Year XXII, n. 1, April 2021

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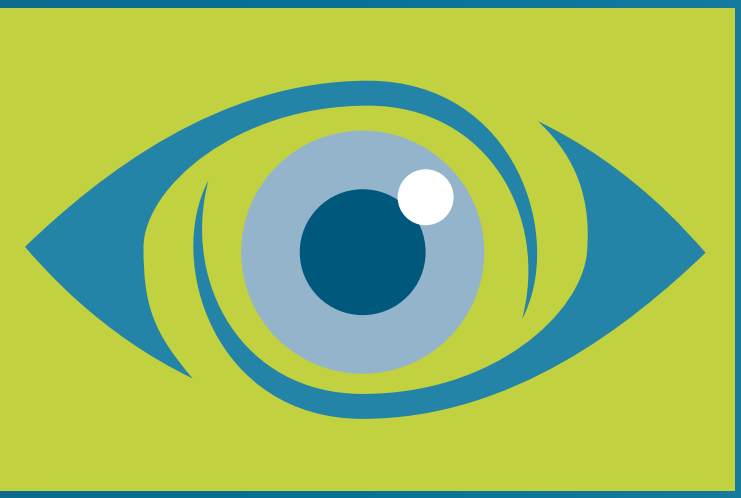

Ophthalmology

Case Reports

Resolution of a case of bullous keratopathy using a hypertonic ointment containing 4.5% sodium chloride and 0.4% hyaluronic acid (Edenight®)

Fedele Passidomo, Francesco Pignatelli, Giuseppe Addabbo

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Valentino de Ruvo

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ISBN 978-88-6756-627-3

ISSN 2035-3812

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Via Decembrio, 28
20137 Milan Italy

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Collections. Registered in Milan - Registration n. 371 - 21 May 1999.

Online version

Publication made possible by an unconditioned educational grant from *NTC S.r.l.*

NTAITZZ501325

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Resolution of a case of bullous keratopathy using a hypertonic ointment containing 4.5% sodium chloride and 0.4% hyaluronic acid (Edenight®)

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ABSTRACT

We report on a case of bullous keratopathy in a woman who developed reduced endothelial cell density several years after cataract surgery and who was on the waiting list for Descemet's stripping automated endothelial keratoplasty (DSAEK). The patient was treated with a hypertonic ointment containing 0.4% hyaluronic acid and 4.5% sodium chloride, and corneal thickness was assessed weekly by optical coherence tomography (OCT) examination. Over the weeks, corneal thickness progressively decreased as the edema reabsorbed, leading to improvements in the patient's quality of vision and perceived pain. For the treatment of corneal edema, hypertonic solutions for daytime use and containing varying concentrations of sodium chloride have been available for several years. The ointment formulation, by contrast, allows administration at night, when fluid accumulation in the cornea is greater, in part as a result of the subject's supine position at night. During the daytime the effect of gravity causes a partial reabsorption of the edema, so the patient experiences a slight improvement in symptoms in the evening. Administration of the treatment at bedtime allows a more targeted action which prevents fluid from accumulating during the night hours. After 3 weeks of treatment, which is still underway, our patient showed almost complete resorption of the edema with a considerable improvement in vision and resolution of the pain. Treatment with the hypertonic ointment was combined with topical steroid therapy (dexamethasone sodium phosphate) and the application of soft therapeutic contact lenses.

Introduction

Bullous keratopathy refers to edema due to excess fluid in the cornea caused by a dysfunction of its inner layer, the corneal endothelium. In this condition, endothelial cell density is reduced and the pump mechanism of endothelial cells is impaired as a result. The cells are no longer able to regulate corneal hydration, leading to a condition known as "corneal decompensation"[1]. Until 10-15 years ago bullous keratopathy was treated with a perforating transplantation, by replacing the entire cornea. In recent years, advanced treatment modalities such as Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK) have been introduced, which allow an early procedure that targets the corneal area involved (corneal endothelium) and improves patient outcomes and chances of visual rehabilitation.

Very often, bullous keratopathy can develop after a complicated cataract surgery or following other surgical trauma. Chronic injury to the endothelial cells may also result from intraocular lenses (IOL) implanted in the anterior chamber or chronic inflammation of the anterior part of the eye. Idiopathic bullous keratopathy or congenital endothelial dystrophies are very rare.

In all these cases, patients complain of reduced visual acuity and the appearance of halos and photophobia, as well as possible intense pain caused by the formation of subepithelial bullae. The characteristic features of bullous keratopathy are therefore epithelial edema with microcysts and increased stromal thickness due to the edema with loss of corneal transparency. Subepithelial and stromal scarring may also be present in long-standing cases.

Surgical approaches include superficial ablation with excimer laser, known as phototherapeutic keratectomy (PTK) and amniotic membrane transplantation[2,3]. Patients with markedly reduced visual acuity are eligible for posterior lamellar keratoplasty and in particular for DSAEK or DMEK. Soft contact lenses may control pain but are considered a short-term solution. Perforating keratoplasty is now regarded as obsolete.

Visual rehabilitation can be successfully achieved, with excellent long-term prognosis. However, the final outcome may be affected by both the general condition of the eye and the duration of the disease itself.

Case report

We present the case of an 80-year-old woman with a history of bilateral phacoemulsification and IOL implantation performed several years before coming to our attention. Preoperatively, the patient had a slightly reduced endothelial cell density compared to normal. Following cataract surgery, a further reduction in endothelial cell density was observed, a situation that can be a physiological effect of cataract surgery but that in this case had led to the development, over a period of 2 years, of bullous keratopathy. The condition had been treated with topical cortisone, 5% hypertonic sodium chloride eye drops and application of a therapeutic soft contact lens, with slight improvement.

When the patient came to our attention she had a residual visual acuity of 1/10, hazy vision, intense pain and marked corneal edema, with microbullae and Descemet's membrane folds. In consideration of the persisting corneal decompensation, corneal edema and pain, it was decided to put the patient on the waiting list for corneal transplant (DSAEK).

The patient was subsequently treated with a hypertonic ointment for corneal edema containing 0.4% sodium hyaluronate and 4.5% sodium chloride to be applied at bedtime, in combination with the topical steroid therapy.

The patient was followed up at weekly intervals with slit-lamp examination and corneal optical coherence tomography (OCT) to assess corneal

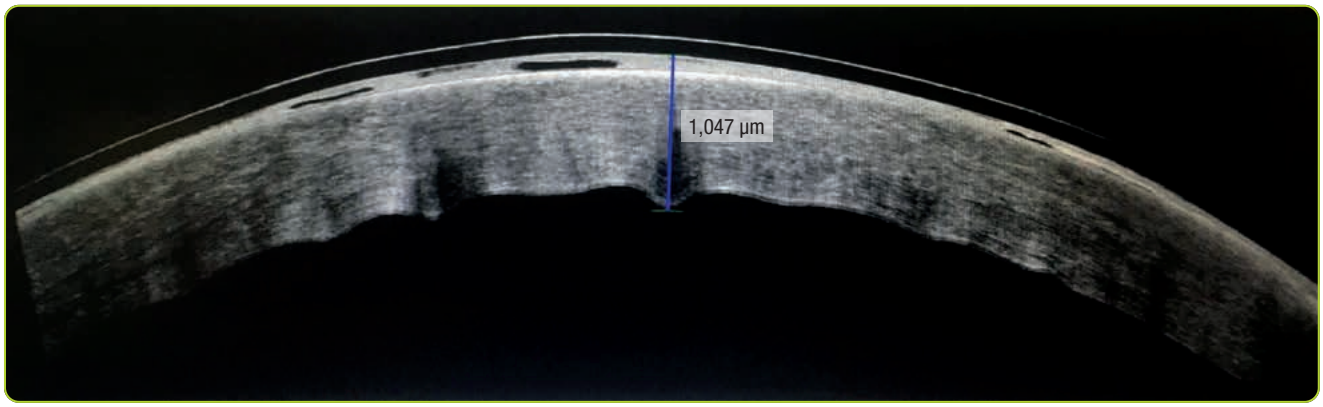

Figure 1. OCT appearance of the cornea at the beginning of the treatment. Epithelial micro- and macrobullae and marked corneal thickening (1,047 µm) are seen.

thickness as an indicator of edema. In addition, the therapeutic contact lens was replaced at each follow-up visit.

Figure 1 shows the OCT appearance of the cornea at the beginning of the treatment. Epithelial micro- and macrobullae can be seen, the rupture of which is the main cause of pain, as well as the therapeutic contact lens. Even more evident is the marked corneal thickening (1,047 µm) due to the edema caused by disruption of the endothelial physiological pump function resulting from the progressive loss of endothelial cells.

Figure 2 shows the considerable improvement observed at follow-up after 1 week of treatment with the hypertonic ointment, which was reflected in a reduction of the patient's symptoms. Slit-lamp examination revealed reduction of the microbullae, conjunctival hyperemia and corneal edema; OCT showed reduction of corneal thickness (1,018 µm). At the second follow-up visit 15 days after the start of the treatment, a further improvement was noted with disappearance of the microbullae and reduction of the corneal edema (807 µm). The patient reported an absence of symptoms (*Figure 3*). At 4 weeks after the start of the treatment (*Figure 4*), there is a further reduction of corneal edema (764 µm), no microbullae, and no conjunctival hyperemia. The patient reported complete disappearance of the symptoms with improved quality of vision (8/10).

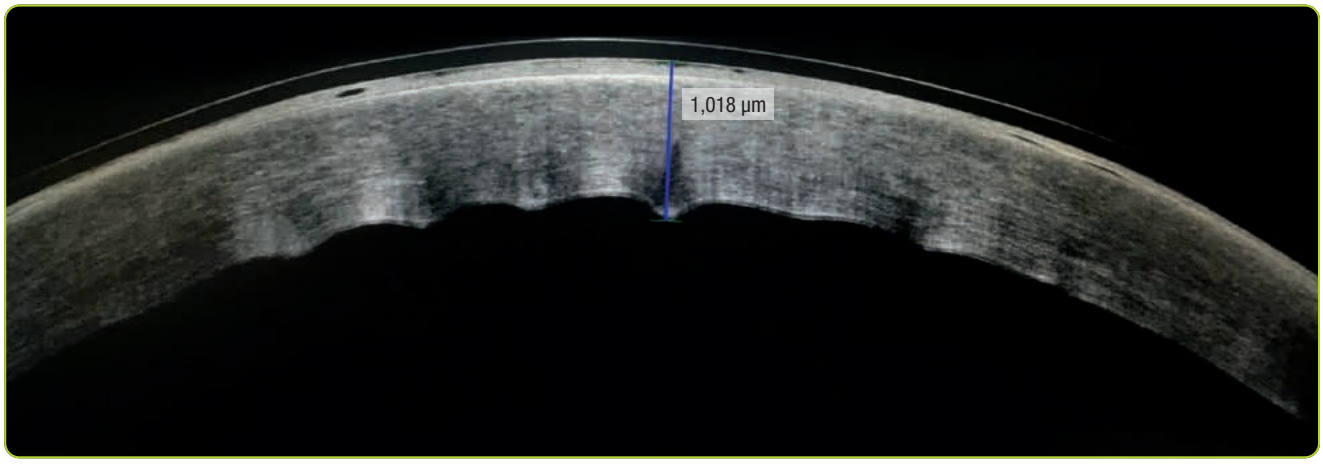

Figure 2. OCT appearance of the cornea after 1 week of treatment with the hypertonic ointment. A reduction of the edema, corneal thickness (1,018 µm), and microbullae can be seen.

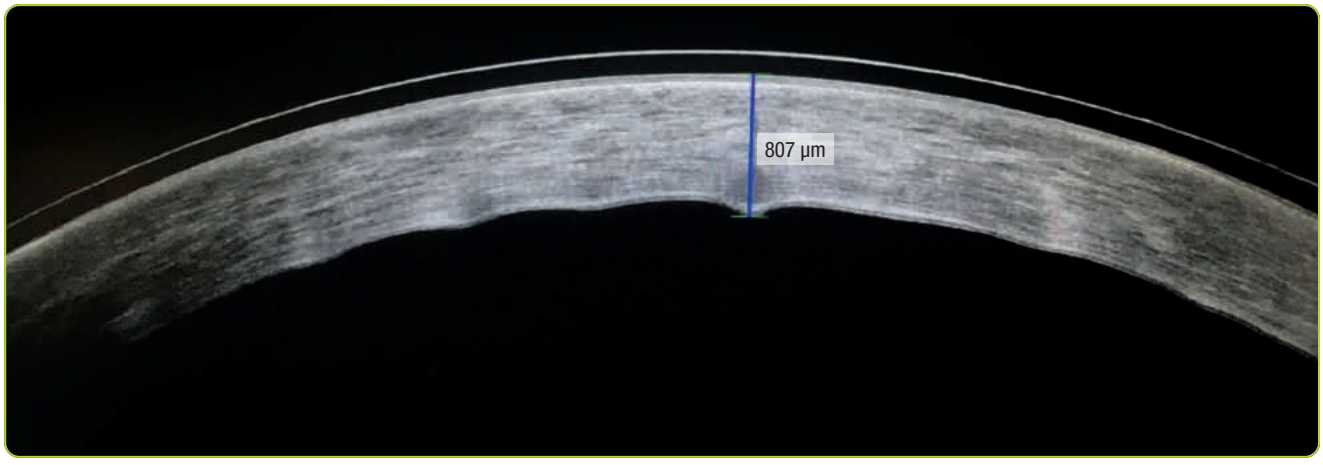

Figure 3. OCT appearance of the cornea at the second follow-up visit (15 days after the start of the treatment). Disappearance of the microbullae and reduction of the corneal edema (807 µm) are seen.

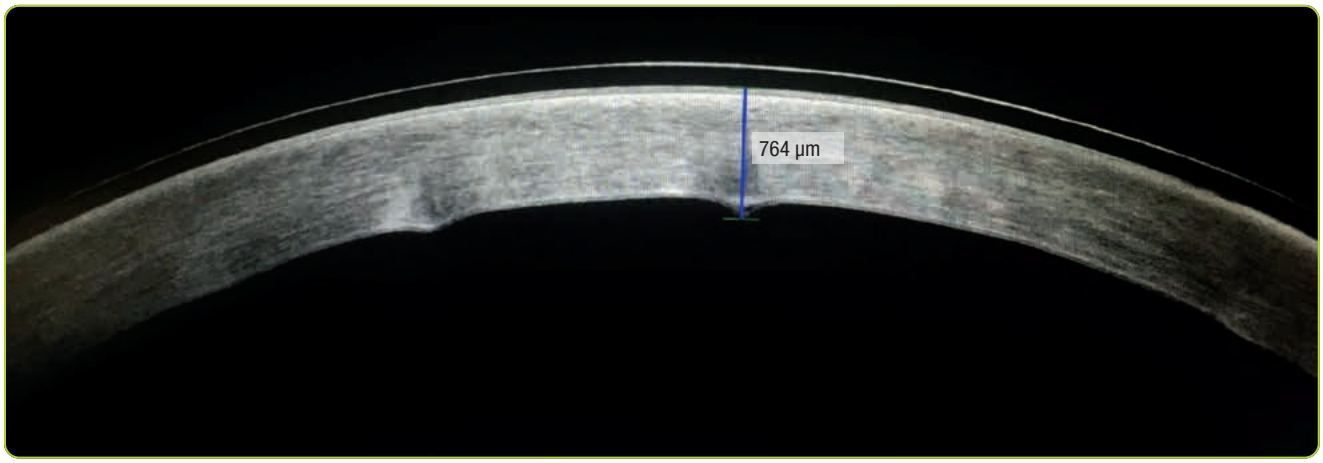

Figure 4. OCT appearance of the cornea at 4 weeks after the start of the treatment. Further reduction of corneal edema (764 µm), no microbullae.

Discussion and conclusions

Corneal endothelium

The corneal endothelium is a single layer of cells that covers the posterior corneal surface and allows water to be transported from the stroma to the anterior chamber. This movement of water counteracts the stroma's natural tendency to swell and ensures corneal transparency. Although the endothelium is able to regenerate after an injury in some species, in humans the main repair mechanism after cell loss is cellular enlargement. Endothelial cell density and function can be clinically estimated by specular microscopy and pachymetry. At birth, the human endothelium is composed of a single layer consisting of up to 500,000 cells, with a density that reaches 7,500 cells/mm^2. Thereafter, cell density decreases progressively, declining sharply during the first year, reflecting the hypertrophy of a fixed endothelial cell population as a reaction to continued corneal growth. Between the ages of 20 and 80 years cell density is estimated to decrease by 0.52% per year on average[1].

Maintenance of corneal transparency

Corneal transparency is maintained by the endothelium creating a condition of relative dehydration of the stroma. The protein matrix around each stromal collagen fiber produces an imbibition pressure (60 mmHg) that drives water into the cornea. The tight junctions between epithelial cells act as a barrier that hinders the flow of water from the tear film to the stroma, but the lack of a continuous tight junction between the endothelial cells allows water to flow freely into the stroma. Accumulation of this water causes stromal swelling and clouding. The pump-leak model of stromal hydration suggests the existence of a dynamic equilibrium between the tendency of stroma to swell and the active transport of ions by an endothelial pump to contrast the inward movement of water. The transport of fluid by the endothelium relies on aerobic metabolism. The movement of water across the endothelium is passive and follows the flux of ions actively transported across the posterior cell membrane. Passive mechanisms aid the metabolically active processes of deturgescence. Evaporation can increase tear film osmolality and draw water from the corneal stroma and, if the endothelium is intact, intraocular pressure may compress the stroma, driving the water out. The number of ionic pump sites per endothelial cell may vary in certain conditions. In Fuchs' endothelial corneal dystrophy (FECD), the endothelial pump function is increased during the early disease stages, but then the pump sites are heav-

ily reduced in the end stages with the development of corneal edema. Water normally enters the stroma across the cells or the intercellular space. Despite endothelial cells being gradually lost throughout life, endothelial decompensation is a rare occurrence. If injury or inflammation reduce endothelial cell density below a critical threshold for the maintenance of corneal stability, physiological function is impaired resulting in corneal edema. This critical density is estimated to be 10-15% of the normal cell count or between 300 and 500 cells/mm^2. This means there is a significant physiological reserve in that 500 cells/mm^2 have the same effectiveness as 3,000 cells/mm^2 in obtaining corneal transparency in the short term[1].

Etiology and treatment of bullous keratopathy

The etiology of bullous keratopathy involves a loss of endothelial cells resulting from a surgical trauma such as that of eye surgery or cataract surgery. However, other ophthalmological surgical procedures may also cause a loss of endothelial cells. These include trabeculectomy for glaucoma and implantation of IOL for correction of refractive errors such as near-sightedness, far-sightedness and astigmatism. These anterior chamber lenses initially featured angle-supported loops that were, however, subsequently found to reduce endothelial cell density leading to corneal decompensation. This complication, coupled with distortion of the physiological shape of the pupil, undermined their use in favor of iris-supported IOL. Another, now superseded, technique possibly responsible for bullous keratopathy is radial keratotomy. Other causes for bullous keratopathy include endothelial dystrophies such as FECD, anterior chamber tumors like mixoma, congenital alterations like microcornea, acute and neurovascular glaucoma, and endothelial herpetic keratitis.

There are many approaches to the treatment of bullous keratopathy, and several topical preparations exist that contain hypertonic solutions[4,5]. Studies have shown that an accurate estimate of pachymetry can help predict the benefit of treatment with sodium chloride, in that central pachymetry values of 613-694 µm and peripheral values of 633-728 µm were found to represent the range within which a 5% sodium chloride solution proved effective. On the other hand, in more advanced disease stages, when both the epithelial and stromal components are involved, hypertonic solutions are less effective.

Despite the advanced stage of bullous keratopathy described in this case report, the patient benefited greatly from the use of the ointment.

The hypertonic solution administered to the patient has the following advantages: the ointment formulation allows a longer persistence of the product on the corneal surface and its night-time use ensures a more effective action when it is most needed; the product also contains 0.4% hyaluronic acid which acts by allowing a longer persistence of the fluid which, absorbed by the corneal stroma, remains on the surface producing greater corneal hydration while reducing the burning sensation associated with hypertonic solutions. The hypertonic ointment containing 4.5% sodium chloride therefore re-establishes the osmotic equilibrium of the cornea by drawing water into the tear film and restoring the corneal endothelial pump function.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors conceived or planned the work and collected the data; drafted the manuscript and critically revised it for intellectual content; finally approved the manuscript to be published; agreed to be accountable for all aspects of the work.

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Fuchs' endothelial corneal dystrophy treated with Edenight®: a case report

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ABSTRACT

Fuchs' endothelial corneal dystrophy (FECD) is characterized by an early loss of corneal endothelial cells which causes corneal edema especially in the early morning[1,2]. Pharmacological treatment plays a major role in the initial stages of disease[3]. We report the case of a woman who was treated with Edenight®, a hypertonic ointment containing 4.5% sodium chloride and 0.4% sodium hyaluronate, achieving a remarkable improvement in visual acuity throughout the day.

Case report

A 74-year-old woman presented to our clinic with a 12-month history of cloudy vision occurring especially in the morning hours and improving over the course of the day. Additionally, she reported seeing halos around lights at night, having a foreign body sensation and increased tearing; she had undergone phacoemulsification with intraocular lens (IOL) implantation in both eyes approximately 7 years earlier. The patient was in good general health.

On slit-lamp biomicroscopy, both eyes showed normal conjunctiva, mild corneal edema, deep and quiet anterior chamber, pseudophakic and well-positioned IOL (***Figure 1***). After vital staining with fluorescein and observation with cobalt blue filter, a mild but diffuse punctate keratitis was detected. Tear film break-up time was normal in both eyes. Specular reflection examination showed a "beaten-metal" appearance of the endothelium. Goldman applanation tonometry revealed 15 mmHg in both eyes.

Best corrected visual acuity (BCVA) at 8 am was 4/10 with - 1.00 cyl = 140° for OD and 3/10 with - 0.75 cyl = 90° for OS; at 6 pm it was 7/10 with - 1.00 cyl = 140° for OD and 5/10 with - 0.75 cyl = 90° for OS.

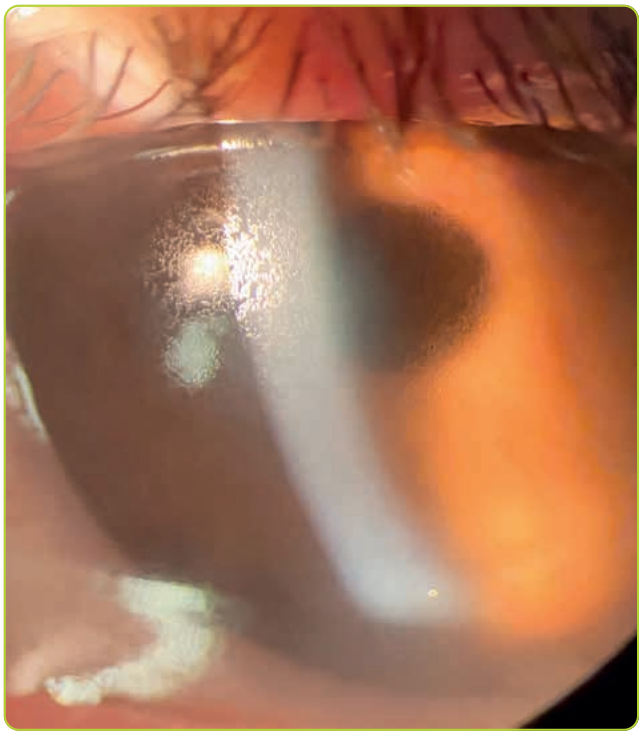

Figure 1. Slit-lamp biomicroscopy showing mild corneal edema in the right eye.

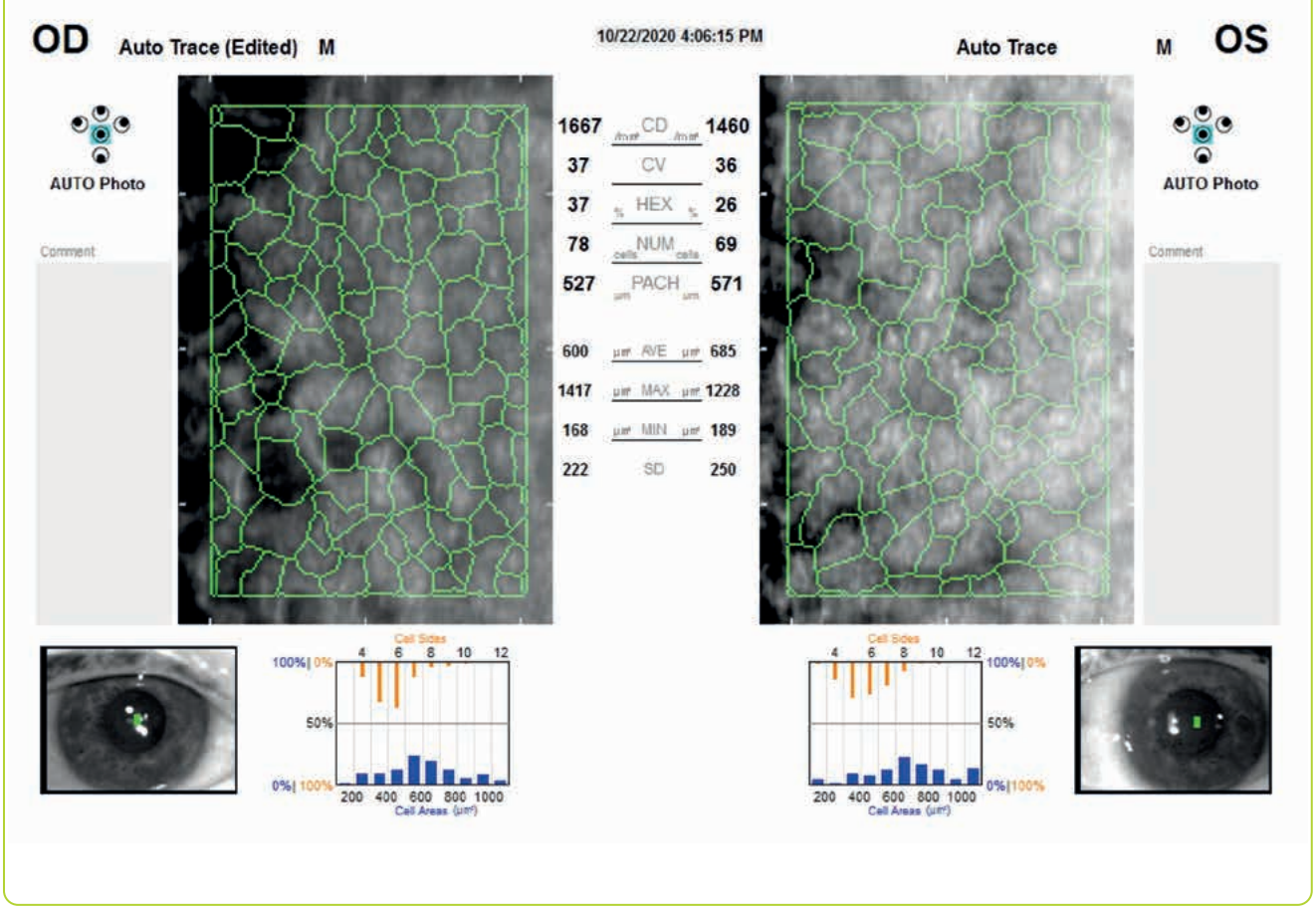

Figure 2. Endothelial biomicroscopy of the central cornea of both eyes.

Biomicroscopy of the central cornea endothelium of both eyes (*Figure 2*) showed a reduced endothelial cell count, polymorphism and polymegathism: cell density (CD) was 1667/mm^2 for OD and 1462/mm^2 for OS; the coefficient of variation (CV) was 37% for OD and 36% for OS; the coefficient of hexagonality was 37% for OD and 26% for OS. Corneal pachymetry was 527 µm for OD and 571 µm for OS.

A diagnosis of Fuchs' endothelial corneal dystrophy (FECD) was formulated.

Treatment and progress

The patient was prescribed Edenight®, a hypertonic ointment containing 4.5% sodium chloride and 0.4% sodium hyaluronate, to be applied once daily at bedtime. A follow-up visit was scheduled after 7 days.

At follow-up the patient reported a substantial improvement in visual acuity, with no side effect or discomfort.

BCVA at 8 am was 7/10 with - 1.00 cyl = 140° for OD, and 5/10 with - 0.75 cyl = 90° for OS; at 6 pm it was 9/10 with - 1.00 cyl = 140° for OD and 7/10 with - 0.75 cyl = 90° for OS.

The BCVA findings demonstrated that the improvement in visual acuity after treatment persisted throughout the day.

Slit-lamp biomicroscopy showed a marked reduction of the mild corneal edema and complete disappearance of the punctate keratitis in both eyes (*Figure 3*).

The patient was advised to continue applying Edenight® every night.

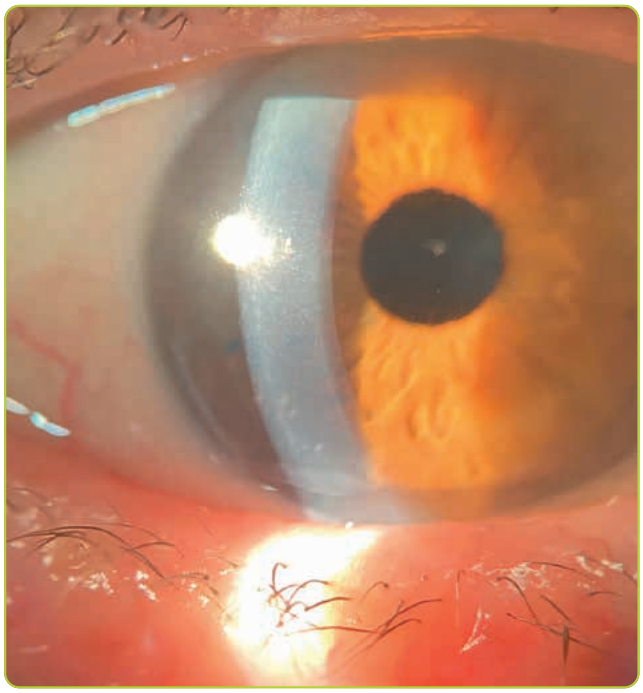

Figure 3. Slit-lamp biomicroscopy at follow-up showing resolution of the mild corneal edema in the right eye.

Discussion and conclusions

FECD is a disease of the corneal endothelium characterized by an early loss of corneal endothelial cells and the accumulation of extracellular matrix in Descemet's membrane, with the formation of focal posterior excrescences called guttae. In a healthy cornea, the correct level of stromal imbibition is regulated by a delicate balance between the passive diffusion of water from the anterior chamber and ocular surface towards the cornea and the active transportation of water and electrolytes from the cornea to the anterior chamber, resulting from the Na^+/K^+ pumps located on the endothelial cells. The progressive loss of endothelial cells causes impairment of the pump mechanism, resulting in corneal edema[1,2]. Corneal edema is more evident in the early morning because of the decreased tear film osmolarity due to reduced tear film evaporation at night when the eye is closed during sleep[2]. In FECD, the presence of corneal edema and guttae on the posterior corneal surface reduces visual acuity and contrast sensitivity even in the early stage of disease[3].

Treatment of FECD

While surgical treatment is the gold standard for severe FECD, patients with early disease are treated conservatively with pharmacological therapy. This consists of hypertonic eye drops which, having higher osmolarity than the tear film, allow passive diffusion of water from the corneal stroma to the ocular surface[4].

Instillation may be necessary every 5-15 minutes in the morning and progressively less frequently over the following hours[5]. By contrast, our patient's case shows that the application of a hypertonic ointment containing 4.5% sodium chloride and 0.4% sodium hyaluronate at bedtime is able to improve visual acuity throughout the day, while significantly reducing the ocular discomfort and burning related to repeated instillation of hypertonic eye drops.

In conclusion, this case report shows that a single administration of a hypertonic ointment at bedtime leads to a substantial improvement of corneal edema, while reducing the ocular discomfort commonly resulting from the use of hypertonic eye drops in patients affected by FECD. These results are related to the higher concentration of sodium chloride in the ointment, which provides it with a greater osmotic power compared to hypertonic eye drops[6] and, second, to the presence of sodium hyaluronate which ensures greater ocular comfort thanks to its lubricating and mechanical protection properties[7].

Conflict of interest

The author declare no conflict of interest.

Author contributions

The author planned the work, collected the data, drafted the manuscript, and agreed to be accountable for all aspects of the work.

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