In Vivo Confocal Microscopy in Patients With Central Cloudy Dystrophy of François

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Objective: To report in vivo corneal confocal microscopic findings of patients with central cloudy dystrophy of François.

Methods: Two unrelated patients, a 78-year-old man and a 75-year-old woman, with central cloudy dystrophy of François were examined using routine slitlamp biomicroscopy and confocal microscopy.

Results: In both cases, slitlamp biomicroscopy showed bilateral polygonal opacities separated by clear spaces. The corneal opacities were most prominent centrally and were located in the deeper stromal layer immediately anterior to the Descemet membrane. By confocal microscopy, normal superficial and basal epithelial layers, midstromal layers, and endothelial layers were noted in both cases. However, small highly refractile granules and deposits were observed in the anterior stromal layer in both cases. Also, multiple dark striae among the extracellular matrix with increased intensities were observed in the posterior stroma adjacent to the corneal endothelial layer in both cases.

Conclusions: Abnormal stromal deposits and multiple dark striae were observed in central cloudy dystrophy of François using in vivo corneal confocal microscopy. Use of confocal microscopy to investigate these abnormal stromal opacities may be helpful in differentiating various corneal stromal pathologic features.


Central Cloudy Dystrophy of François (CCDF) is characterized by polygonal, cloudy gray stromal opacities separated by relatively clear lines, which creates a leatherylike crocodile appearance in the central cornea. This condition is presumably autosomal dominant and usually bilateral. In contrast, similar corneal opacities located at either the central or peripheral cornea in the deep stromal layer are known as “posterior crocodile shagreen” and are usually considered to be age-related corneal degenerations. Other than the hereditary pattern, the central corneal opacities in both conditions are typically located in the axial two thirds of the cornea, are most dense posteriorly, and may extend into the anterior one third of the stroma. To date, the knowledge regarding the pathology of CCDF or posterior crocodile shagreen has been limited. This may be owing to the difficulty in obtaining diseased corneas since the corneal opacities in CCDF or posterior corneal shagreen do not interfere with vision and the corneal opacities or corneal shagreen are usually asymptomatic. Herein, we report the in vivo confocal microscopic findings of 2 cases of CCDF.

METHODS

Two unrelated patients having the diagnosis of CCDF were examined. This study was approved by the ethical committee of the Kanazawa University Graduate School of Medical Science, Kanazawa, Japan. Informed consents were obtained from both patients after a detailed explanation of corneal confocal microscopy. Prior to the confocal microscopy, topical 0.4% oxybuprocaine hydrochloride (Benoxil; Santen Pharmaceutical Co, Osaka, Japan) was instilled in each eye. A corneal confocal microscope (ConfoScan 2; Nidek Technologies, Vigonza, Italy) was used to perform layer-by-layer analyses of the central corneas. Before aligning the lens with the patient’s eye, 1 drop of 0.2% polyacrylic acid (Viscotis; CIBA Vision Ophthalmics, Rome, Italy) was placed on the objective lens of the microscope to protect the patient’s cornea in accord with the manufacturer’s instructions. The objective lens was an × 40 Achroplan (Zeiss, Oberkochen, Germany) water-immersion lens, with a numeric aperture of 0.75.
and a working distance of 1.92 mm. The center of the cornea was aligned to obtain tangential optical sections of the cornea; the z-axis was controlled by a manual joystick. Each corneal confocal microscopic examination was completed within 2 minutes and encompassed 350 serial digital images. No software was used to enhance contrast of the images obtained by confocal microscopy.

**REPORT OF CASES**

**CASE 1**

A 78-year-old man was noted to have bilateral deep stromal corneal opacities during the preoperative evaluation for cataract surgery. Postoperatively, he was referred to us for further evaluation of the corneal opacities. He had well-controlled type 2 diabetes mellitus. Both eyes were pseudophakic and the best-corrected visual acuity was 20/20 OD and 20/16 OS. Intraocular pressure was within normal limits in both eyes. Results of an external examination and a dilated fundal examination were unremarkable in both eyes. On slitlamp biomicroscopy, polygonal stromal opacities separated by clear cracklike lines were observed in the both eyes (Figure 1A). The corneal opacities were most prominent centrally and were located in the deeper stromal layer immediately anterior to the Descemet membrane (Figure 1B). The distribution of the corneal opacities was symmetric in both eyes, and they were best detected by retroillumination. A clinical diagnosis of CCDF was made. Corneal endothelial cell density measured by specular microscopy was 2364 cells/mm² OD and 2109 cells/mm² OS. No other abnormalities were detected in the corneal endothelium. Medical and family histories were noncontributory. There was no clinical evidence of ichthyosis. Both corneas of the patient's 52-year-old son were completely normal, without any evident corneal opacity.

Confocal microscopy in the central cornea of both eyes revealed normal-appearing superficial epithelial layers with typical dark and light cells and basal epithelial layers with polygonal cells. However, in the superficial stromal layer adjacent to the corneal epithelium, small highly refractile granules and deposits were observed (Figure 2A). The midstromal layers showed normal nuclei of keratocytes with a characteristic coffee bean–like appearance (Figure 2B). Most notably, in the deep stroma adjacent to the corneal endothelial layer, multiple dark acellular striae among extracellular matrices with increased intensities were observed (Figure 2C). The width of these microstriae varied from 10 to 20 µm. The directions of these microstriae were highly variable, as they appeared as vertical, horizontal, oblique, or reticular lines. The corneal endothelial layer was normal.

**CASE 2**

An otherwise healthy 75-year-old woman was referred to us for further evaluation of bilateral corneal opacity. She had been complaining of photophobia for a few years. Her uncorrected visual acuity was 20/40 OD and 20/25 OS. Intraocular pressure was within normal limits in both eyes. Findings from a dilated fundal examination showed mild preretinal membrane in the right eye. By slitlamp biomicroscopy, gray polygonal central corneal opacities separated by thin clear spaces in deep corneal stroma anterior to the Descemet membrane were observed in both corneas symmetrically. A clinical diagnosis of CCDF was made. Corneal endothelial cell density by specular microscopy was 2090 cells/mm² OD and 2014 cells/mm² OS. No other abnormalities were detected in the corneal endothelium. Medical and family histories were noncontributory. No evident ichthyosis was noted. The 70-year-old sister of this patient had faint peripheral mosaic opacities without any central cloudiness, and the 50-year-old son of the patient had no discernible corneal opacities.

Confocal microscopy in the central corneas revealed normal-appearing superficial and basal epithelial layers. In the anterior stromal layer, however, small highly refractile granules were observed. Keratocytic nuclei with a typical coffee bean–like appearance were noted in the midstromal layers. In the deep stromal layer, multiple dark striae with increased intensities of the keratocytes and extracellular matrices were noted (Figure 3). The width of the microstriae varied from 15 to 25 µm. These microstriae also oriented toward various directions. The corneal endothelial layer was normal.
The typical findings of CCDF consist of gray-white, polygonal opacities separated by relatively clear thin spaces with indistinct edges in the central cornea. The condition was first described as faint, deep central stromal opacifications occurring in 2 siblings and 6 additional unrelated patients. Two other investigators subsequently described families with multiple affected members and presumed an autosomal dominant inheritance mode.

Others have also noted similar clinical appearances of CCDF, arcus senilis, and anterior or posterior crocodile shagreen. Arcus senilis and anterior or posterior crocodile shagreen are usually seen in the peripheral cornea and are considered to be age-related corneal degenerations. Ichthyosis is also known to cause bilateral cloudy cornea; however, in our patients this possibility was ruled out by a dermatologist.

Karp et al reported histological findings of CCDF. By light microscopy, they noted a faint undulating appearance of the deep stromal lamella with the entire corneal stroma stained positive for acid mucopolysaccharide, most notably in the epithelial basement membrane and in the pre-Descemet stroma. By transmission electron microscopy, thickened epithelial basement membrane intermingled with fibrillogranular materials was observed. Also, numerous extracellular vacuoles with diameters of 250 nm to 6 µm were present throughout the stroma but were most notable in the mid and deep stroma. They noted that the keratocytes contained or were surrounded by fibrillogranular materials. On the other hand, Krachmer et al reported histological findings of concurrent posterior crocodile shagreen and polymorphic amyloid degeneration. Transmission electron microscopy revealed distinctive irregular vertical and unique sawtoothlike configurations of the stromal collagen lamellae, interspersed with patches of 100-nm, widely spaced collagen, corresponding to the central cloudy opacities seen clinically. They did not find extracellular fibrillogranular vacuoles or the presence of acid mucopolysaccharide. Meyer et al also reported a similar sawtoothed pattern of collagen lamellae in a patient with a full-thickness, mosaic pattern, central corneal cloudiness sharing features of CCDF, and posterior crocodile shagreen. However, their sawtooth structures are more prevalent in the anterior one third of the stroma and they also noted numerous lacunae (0.5-2.0 µm in diameter) in the corneal stroma, similar to those reported by Karp et al. The significance of these sawtoothlike collagen lamellae or fibrillogranular vacuoles or lacunae remains unclear.

In vivo corneal confocal microscopy allows better lateral resolution and image contrast of the corneal layers than conventional imaging devices such as slitlamp bio-

Figure 2. Confocal microscopic images of the left cornea in case 1. A, Small highly refractile granules and deposits were observed in the superficial stromal layer beneath the corneal epithelium. B, The midstromal layers showed a typical appearance of keratocytic nuclei. C, In the deep stroma anterior to the corneal endothelium, multiple dark acellular striae among extracellular matrices with increased intensities were noted. Some small refractile granules were also noted in the posterior stroma. Bar indicates 50 µm.

Figure 3. Confocal microscopic images of the left cornea in case 2. In the deep stroma anterior to the corneal endothelium, multiple dark striae among dense extracellular matrices and keratocytes were noted. Some small refractile granules were also noted. Bar indicates 50 µm.
microscopy and specular microscopy.\textsuperscript{11} It also allows a noninvasive, real-time, spatial sectioning of living tissues at the cellular level. Consequently, confocal microscopy has been used successfully to obtain and to differentiate images of normal and abnormal human corneas.\textsuperscript{11} We reported herein the findings of in vivo white-light confocal microscopic analysis of 2 unrelated patients with CDDF. To our best knowledge, this is the first confocal microscopic analysis of CDDF. We found that both cases showed subepithelial and anterior stromal granules with high reflectivities. These granules might correspond to the fibrillogranular materials or localized aggregates of acid mucopolysaccharide beneath the basement membrane of the epithelium, as previously observed by Karp et al.\textsuperscript{3} To our best understanding, these pathological findings of subepithelial or anterior stromal deposits have never been observed or reported in posterior crocodile shagreen.\textsuperscript{3} We also noted by confocal microscopy that similar refractile granules were present in the posterior stroma as well, but to a lesser extent (Figure 2C and Figure 3). Corneal stromal microdeposits can also be observed by confocal microscopy in long-term contact lens wearers\textsuperscript{12}; however, both patients reported herein had no history of contact lens use.

Another striking feature noted in our patients on confocal microscopy was multiple microstriae (10 to 20-µm microstriae in patient 1 and 15 to 25-µm microstriae in patient 2) among extracellular matrices with increased intensities in the deep stromal layer. The increased intensity of the extracellular matrices may correspond to the clinical corneal opacities, caused by extracellular accumulation of mucopolysaccharide and lipidlike materials.\textsuperscript{3} However, the etiology of the microstriae in the deep stroma is unclear. These may correspond to the histological findings of an undulating appearance of the deep lamella.\textsuperscript{3,5} We suspect that some microstriae may reflect the clear spaces interspersed between the opacities, as they are acellular and with optical lucency by confocal microscopy. The presence of similar striae on confocal images has been reported in other conditions such as keratoconus and after penetrating keratoplasty.\textsuperscript{13} Therefore, these findings may represent a common morphological alteration of the stromal lamellae, induced by either a mechanical (such as surgery) or nonmechanical (such as a degenerative process or abnormal stromal deposits) process.

The cause of corneal mosaic pattern remains unknown, but Bron and Tripathi\textsuperscript{14,15} have proposed that anterior mosaic shagreen might result from relaxation of the normal tension of the Bowman layer. They surmise that when tension on the Bowman layer is released, a reproducible polygonal ridge pattern (as clear spaces between the mosaics) can manifest owing to the collagen lamellae inserting obliquely into the Bowman layer and supporting the layer in ridges. A similar anterior mosaic can be seen in the superficial cornea by fluorescein staining after pressure patching of the eye. It can also be observed in a cornea with ocular hypotony, or in a keratoconic cornea that has been flattened by a hard contact lens.\textsuperscript{16} It is also possible that the multiple microstriae we observed in both patients using confocal microscopy may represent microfolds caused by reduced tension of the Descemet membrane similar to that proposed by Bron and Tripathi\textsuperscript{14,15} in the case of anterior crocodile shagreen.

Further studies are necessary to correlate these confocal microscopic findings with relevant histopathological findings. However, using confocal microscopy to investigate posterior stromal opacities may prove useful in differentiating various corneal conditions with primary deep stromal involvements.

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