Corneal Topography and in vivo Confocal Microscopy in Different Types of Posterior Polymorphous Dystrophy

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Abstract: To observe the morphologic changes in the corneas of patients with posterior polymorphous dystrophy (PPMD), using in vivo confocal microscopy and Orbscan Ⅱ corneal topography. Four patients with clinical diagnosis of PPMD, presenting to the Henan Institute of Ophthalmology, were included in this observational case series. The eyes of the 4 patients were examined by slit-lamp biomicroscopy, Orbscan Ⅱ corneal topography, and in vivo confocal microscopy. Two patients presented with corneal steepening on topography, as well as large areas of irregular polymorphous changes of the corneal endothelium on in vivo confocal microscopy consistent with PPMD. Confocal microscopy demonstrated craters, streaks, and cracks over the corneal endothelium surface. Pleomorphism and polymegathism were present in eyes with PPMD. Guttata and clusters of abnormal endothelial cells were also identified in corneas of these PPMD patients. In vivo confocal microscopy is potentially useful for monitoring of disease progression and excluding suspected cases of subclinical PPMD. Abnormalities on the corneal topography were observed, this report brings forth the descriptions of morphologic changes on Orbscan topography.
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1. Introduction

Posterior polymorphous dystrophy (PPMD, OMIM#122000) is a dominantly inherited corneal disorder associated with morphologic endothelial abnormalities in which affected patients are normally asymptomatic, although corneal edema has been reported in cases associated with widespread endothelial dysfunction. In most patients with PPMD, corneal stromal edema does not develop. Instead, the diagnosis is based on the presence of characteristic bilateral endothelial bands, vesicles, and gray opacifications that do not impair visual acuity (Cibis GW,et al, 1997).

Several methods have been used to delineate the structural features of PPMD. These include clinical biomicroscopy, histopathology, electron microscopy, and specular microscopy. Herein, we present four cases of PPMD imaged by in vivo confocal microscopy and Orbscan Ⅱ slit-scanning elevation topography, demonstrating unusual features that have not previously been reported using these two techniques.

2. Material and Methods

Case 1: A 29-year-old male, who presented with a history of intermittent pain in both eyes, was noted coincidentally on slit-lamp examination to have bilateral PPMD. He had neither significant ophthalmic or medical history nor relevant family history. His ocular symptoms had fully resolved at the time of assessment. On examination, he exhibited a best spectacle-corrected visual acuity of 6/5 OU. Slit-lamp biomicroscopy revealed bilateral vesicular lesions at the level of the endothelium forming clusters. Each lesion was surrounded by a gray "halo". Clinically, there was no associated corneal edema (Figure 1A .B). Intraocular pressures (IOP) were 23.6mmHg OD and 20.9 mmHg OS with cup-to-disc ratios of 0.6 OD and 0.3 OS. The remainder of the slit-lamp examination was unremarkable.

Case 2: A 21-year-old female presented for refractive surgery evaluation. She was a soft contact lens wearer who had no ocular history or current symptoms aside from refractive error. On examination, unaided visual acuity was 6/60 bilaterally and her best spectacle-corrected visual acuity was 6/6 OU. Slit-lamp examination of her left cornea demonstrated a curvilinear row of endothelial vesicular lesions 2 mm below the visual axis. Each vesicle was associated with a grayish halo. The remainder of the ocular examination was unremarkable (Figure 2A .B). Intraocular pressures were within normal limits at 14 mmHg OD and 16 mmHg OS.

Case 3: A 26-year-old male presented after a routine preoperative assessment of LASIK. His uncorrected visual acuity was 6/12 in the right eye

and 6/10 in the left. The best spectacle-corrected vision was 6/6 bilaterally. Aside from refractive error, he had no ocular history or current symptoms. On slit-lamp examination, an incidental finding was a "snake like" band at the level of the endothelium superiorly and inferiorly in the right paracentral cornea and "guttata-like" lesions were identified in the left corneal periphery. On retroillumination, his right cornea showed two prominent, oblique band lesions enclosing an area of abnormal endothelium with a rather guttata appearance which were thought to be cause of patient's reduced visual acuity (Figure 3A.B.C.D). Fundus examination was unremarkable.

Case 3: A 30-year-old female was examined for progressive loss of vision (6/7.5) in her both eyes. There was no improvement with refraction or pinhole in her visual acuity. Slit-lamp examination of her both eyes revealed diffuse endothelial changes with pleomorphism. Elliptical pupils were found but no iridial hole was noticed in both eyes. Broad based iridocorneal adhesion extending anteriorly to the Schwalbe's line was found by gonioscopy from 5 o'clock to 7 o'clock. On retroillumination, the posterior cornea has the appearance of beaten metal or peaud' orange. Diffuse opacities presented as irregular thickening of Descemet's membrane with grayish opacities in a swirled pattern (Figure 4A.B.C.D). There was no corneal staining with fluorescein, and intraocular pressures were 16 mmHg in both eyes. Both optic discs were healthy, with a cup-to-disc ratio of 0.3 bilaterally, and fundus examination was otherwise unremarkable.

Orbscan II slit-scanning elevation topography (Bausch& Lomb Surgical, USA) was performed to measure corneal thickness and topography. After explanation of the procedure and obtaining informed consent, in vivo slit-scanning confocal microscopy (Confoscan3.0, NIDEK, Japan) was performed on all patients.

The patient was asked to fixate on a target, and the examination was performed with a 40 × nonapplanating, immersion lens that covers an area of approximately 0.1 mm2. A drop of Vidisic gel (0.2 ％ Carbomer 940, Bausch & Lomb, USA) on the objective lens served as an immersion and contact substance. For all patients, the cornea was examined using a standard setting of four passes, with a scanning range between 700 μ m and 800 μ m(throughout the z-axis) to image the full central corneal thickness and a 150 μ m scanning range to specially image the corneal endothelium and posterior stroma. The maximal light intensity was used for all examinations.

Three patients presenting with clinical signs and symptoms of PPMD were also examined using a new

in vivo laser-scanning confocal microscopy, the HRT3/RCM (Heidelberg Engineering, Heidelberg, Germany). With the addition of the Rostock Cornea Module, the HRT3 is converted to an in vivo laser scanning confocal microscopy. Before examination, one drop of topical anaesthetic (oxybuprocaine chlorhydrate 1.6mg/0.4ml) and one drop of gel tear substitute (0.2 ％ Carbomer 940, Bausch& Lomb, USA) were instilled in the lower conjunctival fornix. The x-y position of the image and section depth were controlled manually.

Qualitative and quantitative analysis using NAVIS (Nidek Advanced Vision Information System) proprietary software was performed. Endothelial cell density was determined by choosing three representative frames in which endothelial cells were clearly visible. A manually adjusted automated cell count was performed on each frame over an area of 0.05 mm2. Mean values for endothelial cell density, cell area, and the percentage of hexagonal cells within each frame were recorded, and mean values for each cornea were calculated.

3. Results

Table1 shows the patient data. The ages of patients ranged from 21 to 30 but didn't correlate with the clinical severity of the dystrophy. Corneal changes in patient of PPMD are usually bilateral but may show marked asymmetry, and typically assume one of the three basic configurations: vesicular lesions (case 1 and 2), band lesions (case 3), and diffuse opacities (case4)

The results of endothelial analysis were showed in Table2. Endothelial densities didn't correlate with the clinical severity of the dystrophy (in terms of number of lesion seen clinically and presence of corneal edema). For example, the most severely affected case (case4) had an endothelial cell density of 1873 ± 155 cells/ mm2. Endothelial polymegathism was noted in all cases, as demonstrated by high coefficients of variation in cell area; however, endothelial pleomorphism was not a prominent feature, with all cases showing low coefficients of variation in cell shape, and high proportions of hexagonality.

Examination of the confocal images revealed that most of the abnormalities were confined to the Descemet's membrane and endothelium. Both of the in vivo slit-scanning and laser-scanning confocal microscopy revealed craters, streaks, and cracks over the corneal endothelium surface. Guttata and clusters of abnormal endothelial cells were also identified in the corneas of these PPMD patients. Interestingly, case 2,3 and 4 exhibited prominent endothelial nuclei, which were well-defined and brighter than the cytoplasm. Some endothelial cells appeared to have

more than two nuclei. In all patients with clinical PPMD, the changes were similar but varied in severity, being more marked in eyes with lower endothelial cell density.

Case1 and 2 demonstrated multiple small focal vesicular lesions (range, 20.1-93.2μm in diameter), which protruded into the anterior chamber. Vesicles may appear in isolation or in clusters throughout the posterior cornea. With the slit-lamp microscopy, the vesicles appeared as small blisters on Descemet's membrane. On confocal microscopy, the vesicles were surrounded by a diffuse gray halo and vesicles were composed of abnormal pleomorphic cells with indistinct borders, creating black areas in the endothelial mosaic that were surrounded by enlarged endothelial cells. Grouped vesicles may aggregate to form larger geographic lesions (Figure 5.6.9A.9B.10A.10B).

Band lesions (case 3) extended across the posterior corneal surface as two scalloped, raised ridges that run roughly parallel to each other. Like the vesicular lesions, band lesion may be present anywhere in the posterior cornea, although they are most commonly found just inferior to the central cornea (Figure7A.7B).

Diffuse lesions of PPMD were confirmed in case 4 by in vivo confocal microscopy. In vivo confocal microscopic images revealed diffuse endothelial changes with pleomorphism and polymegathism. The borders of endothelium were indistinct and the lesions were geographic shaped. The lesions contained hyperreflective areas within them. Around the lesions, we found hyperreflectivity at the level of Descemet's membrane (Figure 8A. 8B. 11A. 11B). Prominent degenerative intrastromal nerves were also noted in case 3 and 4.

Corneal topography revealed asymmetric with-the-rule astigmatism OD and oblique astigmatism OD in case 3 and 4 respectively. Prominent steepening of the posterior corneal surface can also be seen on their corneal topography (Figure 12.13).

Table1. Patient Data

Case	Eye	Age/Sex	Visual Acuity on Presentation	Slit Lamp Signs of PPMD	Confocal Featur of PPMD	Type of Lesion
1	Right	29/M	6/5	+	+	Vesicular
	Left		6/6	+	+	Vesicular
2	Right	21/F	6/60	-	-	-
	Left		6/60	+	+	Vesicular
3	Right	26/M	6/12	+	+	Band
	Left		6/10	+	+	Vesicular
4	Right	30/F	6/7.5	+	+	Diffuse
	Left		6/7.5	+	+	Diffuse

Table2. Results of Endothelial Cell Analysis

Case	Eye	Mean Endothelial Density±SD (cells/mm^2)	Age-Matched Normal Range for Endothelial Density (cells/mm^2)	Mean Endothelial Cell area±SD (μm^2)	Coefficient of Variation(area) (%)	Coefficient of Variation(sides) (%)	Hexagonal Cells (%)
1	Right	2056±102	2056-3594	488±24	30.4	11.4	62.8
	Left	2440±319	2056-3594	417±54	41.6	15.6	48.1
2	Right	3225±72	2291-3873	310±7	36.4	13.5	50.4
	Left	2519±122	2291-3873	398±20	39.8	14.2	51.3
3	Right	1810±147	2102-3641	552±41	31.4	12.9	56.8
	Left	1377±145	2155-3696	715±53	33.0	13.5	57.9
4	Right	1873±155	2035-3572	538±44	48.1	19.3	36.8
	Left	2206±284	2035-3572	458±60	56.4	20.2	34.2
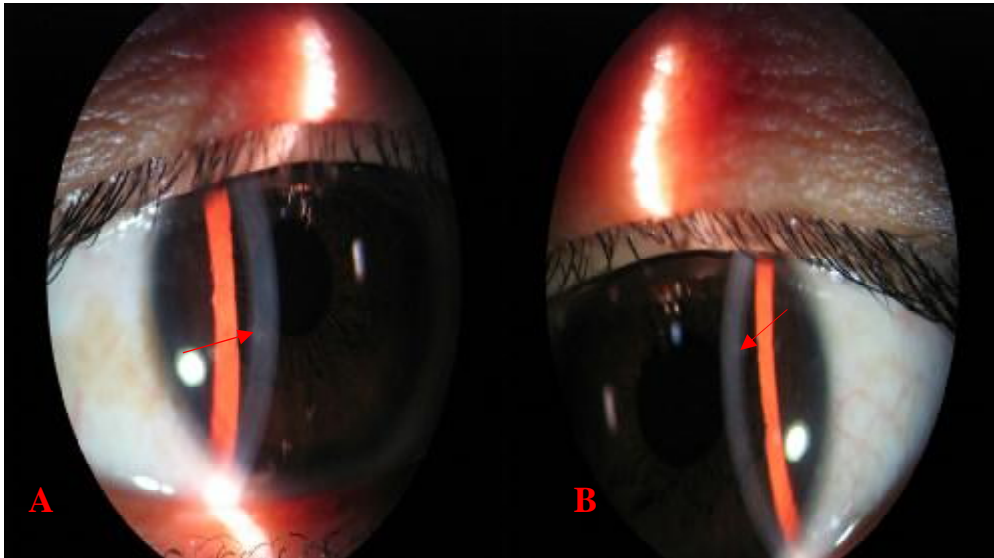
Figure 1 **A** **B**
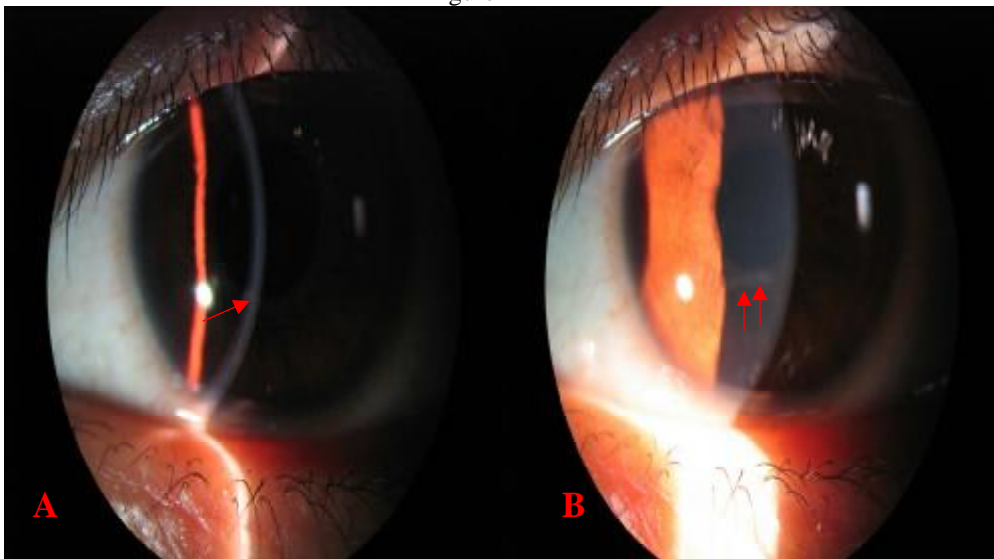
Figure 2 **A** **B**
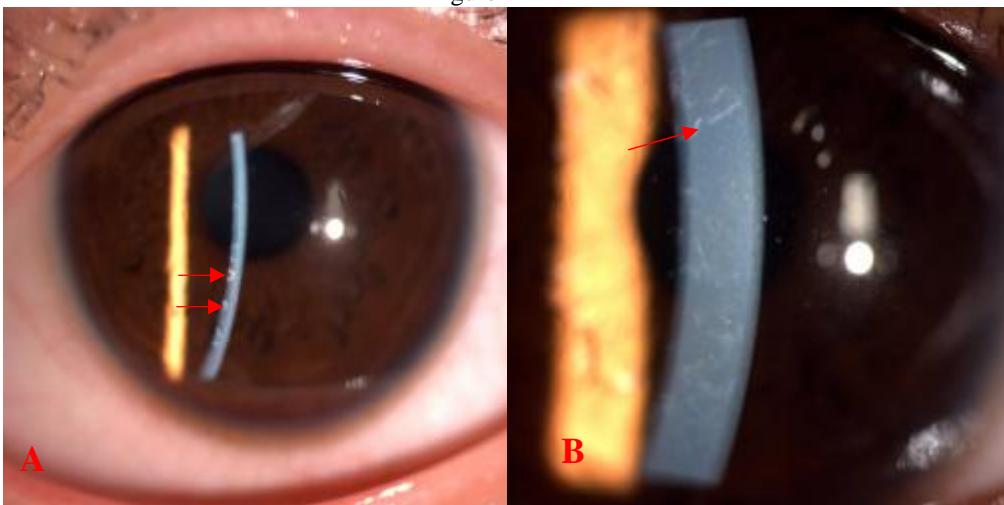
Figure 3 **A B C D**

Figure 4 **A B C D**

Figure 5   Figure 6

Figure 7 **A B**
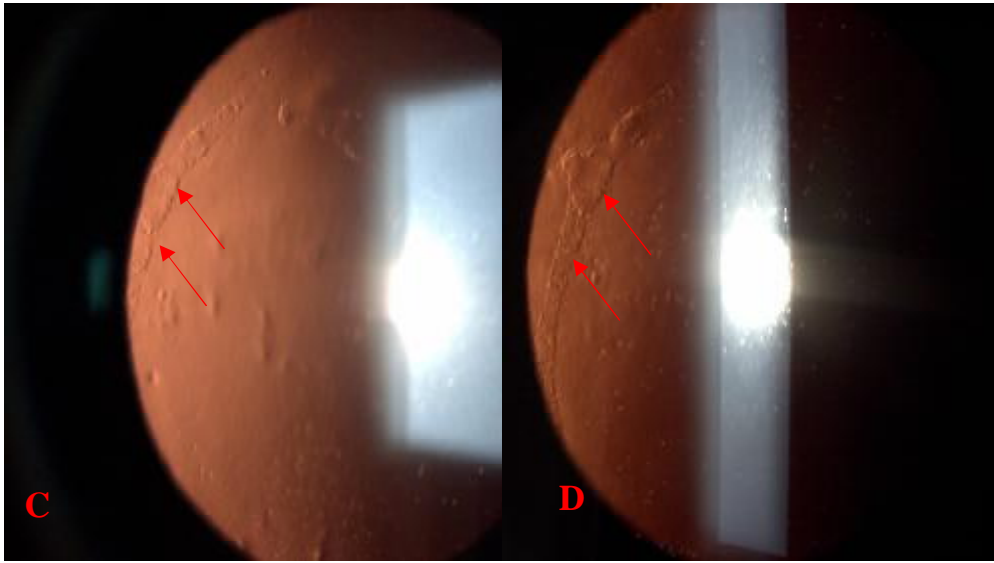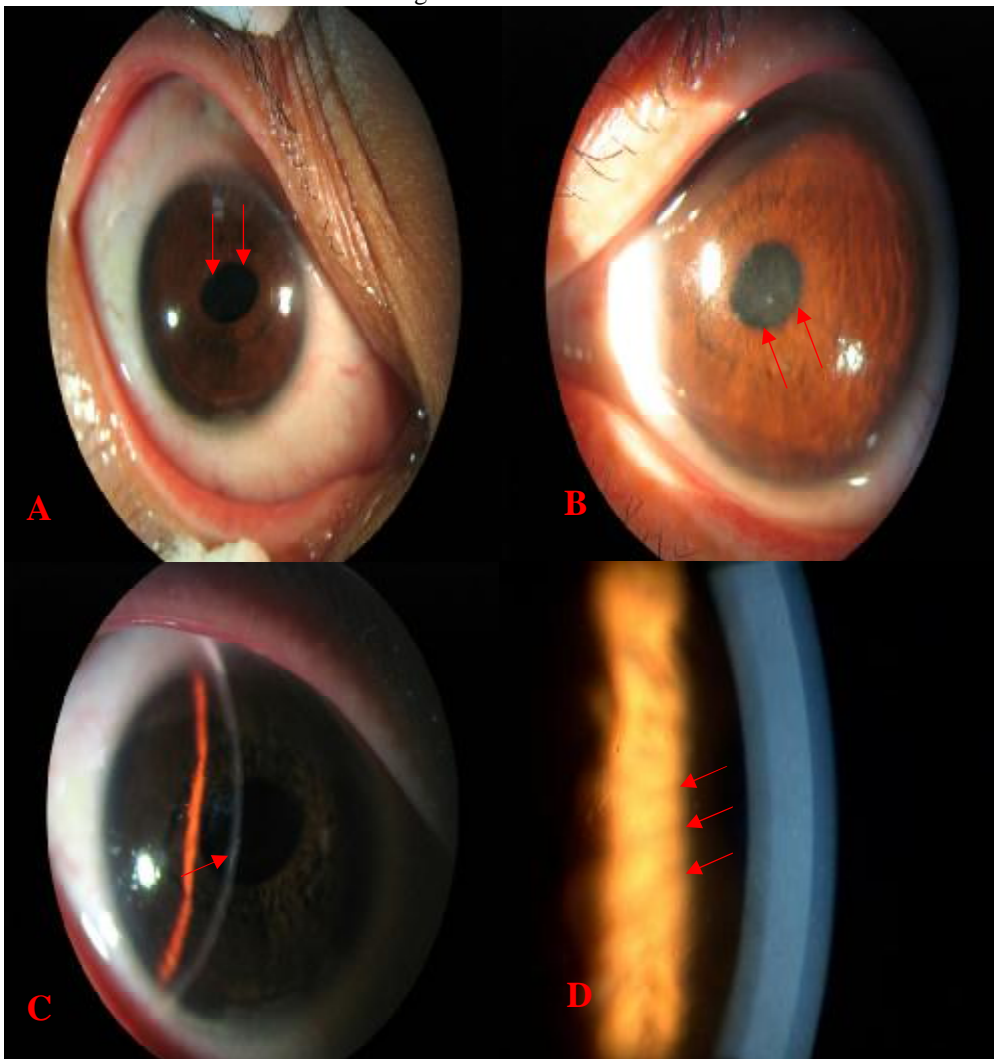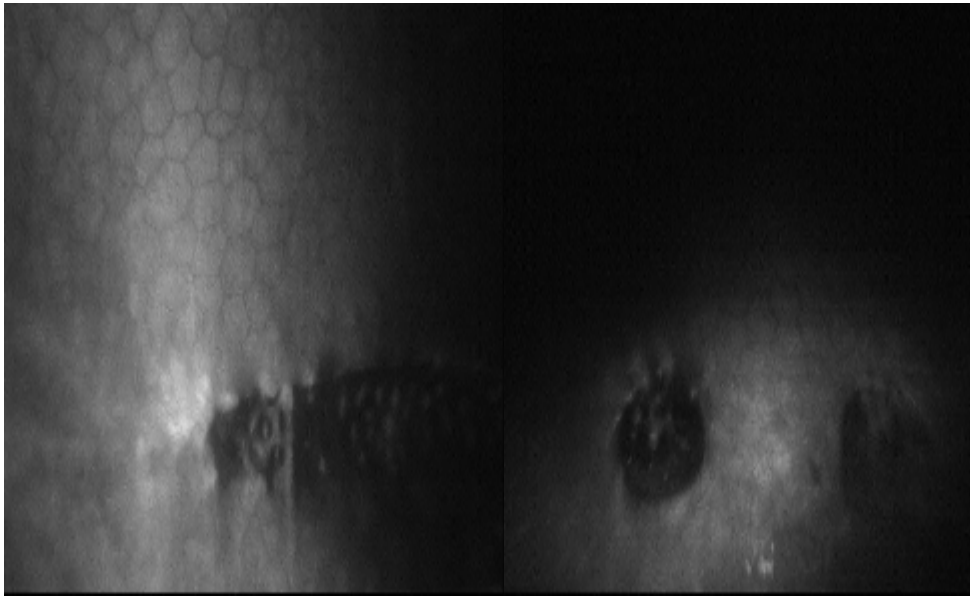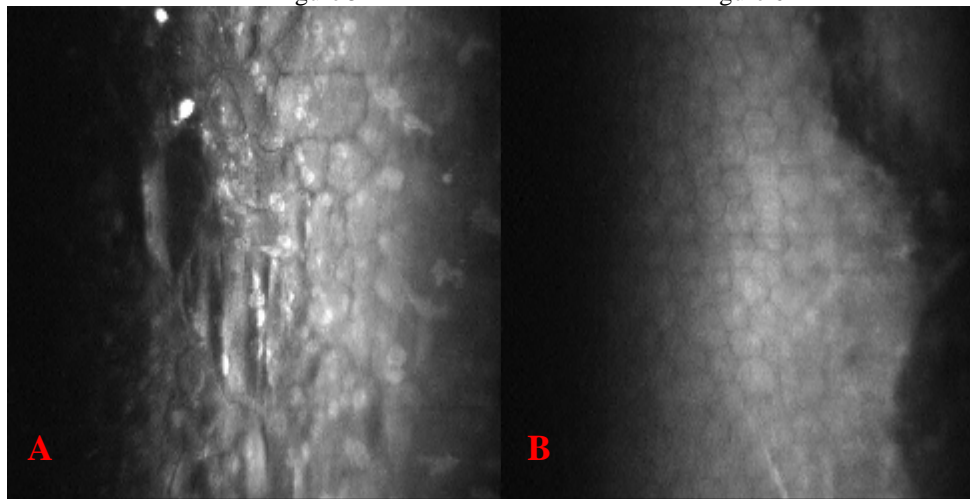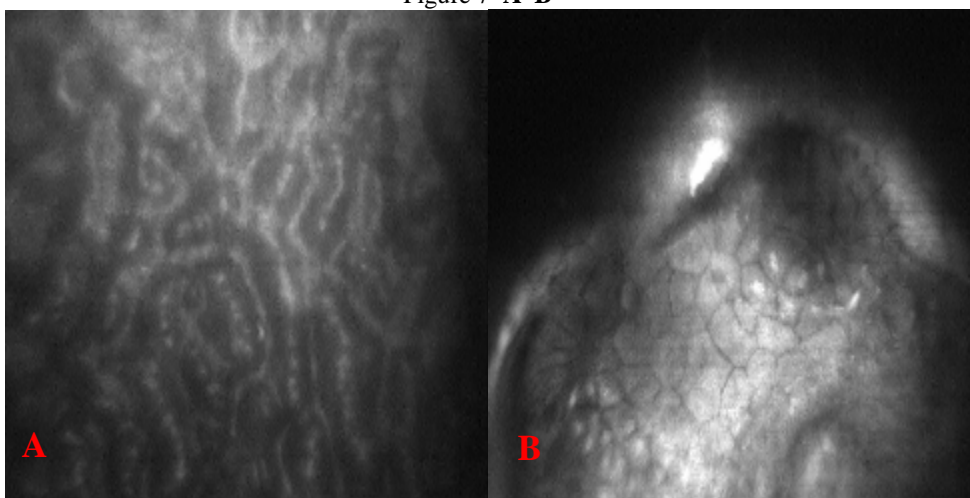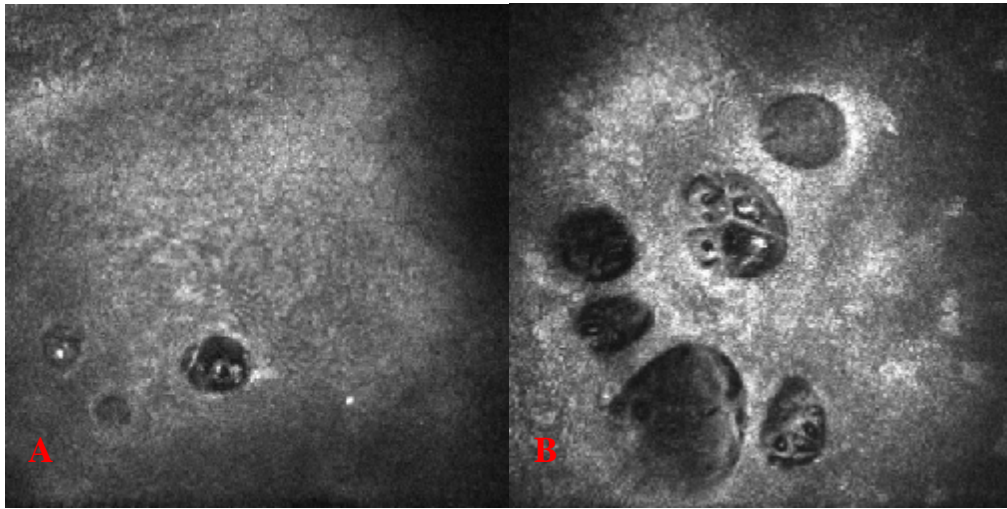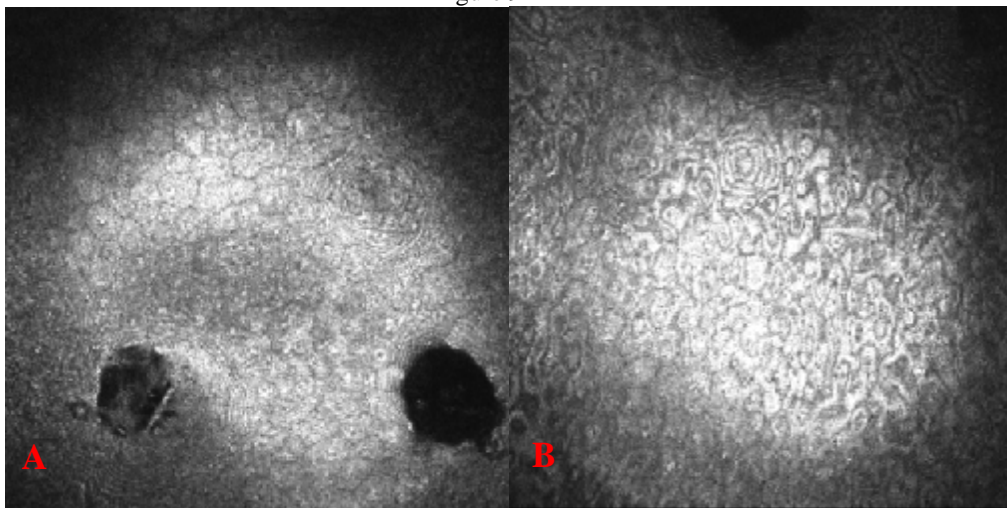

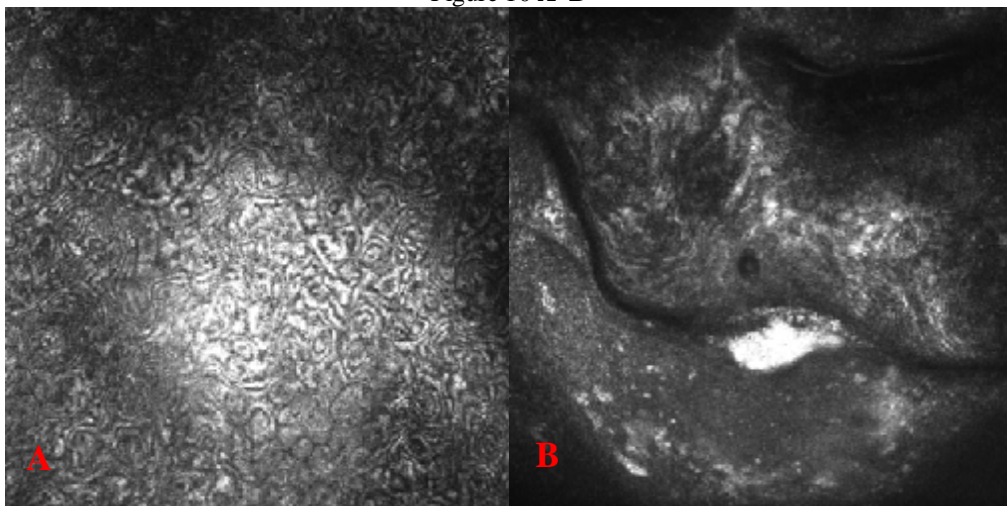Figure 8 A   B

Figure 9 A   B

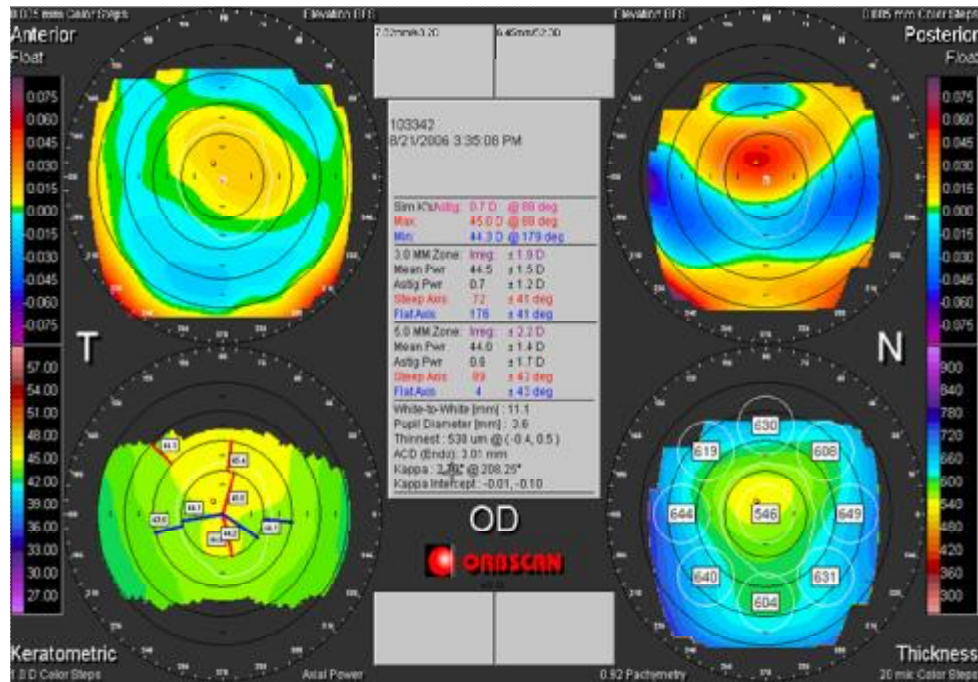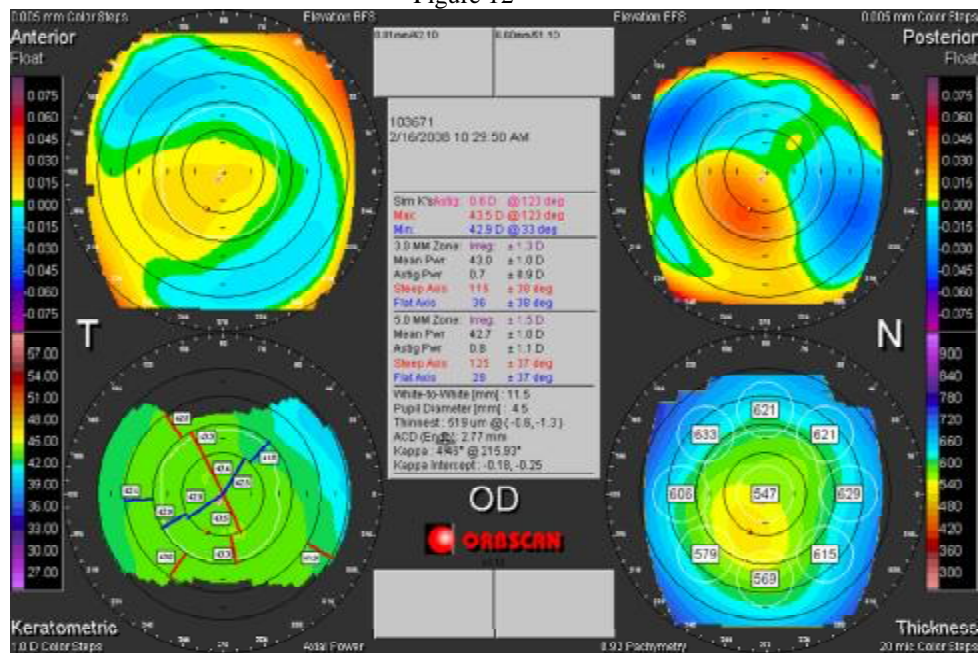Figure 10 **A   B**

Figure 11 **A   B**

Figure 12

Figure 13

Figure 1 (A .B) Case 1 Slit-lamp biomicroscopy revealed bilateral vesicular lesions at the level of the endothelium forming clusters. Each lesion was surrounded by a gray "halo". Clinically, there was no associated corneal edema

Figure 2 (A .B) Case 2 Slit-lamp biomicroscopy demonstrated a curvilinear row of endothelial vesicular lesions 2 mm below the visual axis. Each vesicle was associated with a grayish halo

Figure 3 (A .B.C.D) Case 3 On slit-lamp examination, an incidental finding was a "snake like" band at the level of the endothelium superiorly and inferiorly in the right paracentral cornea and "guttata-like" lesions were identified in the left corneal periphery.

Figure 4 (A .B.C.D) Case 4 Slit-lamp examination revealed diffuse endothelial changes with pleomorphism. Elliptical pupils were found but no iridial hole was noticed in both eyes.

Figure 5 Case 1 / Figure 6 Case2 Confoscan 3.0 and Figure 9 (A .B) Case 1 / Figure 10 (A .B) Case2 HRT3/RCM Show the vesicles were surrounded by a diffuse gray halo and vesicles were composed of abnormal pleomorphic cells with indistinct borders, creating black areas in the endothelial mosaic that were surrounded by enlarged endothelial cells.

Figure 7 (A .B) Case 3 Confoscan 3.0 Show band lesions extended across the posterior corneal surface as two scalloped, raised ridges that run roughly parallel to each other. Like the vesicular lesions, band lesion may be present anywhere in the posterior cornea.

Figure 8 (A .B) Case 4 and Figure 11 (A .B) Case4 HRT3/RCM Confoscan 3.0 In vivo confocal microscopic images revealed diffuse endothelial changes with pleomorphism and polymegathism. The borders of endothelium were indistinct and the lesions were geographic shaped. The lesions contained hyperreflective areas within them. Around the lesions, we found hyperreflectivity at the level of Descemet's membrane

Figure 12 Case 3 and Figure 13 Case 4 Corneal topography revealed asymmetric with-the-rule astigmatism OD and oblique astigmatism OD respectively. Prominent steepening of the posterior corneal surface can also be seen on their corneal topography

4. Discussions

PPMD, a slowly progressive disease of the cornea, was first described by Koeppe (1916). He named the condition "keratitis bullosa interna" to describe the characteristic bullous lesions he noted in the posterior cornea.

A wide spectrum of corneal changes can be seen in PPMD, ranging from a few vesicular lesions to total opacification of the cornea with edema (Levy, et al, 1996). In PPMD, dystrophic endothelial cells exhibit epithelial features, and produce secondary abnormalities in Descemet's membrane (Sekundo, et al, 1994). Iris and anterior chamber angle structures may also be affected in some patients with PPMD (Pardos, et al, 1981; Laganowski, et al, 1991; Hirst, et al, 1983; Krachmer, 1985).

Posterior polymorphous dystrophy typically has an autosomal dominant inheritance pattern, although penetrance of the disease is low. Mutations in VSX1 homeobox (on chromosome 20q11) and COL8A2（on chromosome 1p）genes have been identified in PPMD (Heon, et al, 2002; Biswas, et al, 2001).

In addition, the clinical expression of the disease can vary considerably, even within affected families. For example, one member of the family may only be minimally affected with asymptomatic corneal lesions, whereas a sibling may have severe peripheral synechiae with glaucoma and corneal decompensation.

Clinically, PPMD is characterized by the presence of endothelial lesions, which have been classified into three basic configurations: vesicular lesions, band lesions, and diffuse opacities (Waring, et al, 1978). Vesicles appear as endothelial blisters or blebs on slit-lamp examination and these may be isolated or form clusters or curvilinear patterns (Grupcheva, et al, 2001). Band lesions are characterized by strips of guttata-like irregularities of Descemet's membrane and diffuse PPMD is seen as diffuse irregularities in Descemet's membrane , often associated with corneal edema. One study found that vesicles and bands were twice as common in women as in men, and that vesicles were mostly bilateral (94％) whereas bands were usually unilateral (85％) (Laganowski, et al, 1991). The significance of these findings is not known. The disease can be slowly progressive, but in many cases the findings are static. PPMD can rarely cause visual dysfunction from corneal edema, iridocorneal adhesions, corectopia, and glaucoma (Hirst, et al, 1983). The precise age of onset of PPMD is difficult to determine because most patients have no symptoms. However, a majority of patients are diagnosed in the second or third decade of life. Herein, the ages of our patients ranged from 21 to 30.

From a histological viewpoint, corneal endothelium abnormalities are the hallmark of PPMD. The primary event is believed to be "epithelialization" of the corneal endothelium (Witshcel, et al, 1980; Boruchoff, et al, 1971; Grayson, et al, 1974; Rodrigues, et al, 1980; Henriquez, et al, 1974; De Felice, et al, 1985; Matsumoto, et al, 1988; Rodrigues, et al, 1988). The stimulus for this transformation is not known. The epithelial-like endothelial cells exhibit many morphologic and growth features of the normal epithelium, including a multilaminar pattern, desmosomal junctions, microvilli, cytoplasmic keratin, sparse mitochondria, and rapid growth in tissue culture. They also stain with antisera prepared against human epidermal keratin (Rodrigues, et al, 1988). The transition between endothelial and epithelial-appearing cells can be abrupt (Henriquez, et al, 1984).

The epithelial-like cells are capable of migrating over the endothelial cells without adhering to them and can grow to cover the trabecular meshwork and iris, leading to intractable glaucoma (Rodrigues, et al, 1980). The "epithelialized" cells secrete a thick membrane that resembles an abnormal Descemet's membrane. These cells may even regenerate after corneal transplantation. Descemet's membrane is absent or markedly attenuated in the areas covered by the epithelial-like cells.

In addition to the characteristic epithelial-like cells, many other changes in the endothelium have been noted. Metaplastic fibroblast-like endothelial cells can be seen (Johnson, et al, 1981; Polack, et al, 1980; Boruchoff, et al,1990). Pleomorphism and degeneration of endothelial cells are common findings in PPMD (Polack, et al, 1980; Boruchoff, et al, 1990). Attenuated endothelial cells with disorganized organelles, large vacuoles, phagosomal inclusions, and disrupted cell membranes have been described using transmission electron microscopy. Areas of hypertrophic endothelial cells coexist with areas of focal endothelial cell loss, suggesting competing degenerative and regenerative processes (Polack, et al, 1980).

Alterations in Descemet's membrane, including deposition of abnormal collagen, guttata, and pits, are a common finding in PPMD (Rodrigues, et al, 1982). The changes are believed to be secondary to the primary alterations in the endothelium. Thickening of Descemet's membrane is the typical finding, although attenuation of this layer has occasionally been noted (Hanna, et al, 1977). The posterior collagenous layer can be interrupted by irregular excrescences, which resemble the cornea guttata observed in Fuch's endothelial dystrophy.

The pathogenesis of PPMD likely involves abnormal transformation and migration of the endothelial cells with secondary alterations in Descemet's membrane, but the stimulus for these events is unclear. The concept of metaplasia has been proposed to explain the endothelial changes in PPMD. Epithelial or fibroblastic transformation in PPMD may represent a metaplastic response of endothelial cells, although the trigger is not known (Johnson, et al, 1976). Differential staining patterns with specific epithelial and endothelial antibodies support the idea that endothelial cell transformation occurs in PPMD (Ross, et al, 1976). Some endothelial cells stain only with the endothelial antibody, some stain with both types of antibodies, and others stain only with epithelial antibody, suggesting that endothelial cells progress from a normal phenotype to a transitional phenotype, and finally to an abnormal epithelial phenotype.

Unfortunately, histologic studies have only been performed on corneal buttons after penetrating keratoplasty and therefore represent only severe cases of PPMD with corneal edema. Both specular and confocal microscopy enable imaging of the cornea in vivo and may be used to examine earlier or mild cases that represent the most common form of PPMD.

In vivo confocal microscopy is an invaluable additional tool for further investigation of PPMD. Due to a combination of high resolution and magnification, it highlights pathological findings at a cellular level in all corneal layers, not just the endothelium and Descemet's membrane. In vivo confocal microscopy provides a unique opportunity for clinicopathological assessment of corneal dystrophies such as PPMD that do not generally progress to penetrating keratoplasty.

To our knowledge, there are only a few published reports of in vivo confocal microscopy in PPMD. Chiou et al (1999) identified patchy, round hyporeflective areas at the level of Descemet's membrane in one subject and hyporeflective bands with marginal hyperreflective structures at the level of Descemet's membrane in a second subject. Unfortunately, although vesicular and band-like lesions were identified by slit-lamp microscopy, the authors didn't comment on any endothelial structures visualized by in vivo confocal microscopy. Grupcheva, et al, (2001) identified endothelial vesicular lesions composed of optically dense material, forming in deep stromal keratocyte density was noted. An interesting finding in this case was protrusion of endothelial vesicles into the anterior chamber. Confocal microscopy demonstrated craters, streaks, and cracks over the corneal endothelium surface. Pleomorphism and polymegathism were present in eyes with PPMD. Guttata and clusters of abnormal endothelial cells were also identified in corneas of our PPMD patients.

A striking feature of two of our cases presented is the abnormal changes on corneal topography. Prominent steepening of the posterior corneal surface can be seen in case 3 and 4. The lesion type of case 3 and 4 are band and diffuse respectively. This may be caused by the larger area of abnormal endothelium. PPMD has been associated with keratoconus in several reports (Gasset, et al, 1974; Weissman, et al, 1989; Bechara, et al, 1991; Blair, et al, 1992; Driver, et al, 1994). Keratoconus (OMIM#148300) is a frequent corneal dystrophy with a reported incidence that varies from 50 to 230 per 100,000 (approximately1/2000) (Rabinowitz and Keratoconus, 1998). Characteristically, the cornea assumes a conical shape as a result of progressive noninflammatory thinning of the corneal stroma. The thinning of the cornea causes irregularity in its curvature (astigmatism) and corneal protrusion resulting in a variable degree of visual impairment. Depending on the stage of the disease, every layer of the cornea may become involved in the pathological process. Although Descemet's membrane and endothelial cells may show minor changes, the major pathological defects lie in the anterior cornea, with compaction of the stroma and breaks in Bowman's membrane (Rabinowitz,1998). In case 3 and 4, the epithelium and Bowman's membrane appeared unremarkable. Subepithelial nerve plexuses with normal configuration and density were present subjacent to the Bowman layer. We also observed prominent degenerative intrastromal nerves by in vivo confocal microscopy, the relevance of which, if any, has not previously been assessed in PPMD.

Most patients with PPMD remain asymptomatic. This disease is only rarely progressive or visually impairing. Therapeutic intervention is not typically required. If epithelial edema occurs, it may be treated with hypertonic agents. Penetrating keratoplasty may be required in patients with severe disease. Overall, the prognosis for surgery is good, unless iris adhesion or glaucoma are present. Recurrence of PPMD following corneal transplantation has been reported, typically manifesting as a retrocorneal membrane or thick fibrous deposits between the epithelialized cells and Descemet's membrane (Sekundo, et al, 1994).

To the best of our knowledge, this is the first time we study the Chinese patients with PPMD by using in vivo confocal microscopy and Orbscan Ⅱ corneal topography. As there might be variations between cases, further studies, particularly about Orbscan Ⅱ corneal topography and in vivo confocal microscopy, are called for to define the distinctive features of this dystrophy.

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