SHORT COMMUNICATION

Keratoconus associated with corneal macular dystrophy: *In vivo* confocal microscopic evaluation

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PURPOSE. *The authors present a case, studied through in vivo confocal microscopy, of concomitant keratoconus and macular corneal dystrophy (MCD).*
METHODS. *A 29-year-old man underwent a penetrating keratoplasty in the right eye in May 2005. Confocal microscopy was performed to examine the cornea of the right eye.*
RESULTS. *A diagnosis of concomitant keratoconus and MCD was suspected, due to the simultaneous findings of corneal ectasia and stromal opacities.*
CONCLUSIONS. *In this case, using in vivo confocal microscopy, morphologic changes were detected in many corneal layers and compared with the histopathologic findings. The morphologic alterations were found mainly in the area of the cornea apex. (Eur J Ophthalmol 2006; 16: 745-50)*

KEY WORDS. *Cornea, Keratoconus, Corneal macular dystrophy, Confocal microscopy*

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INTRODUCTION

Macular corneal dystrophy (MCD) is an autosomal recessive disorder characterized by corneal opacities resulting from intracellular and extracellular deposits within the corneal stroma (1).

This dystrophy usually begins in the first decade of life and leads to progressive visual deterioration as the stroma becomes generally cloudy, dense, and with gray-white spots. The macular spots have fuzzy edges and the intervening stroma is not clear. Young patients exhibit axial lesions in the superficial layers of the cornea, but with time, lesions approach the periphery and extend throughout the entire stromal thickness.

Patients experience progressive loss of vision as well as attacks of irritation and photophobia.

Keratoconus is a noninflammatory ectatic and degenerative corneal pathology. The cornea assumes a conical shape because of thinning and protrusion. It is usually bilateral. The etiology is unclear but probably multifactorial, and the pathogenesis is characterized by an area of protrusion associated with loss of stromal substance (2).

Stromal thinning usually involves the center or the inferior paracentral area.

This process results in mild to marked impairment of visual function.

Keratoconus can occur in association with a variety of ocular and systemic diseases. Systemic associations include atopic dermatitis, Down syndrome, Ehlers-Danlos syndrome, mitral valve prolapse, Marfan syndrome, osteogenesis imperfecta type I, and other disorders of the connective tissue (3-7).

Keratoconus can also appear in the presence of isolated ocular pathologies such as retinitis pigmentosa, Leber's congenital amaurosis, retinopathy of prematurity, aniridia, vernal keratoconjunctivitis, iridocorneal endothe-

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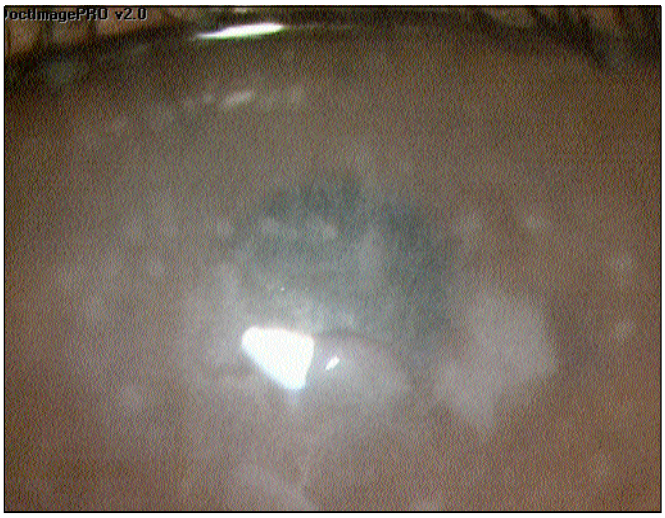

Fig. 1 - *Eye image of macular corneal dystrophy associated with keratoconus.*

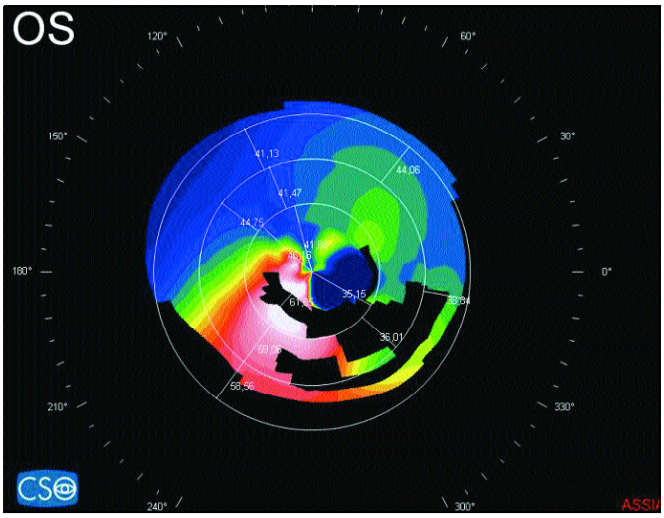

Fig. 2 - *Corneal topography (Eye-Top, CSO, Italy).*

lial syndrome, and corneal dystrophies (8-15).

Reported associations with corneal dystrophies include granular dystrophy, posterior polymorphous dystrophy, fleck dystrophy, Fuchs endothelial dystrophy, and lattice dystrophy.

The association between MCD and keratoconus has been recently described for the first time in two patients (16).

In recent years, several studies have investigated the microscopic abnormalities visible by confocal microscopy in eyes affected by keratoconus (17, 18).

To our knowledge, the confocal microscopic appearance of MCD has not been previously described in the ophthalmologic literature. Moreover, the examination of the association between MCD and keratoconus has not been described through confocal microscopy.

We present a case, studied through in vivo confocal microscopy, with concomitant keratoconus and MCD.

Case report

A 29-year-old man with decreased vision in the right eye was referred to us for a clinical evaluation in November 2004.

He had a history of undefined corneal disease for which he underwent, at another ophthalmologic center, a penetrating keratoplasty in the left eye in 1997 because of severe visual disability.

His general health was good and his familial history was negative for corneal disease.

His best-corrected visual acuity was 40/200 in the right eye. The patient had poor visual acuity in this eye.

Slit-lamp examination revealed an evidence of stromal corneal dystrophy in the right eye. Focal grayish-white opacities were noted in the superficial and deep corneal stroma. Lesion borders were indistinct. The haziness extending to the corneal periphery was more severe in the center. There was also corneal thinning with moderate protrusion of the central thinning areas (Fig. 1).

Central corneal thickness measured by ultrasonic pachymetry was 410 µm on the right eye.

Keratometric mires were irregular and poorly formed.

Corneal topography (EyeTop, CSO, Italy) showed a characteristic pattern of keratoconus (Fig. 2).

A diagnosis of concomitant keratoconus and MCD was suspected due to the simultaneous findings of corneal ectasia and stromal opacities.

Preoperative confocal microscopy was performed to examine the cornea of the right eye (HRT II, Heidelberg Engineering, Germany).

Before the confocal microscopic examination, topical anesthetic 0.4% oxibuprocaine chlorohydrate (Novesine, MSD) was instilled into the lower conjunctival fornix. A drop of sodium hyaluronate gel on the objective tip served as coupling medium.

Confocal microscopy examination of the right cornea showed normal superficial and intermediate epithelium layers, together with n evident distortion of the basal epithelium. Irregularities and areas with undefined cell borders were visible. Highly reflective irregular deposits were also evident (Fig. 3).

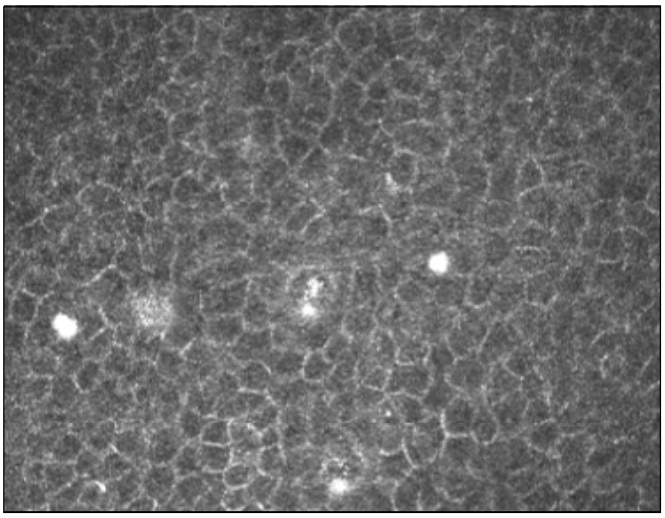

Fig. 3 - *Confocal microscopy of epithelium layers.*

In the Bowman layer region important alterations were evident. There was a highly reflective scar tissue extending from the basal membrane to the immediately underlying stroma. Bright and dense structure at the level of the basal membrane was found at 60 µm of depth (Fig. 4A).

Besides the subepithelial, nerve plexus was undetectable. Anterior stroma showed the presence of bright and dense structures that were separated by bands of normal stroma.

The main stromal abnormalities were microstriae that appeared as multiple, thin, dark lines in contrast with the brighter reflectivity of the stroma. The striae were extracellular, and presented different orientation and thickness. This alteration was found in the whole stroma. The keratocytes nuclei were barely distinguishable within the edge of these linear structures (Fig. 4B).

In the stroma, irregular reflective intra- and extracellular material was interspersed with the unclear keratocytes nuclei (Fig. 5A).

Another microscopic feature was the presence of microlacunae, which appeared as dark, cystic nonreflective structures in the extracellular connective tissue (Fig. 5B).

The endothelium was normal.

Corneal alterations were mainly found in the area of the corneal apex.

These images were compatible with the clinical pictures of the disease.

In May 2005 the patient underwent a penetrating keratoplasty in the right eye.

The pathologic examination of the button revealed epithelial and stromal thinning with irregularities and multiple breaks in the Bowman layer, together with multiple zones of scarring. Moreover, non-hyaline material, especially associated with keratocytes, was found.

The Alcian blue (Fig. 6A) and colloidal-iron (Fig. 6B)

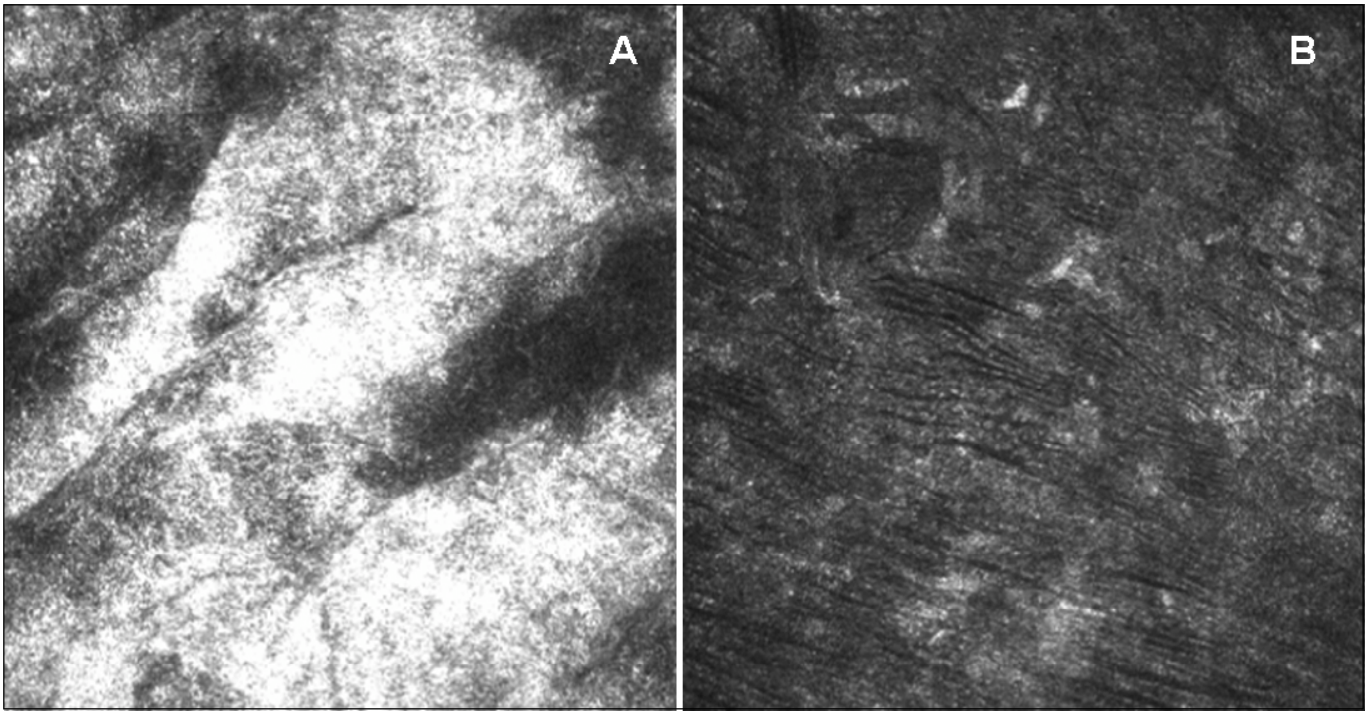

Fig. 4 - *Confocal microscopy of Bowman layer region* (**A**) *and of the superficial stroma* (**B**).

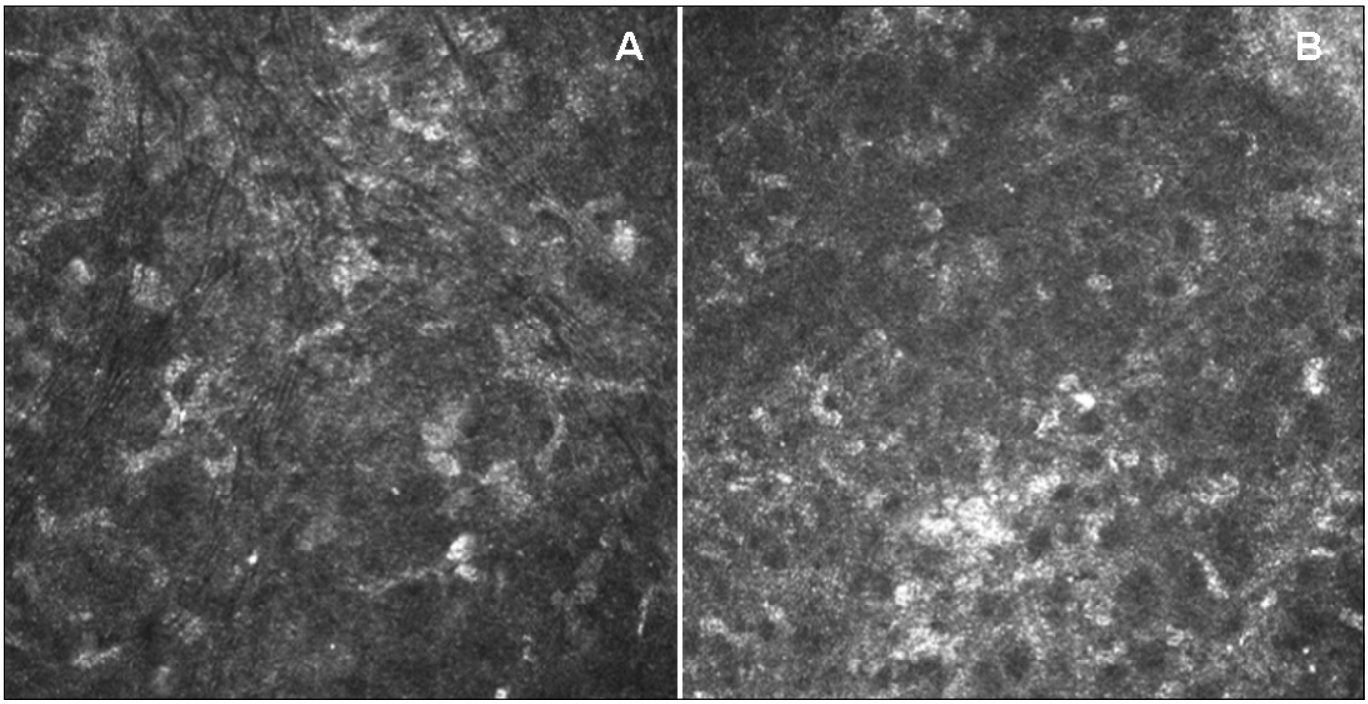

Fig. 5 - *Stromal keratocytes nuclei* (**A**) *and microlacunae by confocal microscopy* (**B**).

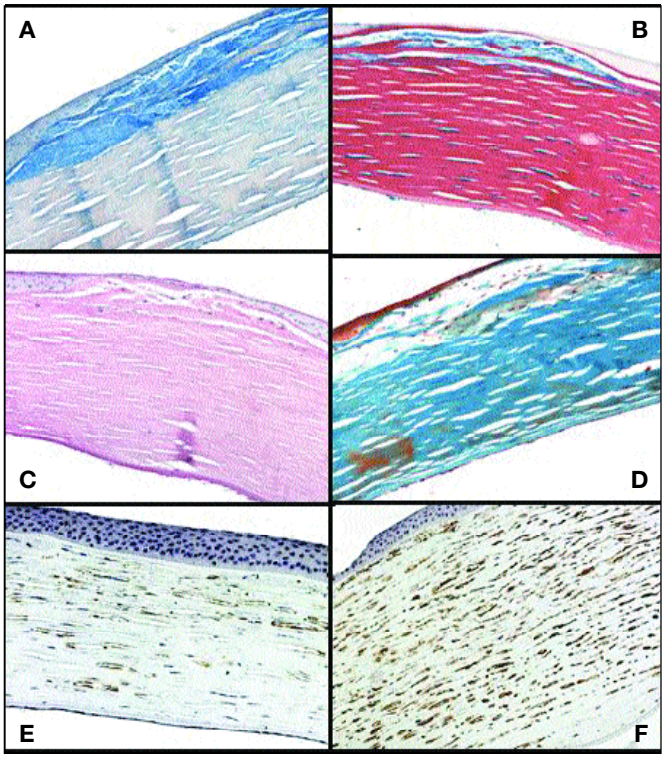

Fig. 6 - *Alcian blue* (**A**) *and colloidal iron* (**B**) *positive staining; PAS* (**C**) *and Masson* (**D**) *negative staining; immunohistochemistry diffuse loss of CD-34 expression* (**E**) *in donor cornea and strong immunoreactivity* (**D**) *in recipient bed.*

positive staining, associated with PAS (Fig. 6C) and Masson negative (Fig. 6D) staining, confirmed the typical appearance for macular dystrophy.

The expression of CD-34 in stromal corneal cells was also examined by immunohistochemistry analysis (19). Diffuse loss of CD-34 expression was present in central stroma (Fig. 6E), while in peripheral cornea, keratocytes were presenting strong and substantial immunoreactivity (Fig. 6F).

DISCUSSION

We report a rare case of keratoconus in association with MCD diagnosed histopathologically.

Explanations for this association remain unknown. These could include a poorly understood molecular mechanism, genetic linkage, or other causes.

Javadi et al hypothesized a biochemical alteration in collagen fibril size or packing induced by abnormal deposits in MCD which may predispose to thinning and ectasia (16).

On the other hand, this association might be caused by a single genetic alteration. Other molecular and genetic studies in the future may shed light on this association.

The use of confocal microscopy has been reported for various corneal diseases. This tool allows for real time in vivo examination of all layers of the cornea, and thus visualization of microscopic alterations.

To our knowledge, we describe the first confocal features of a macular corneal dystrophy associated with keratoconus.

In this case, using in vivo confocal microscopy, morphologic changes were detected in many corneal layers.

The basal epithelium presented irregularities and distortion, as previously found in keratoconus, even if in MCD the epithelium was also seen to be irregular through phase-contrast microscopy (20). Abnormal and reflective material was present near basal epithelium cells. This material could describe glycosaminoglycans deposits. In fact, histologically, macular dystrophy is characterized by the accumulation of glycosaminoglycans in the epithelium cells and between the stromal lamellae (21, 22).

We found a highly reflective scar tissue that extended from the basal membrane to the immediately underlying stroma. This could be a focal rupture of the Bowman's membrane that is visible both in keratoconus and in MCD (2, 20). In fact, the main histopathologic alteration of the MCD is represented by focal ruptures of Bowman's membrane that may be irregular, thinned, or absent in some areas (20).

Transmission electron microscopy shows irregular thinning and breaks of the basement membrane, and a large extracellular accumulation of abnormal material (23).

In the stroma, confocal microscopy showed dark striae with different orientation, together with an alteration of the density and the shape of the keratocytes nuclei. The microstriae appear as hyporeflective lines, in contrast with the brighter reflectivity of the stroma. Those are typical findings of confocal examination of the stroma in patients with keratoconus (17).

In addition, we found in the whole stroma the presence of abnormal, reflective irregular extra- and intracellular material. Since MCD is a stromal dystrophy that is histopathologically characterized by an accumulation of glycosaminoglycans between the stromal lamellae, we hypothesized that the deposits are a large extracellular accumulation of abnormal material. Electron microscopy on MCD shows accumulation of mucopolysaccharide within stromal keratocytes, which are distended by numerous intracytoplasmic vacuoles with pyknotic nuclei (23).

The morphologic alterations were mainly found in the area of the cornea apex.

In conclusion, confocal microscopy may provide new information on corneal microanatomy and histopathology of corneal dystrophies. Moreover, this technique may allow for early and noninvasive confirmation of diagnosis. Other studies have been carried out to evaluate confocal microscopic findings in MCD.

None of the authors has proprietary or financial interest in any material or device mentioned.

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