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Pre-Descemet Corneal Dystrophy – Changes in Corneal Morphology in Confocal Microscopy

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Abstract: **Purpose:** To identify and describe the in-vivo microstructural changes in the cornea of patients with pre-Descemet's membrane corneal dystrophy. Method: Ten patients (20 eyes) were examined in the Laser Microsurgery Centre in Warsaw. The ophthalmic examination, including visual acuity and slit lamp biomicroscopy, was carried out. Because of suspicion of corneal dystrophy, in vivo confocal microscopy of the cornea was also performed.
Results: Biomicroscopy revealed bilateral, dust-like fine opacities in the deep parts of the corneal stroma. Confocal microscopy showed pleomorphic structures (enlarged keratocytes) containing dense, hyperreflective, granular inclusions in the posterior stroma, next to the Descemet's membrane. In 3 patients (6 eyes) punctate particles were seen extracellularly also in the mid stroma. Superficial and basal epithelial layers, anterior stroma and endothelium cells appeared normal.
Conclusions: 1. In vivo confocal microscopy findings of cornea with pre-Descemet's membrane dystrophy are characteristic. 2. In vivo confocal microscopy is a useful tool in diagnosing rare corneal dystrophies in cases where classical examination methods give inconclusive results.

Key words: pre-Descemet corneal dystrophy, in vivo confocal microscopy.

Introduction

Corneal dystrophies are a group of congenital diseases that usually manifest bilaterally. The progression of the lesions is not always symmetrical. They show slow progression and are unrelated to systemic and environmental factors [1]. The term 'corneal dystrophy' was first introduced by Grenouw, who in 1890 described 2 patients with a 'nodular cornea' [2].

Pre-Descemet corneal dystrophy (PDCD) is a rare corneal dystrophy. According to the International Classification of Corneal Dystrophies (IC3D), there are two subtypes of PDCD: 1 – an isolated form of PDCD with unknown locus of the gene responsible for the lesions, and 2 – PDCD associated with X-linked ichthyosis. In this case, a deletion of the steroid sulfatase gene located on chromosome Xp22.3 (MIM#30 8100) is responsible for the lesions [3]. The dystrophy is usually asymptomatic and the diagnosis is made incidentally during an ophthalmological examination for which the patient has presented for another reason. The abnormality affects the posterior corneal stroma and typically appears in both eyes. The picture is not always unambiguous.

Fine-particle opacities visible biomicroscopically in the immediate vicinity of Descemet's membrane are sometimes the reason for referring a patient for confocal microscopy to confirm the diagnosis or to differentiate with pathology within the corneal endothelium, e.g. endothelial dystrophy or the presence of inflammatory cells on the endothelial surface. The disease has a slow and benign course, which is associated with the lack of need to implement treatment.

The aim of this study is to analyze changes in the structure of individual corneal layers in patients with pre-Descemet's dystrophy observed using confocal microscopy (in vivo confocal microscopy, IVCM). Due to its high magnification and high resolution, it allows non-invasive and accurate imaging of all corneal layers at the cellular level.

Material and methods

The study group consisted of 10 patients (20 eyes) of the LASER Eye Microsurgery Centre in Warsaw (4 women and 6 men) aged 34 to 43 years (mean age 39 years) referred to the confocal microscopy laboratory with a suspicion of stromal or endothelial corneal dystrophy raised on the basis of slit-lamp examination (Tab. I). Visual acuity and slit-lamp evaluation of the anterior segment of the eye were performed in all patients. Because corneal dystrophy was suspected, the examination was extended to include confocal microscopy with a Confoscan4 instrument from Nidek Technologies (Italy). The procedure for this examination has already been described in detail [4].

Results

In all patients, the best corrected visual acuity for distance was 1.0; best corrected visual acuity for near was Sn = 0.5. Slit-lamp examination revealed the presence of small, multiform, light-grey, discrete opacities in the posterior corneal stroma, immediately anterior to Descemet's membrane (Fig. 1, 2). The density/ severity of the lesions varied slightly between patients. No other abnormalities were found in the anterior segment of the eye.

Confocal microscopy results: individual epithelial cell layers (Fig. 3A, B) and subepithelial nerve plexuses within normal limits (Fig. 3C). Anterior (Fig. 4A) and mid (Fig. 4B) stroma with normal morphology. In 3 patients (6 eyes), scattered extracellular small hyperreflective granules were found within the intermediate part of the stroma. In all patients (20 eyes), pleomorphic structures (enlarged, excited keratocytes) measuring 20–60 μm filled with hyperreflective, fine-grained deposits of heterogeneous size were visualized in the posterior part of the corneal stroma (Fig. 5), adjacent to Descemet's membrane (Fig. 6) (Fig. 7A, B). In eight patients (16 eyes), fine deposits with increased reflectivity were also present extracellularly (Fig. 8).

Nr	1	2	3	4	5	6	7	8	9	10
Age	34	37	40	41	38	35	43	38	41	42
Sex	M	M	M	M	F	F	F	F	M	M
Bilateral changes	+	+	+	+	+	+	+	+	+	+
Endothelial cell density RE/ LE	3328/ 3182	3290/ 3108	2856/ 2978	2956/ 3086	2987/ 3197	3045/ 3216	2889/ 2718	2912/ 3176	3019/ 2896	2693/ 2789
Endothelial cells morphology	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
Intracellular hyperreflective particles	+	+	+	+	+	+	+	+	+	+
Extracellular deposits	+	+	+	+	+	-	+	+	+	-
Involvment of medial parts of corneal stroma	-	-	+	-	-	-	+	+	-	-

Tab. I. Patients data and confocal microscopic findings.

The described changes occurred only in the part of the stroma immediately anterior to Descemet's membrane (at a maximum distance of 90 μm from the endothelium) and corresponded to biomicroscopically visible fine haze. Their number increased posteriorly and the maximum degree of semen varied among patients (Fig. 7A–D). In one patient (2 eyes), polymorphic cells filled with fine granules were interconnected, giving the impression of a net (Fig. 7C, D). There were no abnormalities in Descemet's membrane or endothelial cells (Fig. 9). Endothelial cell density in the study group assessed in the center of the cornea ranged from 2693 cells/ mm^2 to 3328 cells/ mm^2 and was within the normal limits for age.

In view of the negative history for X-linked ichthyosis, the diagnosis of isolated pre-Descemet corneal dystrophy was either diagnosed or confirmed in all patients studied.

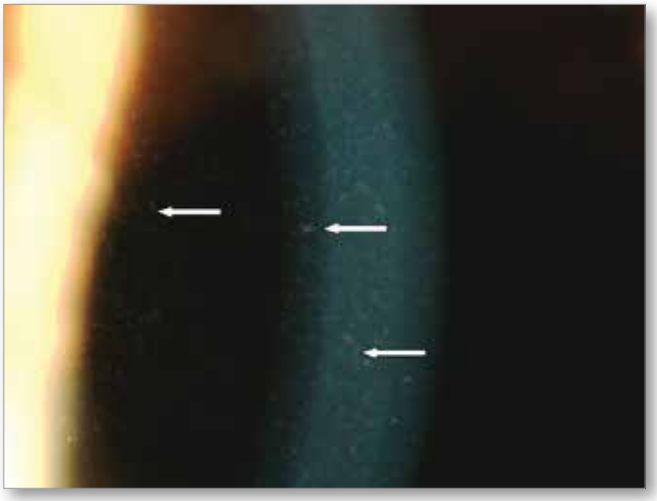

Fig. 1. Small, grey-white and scurf-like corneal opacities.

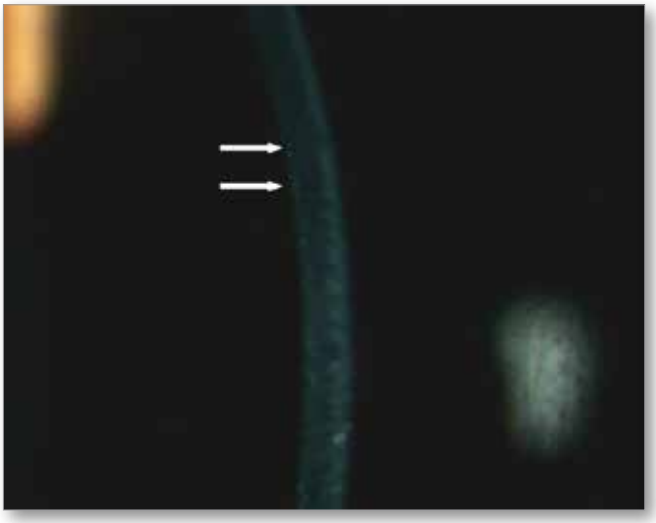

Fig. 2. Opacities located in posterior stroma, near Descemet's membrane.

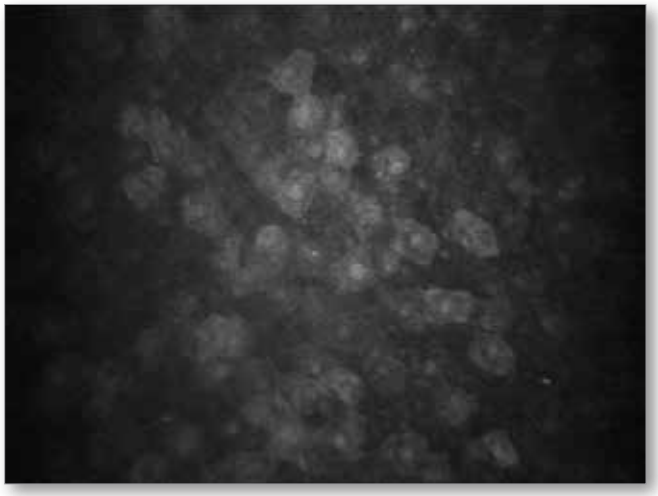

Fig. 3A. Normal surface epithelial cells.

Fig. 3B. Normal basal epithelium.

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Fig. 3C. Normal appearance of subepithelial nerve fibers.

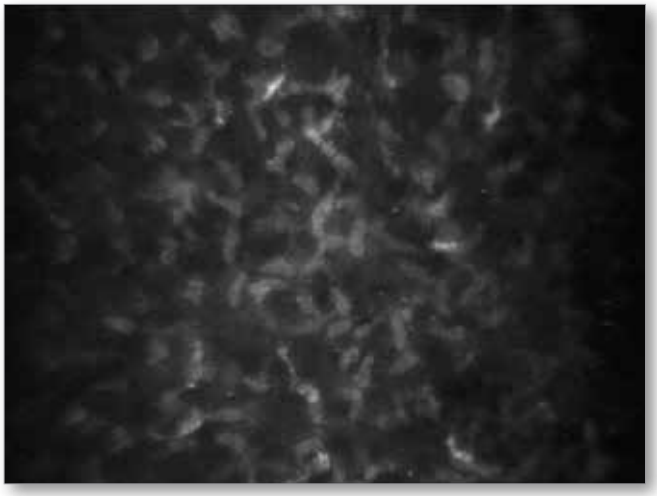

Fig. 4A. Image of unchanged anterior and medium stroma.

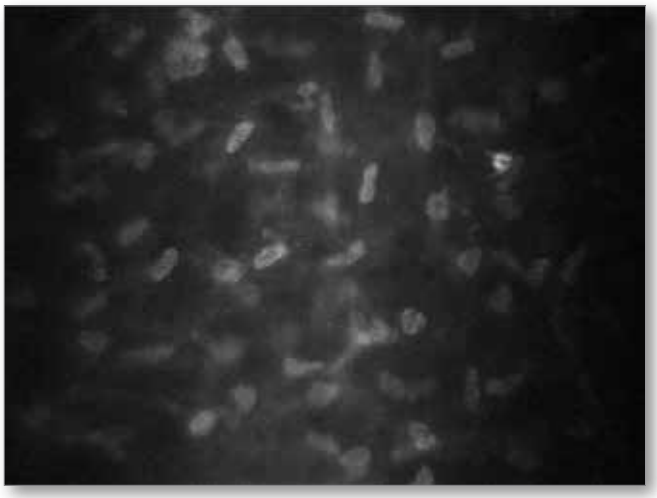

Fig. 4B. Image of unchanged anterior and medium stroma.

Discussion

Pre-Descemet corneal dystrophy (PDCD) is a rare, binocular, corneal disorder. The diagnosis is usually made around 30–40 years of age. Its course is usually asymptomatic. The diagnosis is usually made incidentally during an examination for another reason. It is estimated that many patients remain undiagnosed,

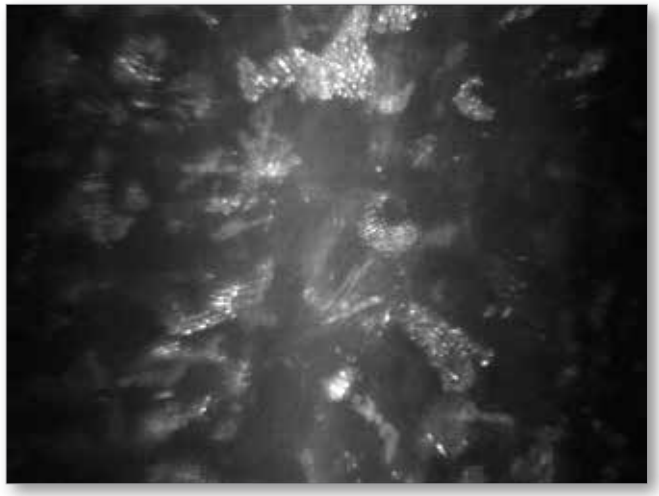

Fig. 5. Posterior part of corneal stroma.

Fig. 6. Opacities near Descemet's membrane layer.

which makes it difficult to accurately determine the prevalence of the disease in the population. It was first documented in 1947 by Maeder and Danis [5]. They described a patient suffering from keratoconus, in whom, in addition, filiform, discrete changes were observed in the deep layers of the corneal stroma. In the following years, there were descriptions of similar corneal changes in patients with congenital ichthyosis [6] but also without accompanying conditions. Collier [7] followed by Grayson and Wilbrand [8] described the familial occurrence of corneal lesions and proposed a morphological classification of opacities located in the posterior stromal layers, adjacent to Descemet's membrane.

They divided them into groups: 1. fine-particle haze ('cornea farinata'); 2. larger, more pleomorphic opacities; 3. opacities in the posterior stroma accompanying other corneal conditions or systemic diseases. They observed that small, fine lesions can occur alone or accompany pleomorphic opacities within the same eye or in a companion eye. They speculated that they may be an earlier stage of these. Currently, according to the 2015 International Classification of Corneal Dystrophies (IC3D), there are two subtypes of PDCD: 1 – the isolated form of PDCD and 2 – PDCD associated with X-linked ichthyosis. Alió et al. reported the presence of mutations in the PRDX3 gene in 12 of 21 members of three families with clinically diagnosed punctiform and polychromatic pre-Descemet corneal dystrophy, a variant of isolated PDCD [9].

The most characteristic changes are observed in the posterior part of the corneal stroma. These are binocular pleomorphic (punctiform/ filiform) opacities visible in the immediate vicinity

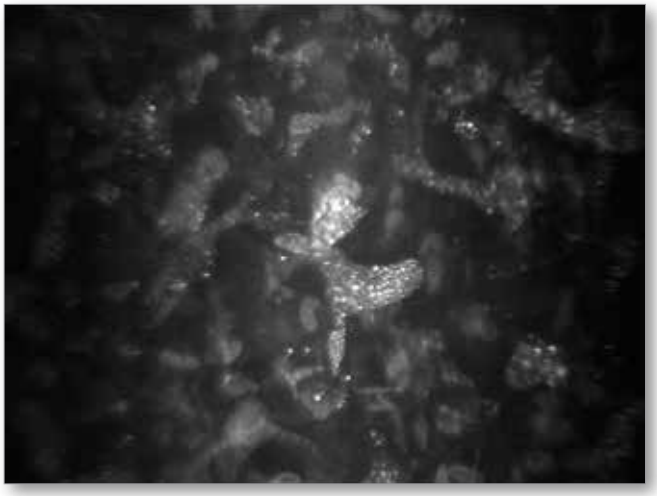

Fig. 7A. Hyperreflective dot-like intracellular inclusions observed in keratocytes.

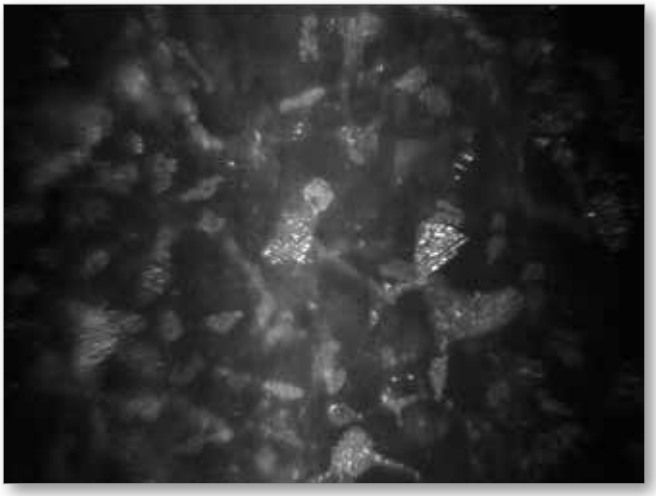

Fig. 7B. Numerous tiny, pleomorphic opacities located anterior to Descemet's membrane.

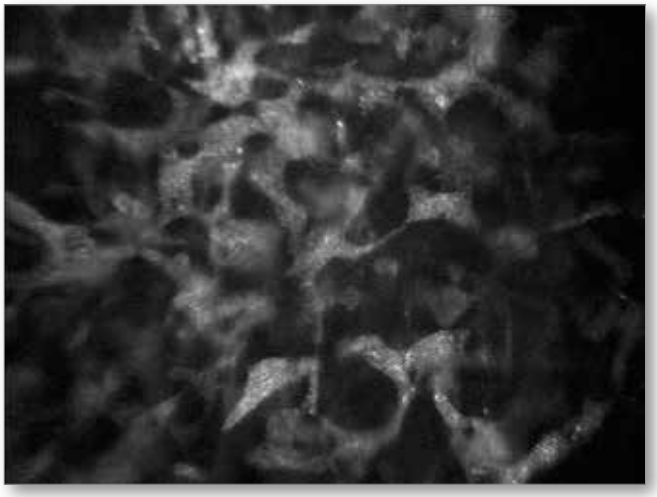

Fig. 7C. Network-like appearance of numerous keratocytes filled with small, granular particles.

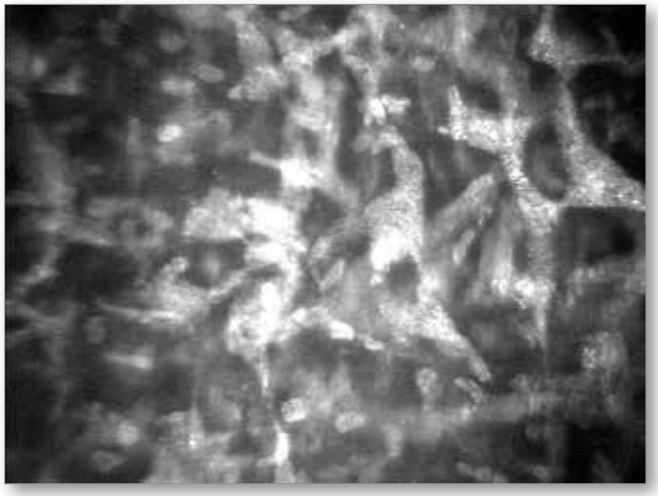

Fig. 7D. Network-like appearance of numerous keratocytes filled with small, granular particles.

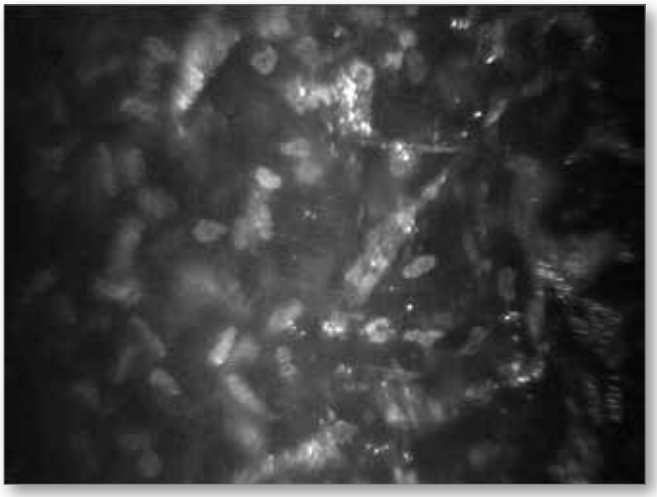

Fig. 8. Small extracellular dots in posterior stroma.

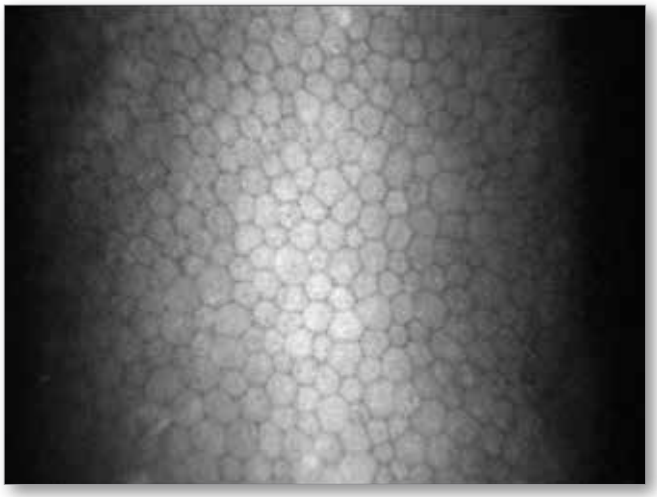

Fig. 9. The density and morphology of endothelial cells are normal.

of Descemet's membrane. These can be assessed using a variety of diagnostic equipment, from biomicroscopic examination, through confocal microscopy, to histology and electron microscopy. Due to the practical lack of impact on visual acuity, the availability of corneal tissue for histopathological examination is severely limited. Curran et al. [10] were the first to describe the results of histological and electron microscopic examination, which allowed a more accurate definition and understanding of the corneal morphology of patients with pre-Descemet's dystrophy.

They described the presence of enlarged keratocytes whose body was filled with numerous vacuoles filled with lipofuscin-like lipids. The altered cells were located in the posterior part of the cornea. The image obtained by confocal microscopy is very consistent with that described above. In all patients, it was possible to

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confirm the presence of pleomorphic structures with a cell nucleus, homogeneously filled with very fine granules (Fig. 5, 6, 7). In all likelihood, these are enlarged/activated keratocytes. The hyperreflective granules within the cytoplasm are consistent with those described by Curran et al. and Kempster et al. [11].

In the present study, in 3 patients (6 eyes), in addition to the typical changes in the posterior stroma, the presence of small granules located extracellularly in the more anteriorly located layers of the cornea was observed. Similar changes were reported in the literature. Shi et al. [12] described the case of a 34-year-old patient with PDCD associated with ichthyosis. On confocal microscopy, in addition to the typical keratocytes filled with fine granules seen in the posterior stroma, they found similar granular deposits in the extracellular space also in the anterior stromal layers.

Malhotra et al. [13] in their study also confirmed the involvement of the anterior layers of the cornea in the disease process. Biomicroscopic examination and anterior segment optical coherence tomography (AS OCT) indicated involvement of not only the stromal layers immediately anterior to Descemet's membrane. Confocal microscopy confirmed the presence of typical fine-grained hyperreflective deposits throughout the thickness of the stroma. The intensity of the substitutions gradually increased posteriorly from fine-grained deposits located extra- and intracellularly, not affecting cell size in the anterior layers, to the presence of enlarged, activated keratocytes with cytoplasm overflowing with hyperreflective deposits in the posterior layers.

Alafaleq et al. [14]. Analyzing AS OCT images from 4 patients with PDCD, in addition to the typical hyperreflective line directly anterior to Descemet's membrane corresponding to biomicroscopically visible opacities, they observed a thinner hyperreflective line directly under Bowman's layer and very fine bright reflections throughout the thickness of the stroma. These changes were consistent with the presence of activated keratocytes in the stromal layers immediately below the epithelium. The authors noted that the abnormalities observed on AS OCT were visible not only in the central, but also in the peripheral part of the cornea extending to the corneal limbus.

The microscopic image confirmed the involvement of the entire thickness of the stroma in the pathological process, with the greatest intensity of deposits directly anterior to Descemet's membrane, leaving an unchanged epithelium and endothelial cell layer.

In the present study, corneal endothelial abnormalities were not found in any of the 10 patients studied. There are isolated reports in the literature of endothelial changes in eyes with PDCD. Malthora et al. [13] described 1 patient in whom, in addition to stromal changes, hyperreflective deposits scattered on the endothelial surface were visualized in the IVCM. The morphology of the deposits was similar to that of deposits observed in the corneal stroma. The density and morphology of the endothelial cells remained within normal limits. Alka et al. [15] described 1 patient with PDCD with typical biomicroscopic and confocal images of the corneal stroma. They further noted an increased rate of polymorphism and polymegethism of the cells while maintaining normal cell density. The co-occurrence of pre-Descemet's dystrophy with other endotheliopathies is also possible. Yeh et al. [16] presented the results of a patient with PDCD and Fuchs endothelial dystrophy confirmed by confocal microscopy.

The changes observed biomicroscopically in the cornea of patients with pre-Descemet's dystrophy do not tend to progress rapidly. This is reflected in confocal microscopic examination. Shi et al. [12] found no change in corneal morphology in a patient with PDCD (a form associated with X-linked ichthyosis) at one-year follow-up.

Kontadakis et al. [17] also documented a one-year follow-up in 2 patients (4 eyes), finding no significant corneal morphology change over time using IVCM. Interestingly, these were patients who had undergone photorefractive keratectomy (PRK) with mitomycin C (MMC) due to an accompanying bilateral refractive defect. Full unaided visual acuity was achieved postoperatively in all cases, and the postoperative course was without complications. A confocal microscope examination performed 12 months after surgery showed no significant difference in corneal morphology compared to the preoperative examination.

Conclusions

Due to its high magnification and high resolution, confocal microscopy allows an accurate and non-invasive evaluation of all layers of the cornea at the cellular level. This makes it possible to differentiate and diagnose corneal disorders in cases where classical examination methods give inconclusive results. The changes observed in eyes with pre-Descemet's dystrophy using confocal microscopy are characteristic, which, in combination with the low invasiveness and the examination being performed intravitally, determines the importance of this test in diagnosis and differentiation.

Disclosure
Conflict of interests: none declared
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