TROPHY CONTEST

THEA INTERNATIONAL CONTEST OF CLINICAL CASES IN PATHOLOGIES OF THE EYE

EDITION 2017 - 2018

NOVEL MANAGEMENT OF OCULAR SURFACE DISEASE

THE BEST CLINICAL CASES

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Théa

PREFACE

Mr. JEAN-FRÉDÉRIC CHIBRET

M. Jean-Frédéric CHIBRET
President of Laboratoires Théa

Education and sharing knowledge have always been an important tradition for the Chibret family. Théa supports many projects and educational activities, for example the European Meeting of Young Ophthalmologists (EMYO) since their first meeting in 2014. Théa is also an institutional partner of the European Board of Ophthalmology (EBO).

In 2012, Théa launched "TROPHY", the "Théa inteRnational cOntest of clinical cases in PatHologies of the eYe". TROPHY is an annual contest which aims to encourage fellows and residents to actively participate in their speciality by sharing the results of their clinical cases and experience.

Each year there is a specific theme. Three winners are invited by Théa to present their clinical cases at the Théa symposium organized alongside the ARVO congress. These winners are confidentially and objectively chosen by a board of experts

More and more participants are competing for the chance to submit their latest research and present their cases during this international symposium. In 2017 more than 220 ophthalmologists applied to one of the 3 winners of the TROPHY contest..

After "Glaucoma", "Glaucoma and Ocular Surface", "Persistent or recurrent corneal ulcers", "Management of Corneal Disorders" and "Non-surgical treatment of corneal disorders", last year's topic was "Novel management of ocular surface disease"

The cornea is the gateway to the eye; a healthy cornea is vital for maintaining eye health and good, clear vision. It can be damaged through a range of conditions induced by several diseases involving various processes such as inflammation, infection, degeneration, injuries, and inherited dystrophies.

This means that there is a wide scope for talking points and research surrounding this topic, which has led to a varied and closely fought competition.

We would like to thank all the judges, both national and international, who have helped to review all the many cases submitted each year.

Finally, we would like to thank all the participants in past TROPHY competitions and warmly invite any young residents and fellows in ophthalmology to take part in the coming years. In this way, we are pleased to inform you that the topic of the 2018-2019 TROPHY edition will be "managing ocular surface inflammation"

PREFACE

Prof. ELISABETH MESSMER

Professor Elisabeth Messmer
Head of the department of ophthalmology,
LMU Munich, Germany

Laboratoires Thea's involvement in education in ophthalmology is long-standing, and the TROPHY contest is just one example. The first edition of the TROPHY contest for clinical cases in ophthalmology took place in 2012 and was an instant success. TROPHY is one of the best examples of encouraging young ophthalmologists and offering them the opportunity to share their experience in treating complex cases.

I was honored to be chair of the 6th edition of TROPHY, which covered a specific topic of personal interest to me: "NOVEL MANAGEMENT OF OCULAR SURFACE DISEASE".

This particular subject was chosen because management of corneal problems has evolved rapidly during recent years. Corneal research is currently on the rise, mainly due to the fact that diagnosing and treating problems of the cornea and ocular surface have high priority in modern ophthalmology and hold the key to maintaining and restoring vision. We received 117 entries from 23 countries this year. The three winners were chosen by a jury of international experts.

The three cases were of high quality, very interesting, and presented and discussed well by the candidates. You can read for yourself all the details in this brochure.

I hope you will enjoy this brochure as much as I did. Please remember to share this with your colleagues, emphasize the opportunity TROPHY presents and encourage them to apply for the next edition.

TROPHY WINNERS AT THÉA 2018 ARVO SYMPOSIUM

Théa gave 3 applicants the opportunity to present an unpublished clinical case to an international audience during the Théa symposium at the 2018 ARVO meeting.

TROPHY winners at Théa ARVO symposium in Honolulu on May 2018

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Necip Kara, MD, FEBO, received a medical degree from Meram Medical Faculty of Selcuk University in Konya, Turkey and specialized in Ophthalmology in the Beyoglu Eye Training and Research Hospital. Dr Kara is is currently working in the Deparment of Ophthalmology in the Gaziantep University School of Medicine, Turkey. His main research interests include cornea and external eye diseases, ophthalmic lasers, cataract and refractive surgery.

AMNIOTIC MEMBRANE TRANSPLANTATION WITH MODIFIED OCULAR SURFACE RING: A SUTURELESS OCULAR SURFACE RECONSTRUCTION TECHNIQUE

★ INTRODUCTION ★

Human amniotic membrane has been used in the management of ocular surface diseases. The usefulness of amniotic membrane has been attributed to its anti-inflammatory, anti-fibrotic, and anti-vascularization effects and also to its ability to enhance epithelial healing.

Symblepharon is one of the most challenging problems of ocular surface diseases and can result in restriction of ocular motility, inadequate blinking, entropion, ptosis and secondary harmful effects on the ocular surface, including the cornea. It can be caused by problems such as chemical burn, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and dry eye.

Symblepharon rings are commonly used in the prevention of symblepharon formation. The ring exhibits beneficial effects by reducing scarring and keeping the eyelids away from the damaged ocular surface. In this study, a novel surgical technique for amniotic membran transplantation (AMT) with a modified ocular surface ring (MOSR) using a feeding tube is described in cases of severe ocular surface diseases.

★ CASE REPORT ★

The patients underwent placement of the amniotic membrane and modified symblepharon ring implantation to treat the ocular surface diseases. In cases with symblepharon, lysis of symblepharon and all adhesions were performed, followed by AMT onto the entire ocular surface with the MOSR implantation. In cases with limbal stem cell deficiency, limbal stem cell transplantation was also performed, followed by AMT with MOSR.

AMT with MOSR procedure

The surgical technique is shown in detail in video 1, video 2, Fig. 1, and Fig.2. The modified ring was formed using the custom dimension of each eye using a feeding tube. After adjusting the length of the tube by positioning the fornices, it was cut from the marked point. The feeding tube opening was enlarged using a forceps to insert the other end, and then the ends were nestled to form the MOSR. A large piece of amniotic membrane graft was prepared to cover the entire cornea, conjunctiva, fornix, and palpebral conjunctiva. The amniotic membrane graft was spread onto the ocular surface and eyelid, with the epithelial side facing down. The MOSR was gently placed on the amniotic membrane graft in the palpebral aperture. The MOSR held using a forceps was first pushed into the inferior fornix, followed by pushing into the superior fornix. The excess membrane was trimmed at the lid margins. Postoperatively, the patient first received topical moxifloxacin, topical loteprednol etabonate 0.5%, artificial tear eye drops, autologous serum eye drop, and followed by regulated according to ocular condition of patient.

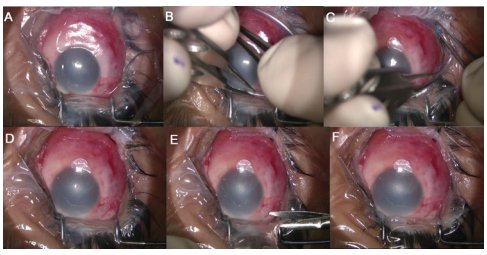


Figure 1. Preparation of the MOSR. A: A feeding tube; B: the adjustment of the tube length by positioning the fornices; C:Cutting of the feeding tube from the marked point; D: Enlargement of the feeding tube opening using a forceps; E: Nestling of the tube ends to form the MOSR; F: Appearance of the formed MOSR

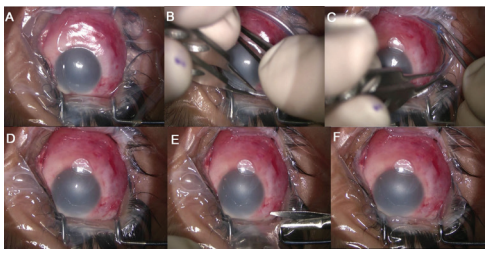
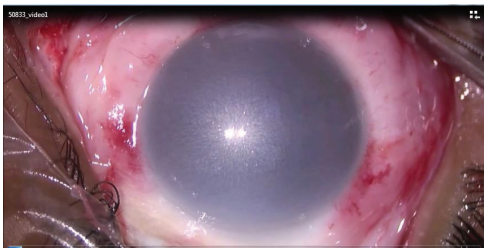
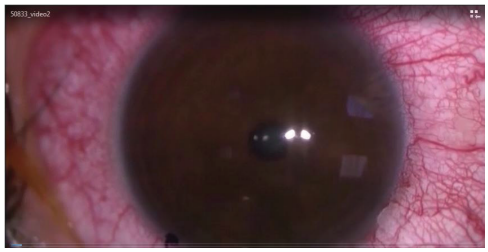


Figure 2. Implantation of the MOSR in a patient with severe ocular chemical burn (case 1). A: Covering the entire ocular surface with a large piece of amniotic membrane graft; B: Positioning of superior part of the MOSR in the superior conjunctival fornices above the amniotic membrane graft; C: Positioning of inferior part of the MOSR in the inferior conjunctival fornices and medial canthus above the amniotic membrane graft; D: Appearance of the ocular surface after the MOSR implantation; E: Trimming of the excess amniotic membrane at the lid margins.



Video 1. =(Case 1). Amniotic membran transplantation with a modified ocular surface ring (MOSR) in a patient with severe ocular chemical burn.



Video 2. (Case 6). Conjunctival limbal autograft implantation, amniotic membran transplantation with a modified ocular surface ring, and simple limbal epithelial transplantation from a cadaveric donor in patient with severe limbal stem cell deficiency secondary to ocular chemical burn.

RESULTS

AMT combined with MOSR were analyzed retrospectively. Additionaly, symblepharon release was applied in two eyes and limbal stem cell transplantation was performed in three eyes. Postoperatively, complete epithelialization was achieved without symblepharon formation. The demographic information and clinical data of the patients are summarized in Table 1.

Case no	Age/sex	Ocular surface disease	Surgery	Follow-up (Mo)	Last visit Results
1	13/F	Chemical burn, large stem cell loss	AMT+MOSR	2	No symblepharon, no epithelial defect
2	30/F	Symblepharon	Symblepharon	4	No symblepharon recurrence
3	50/M	Chemical ocular burn, limbal stem cell loss	Limbal stem cell tx+AMT+MOSR	9	No symblepharon, no epithelial defect
4	62/F	Symblepharon	Symblepharon	6	No symblepharon recurrence
5	40/M	Severe chemical ocular burn, limbal stem cell loss	Limbal stem cell tx+AMT+MOSR	6	Lid deformation, entropion, no epithelial defect, no symblepharon
6	35/M	Severe chemical ocular burn, 360° limbal stem cell deficiency with conjunctivalization, corneal opacity	Limbal stem cell tx+AMT+MOSR	3	no epithelial defect, no conjunctivalization and limbal stem cell deficiency, but corneal stromal opacity remain

★ DISCUSSION ★

Severe ocular surface diseases such as chemical burns and ocular cicatricial diseases can lead to severe ocular morbidites, including symblepharon formation and limbal stem cell loss. Maintenance or restoration approaches for ocular surface management are very important to prevent loss of vision or to perform sequential surgical treatment, including keratoplasty and keratoprosthesis. It has been reported that early intervention with AMT in severe ocular surface diseases such as Stevens–Johnson syndrome and acute chemical burns leads to better long-term results.[1,2]

The amniotic membrane is usually sutured onto the ocular surface using running or interrupted sutures for fixation.[3] However, the placement of sutures inflicts trauma to the ocular surface with prolonged operative time, and hence technical skills are required for an effective suture placement. AMT with MOSR does not require any sutures and eliminates several problems resulting from sutures, such as subconjunctival hemorrhage, infection due to sutures, tissue necrosis, foreign body reaction, and irritation. Using AMT with MOSR relieves patient symptoms and decreases surgical time.

Recently, several sutureless amniotic graft implantation procedures have been described. The Prokera ring (Bio-Tissue, Inc, Doral, FL) is an FDA-approved device that consists of a cryopreserved amniotic membrane circle clamped into a dual polycarbonate ring. However, it has a relatively high cost. Liang

et al created a modified symblepharon ring using a polymethylmethacrylate ring to apply the amniotic membrane for patients with ocular chemical burns.[4] They showed that sutureless AMT using MOSR had better efficacy than the conventional sutured AMT in the treatment of acute ocular burns.

Symblepharon formation is one of the most challenging problems of severe ocular surface diseases. Various procedures have been evaluated to prevent symblepharon formation, such as the conformer or conventional symblepharon ring combined with AMT. Commercially available amniotic bandage tissues such as the Prokera ring cover just the corneal and limbal surfaces, leaving the deep fornix unreachable, and fail to prevent symblepharon formation. AMT with MOSR procedure expands the effective coverage of the amniotic graft to the entire ocular surface, including the cornea, bulbar conjunctiva, fornices, and palpebral conjunctiva, and prevents significant ocular surface scarring and symblepharon formation. When compared with other options, the MOSR is an inexpensive and an easily accessible option. It can also be customized for each individual. As the MOSR is placed into fornices, it does not cause any cosmetic view. Central aperture of the MOSR allows oxygen and drops to reach the ocular surface, and examination of the ocular surface during the postoperative period. Postoperatively, the MOSR can be easily removed from the ocular surface in the office room.

F:Female, M:Male, Mo: Month, AMT: amniotic membrane transplantation, MOSR: modified ocular surface ring, Tx:Transplantation, PK: Penetrating Keratoplasty

★ CONCLUSION ★

This study demonstrated a simple, effective, and safe technique using AMT combined with MOSR for ocular surface rehabilitation without the need for suturing. This modified technique is economically advantageous and may be an alternative to conventional symblepharon ring or other sutureless AMT techniques.

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Dr. Nikolaos MAMAS

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Nikolaos Mamas was born in Greece. After graduating from the Medical School of Athens, Greece, he was trained in Ophthalmology and aquired his higher academic degree and specialty medical qualification at the Department of Ophthalmology of RWTH Aachen University in Germany. Between 2016 and 2018 he continued his training at the 1st Department of Ophthalmology at the University of Athens. Currently, he is working as a Medical Retina Fellow at Moorfields Eye Hospital in London, UK.

EQUINE PERICARDIUM FOR TECTONIC REPAIR OF CORNEAL PERFORATIONS

★ INTRODUCTION ★

Corneal perforation can be the result of trauma, severe burn or corneal ulcerative disease. It can cause devastating acute complications, which in the longer term can lead to phthisis and blindness. Therefore, promt diagnosis and management of this ophthalmologic emergency is crucial in order to maintain globe integrity.[1]

Several factors determine optimal management; the cause of perforation, size and location of the defect, as well as extent of stromal and scleral involvement. Smaller corneal perforations can be adressed with a bandage contact lens, tissue adhesives, conjuctival flaps or amniotic membrane transplantation, whereas larger perforations may require patching with more stable materials, such as scleral and corneal allografts.[1]

Human corneal or amniotic membrane grafts are not always available, necessitating the need for alternative biomaterials when facing emergencies. Pericardium is a collagen-rich biological tissue widely used as a biomaterial for tissue enginneering applications, mostly the construction of bioprostheses in neurosurgery and cardiovascular surgery. In ophthalmic surgery, bovine and human donor pericardium has been applied for the management of exposed glaucoma shunts[2-4] and orbital implants[5,6] as well as scleral thinning.[7] Recently, the use of bovine pericardium for the urgent management of corneal perforations was reported.[8,9]

Equine pericardium has been assessed or is currently used in clinical practice, e.g. as a dura substitute in neurosurgery,[10] for reconstruction of calcified mitral annulus and aortic aneurysms in cardiovascular surgery[11,12] and for treating bone defects in dental surgery,[13,14] however, to our knowledge there is no report to date on the use of this novel biomaterial in ophthalmic surgery. Herein, the successful use of equine pericardium for sealing corneal perforations is described.

★ CASE PRESENTATION ★

A 38-year old male was referred to our department with a bilateral non-infectious perforated corneal melt due to presumed ocular nonsteroidal anti-inflammatory drugs (NSAID) abuse. The patient reported regular chronic use of 'unknown' eye drops, without medical monitoring, for his chronic bilateral eye irritation. He denied any previous ocular surgery, while his medical history was insignificant.

Visual acuity was hand motion in both eyes. No lid or lash abnormalities were present. Slit lamp biomicroscopy showed a moderate conjuctival injection and a bilateral melting of the inferior half of the cornea. A mild inflammatory stromal infiltrate surrounded the area of ulceration, while a focal perforation of approximately 4mm caused iris prolapse and athalamia (Figures 1a and b). Intraocular pressure, estimated digitally, was in hypotonic levels. Ophthalmoscopy showed an unremarkable fundus in the periphery, B-scan revealed normal posterior segment findings.

As amniotic membrane or corneal allografts were not readily available, we decided to use lyophilized equine pericardium to seal the corneal defect temporarily and delay corneal grafting until control of the associated inflammation would allow survival of the graft. Informed consent was obtained from the patient prior to surgery. The procedure was performed under topical anaesthesia. According to the manufacturer's recommendations, the dry patch was moistened in physiological saline solution for 1 minute to soften and recover its original consistency. After debriding the necrotic tissue, the extent of the defect was measured and the pericardium sheet (40 mm x 50 mm) was trimmed to the appropriate size and shape and fixated with interrupted 10-0 Nylon stitches (Figures 1c and d). Cultures and corneal tissue specimens were additionally obtained for microbiological and histopathological examination. Finally, cefuroxime at a concentration of 1mg/0.1ml was injected into the anterior chamber.

During the postoperative period, oral and local antibiotic as well as local anti-inflammatory treatment was given. Both eyes were regularly treated with preservative-free lubricating eye drops. The patient was examined on a daily basis for signs of infection or hypotony. Intraocular pressure was carefully estimated digitally. Bacterial and fungal cultures were negative, whereas the histopathological examination did not provide any specific findings apart from the presence of neutrophils.

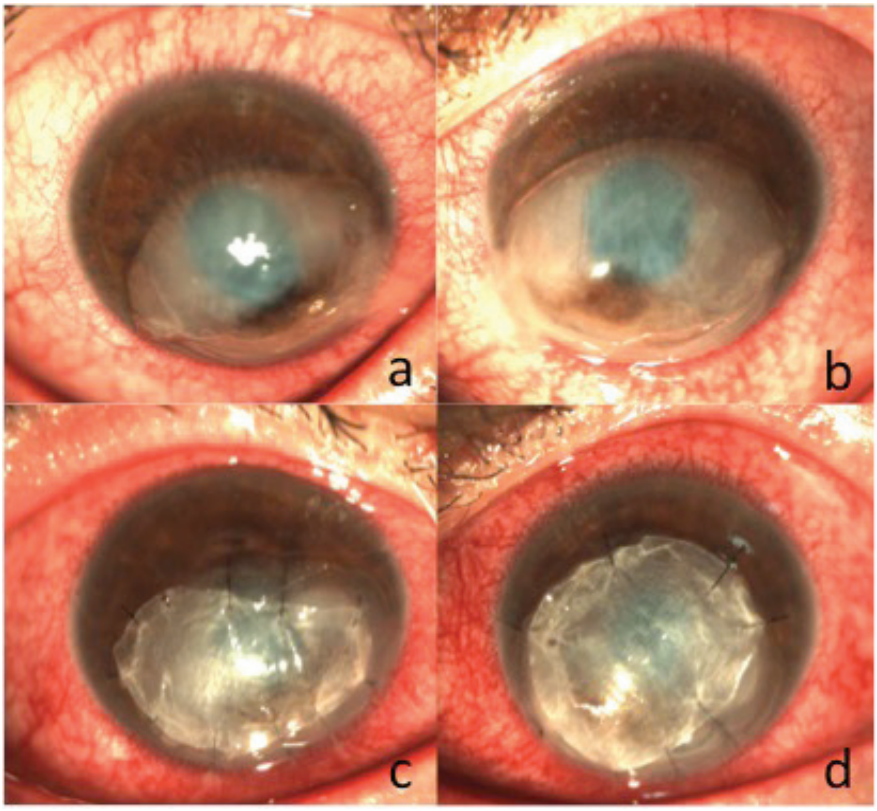

Fig. 1 Photo collage of slit-lamp pictures of both eyes. Perforated corneal melt causing iris prolapse and athalamia in the right (OD) (a) and left eye (OS) (b) at presentation. Management of the perforation with a single layer of equine pericardium fixated with nylon 10-0 sutures OD (c) and OS (d)

An immediate watertight closure of the corneal perforation was achieved and maintained throughout an observation period of 6 months with no evidence of infection or recurrent melting. The intraocular pressure remained stable and the patient did not complain about pain or significant discomfort.

A self-limiting partial degradation of the pericardium and loosening of sutures was observed at 2 months in both eyes (Figures 2a and b). During suture removal, the pericardium dislodged exposing tectonically stable vascularized scars (Figures 2c and d).

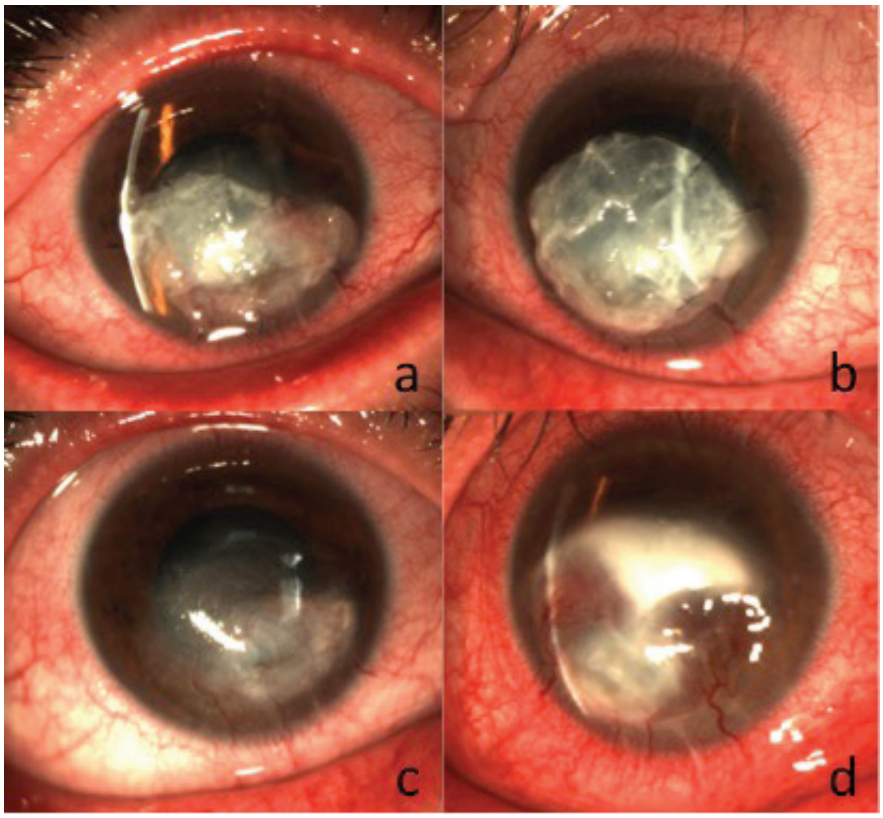

Fig. 2 Partial degradation of the pericardium at 2 months OD (a) and OS (b) and a tectonically stable vascularized scar 5 months after surgery OD (c) and OS (d).

★ DISCUSSION ★

The successful employment of lyophilized equine pericardium for the urgent management of non-infectious corneal perforations is reported. This is to our knowledge the first report on the use of this reconstructive biomaterial in ophthalmic surgery.

Equine pericardium undergoes industrial processing prior to transplantation; the cellular components of the tissue are removed (decellularization) through physical, enzymatic or chemical treatments resulting in an antigenically neutral biomaterial, while the integrity of the extracellular matrix is preserved. The purified collagen network is then fortified by means of cross-linking, coating with biopolymeric films or lyophilization (freeze drying). Finally, it is chemically sterilized and irradiated with X-rays.[15]

Processing offers to pericardium properties that render it suitable for sealing corneal tissue defects. The cell-free pericardial tissue composed of extracellular matrix proteins, which are generally conserved among species, can be easily used as a guide for host cell attachment, migration and

proliferation.[16] This property is important for the promotion of corneal wound healing, as pericardium ensures a watertight closure of the perforation, while acting as a scaffold for stromal remodeling and epithelial surface closure. Moreover, the collagen network aquires a high mechanical resistance, it becomes easy to handle and its transparency allows visibility of the underlying tissues (Figures 1c and d). Due to its equine origin, there is no risk of prion transmission. Finally, it is considered as biocompatible and is not expected to show any toxicity or hypersensitivity reaction.[16] All these qualities render lyophilized equine pericardium a reasonable off-label choice for corneal sealing, when donor grafts are not readily available.

First-line choices for tectonic repair of corneal perforations include gluing, conjuctival flaps, amniotic membrane and corneal transplantation in the form of penetrating keratoplasty, corneal patch graft, lamellar keratoplasty or tectonic epikeratoplasty.[1]

The extent of the perforation in our patient, as well as the instability of the surrounding cornea did not allow application of cyanoacrylate adhesive as this is indicated for smaller defects.[17] Conjunctival flaps are not suitable for active keratitis with severe stromal thinning or in cases of a frank perforation, as they cannot always control the leakage.[18]

Amniotic membrane or corneal allografts are established biomaterials for sealing corneal defects, however they were not available at that point in our clinic.

In the herein described case, equine pericardium patch was shown to be effective for sealing corneal perforations. A significant superficial and deep corneal neovascularization at the area of the pericardium graft especially on the left eye was established between the second and fifth month of follow-up (Figures 2c and d). Since host bed vascularity is a cardinal risk factor for corneal graft rejection,[19] further management of neovascularization is essential prior to keratoplasty. Additional studies are needed to determine the overall safety and effectiveness of this biomaterial, as well as any differences in the properties and surgical outcomes among pericardial membranes from different species or newer tissue engineered biomaterials.

★ CONCLUSION ★

This is the first report on the use of equine pericardium for sealing corneal defects. Corneal integrity was achieved and maintained in both eyes of our patient with no signs of aqueous leak, hypotony, infection or recurrence. Considering its easy access and safety, it may be considered for the urgent management of corneal perforations when other donor tissue is not available.

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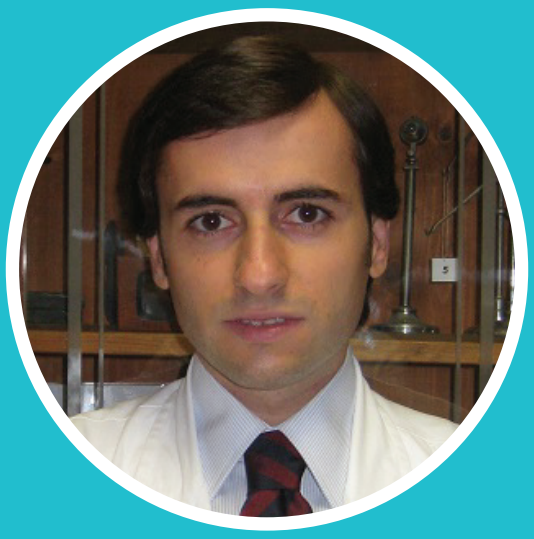

3

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IN VIVO CONFOCAL MICROSCOPY DEMONSTRATES THE RECOVERY OF THE NORMAL MORPHOLOGY OF SUB-BASAL NERVE PLEXUS AFTER CORNEAL NEUROTIZATION FOR THE TREATMENT OF SEVERE NEUROTROPHIC KERATITIS

★ INTRODUCTION ★

Neurotrophic keratitis is a degenerative disease caused by damage of trigeminal innervation, leading to corneal epithelial breakdown, impairment of healing and, in severe cases, corneal ulceration, melting and eventually perforation. The hallmark of the disease is a decreased or absent corneal sensation.1 Trigeminal nerve provides not only sensitivity but also trophic factors, thus playing a key role in maintaining the integrity and function of the entire ocular surface. The most common causes include, among others, herpetic keratitis, corneal surgery and diabetes. Medical management consists of supportive measures such as unpreserved tear substitute to moisten the ocular surface, antibiotic to prevent infections, and contact lens to protect the cornea. Novel therapies, including recombinant human nerve growth factor and Regenerating Agent eye drops, are currently under investigation in ongoing Clinical Trials with promising results (respectively NCT01756456 and NCT01242839).

However, to date no satisfactory medical options are available for the treatment of severe neurotrophic keratitis, while surgery is reserved for refractory or complicated cases. Recently a novel surgical technique consisting of the transposition of contralateral supratrochlear and supraorbital nerves to the sclero-corneal limbus of the affected eye with the aim of restoring corneal innervation and sensivitity was introduced.2-3 To the best of our knowledge, the postoperative recovery of corneal innervation and sensitivity has been investigated and confirmed only indirectly by means of corneal esthesiometry. We describe herein for the first time the process of reinnervation as it progresses over the time after corneal neurotization by means of in vivo confocal microscopy (IVCM).

★ CASE PRESENTATION ★

Patient history

A 46-year-old woman with a 3-year history of recurring chronic neurotrophic keratitis in her right eye due to facial and trigeminal palsies secondary to surgical removal of homolateral statoacoustic nerve neurinoma of pontocerebellar angle was referred to the Cornea Service of our Institution. Lateral tarsorraphy had been performed soon after the palsies' onset to protect the cornea from the exposure. Upon presentation, slit lamp examination revealed a central corneal neurotrophic ulcer (stage III Mackie Classification) with a diameter of 3 x 3 mm, accompanied by stromal melting and tortuous corneal neovessels. The patient was treated with unpreserved tear substitutes and vitamin A ointments, and followed-up for an additional period of 1 year, but the clinical picture remained stable and the corneal ulcer did not heal. Corneal esthesiometry and IVCM were performed three times over the year, and confirmed the complete absence of respectively corneal sensitivity and nerve fibers in the sub-basal plexus. One week prior to corneal neurotization, Schirmer test type I was 1mm/5', break-up time (BUT) was 1 second, ocular surface disease index (OSDI) score was 32. Best-corrected visual acuity was limited to hand motion at 1 foot. Corneal esthesiometety evaluated quantitatively by the Cochet-Bonnet esthesiometer was null in all the 5 corneal regions (Figure 1, part A). IVCM confirmed the complete absence of the corneal sub-basal nerve plexus (Figure 2, part A).

Surgical procedure

The left supraorbital and supratrochlear nerves, along with their main branches which run with different depth and path in the subdermal plane, were identified and dissected through a coronal incision from the undersurface of the frontal skin, in order to harvest a minimal nerves length of 12 cm. The dissected nerves were then tunnelled over the nasal bridge to reach a 10 mm incision in the right superior eyelid. Using a Wright needle, four distal nerve branches were retrieved in the ocular surface (Figure 3). By means of a conjunctivotomy and tenonectomy, the nerves were tunnelled to gain access to the subtenonian area. Each distal branch was passed into the prepared perilimbal space and finally distributed at the four cardinal points. The branches were not fixed to the sclera by sutures in order to avoid possible damage of nerve fibers, but were only positioned in the cardinal points. Four centripetal intra-corneal tunnels (one for each branch) were done in order to facilitate the nerve sprouting towards the central cornea. The conjunctiva was then sutured with 8-0 vicryl suture.

Patient follow-up

After surgery, patient was instructed to instill Tobramycin plus Dexamethasone eye drops four times a day for 4 weeks. Transposed nerves were visible in the desired positions passing around the sclero-corneal limbus under the bulbar conjunctiva by slip lamp examination and anterior segment optical coherence

tomography (Figure 4, parts A-B). Three months postoperatively, clinical picture improved significantly with the complete healing of the epithelial defect, the decrease of conjunctival hyperemia and of area and tortuosity of corneal neovessels, and the increase of Schirmer Test type I and BUT to the lower limits of normal range (respectively 8 mm/5' and 5 seconds). IVCM detected few thin and tortuous nerve fibers in the corneal sub-basal plexus (Figure 2, part B), while corneal esthesiometry continued to be null. Six months postoperatively, IVCM detected a higher density of nerve fibers which appeared with a near-normal morphology (Figure 2, part C), while corneal sensitivity was still totally absent. Nine months postoperatively, IVCM detected nerve fibers in the corneal sub-basal plexus with normal density and morphology (Figure 2, part D), and corneal esthesiometry measured 30 to 35 mm in all the 5 corneal regions examined. Currently one year postoperatively, sub-basal plexus continues to be normal in terms of density and morphology, while corneal esthesiometry improved to 40 mm in all the 5 corneal regions (Figure 1, part B).

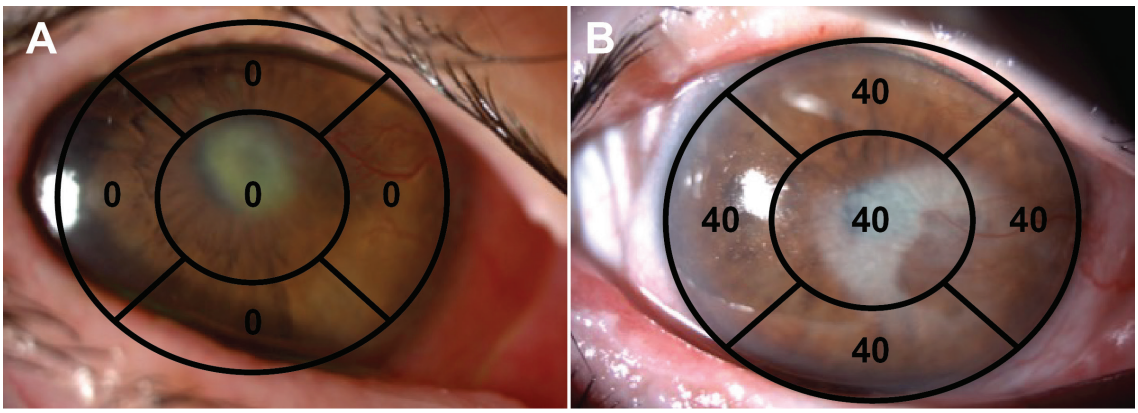

Figure 1: Slit lamp examinationand corneal esthesiometry before (part A) and 1 year after surgery (part B).

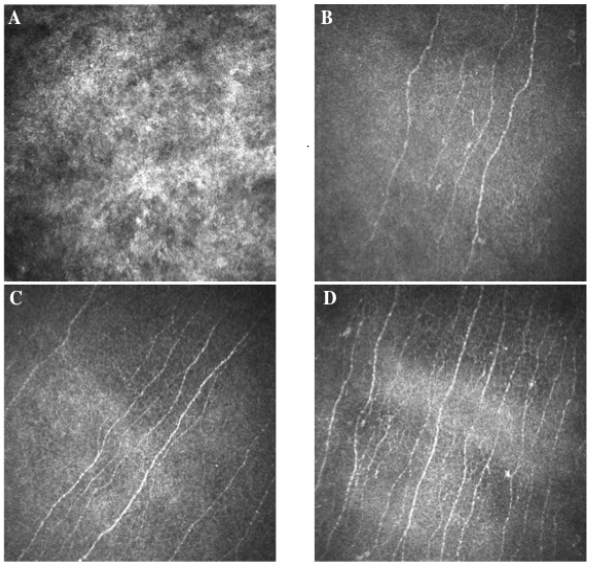

Figure 2: In vivo Confocal Microscopy images preoperatively (part A) and 3 (part B), 6 (part C) and 9 months postoperatively (part D)

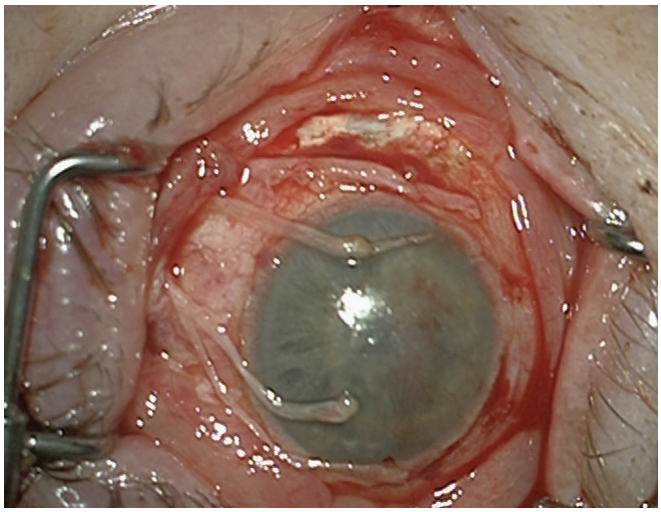

Figure 3: Intraoperative picture of the four distal nerve branches positioned upon the ocular surface

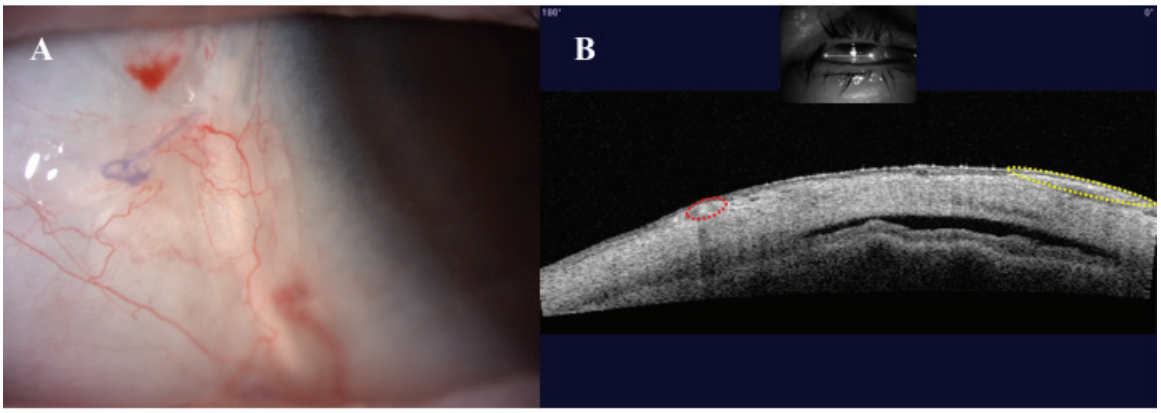

Figure 4: Slit lamp examination showing one branch of the transposed nerves underlying the bulbar conjunctiva and surrouding the temporal sclero-corneal limbus (part A). Anterior-segment Optical Coherence Tomography cross-sectional scan showing the vertical temporal branch (red dashed area) and the horizontal inferior branch (yellow dashed area) (part B)

★ DISCUSSION ★

Denervation of the cornea impairs wound healing, leading to chronic ulceration; in addition it represents a contraindication for corneal transplantation, because the new graft would be affected by the same detrimental processes. Recently, novel surgical techniques consisting of different nerves transpositions to the denervated cornea have been proposed in order to restore corneal sensation in severe cases of neurotrophic keratitis.2-5 Corneal neurotization can be performed through two different surgical techniques, based on the transposition of the contralateral or ipsilateral supraorbital and/or supratrochlear nerves (direct neurotization),2-4 or on the sural nerve graft (indirect neurotization).5 This approach allows to restore corneal sensitivity, and to perform successful subsequent corneal surgery, when required.

To date corneal reinnervation after surgical neurotization has been determined only clinically by Cochet-Bonnet esthesiometer, while the direct evidence of the ingrowth of the transferred nerves from the sclero-corneal limbus to the central recipient cornea has not been provided. Thus, it was still not clear if postoperative improvement of ocular surface condition along with the reduction of inflammation occurred after corneal neurotization were related to the action of chemical neuromediators supplied to the ocular surface by the transferred nerve branches anchored to the sclero-corneal limbus, or to an ingrowth of the distal nerve fascicles towards the recipient cornea.

In the case presented herein, we used for the first time in vivo confocal microscopy to objectively observe the process of corneal reinnervation as it progressed over the time after corneal neurotization. We detected new thin corneal nerves in the subepithelial plexus as soon as 3 months postoperatively, which acquired a near-normal morphology and density six months after surgery. However corneal sensitivity measured by Cochet-Bonnet esthesiometer remained null at those time intervals. Different hypotheses can be postulated to explain the structure-function discrepancy between corneal nerves detection by IVCM and the lack of functional response. First of all, although Cochet-Bonnet esthesiometry is considered the gold standard, it is far to be an ideal tool for measuring overall corneal sensitivity; in fact the direct physical pressure of the nylon thread against the cornea results in stimulation of Ad fibers, exploring only the mechanical sensitivity while neglecting chemical and thermal receptors.6 The second hypothesis concerns the central nervous system remodeling that likely takes place after nerve transfers with a variable time line. Indeed, after corneal neurotization the patient has to shift his/her perception to recognize mechanical stimulation of the cornea as true corneal sensation.

Corneal esthesiometry was partially regained in all regions after nine months, and increased further one year postoperatively. IVCM demonstrated the recovery of the normal morphology of the sub-basal nerve plexus of the cornea as soon as nine months postoperatively. As spontaneous corneal nerve regeneration has been demonstrated in a case of neurotrophic zoster keratopathy after few years of follow-up,7 we studied over the time the sub-

basal nerve plexus by serial IVCM scans and corneal esthesiometries before to proceed with surgical neurotization, which was performed 4 years after the onset of the palsy.

Interestingly, the patient did not report any unpleasant sensation of neuropathic pain, allodynia or disesthesia during the entire follow-up period. However, a stromal leukoma covering completely the visual axis is still present and deep anterior lamellar keratoplasty would be necessary to restore patient's visual acuity. This surgery would provide not only a significant gain in terms of visual acuity, but also the the histopathologic assessment of nerves in the corneal button excised by using the Karnovsky and Roots modification of nonspecific acetylcholinesterase method, with the ex vivo demonstration of the distribution and spatial arrangement of the nerve bundles that repopulated the cornea after surgical neurotization.[8]

★ CONCLUSION ★

This case report provides new insight supporting the efficacy of corneal neurotization as a definitive treatment option in severe neurotrophic keratitis, representing the first anatomical in vivo validation of reinnervation after corneal neurotization thanks to in vivo confocal microscopy imaging. Corneal sensitivity and normal morphology of the sub-basal nerve plexus were regained within the first postoperative year. In case of concomitant corneal opacity, we advocate a staged approach (corneal transplantation at least 1 year after corneal neurotization) in order to provide an optimal recipient bed for the success of the graft. Prospective randomized clinical trials comparing direct and indirect corneal neurotization are desiderable to establish the "gold standard" technique. Future perspectives of corneal neurotization may include also endoscopic minimally invasive procedure,10 and the use of either natural or recombinant nerve growth factor-based eye drops to further stimulate nerve fibers growth after surgery.

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BEST NATIONAL CASES

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CACICOL: A NOVEL TREATMENT FOR LIGNEOUS CONJUNCTIVITIS?

★ INTRODUCTION ★

We present a case of ligneous conjunctivitis which was treated with Cacicol (PolyCarboxyMethylGlucose Sulfate)) with good control of symptoms and signs. We believe that this is the first reported case of ligneous conjunctivitis to have been treated with Cacicol.

Ligneous conjunctivitis (LC) most frequently occurs in the setting of hypoplasminogenaemia, a rare autosomal recessive disorder resulting in a lack of plasminogen. This can be either type 1 hypoplasminogenaemia in which LC and poor wound healing predominates or type 2 dysplasminogenaemia which is not felt to cause any symptoms (1). Ligneous conjunctivitis may in some cases be part of a systemic condition, which can present with dental, respiratory, kidney, ear and female genital involvement. It is important to diagnose quickly as respiratory involvement can be fatal. LC is characterised by chronic conjunctivitis with hard fibrin rich "woodlike"otarsal pseudomembranes with a thick mucoid discharge. (2) It does not respond to conventional treatment for conjunctivitis and recurs quickly following pseudomembrane excision. Histopa-

thological diagnosis is made on the basis of subepithelial deposits of amorphous eosinophilic hyaline with granulation tissue and inflammatory cells, immunoreactive for fibrinogen in subtarsal conjunctival pseudomembranes. (3) Patients will also show low levels of plasminogen on blood tests.

Conventional treatment is with pseudomembrane excision followed by intensive heparin and steroid eye drops with topical ciclosporin long term to prevent recurrence (2). However the use of plasminogen and fresh frozen plasma (FFP) drops is also described in case reports to good effect (1,4,5,6,7) along with the use of amniotic membrane grafts (3,8). This treatment presents some difficulties as plasminogen drops are not yet available commercially, FFP requires local blood bank cooperation, and to be kept frozen until used while Heparin drops require special sterile pharmacy preparation. In our case we found it impossible to quickly source these agents and decided to empirically try Cacicol eye drops. Cacicol is a heparan sulfate analogue (heparan sulfate itself being an analogue of heparin) and is marketed as a matrix regeneration therapy agent (RGTA).

Cacicol was initially developed for use in the treatment of neurotrophic corneal ulcers (9, 10) and is licensed for use in the UK as a medical device to individual patients on a case by case basis. Heparan sulfate and heparin are structurally similar and have been shown to act in similar ways (11). As such it was postulated that it may work as heparin does in this condition by inactivating factor Xa, stopping the production of thrombin and accelerating the combination of antithrombin III with thrombin and as such preventing the build up of fibrin from fibrinogen which forms the thick pseudomembranes (12).

★ CASE REPORT ★

A three and a half year old girl of Middle Eastern, non consanguineous parents presented to clinic with persistent bilateral red, painful eyes with mucoid discharge. On examination she had severe papillary conjunctivitis with thick pseudomembranes and some minor limbitis. She was diagnosed with pseudomembranous conjunctivitis and started on a trial course of steroid and ciclosporin 0.2% eye drops. Routine conjunctival swabs were performed but these all proved negative. After a few weeks of treatment only mild improvement had occurred and in the right eye a large hard lesion was noted to be firmly adherent at the upper edge of the tarsal plate (image 1).

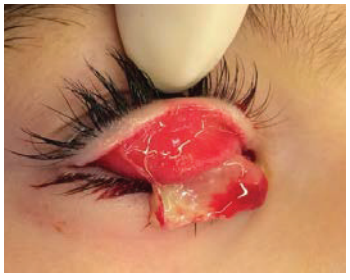

Image 1: Ligneous conjunctivitis pseudomembrane

It was decided to perform an examination under general anaesthetic during which excision of this lesion was performed and sent to histopathology. This confirmed a diagnosis of ligneous conjunctivitis which was already clinically suspected and because of the known association with plasminogen deficiency a blood sample was also taken for analysis of plasminogen levels.

Blood plasminogen level was found to be severely reduced at 0.08 IU/ml (10% of normal level). A referral was made to Paediatric Haematology who performed genetic testing and also to general paediatrics for assessement for involvement of other organs. The patient was recommenced on Loteprednol and Ciclosporin (0.2%) eye drops, however she soon had a recurrence of her pseudomembranes and developed corneal deposits associated with a reduction in her visual acuity. Plasminogen, FFP and heparin eye drops proved impossible to source and as such Cacicol drops were commenced on alternate days. This resulted in a dramatic improvement in the clinical picture over 48 hours, with a reduction in inflammation, improvement in visual acuity and increasingly less ligneous deposits on each subsequent visit. Ciclosporin and loteprednol drops were reduced and stopped and the condition remained relatively stable over the course of 3 years follow up.

Unfortunately the patient stopped her Cacicol drops on 2 occasions with a resultant flare in her ligneous conjunctivitis. This was quickly calmed each time with once daily usage of Cacicol drops for 4 days followed by alternate days and then reduced to one drop 2 to 3 times a week (image 2). This strengthened our belief in the clinical effectiveness of this agent.

image 2: Top: Flare up after non compliance with Cacicol.
Bottom: Appearance after 1 week of cacicol use

★ DISCUSSION ★

The case presented here is the first we are aware of where Cacicol has been used successfully to treat ligneous conjunctivitis.

Ligneous conjunctivitis is a rare condition, of which the incidence is not known, however there are over 120 cases reported in the literature. Topical Heparin is used conventionally for itgn anti-fibrin action as previously described, however as this is a rare condition, these eye drops are not easily accessible and require preparation from systemic heparin in a sterile preparation pharmaceutical unit. (13).

Cacicol is a heparan sulfate analogue which itself is an analogue of heparin and was chosen on an empirical basis in the hope that it would also have an anti-fibrin action in this condition. In addition where the use of heparin has been described administration has been from half hourly on a reducing course (12), while Cacicol appears to be effective when used twice weekly in a similar way to which it is directed to be used in non healing corneal epithelial defects. This is due to the limited availability of heparan-binding sites. Once these binding sites are filled, excess Cacicol can actually reduce wound healing ability by removing heparan bound growth factors and cytokines (14). It is anticipated that treatment will be life long, or at least until another treatment becomes available, so ease of use and ease of dispensing is we feel very important in achieving good compliance. The patient's Mother collects supplies of Cacicol at her local hospital pharmacy on a monthly basis after a named patient application for funding and supply of this relatively inexpensive "medical device" was made.

Cacicol being an analogue of a naturally occurring proteoglycan is also felt to be very safe and to date no significant side effects have been reported. We propose that at present Cacicol has a role to play in the management of this condition, however experience with more cases are required to confirm this.

★ CONCLUSION ★

Cacicol has proven to be an effective method of managing acute flares and maintaining stability in this case of ligneous conjunctivitis. The conventional treatments of heparin or plasminogen eye drops are difficult to source and to supply. Cacicol potentially presents a safe, effective and readily available, stable therapeutic agent for this condition and by the low frequency of installation required a very acceptable treatment to the patient.

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USE OF AUTOLOGOUS ORAL MUCOSA TRANSPLANT TO TREAT CONJUNCTIVAL AND LEAKAGE AFTER TRABECULECTOMY

★ INTRODUCTION ★

Trabeculectomy is the most commonly performed filtration surgery. Although it is relatively easy to perform and effectively lowers intraocular pressure, it is not always without complications. To prevent scarring mitomycin C is sometimes used as an adjunct which can additionally lead to an increased incidence of ocular hypotony due to thinner and leaking blebs[1].

Treatment options for late-onset leaking and overfiltrating blebs include a multitude of surgical and non-surgical procedures.

We report of a patient who suffered from recalcitrant hypotony due to repeated necrosis of the sclera and conjunctiva after trabeculectomy refractory to conservative measures as well as multiple amnion grafts, conjunctival flaps and pericard reconstructions who finally was treated successfully with an autologous oral mucosa graft onto the globe.

★ CASE REPORT ★

A 58 year old man with a narrow angle glaucoma and plateau iris configuration underwent a conventional trabeculectomy with mitomycin C on the right eye in 2009. A structurally normal to large bleb was its result and his pressures were between 4 to 9 mmHg for years. Beginning 2016 his right eye became progressive hypotone without Seidel/leakage and the diagnosis of overfiltration was made. A slow reduction of visual acuity due to macular folds was noted reason why surgical revision with transconjunctival fixation of the sclera as well as tamponade of the anterior chamber with a dispersive viscoelastic (endocoat Healon) was performed in April 2016 due to severe persisting ocular hypotony.

After the intervention hypotony still persisted. An open revision of the scleral flap with pericard-patch (Tutopatch) two weeks later was done which resulted in an uncontrollable hypertony with consecutive operative lavage of the anterior chamber. Finally conjunctival necrosis over the implanted pericard-patch developed and further melting of the sclera and pericard led to open fistulisation. Hence two weeks after the first attempt to reduce filtration another pericard-patching was repeated combined with amniotic membrane transplantation (Figure 1 a).

No leakage was documented even after the removal of bandage contact lens in the first days after the surgery. One week postoperatively a new positive Seidel on the nasal rim of the amnion graft, repeated necrosis of the scleral flap and progressive retraction reaction of the amnion graft with consecutive shallowing of the anterior chamber were noted (Figure 1 b). An initial successful postoperative result had failed again and another new revision with pericard-patch and amniotic membrane transplantation had been performed in July 2016 with further revisions to close persisting conjunctival defects three months later in October 2016.

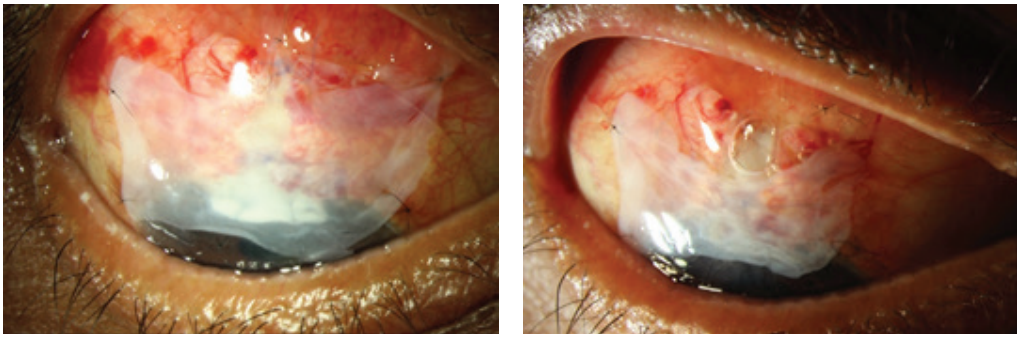
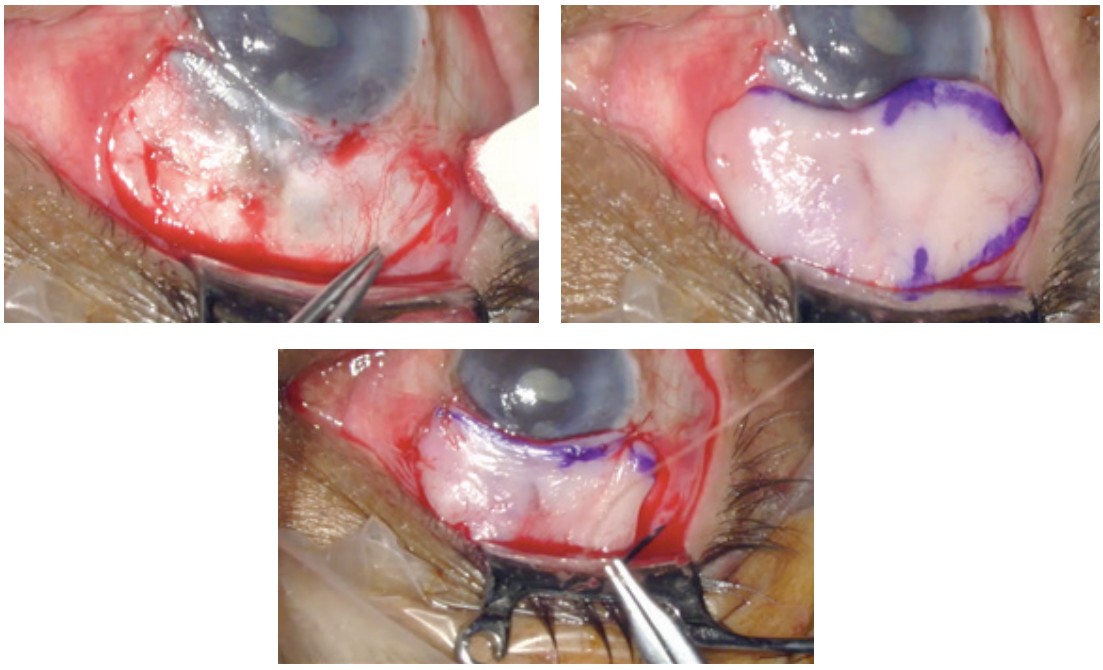


Figure 1a and b. Amnion graft and large diameter bandage contact lens 5 days postoperative after pericard-patch and

amniotic membrane transplantation. New beginning retraction reaction of the amnion graft on the inferior and superior parts with conjunctival necrosis one week later (b).

Due to repeated scleral necrosis and unsuccessful operative treatment results with pericard-patching and amniotic membrane transplantations an alternative option to close the leaking ocular surface had to be developed. Hence autologous oral mucosa transplantation on to globe was performed in March 2017.

A 2.5 x 1 cm piece of oral mucosa from the central area of the lower lip was taken. The globe was prepared and any remaining old sutures, amnion-graft and, pericard remnants had been removed. The oral mucosa was tightly sutured edge to edge with absorbable 6-0 and 8-0 Vicryl simple interrupted and U-sutures (Figures 2a – c). A temporary tarsorrhaphy was done at the end of the surgery.



Figures 2a – c.
Figure 2a. Intraoperative bare sclera; Figure 2b. Prepared mucosa in situ; Figure 2c. Suturing of mucosa.

The procedure was performed without any complications and topical antibiotics and steroids were administered.

The opening of the tarsorrhaphy was successfully performed after 5 days.

A fine leakage on the temporal oral mucosa-conjunctiva rim was noted 2 months after transplantation. A corneal U-suture to close the leaking area had been successfully performed.

Over the whole follow-up time of 7 months the graft remained intact (Figures 3 and 4).

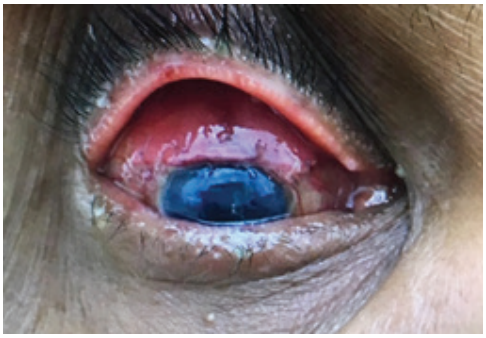
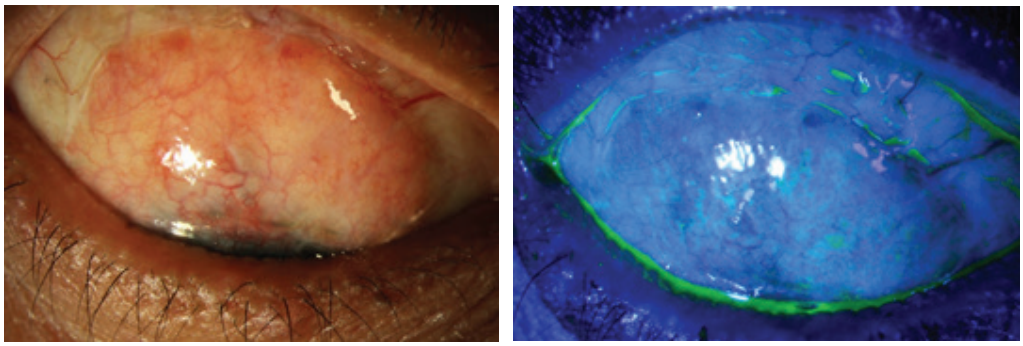


Figure 3. Oral mucosa graft 1 week postoperatively.

Figure 4. Oral mucosa graft 6 weeks postoperatively.

At the last follow-up 7 months after oral mucosal grafting the patients best corrected visual acuity on the affected eye was actually 20/200 (LogMAR 1.00). No topical therapy is actually applied in the right eye and his pressure remains at around 9 mm Hg. The oral mucosa graft is viable (Figures 5a and b).

Noteworthy is that the patient was checked several times for systemic autoimmune/rheumatoid diseases and nothing was found explaining the scleromalacia and necrosis of his conjunctiva.



Figures 5a and b. Figures showing viable graft 7 months postoperatively after oral mucosa transplantation (a native; b fluorescein stained).

★ DISCUSSION ★

This case describes a successful treatment of repeated conjunctival necrosis and leakage with an oral mucosa graft after trabeculectomy with mitomycin C. In our case, repeated scleral melting in the bleb area led to open fistulation. This situation required a definitive surgical management. In our case, transconjunctival fixation of the scleral flap with sutures, repeated pericard patching and also amniotic membrane transplantations, did not sufficiently stop the leakage. The incidence of a bleb leak increases at a fairly constant rate over time. The rates of incidence differ in the literature from 2.5% to 10%[1, 2].

Aqueous leakage from a filtering bleb may occur as an early or late complication of glaucoma filtration surgery. If untreated, vision threatening complications may result, such as ocular hypotony with or without maculopathy, shallowing of the anterior chamber, peripheral anterior synechiae, cataract formation, corneal decompensation, choroidal effusion, suprachoroidal hemorrhage, and endophthalmitis[1].

The non-surgical treatment includes a wide variety of strategies like aqueous suppressants, reduction of corticosteroids, pressure patching or bandage contact lens, cyanoacrylate glue, laser application on bleb or injection of autologous blood beneath the bleb.

The surgical treatment can be performed by conjunctival advancement, scleral flap re-suture, free autologous conjunctival flap or patch, amniotic membrane graft[3], donor scleral or corneal patching, reconstruction with bovine or human pericardium (Tutopatch)[4, 5].

As an alternative for bleb and leaking sclera reconstruction remains the oral mucous membrane. Oral mucous membrane transplants are widely used in the management of ocular surface diseases, including postenucleation socket syndrome, conjunctival replacement following tumor resection[6], cicatricial ocular surface diseases[7], treatment of refractory pterygium[8] and conjunctival insufficiency after filtration surgery[10].

The advantages of oral mucosa transplantation include easily accessibility, high stability of grafts and cheap grafting[9].

In the most cases, the repair with one of the conjunctival techniques is recommended in the literature for the initial therapy. The use of oral mucosa may allow the effective closure of the leaking trabeculectomy blebs, if the

conjunctival techniques are without satisfactory result.

The oral mucosa tissue differs from a conjunctiva in which it heals differently. It is thicker than the conjunctiva and it forms a flatter bleb. An additional advantage is the saving of the conjunctiva for further glaucoma surgeries if indicated9. In the last years, a combination of two tissues in one eye was gaining importance, such as amnion membrane and oral mucosa.

Due to uncontrollable leakage of the sclera after multiple unsuccessful surgical attempts we indicated an autologous oral mucosa transplant as an option to treat this chronic problem.

★ CONCLUSION ★

This case illustrates the treatment difficulties of a relatively common late complication of trabeculectomy. The incidence of scleral necrosis and bleb leaks after trabeculectomy increases after time. There are many treatment options of late bleb leaks, including a non-incisional therapy and also a surgical treatment.

Our case is illustrating a well-known technique which had been adapted in this case for the treatment of conjunctival insufficiency with leakage10 and scleral necrosis after filtration surgery. With this case we hope that the use of autologous oral mucosa may provide a major alternative for effective closure of aqueous leakage and repeated scleral necrosis.

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REFRACTORY MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE-LINKED CRYSTALLINE CORNEAL DEPOSITS TREATED BY TOPICAL N-ACETYLASPARTYLGLUTAMIC ACID

★ INTRODUCTION ★

Corneal crystalline deposits of immunoglobulin origin or paraproteinemic crystalline keratopathy (PPCK) have been reported to occur in a variety of hypergammaglobulinaemic states or lymphoproliferative affections, including monoclonal gammopathy of undetermined significance (MGUS)[1-2], multiple myeloma[3-4], cryoglobulinaemia[5], Waldenström's macroglobulinaemia[6], rheumatoid arthritis[7], other plasma cell dyscrasias, and after immunoglobulin therapy[8]. Meesmann, in 1934, was the first to report corneal deposits in a patient with Bence-Jones proteinuria[9]. Prospective studies concerning the incidence of corneal involvement in monoclonal gammopathies have found only a very low incidence[10]. Due to the rarity of this phenomenon, patients without a known systemic disease who present with PPCK are often misdiagnosed. Examples of differential diagnoses include lattice dystrophy, Schnyder's crystalline dystrophy, deep filiform dystrophy and ocular cystinosis[11]. Although uncommon, PPCK can be the first clinical sign of these general disorders. Treatment of this corneal condition is challenging. We report a case of refractory MGUS-linked PPCK treated with success with N-acetylaspartylglutamic acid (NAAG).

★ CASE REPORT ★

A 40-year-old male presented in July 2016 at ophthalmologic emergency of Adolphe de Rothschild Foundation Hospital, Paris, France for a history of bilateral mild ocular irritation and photophobia. The patient stated that his ocular symptoms began 6 years ago and experiences several recurrent crises. He was followed by his referring ophthalmologist and was treated since then with local azithromycin for supposed ocular rosacea. As crises continue to occur, patient decided to consult to our center. Best corrected visual acuities were 20/20 in both eyes. Ocular examination revealed irritated conjunctivas on both eyes. Slit lamp examination revealed bilateral, white, translucent, thin, crystalline-like deposits throughout the entire depth of both corneas, predominantly in the epithelial and the subepithelial layers (figures 1, 2 and 3). Fundoscopic examination (figure 4) and macular OCT were normal on both eyes. The remainder of the ocular examination was unremarkable. As clinical examination was not consistent with ocular rosacea, the patient was referred to the cornea department for further investigations. Laser scanning in vivo confocal microscopy (Heidelberg Retina Tomograph II, Rostock Cornea Module; Heidelberg Engineering GmbH®) confirmed a massive amount of highly reflective crystalline deposits throughout epithelium, Bowman's layer and with some extension into the superficial stroma of both eyes (figure 5), sparing the endothelial layer. Systemic examination was normal and paraclinic workup disclosed normal cell blood count, normal electrolytes including calcemia, creatininemia and normal complement C3 and C4 levels. Serum immunoglobulin levels showed an elevation of IgG to 1010 mg/dl (normal 158–358 mg/dl). IgA and IgM levels were within normal range (figure 6). Full-body X-rays revealed no osteolytic or abnormal lesions. Urinalysis for Bence–Jones proteins was negative. Serum immuno-electrophoresis demonstrated a monoclonal IgG-kappa band. Bone marrow smears depicted a plasma cell concentration less than 10%, and there were no morphological abnormalities. The patient was diagnosed with type IgG-kappa MGUS.

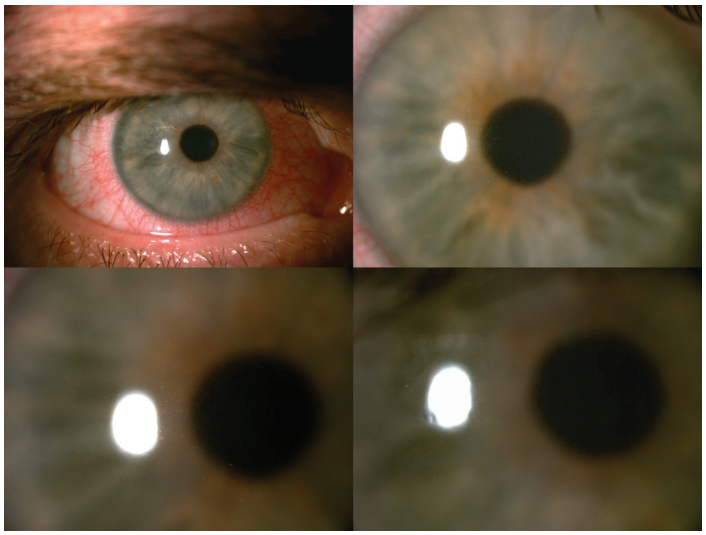

Figure 1: Corneal crystals— diffusely throughout the cornea

Initial treatment consisted of topical dexamethasone eyedrops with rapid improvement of his ocular symptoms. Unfortunately, our patient developed corticodependance with recurrent crises during ongoing low-dose topical corticosteroid treatment. We decided to undergo a treatment with topical NAAG eyedrops four times a day as a steroid sparing agent in order to treat this refractory MGUS-linked PPCK. Topical steroid withdrawal was attempted successfully shortly after initiating treatment.

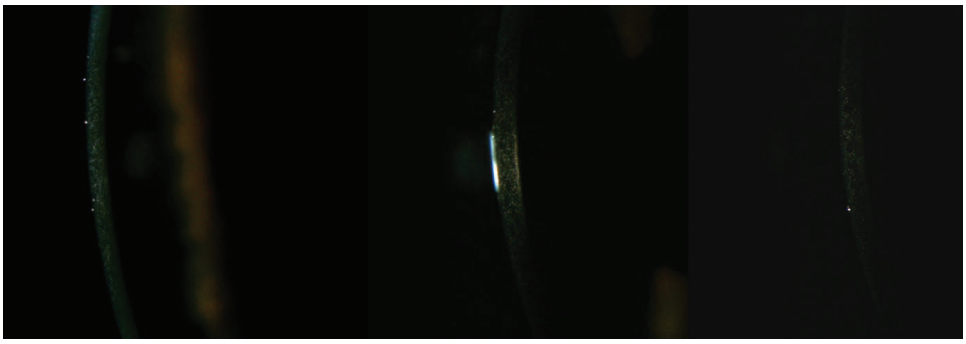

Figure 2: Slit-lamp biomicroscopy reveals greyish-white deposits in the entire cornea of both eyes.

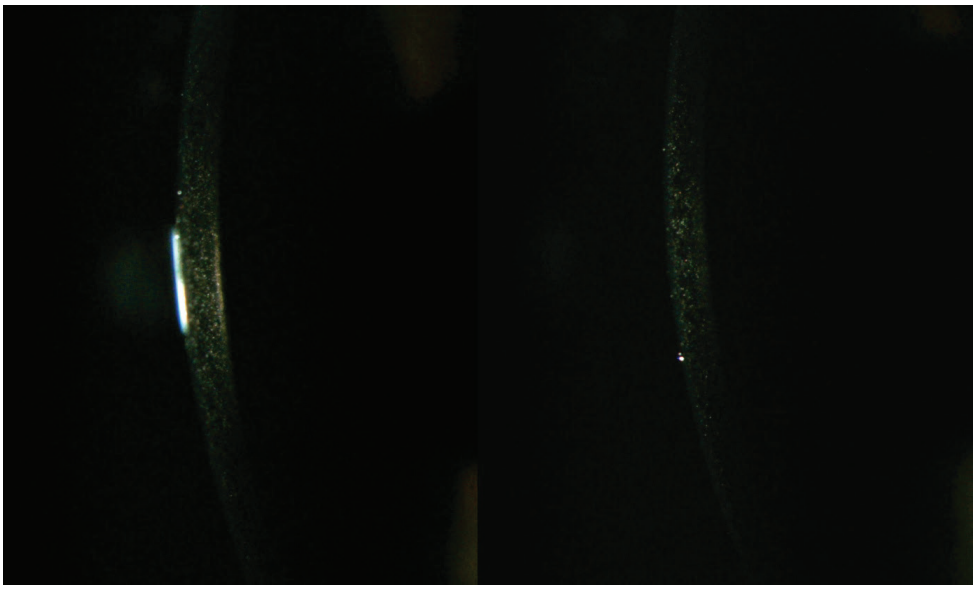

Figure 3: Magnified view of refractile corneal crystals optic section, predominantly located in the anterior stromal and subepithelial layers.

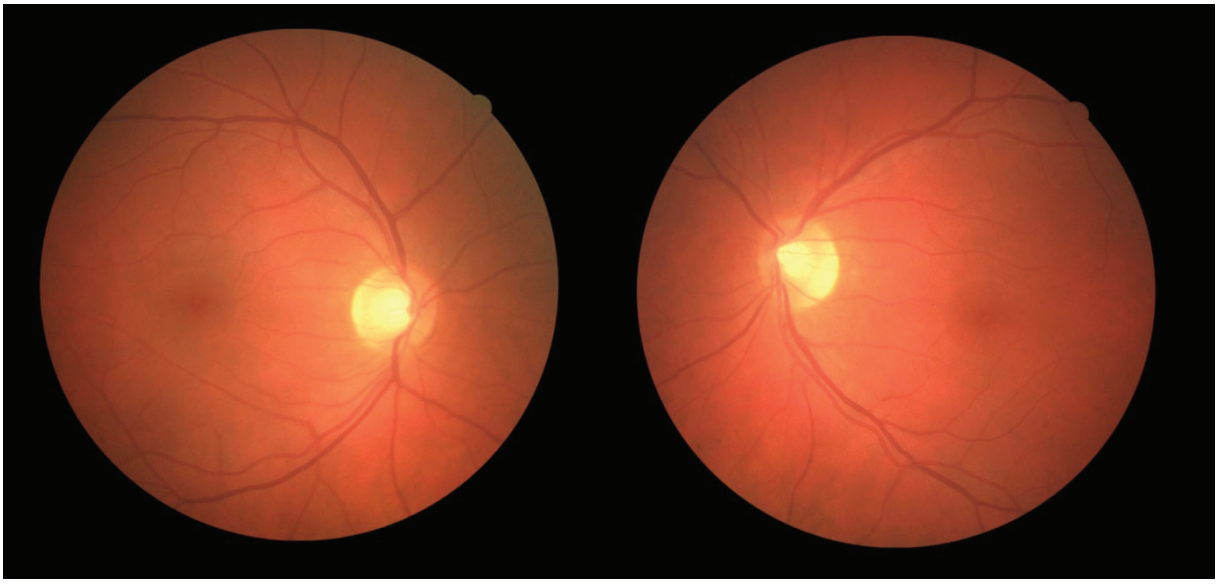

Figure 4 : Normal fundus examination on both eyes

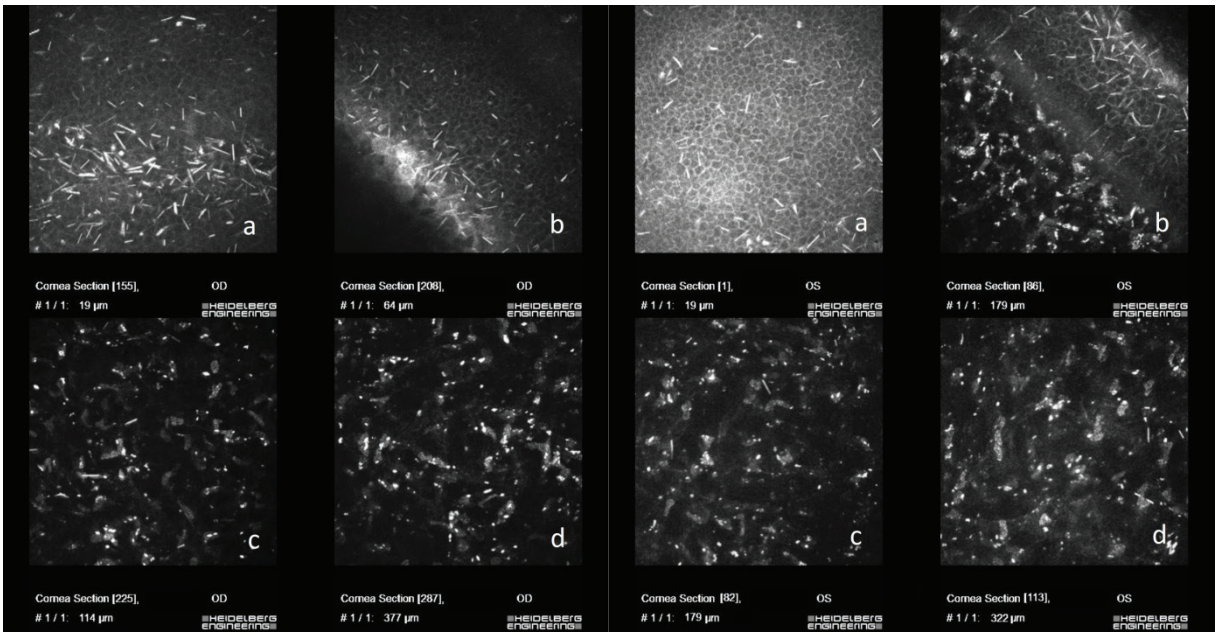

Figure 5 : In vivo HRT II scanning laser confocal microscopy.
a Numerous randomly oriented needle-shaped hyper-reflective crystals within the epithelial layer.
b Extension of the deposits into the Bowman's membrane, the subepithelial plexus nerve fibres and the superficial stroma.
c Rare randomly oriented needle-shaped hyper-reflective crystals variably spreading in the anterior stroma starting under Bowman's lamina.
d Sparing of the posterior stroma and the endothelium layer

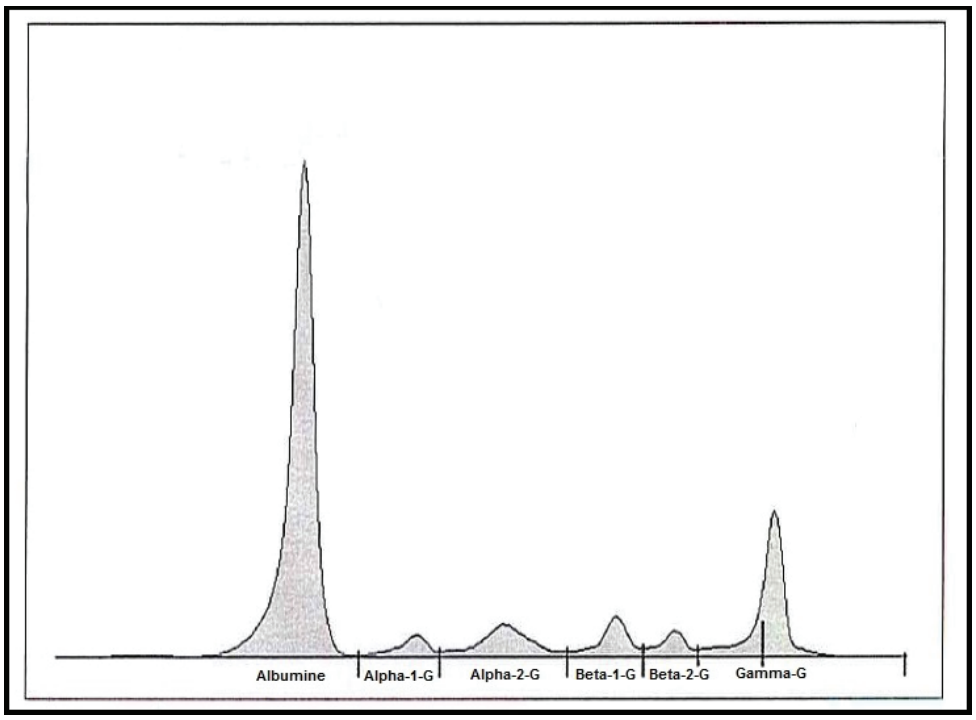

Figure 6: Serum immunoglobulin levels showed an elevation of IgG to 1010 mg/dl (normal 158–358 mg/dl).

★ DISCUSSION ★

Our patient was probably hyper-gammaglobulinaemic for over 6 years before diagnosis. His ocular symptoms were mild, without the severe photophobia or loss of visual acuity reported by other workers. Involvement of ocular structures such as the ocular surface and the cornea secondary to hypergammaglobulinaemic states, lympho-proliferative affections or other plasma cell dyscrasias, is widely reported in the literature[1-10]. In particular, the whole cornea may be affected by crystalline deposits. In vivo confocal microscopy represents a low-invasive high-resolution diagnostic technique to explore corneal microstructures. For instance, in our case, in vivo confocal microscopy aspect was consistent with typical PPCK as described in the literature. We therefore did not perform any invasive procedures to confirm the diagnosis.

The precise mechanism of corneal immunoprotein deposition in the setting of paraproteinemias is not completely elucidated and has been discussed in the literature. It is believed that the different locations of the abnormal immunoglobulin deposits reflect plurality in intra-corneal paraprotein deposit mechanisms. Three main ways, either working alone or in combination,

have been described in the literature: the intracellular immunoglobulin fragments may entered the corneal and conjunctival epithelium by way of the tear film, the keratocytes by way of the corneoscleral limbus vasculature, and the endothelial cells by diffusion from aqueous humor from the anterior chamber [12-13]. Immunoglobulin deposits in the cornea can be exclusively intracellular, extracellular or a combination of both types[14].

The complement system plays important roles in a variety of chronic ocular diseases. In his study, Montalvo et al showed that ocular tissues adjacent to inflammatory sites undergo changes that facilitate complement deposition[15]. The complement system is also considered as one of the major effector mechanisms involved in initiation of the subclinical inflammation that leads to IgE-independent eye irritation. In 2003, in a comparative study about the capability of nine antiallergic eyedrops commonly used in the treatment of allergic conjunctivitis to inhibit complement activation, Blondin et al proved that only topical 4.9% N-acetyl aspartic acid-glutamic acid and topical 2% nedocromil were found to significantly inhibit complement activation triggered by particulate matters or pollen allergenic extract[16].

Corneal crystalline deposits associated with Bence-Jones proteinuria were first described by Meesmann, in 1934[9]. In 1958, Burki reported the first description of PPCK associated with multiple myeloma[17]. Since then, a variety of immunoprotein deposits have been described in the cornea, among which, IgG-kappa lightchain deposition is most frequently reported. Presenting initially as crystalline keratopathy has also been reported to occur in patients of IgG MGUS. MGUS is a benign asymptomatic plasma cell neoplasm containing monoclonal protein (M protein). MGUS is defined as a serum M protein level less than 3.0 g/dL and bone marrow plasma cell level less than 10%. Diagnosis of this disease is made by detection of M protein in blood or urine samples. In his study, Kyle showed that 19% of patients with a diagnosis of benign monoclonal gammopathy developed myeloma, or a related disorder when followed for 10 years or more[18].

★ CONCLUSION ★

There is very little information in the literature regarding treatment options and the prognosis of the corneal involvement. Many of the presented cases are associated When patients presented with only minimal visual symptoms and require no specific ocular therapy, control of the systemic condition usually improves the ocular symptoms. In the very few cases of severe and lasting corneal involvement, penetrating keratoplasty seems to be the treatment of choice[19]. We proposed the hypothesis that immunoglobulin deposits into the cornea trigger the complement system. Therefore, this condition can lead

to recurrent ocular surface inflammation. This ocular inflammation can be successfully treated with complement activation inhibitors such as topical NAAG.

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EX VIVO CULTIVATED LIMBAL STEM CELL TRANSPLANTATION: CARING FOR THE GRAFT AFTER THE SURGERY

★ INTRODUCTION ★

The integrity of the corneal epithelium is maintained by a population of stem cells located in the basal layer of the limbus: the limbal epithelial stem cells (LSCs)[1,2]. Diseases or injuries that destroy LSCs, can result in a condition known as limbal stem cell deficiency (LSCD). In these cases, the corneal epithelium degrades and is rendered susceptible to invasion from the surrounding vascular conjunctiva. This can lead to corneal neovascularization, chronic inflammation and stromal scarring. As a result, patients with LSCD suffer from pain, photophobia and blindness[2].

The current gold standard for total or severe LSCD is to transplant limbal tissue or limbal epithelial cells to repopulate the cornea. This can be achieved by the transplantation of healthy limbal epithelium, using either large tissue limbal epithelial grafts[3,4] or, more recently, using ex vivo expanded limbal epithelial grafts from small limbal biopsies[5].

Once the stem cells have been transplanted, the health of the recipient bed and ocular surface play a crucial role in the survival of graft and the outcome of the surgery[6].

While different protocols and surgical techniques have been extensively reported, there is very little focus on pre- and post-operative management providing an optimal environment for the cells to survive.

We report the case of total limbal stem cell deficiency treated with

Cultivated Limbal Epithelial Transplantation (CLET) and aim to focus on the importance of topical medications in the preservation of a good surgical outcome.

★ CASE REPORT ★

A 66-year old female patient was referred to our center because of iatrogenic limbal stem cell deficiency in her right eye. She had a history of a conjunctival melanoma for which she underwent 22 surgical excisions with cryocoagulation and treatment with mitomycin-C over a time-course of 12 years. While she was free from melanoma, the medication led to LSCD and an ingrowth of blood vessels over her limbus. She had no pain, but suffered from intense photophobia and her best-corrected visual acuity (BCVA) had dropped from 1,0 to 0,1. Cataract surgery and a scleral lens could barely improve the visual acuity and the patient continued to suffer from the sequelae of iatrogenic LSCD.

She was then referred to our center. Slit lamp examination revealed corneal neovascularisation over 360°, which was more extensive in the superior and inferonasal quadrants. Centrally, the cornea was avascular, but the epithelium was very irregular and there was a paracentral opacity. (Fig 1, 2) There were no eyelid abnormalities and Schirmer test of the right eye was 13mm after 5min. Since a penetrating keratoplasty would only be a temporary solution in this vascularized bed, a cultivated limbal stem cell transplantation was proposed in order to regenerate her anterior cornea and reform the limbal epithelial barrier.

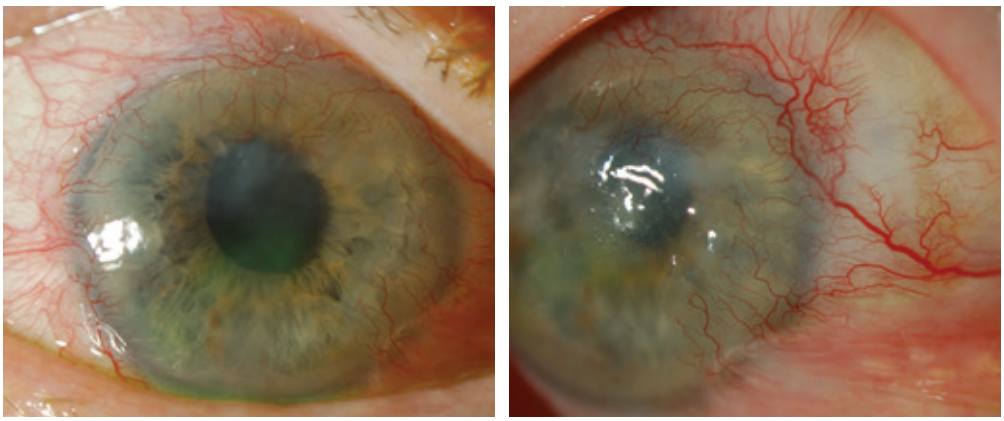

Fig 1 and 2: Pre-opeartive slit lamp images of the right eye showing peripheral corneal neovascularisation, more extensive superiorly and inferonasally

A small biopsy (1x2mm) was harvested from the limbus of the healthy left

eye under topical anaesthesia. The cells were cultured on a denuded human amniotic membrane using a standardized protocol[7]. After a culture period of 14 days, the cells achieved an outgrowth of 17mm and the composite graft was transplanted using a minimal manipulation technique. Briefly, a 360° conjunctival periotomy was performed followed by dissection of the pannus tissue. The graft was consequently applied to the surface of the cornea, using fibrin glue. A secondary amniotic membrane covering the whole graft, was secured to the surrounding conjunctiva using four 10–0 nylon sutures[7].

Post-operatively, the patient was prescribed a preservative-free local treatment with 0.3% ofloxacin 0,3% 4×/day, dexamethason drops 0,1% 8×/day and autologous serum drops 20% 16x/day. One week post-operatively the conjunctival sutures holding the amniotic membrane "patch" in place were removed. At three weeks post-operatively, a small corneal epithelial defect inferiorly was diagnosed. (Fig 3) A bandage lens was placed on the cornea which resulted in a closed epithelium when the patient was seen 6 days later.

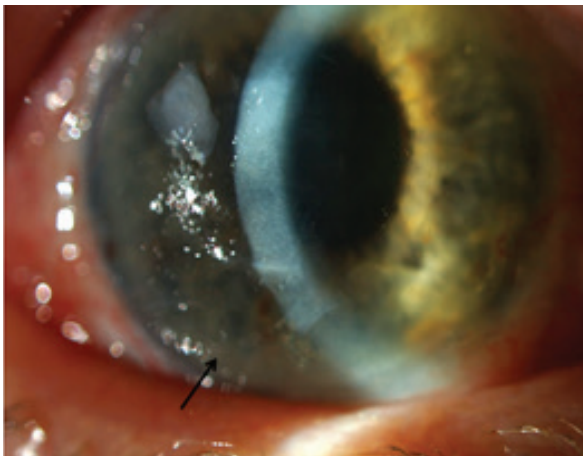

Fig 3: Presence of a corneal epithelial defect inferiorly (arrow)

Two months post-operatively, autologous serum drops were replaced by preservative-free teardrops containing trehalose (16x/day). Dexamethasone eye drops were reduced gradually to 5x/day and the antibiotic treatment was ceased. This treatment was continued for 4 months and a good incorporation of the graft was seen. Six months post-operatively, the patient presented with a raised intra-ocular pressure (IOP) (28mmHg) and glaucoma therapy with preservative-free timolol 0,1% was initiated. Dexamethasone eye drops were tapered further to 1x/day. The trehalose containing teardrops were continued at a 4x/day frequency. The IOP normalized during the following 8 weeks, after which timolol could be ceased.

One year after stem cell transplantation, the BCVA had improved to 0,3 under a maintenance treatment of the regular artificial teardrops 4x/day and dexamethasone 1 drop alternating every day. Slit lamp examination revealed a closed epithelium without vascularisation but remnants of the stem cell graft were still in place, interfering with BCVA. (Fig 4)

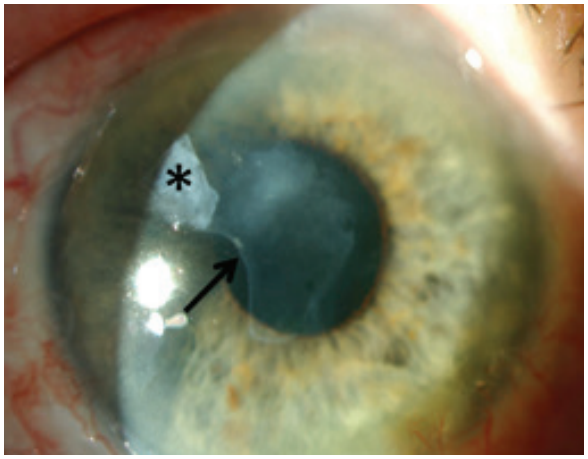

Fig 4: Remnants of the graft (arrow) and biopsy (asterisk) present on the central cornea

The patient desired a further visual improvement, and therefore a superficial keratectomy was considered to clear the visual axis of the remnants of the graft (amniotic membrane and biopsy) that had integrated into the anterior stroma. However, while awaiting this procedure, the stroma showed gradual clearing under her local treatment and 19 months after stem cell surgery, the BCVA had improved to 0,5. (Fig 5)

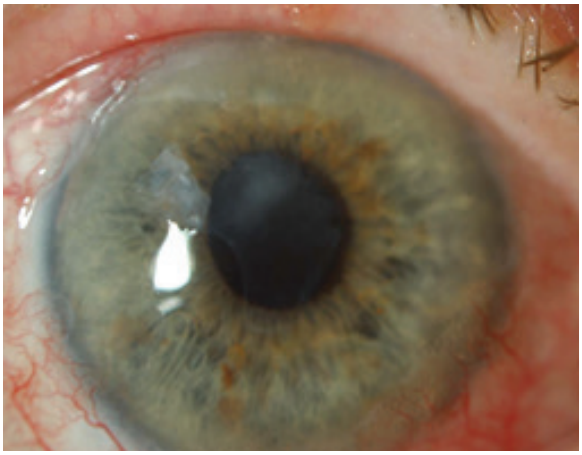

Fig 5: Gradual clearing of the anterior stroma,19 months post-CLET

In vivo confocal microscopy (HRT-III) of the cornea was performed which revealed epithelial cells of corneal phenotype (Fig 6).

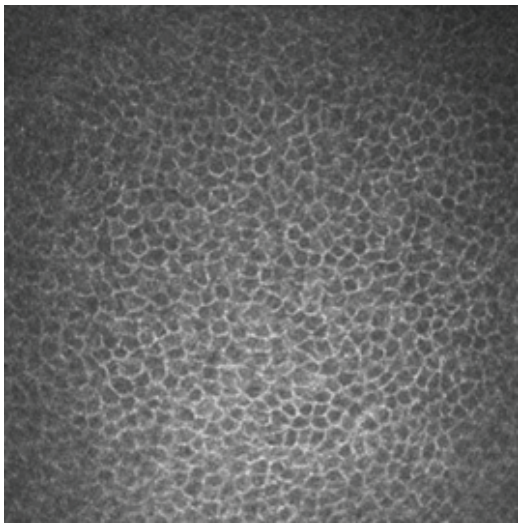

Fig 6: In vivo confocal image of the epithelial wing cell layer

Therefore no further surgery was required to improve BCVA and local treatment with regular artificial preservative-free tears and dexamethasone 1 drop alternating every day was continued. At present, two years after limbal stem cell transplantation, the patient shows a stable, smooth and intact ocular epithelium. (Fig 7) The BCVA remains at 0,5 and the patient recently became a member of a book club.

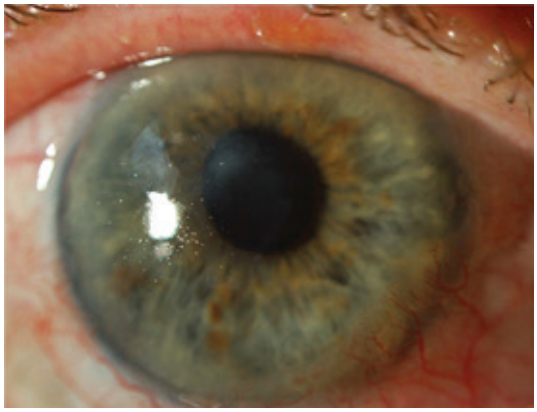

Fig 7: Intact corneal epithelial layer, 2 years post-CLET

★ DISCUSSION ★

Ex-vivo cultivated limbal stem cell transplantation is a relatively new technique for the treatment of total or severe LSCD. This technique has been used with good results in various centres worldwide [8–10]. So far, there is no consensus on the best care for the epithelial cells postoperatively. Here we report a successful anatomical and functional outcome using a standardized protocol and stress the importance of pre- and post-operative care tailored to the patient.

The stem cells may be considered as seeds, while the ocular surface is the soil in which they are embedded [11]. (Fig 8) The seeds will only grow in an optimal environment with the right nutrients. Therefore, prior to stem cell transplantation, it is important to prepare the best recipient bed for the cultivated cells and to restore the ocular surface's defences.

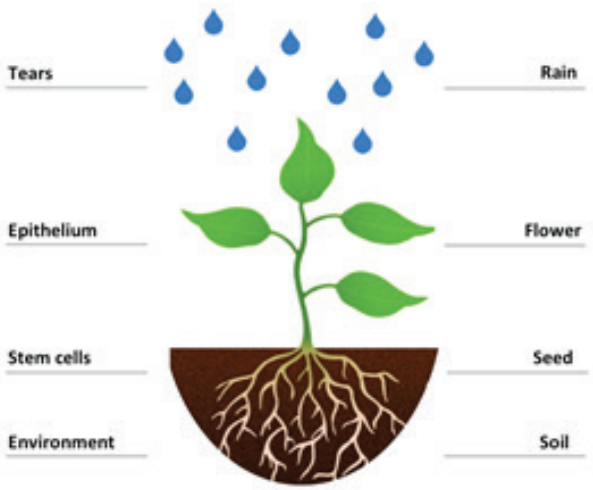

Fig 8: Similarity in maintaining ocular surface health and growing a plant in soil (Analogy to Tseng and Tsubota [11])

Eyelids and fornices should be clinically evaluated and treated in case of abnormalities. An abnormal eyelid function will lower the chances of survival of the stem cells and therefore the patient should not be transplanted if no normal eyelid function can be obtained. Additionally lid margin disease should be treated prior to intervention, as the eyelids are crucial for the preservation of ocular surface integrity, as well as for maintaining a healthy pre-ocular tear film [12]. These anterior segment issues should not be considered trivial as they can mean the difference between graft success and failure.

A healthy tear film provides the cornea with essential "rain" needed for to grow [11]. (Fig8) Schirmer test, phenol red test, biomicroscopic tear film evaluation and osmolality testing are examples of tests that can be used to estimate quantity and quality of the tears [13–15]. In this case, apart from a biomicroscopic evaluation, the Schirmer test was used to quantify the tear production. However, a limitation of this test is its inability to provide

information about the tear film quality which might be even more important than quantity.

Additionally, any inflammation of the ocular surface should be carefully evaluated and treated if necessary. Inflammation disturbs the normal milieu of the (remnants of the) limbal niche and lead to dysfunction or aberrant differentiation of the stem cells [16]. At present, grading of redness of the bulbar conjunctival blood vessels is the most relevant driver for assessment of ocular surface inflammation [17].

Conjunctival redness can be assessed using different methods including grading scales [18,19], manual qualitative methods or (semi-) automated techniques [20]. In this case, inflammation was assessed using a four-stage grading scale based on redness and dilatation of the blood vessels. This is a subjective but relevant method in order to standardize the assessment before treatment and during follow-up. However in order to overcome the limitations of observer variability and more objectively measure inflammation, we aim to develop and implement a sub-clinical ocular surface inflammation monitoring tool based on inflammatory biomarkers in tear samples.

In this case, there was no clinically detectable inflammation, no lid margin disease nor malocclusion, and the Schirmer test revealed a tear film secretion of adequate quantity (>10mm). The recipient was considered an ideal candidate for limbal stem cell transplantation.

In cases where the Schirmer test is <10mm, we add punctum plugs in order to enhance the tear film stability. Treatment options for controlling inflammation include topical steroids, topical cyclosporine or oral doxycycline [16].

Post-operative care should also be focused on providing and maintaining an ideal environment for transplanted limbal epithelial stem cells, since this ensures the best chances of epithelial healing and stem cell survival [21]. In addition to the preoperative preparations, alternatives include a temporary closure of the eyelids such as tarsorraphy or botox ptosis induction post-transplantation, These techniques additionally prevent mechanical damage

from blinking, apart from enhancing a stable tear film.

The use of preservative-free eye drops is crucial in the post-operative management. Benzalkanium chloride (BAC), the most frequently used preservative in topical drops, has been shown to profoundly modify the ocular surface of the anterior segment, including the tear film, cornea and conjunctiva [22]. Its cellular toxicity includes a risk for both the stem cells and the surface microenvironment. Therefore, 'preservative-free' is the gold standard in the management of limbal stem cell patients, including during treatment of ocular comorbidities. In this case, the patient followed a long-term maintenance therapy with preservative-free eye drops and her raised IOP was effectively treated with the use of a preservative-free beta-blocker. The corneal epithelium remained stable during the entire course of this treatment.

In addition, we have the tendency to prescribe a trehalose-containing drop after stem cell grafting, since trehalose has been shown to be effective in protecting corneal epithelial cells against a variety of stressful environmental conditions such as dessication, dehydration and oxidation [23–25]. Based on our experience, we hypothesize that this approach offers the best optimization for the stem cell microenvironment post-CLET.

This surgical and medical approach resulted in a smooth, intact epithelium and an improved BCVA without the need of extra sight restoring surgery.

★ CONCLUSION ★

This case showed that autologous transplantation of cultivated limbal epithelial stem cells offers a safe and effective method for corneal surface reconstruction in iatrogenic LSCD. A careful pre-operative evaluation and preparation of the ocular surface together with a post-operative medical management provides the ideal environment for the transplanted cells and as such ensures the best chance on a successful grafting. Preservative-free is the golden standard and the peri-operative treatment should be tailored to the patient.

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OCULAR ROSACEA, MYCOTIC KERATITIS AND EPITHELIAL DEFECT REFRACTORY TO CONVENTIONAL TREATMENTS: THE QUEST FOR INNOVATIVE TREATMENTS FOR COMMON PATHOLOGIES

★ INTRODUCTION ★

Rosacea is a common cutaneous inflammatory condition that represents a significant cause of morbidity for patients who suffer from it and remains to date incurable. This disorder affects mainly the skin in the centrofacial and periocular regions and results in significant inflammation of the eyelids and the ocular surface.3 It is estimated that only 60-70% percent of patients with rosacea develop ophthalmic findings. Ocular involvement may occur concurrently or independent of centrofacial features.20

Etiology remains unknown. Pathophysiology of the disease includes inflammatory changes, altered immune system responses and vascular dysregulation. It may occur at any age but it is more frequent in patients over 35 years. The most commonly associated symptoms and findings include pain, photophobia, blurry vision, irritation, dryness, foreign body sensation, vascularization, recurrent epithelial defects and potential devastating complications like keratitis that can lead to visual loss.3 If left untreated, signs and symptoms may progress in severity over time. In its most extreme state, the ocular surface disease may even lead

to recurrent erosions, ulceration, and corneal perforation.15 This disorder not only remains without cure but is also difficult to treat and stabilize.

The most common clinical presentations in ocular rosacea are blepharitis and conjunctivitis. Frequent findings include inflamed eyelids with recurrent chalazion and Meibomian gland dysfunction, conjunctival hyperemia, telangiectasias and dry eyes.15 This potentially incapacitating disorder may also manifest with scleritis, iritis and keratitis.20 Patients with chronic blepharitis and Meibomian gland dysfunction are at higher risk of dry eye and infectious keratitis.15,8 Extensive Meibomian gland dysfunction and acne rosacea are associated with recalcitrant recurrent corneal erosions.17 It appears that Meibomian gland inflammation affects the health of the corneal epithelium.18

The pathogenesis of impaired epithelial healing may be multifactorial. Lipases produced by Staphylococcus epidermidis that colonize the lid margins of acne rosacea patients produce toxic free fatty acids that interfere with the healing process.3 Furthermore, increased concentrations of matrix metalloproteinases, especially MMP-9, known to be critical extracellular-remodeling enzymes in wound healing have been found in these same patients.20 Rosacea patients with recurrent erosions, peripheral infiltrates, and corneal ulcers have elevated gelatinase B activity, suggesting a role of this enzyme in the pathogenesis of these conditions.7,8

Complications of recurrent corneal epithelial defects are uncommon but may include microbial keratitis. A damaged epithelium provides adherence sites for pathogen access to the corneal stroma. Ocular surface disease is a recognized risk factor for the development of microbial keratitis. Therefore, epithelial defects elude the natural resistance mechanisms of the cornea to infection.7 Chronic ocular surface inflammation by itself predispose to surface changes that in turn may create a favorable environment for infection.8

We here present a patient with a severely compromised ocular surface from a combination of surface alterations and systemic factors. The cornerstone of this patient's pathology is ocular rosacea and the subsequent alterations in the course of his disease derived from it. Ocular surface alterations due to rosacea resulted in an epithelial defect that in the context of an immunocompromised state led to infectious keratitis. Due to early exposure to several treatments it resulted in therapy resistance that complicated the clinical course. Complex corneal defects that are restricted in their curability, require thinking out of the box and explore available treatments in more rigorous ways and opt for new therapeutic options as described in the present case.

★ CASE REPORT ★

A 57-year-old male presented with a six-week history of cloudy vision on the right eye associated with redness, photophobia, pain and foreign body sensation. He reported a medical history of Diabetes Mellitus type II of 12 years of evolution, uncontrolled. The patient referred alcohol abuse and he was currently working as a gardener. On ocular history he reported cataract surgery by phacoemulsification on both eyes two years ago and proliferative diabetic retinopathy treated with three sessions of argon laser pan photocoagulation on both eyes. Upon symptom presentation, he attended to an ophthalmologist who prescribed 0.3% gatifloxacin drops and vancomycin drops every two hours. He decided to get a second opinion after six weeks of treatment without improvement of symptoms.

Visual acuity on the right eye was 20/300 Snellen (1.17 LogMar) and 20/40 (0.030 LogMar) on the left eye. Clinical examination of the right eye on slit lamp revealed posterior blepharitis with Meibomian gland dysfunction, telangiectasia on the lid margin, conjunctival papillary reaction, hyperemia, ciliary injection, nasal pingueculitis, tortuous nasal vascularization, tear breakup time 3 seconds and a corneal perilimbal epithelial defect of 2.5mm x 1.5mm with underlying stromal infiltrate (figures 1). Oral medication with minocycline 100mg bid was initiated. Lid hygiene was recommended. Topical medication was modified by adding netilmicin drops every two hours and 1% tropicamide phenylephrine eye drops every 8 hours to the previous treatment. Corneal scrapes were taken for culture.

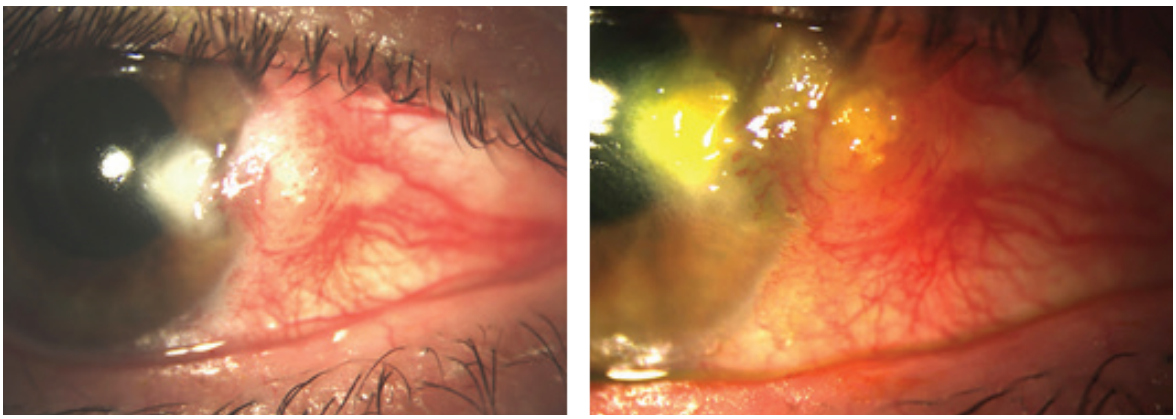

Fig. 1 Anterior segment of the right eye at first consultation. The image shows in detail conjunctival hyperemia and a perilimbal epithelial defect with an underlying deep dense infiltrate.

After a week of treatment, the epithelial defect with the stromal infiltrate remained without change and an adjacent paracentral triangular epithelial defect of 2mm x 2.5 mm appeared. Corneal culture reported Fusarium solani. With the identification of the pathogen, topical treatment was changed to 0.3% gatifloxacin , 5% natamycin hourly and 1% tropicamide phenylephrine every 8 hours.

Two weeks later the patient referred a slight improvement in symptoms but clinical examination on slit lamp and visual acuity remained unchanged. Treatment was modified adding 1% voriconazole hourly and sodium hyaluronate every 3-4 hours.

The epithelial defect increased in extension after 72 hrs. to 2.5 x 3mm and the borders appeared irregular with underlying and perilesional stromal edema. Visual acuity was 20/800 Snellen (1.60 LogMar). The rest of the clinical examination showed no improvement. Due to lack of response, the therapeutic approach was modified. At this point we theorized that there was little to no penetration of the antimycotic treatment and we decided to use a very different adjunctive therapy. Argon laser absorption by the ocular tissue targets is maximally achieved by melanin and hemoglobin present in the retina not in the cornea. To be absorbed by the cornea we stained it with fluorescein dye. Green 532 nm wavelength argon laser (Carl Zeiss LSL 532s AG; Meditec, Inc) was applied to the peripheral corneal ulcer after applying 0.25% fluorescein sodium staining at a potency of 900mW with a 100µ spot and 0.10 sec duration (figure 2). The laser was applied until we noticed blanching of the corneal stroma and small bubble cavitations appeared.

Immediately after treatment, epithelium appeared irregular and was friable to the touch. Topical treatment was established with 5% natamycin every two hours, 1% voriconazole every two hours, 0.15% sodium hyaluronate every 2-4 hours and 1% tropicamide phenylephrine every 8 hours. To address the epithelial pathology and improve epithelial healing, 3% trehalose was initiated every 4 hours.

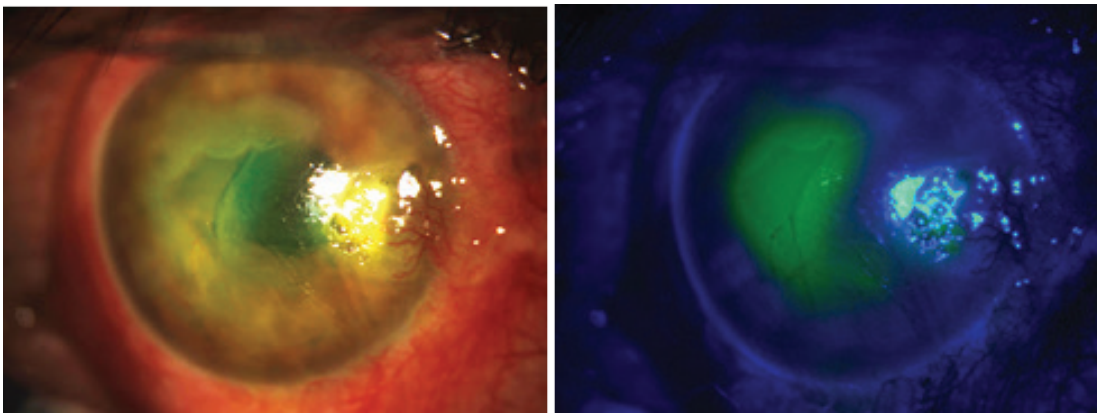

Fig. 2 Anterior segment of the right eye immediately after argon laser application. The image shows a paracentral epithelial defect and laser spots on the surface of the infiltrate. Vascularization arising.

hours, clinical examination showed a well-defined, smaller and less dense infiltrate and a lightly reduced epithelial defect with regular borders. The overall appearance of the epithelium was smoother (figure 4). The same topical treatment was continued.

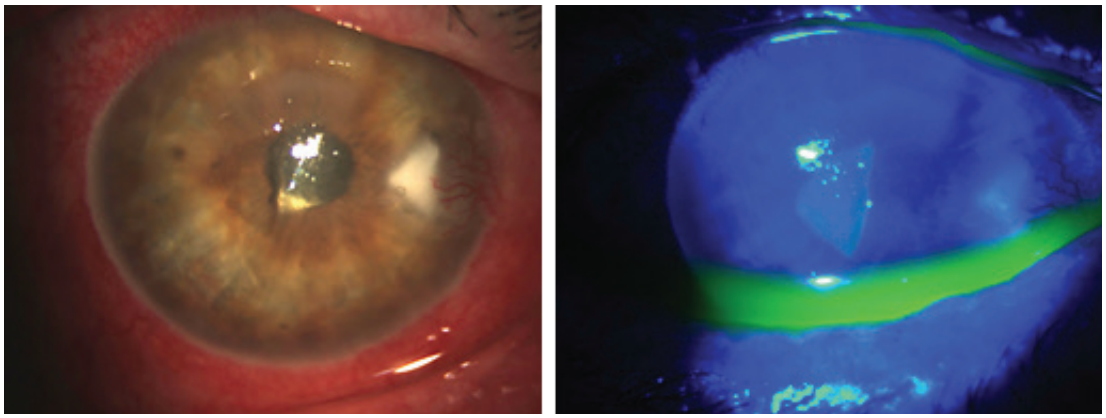

Fig. 3 Anterior segment of the right eye 72 hours after argon laser application. The image shows a reducing paracentral epithelial defect and a less dense infiltrate.

Follow up was done weekly. Symptoms were drastically improved after two weeks of treatment. Examination showed less ciliary injection, absolute resolution of the epithelial defect with no perilesional edema , and a fully epithelized diminished perilimbal infiltrate (figure 4). Another session of photocoagulation was applied over the infiltrate to promote once again penetration of the topical antifungal.

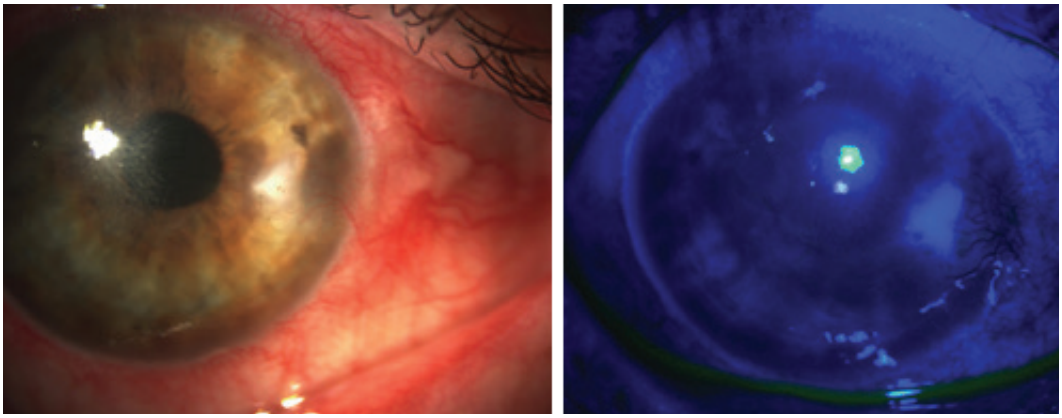

Fig. 4 Anterior segment of the right eye two weeks after argon laser. The image shows a completely healed epithelium and a reduced infiltrate in density and extension.

One week later, visual acuity improved to 20/150 (0.87 LogMar). Slit lamp examination showed slight hyperemia with no ciliary injection, no epithelial defects and noticeable improvement of the perilimbal infiltrate with

photocoagulation scars. (figure 5) Topical treatment consisted of 5% natamycin every two hours alternated with 1% voriconazole every two hours, 0.15% sodium hyaluronate every 2-4 hours and 3% trehalose every 4 hours.

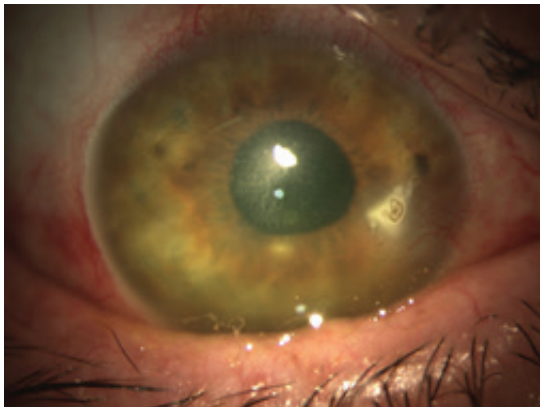

Fig. 5 Anterior segment of the right eye after second application of argon laser. The image shows a reduced infiltrate in density and extension with laser spots.

Three weeks after the last photocoagulation session, complete resolution was observed. The patient reported no symptoms and visual acuity was restored to 20/60 (0.47 LogMar). Lid margin appeared unaltered, conjunctival hyperemia decreased, a smooth and uniform corneal epithelium was observed, nasal vascularization diminished and a less than 0.5 mm leucoma was left on the site of the infiltrate (figure 6).

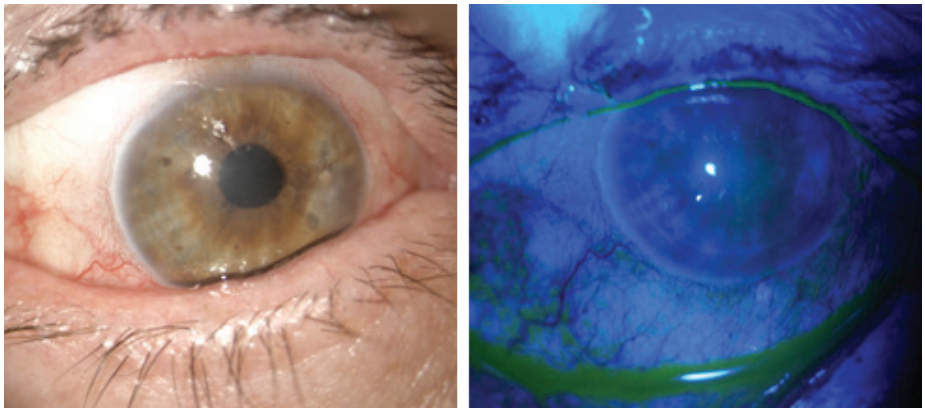

Fig. 6 Anterior segment of the right eye at resolution. The image shows a less congestive lid margin, clear cornea with a slight nasal leucoma and a smooth epithelium with no defects.

★ DISCUSSION ★

Rosacea deeply affects the ocular surface making it vulnerable to other ailments. Management and stabilization of ocular rosacea and is potential consequent anomalies are challenging.3 In the present case a weak immune system as a consequence of a history of uncontrolled diabetes mellitus and alcohol abuse in combination with the chronic inflammatory state caused by rosacea and certain environmental conditions led to a complex ocular surface disease that proved resistant to conventional therapies such as lid hygiene, topical antimicrobial drugs and artificial tears.19,22 A recalcitrant epithelial defect and a not healing mycotic ulcer forced us to reconsider our treatment options. If left untreated those relatively common ocular affections in this patient could have devastating effects and endanger vision. Thus, we started the quest for innovative treatments for common pathologies.

Mycotic keratitis occurs due to invasion by the pathogenic fungal strains and helped by poor host immunity and defense mechanisms due to local or systemic causes.6 Addressing the mycotic corneal ulcer management, our first approach with a cultured based diagnosis was to treat with natamycin which belongs to the polyene class of antifungals and is known to be highly effective against Fusarium.2 The infiltrates in fungal keratitis are usually deep and they can even reach the Descemet membrane and further.6 The first challenge we encountered was that even though we were using the correct antimicrobial , it was not being adequately distributed into and through the corneal stroma. We hypothesized that maybe if we needed to aid somehow the penetration of the drug into the corneal stroma.

Ophthalmic applications of lasers are widely used nowadays. Recently argon laser photocoagulation was introduced as an adjunctive therapy in the treatment of resistant infectious corneal ulcers including fungal cases with favorable results.16 The mechanism of action consists on a thermal damaging effect that results in suppression of cellular enzymes, damage of the cellular proteins and DNA damage.10 Special care needs to be taken in the estimation of pulses that should be used during a treatment and its localization, as overheating may damage both the host and the pathogen. Tissue debridement of the ulcer bed may enhance penetration of antifungal drugs.9 But unlike manual debridement, argon laser treatment produces a fungicidal effect. In this case argon laser corneal photocoagulation as an adjunctive therapy for topical natamycin resulted in reduction of the infiltrate since the first application and later complete healing of the corneal ulcer.

Regarding the corneal epithelial defect, we had to think of its treatment in the context of ocular rosacea. As other studies have demonstrated, Meibomian gland dysfunction has a profound effect on the homeostasis of the ocular surface. Chronic blepharitis is associated with the release of bacterial lipases, fatty acids, interleukins and matrix metalloproteinases from the inflamed Meibomian glands that may impair corneal epithelial healing. Previous studies have shown direct association between corneal erosions, chronic blepharitis and acne rosacea.17 Therefore, our initial approach was to indicate lid hygiene

and oral minocycline. Tetracyclines reduce the free fatty acids in the tear pool of patients with Meibomian gland dysfunction. Blepharitis associated with acne rosacea may require treatment for prolonged lengths of time, as discontinuation of tetracyclines is commonly associated with recurrences of rosacea.21 To this initial approach we added topical lubricants. Besides all the efforts the corneal epithelial defect showed no healing signs and appeared to increase. At this point we needed to enhance protection of the epithelium, so we prescribed 3% trehalose due to its bioprotective characteristics. Trehalose is a nonreducing disaccharide of glucose, naturally produced, and accumulated in many living organisms, but not in mammals. It was identified as a key response element needed to protect the cells against a great number of environmental stresses, such as desiccation, dehydration, cold, heat, and oxidation.11 Trehalose protects corneal epithelial cells from experimental drying and was shown to be effective in the treatment of moderate to severe human dry eye.12 Trehalose eyedrops were found by a previous study to be safe and effective compared with saline in the treatment of moderate-to-severe dry eye syndrome.13,14 The promoting effect of trehalose on corneal wound healing is likely to be related to a decrease in the hypoxia response injury of the cornea.4 Furthermore, during desiccation in vivo, it was also demonstrated that it could effectively suppress apoptotic cell death on the ocular surface.1,5 This findings may explain why the corneal epithelium in this patient didn´t present any further damage and started to heal even though it was exposed to high temperatures (above 70° C) with argon laser photocoagulation.

★ CONCLUSION ★

Rosacea is a chronic cutaneous inflammatory disorder with a large spectrum of presentations and is responsible for various significant changes in the ocular surface. It remains an incurable pathologic entity and treatment consists in addressing each of its clinical manifestations. When combined with other predisposing factors for ocular surface disease it may become a complex entity and a challenge for the ophthalmologist. Sometimes conventional treatments stay insufficient in treating these challenging cases. Fortunately, treatment options for ocular surface diseases have expanded dramatically over the past several years. Recent innovations are intended amongst other things, to expand our armamentarium of treatment against atypical presentations of common diseases. In certain cases, we are required to implement an unusual approach to the common thinking structure as in the development of new treatment techniques or the appliance of known treatments to a different pathology than the one it was initially intended for.

- In this case argon laser photocoagulation proved to be useful as an adjunctive treatment of refractory fungal keratitis by acting as a fungicidal and by aiding antifungal drug penetration.

- On the other hand, trehalose due to its protective properties and its action

in protein stabilization of membranes is an effective medication for dry eye syndrome disease and it allows epithelial healing under stress conditions.

- To the best of our knowledge trehalose has never been used in the treatment of epithelial defects associated with an infectious concomitant disease.

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"SCLERO-DALK": NEW APPROACH FOR TREATMENT OF SUPERFICIAL CORNEAL LEUKOMA

★ INTRODUCTION ★

Corneal scarring is a frequent cause of visual loss.[1,2] It can be caused by different factors, such us dystrophies, infections, and ocular trauma

Traditionally, penetrating keratoplasty (PK) has been the procedure of choice in such cases of severe corneal scarring.[3,4] However, in pathologies where there is no endothelial involvement, deep anterior lamellar keratoplasty (DALK) may be a better alternative.[5,6]

Postoperative complications including rejection and intraocular pressure elevation are more frequent in PK.[7] DALK offers an alternative procedure that may lessen those risks because the recipient Descemet's membrane (DM) and endothelium are preserved.[8] However, intraoperative perforation of the DM is a significant complication . At the same time, DALK carries the potential danger of decreased visual acuity due to possible opacification at the interface layers.[9,10,11]

We report a new approach for treatment of corneal leukoma which can decrease the risk of DM perforation and may report better postoperative visual acuity, since less residual estroma is remained.

★ CASE REPORT ★

The case concerns a 48 years old man referred to the Corneal Diseases Department for superficial corneal leukoma in the left eye (LE) secondary to ocular trauma 14 years ago.

The initial clinical findings showed an uncorrected visual acuity (UCVA) of 1 in the right eye (RE) and 0,3 in the LE, with previous refraction of +0.75 (RE) and +2.50 -2 x 10° (LE). In the slit lamp evaluation we objectify a central corneal leukoma with anterior stromal opacities and epithelial edema in temporal area, in his LE.(Figure 1) The RE showed no alterations.

Intraocular pressure and fundus were normal in both eyes.

The patient complains of low vision in his LE . A deep anterior lamellar keratoplasty with a scleral approach (Sclero-Dalk) is proposed and he accepted.

Corneal thickness as measured by anterior segment optic coherence tomography (OCT) was 530 µm. Non-contact specular microscopy showed normal endothelial mosaic pattern and a cell density of 2473.4 cells/mm^2

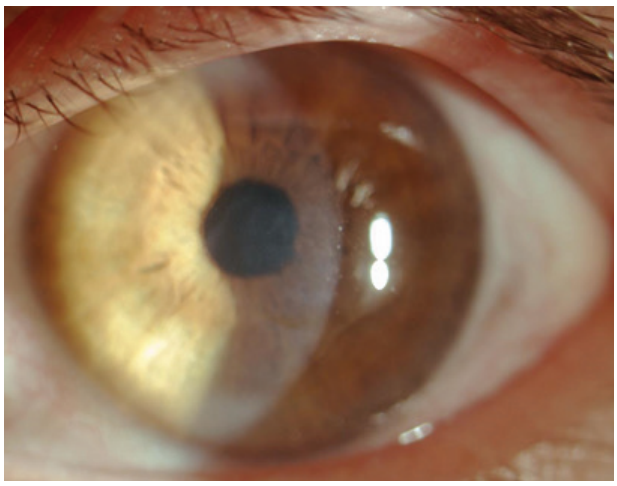

Figure 1: Slit-lamp biomicroscopy showing superficial corneal leukoma before surgery.

Sclero-DALK is performed under general anesthesia. It consists of the creation of a deep sclerotomy through which we directly approach the predescemetic space. Using a Mermoud spatula, we penetrate this space and introduce a cannula with viscoelastic, achieving dissection of the DM. Subsequently the same process is continued as for the realization of a conventional DALK. As a postoperative treatment, we used dexamethasone and tobramycin drops every 4 hours.

The day after surgery, the corneal graft was transparent with a small air bubble in the anterior chamber; UCVA was 0.2 (Figure 2).

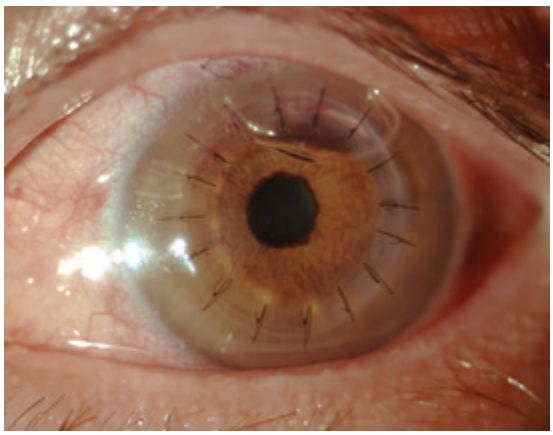

Figure 2: 24 hours after Sclero-DALK surgery

One week after surgery VA had improved to 0.3. Slit-lamp biomicroscopy showed diffuse edema in the temporal area of the cornea (Figure 3). The anterior segment OCT revealed a small detachment of DM in the temporal periincisional zone (figure 4), so it was decided to introduce an air bubble in the anterior chamber, through a lower temporal paracentesis, obtaining the repositioning of the membrane. The patient was left in absolute rest in supine position for 2 hours and then, half of the air was removed. (Figure 5,6).

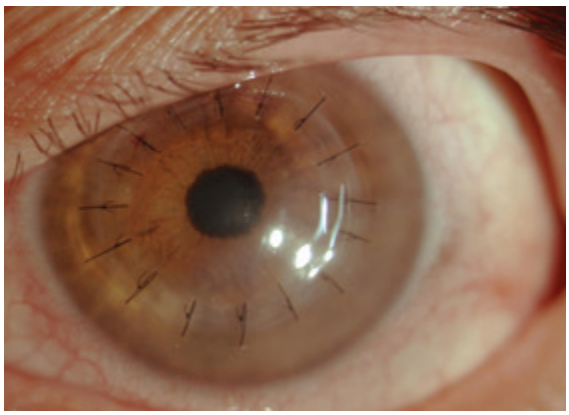

Figure 3: One week after Sclero-DALK surgery. Slit-lamp biomicroscopy showing diffuse edema in the temporal area of the cornea

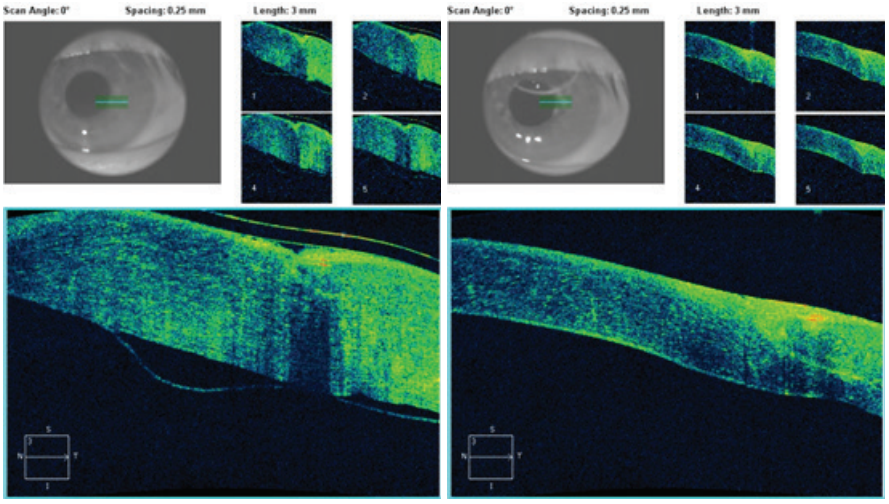

Figure 4: Anterior segment OCT of the left cornea. Descemet membrane detachment in the periincisional zone (left image) and Descemet membrane reposition after air injection (right image) .

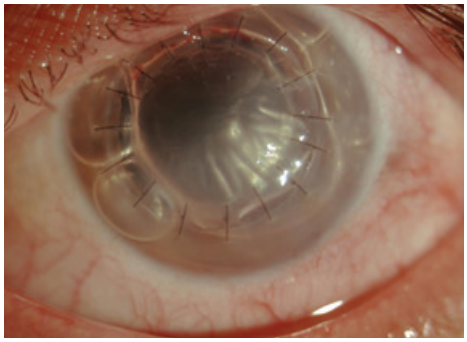

Figure 5: Immediatly after air injection.

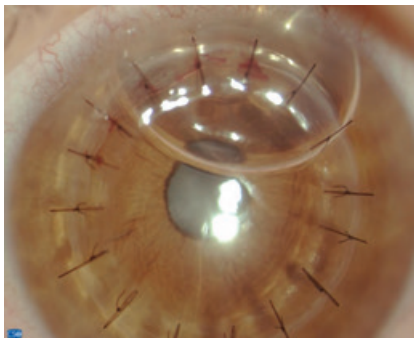

Figure 6: Two hours after air injection.

At 4 weeks postoperatively, corneal transparency was recovered. (Figure 7). UCVA was 0.4. The treatment is modified to fluorometolone eye drops every 6 hours.

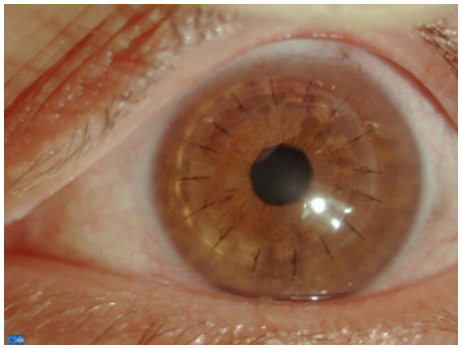

Figure 7: Transparent corneal graft, one month after surgery.

Three months after surgery, UCVA was 0.5. Keratometry in LE was 48.12 / 44.37 x 183°. Suture removal was initiated. (Figure 8)

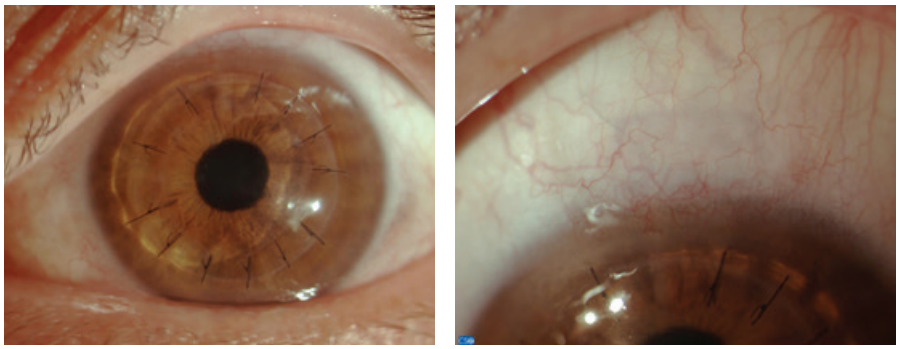

Figure 8: Transparent corneal graft, 3 months after Sclero-DALK surgery.
The image on the right shows the scleral approach area.

At present, the patient does not refer any symptoms. His best corrected visual acuity (-1.50 -4.50 x 50°) is 0.8 and he does not need any treatment. (Figure 9)

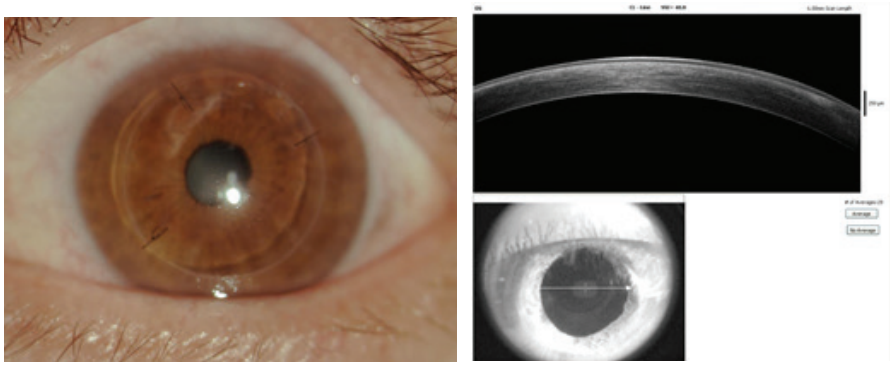

Figure 9: Slit lamp biomicroscopy and anterior segment OCT at 8 months after Sclero-DALK surgery

★ DISCUSSION ★

The Sclero-Dalk technique come up in order to find an alternative to the "Big Bubble" technique for deep lamellar corneal transplants realization. It is performed under general anesthesia. We begin the surgery by performing a limbic peritomy and a 4x4mm deep sclerotomy wich allows us to get to the schlemm canal. (Figure 10)

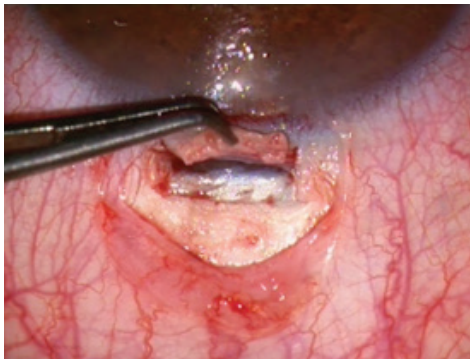

Figure 10: Creation of the deep sclerotomy

A paracentesis is performed and the aqueous humor of the anterior chamber is evacuated. Once we visualize Schlemm canal, we are certain that we are in predescemetic space level which is further dissected by penetrating into the cornea with the Mermoud spatula. Sodium hyaluoronate can be injected through a flat cannula deep into the predescemetic space. Injection of the viscoelastic substance between the deep stroma and Descemet's membrane facilitates the separation of the layers. (Figures 11,12)

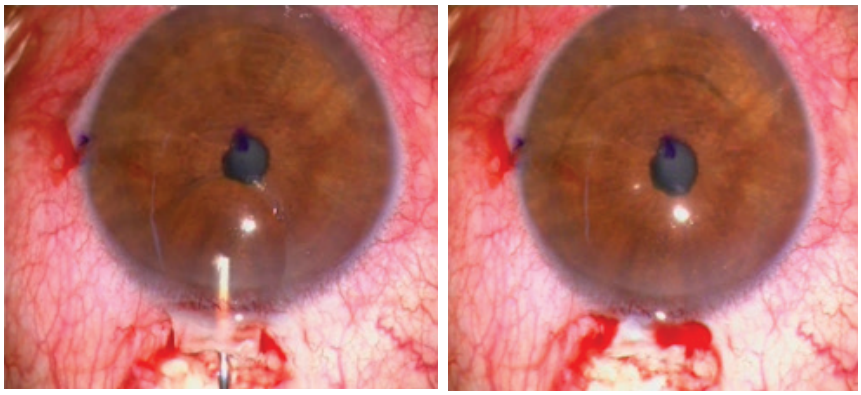

Figure 11, 12: Viscodisection through the sclerotomy approach.

The anterior corneal surface is cut with a suction trephine set and is completed with Vannas scissors. (Figures 13,14). The stromal lamella is removed and the DM is exposed.

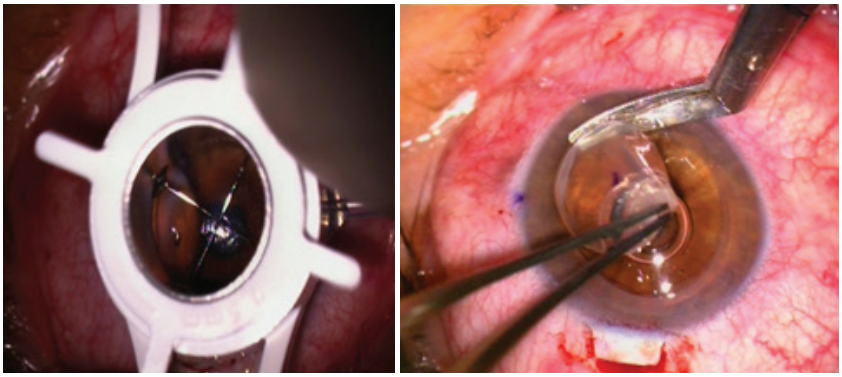

Figure 13, 14: Preparing the recipient cornea.

The DM is irrigated until the viscoelastic is completely removed (Figure 17). A descemet stripped donor corneal button (0.25 mm greater than the size of the corneal receptor trepanation performed) from a fresh cornea, is prepared by the surgeon (figures 15, 16), and subsequently placed at the predescemet's level of the recipient one and sutured to the host cornea by 16-interrupted 10–0 monofilament nylon sutures. (Figure 18). Sclera and conjunctiva are sutured and cefuroxime intracamerular (0,1ml) is injected at the end of surgery.

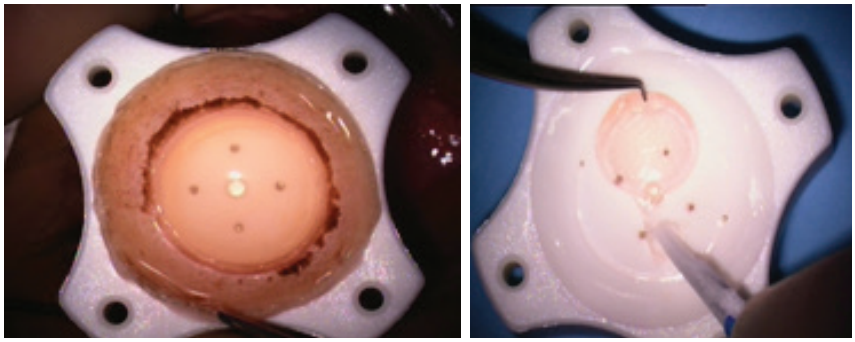

Figure 15: Donor scleral corneal ring on the Hessburg-Barron Punch block (left image)
Figure 16: Endothelium is removed with its Descemet Membrane by tweezers (right image)

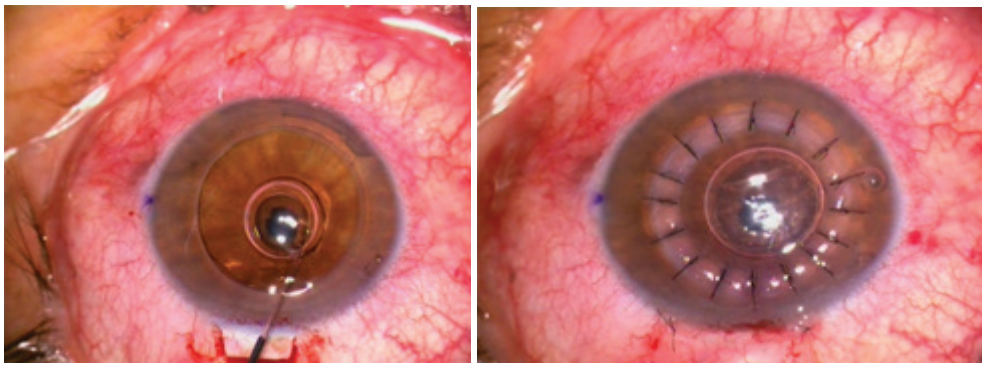

Figure 17: Irrigation to remove viscoelastic
Figure 18: End of the surgery

The main advantage of this new surgical technique is that it allows us to approach the predescemetic space by direct vision from the Schlemm canal. The conventional DALK or the "Big Bubble" technique use a reflex produced by the air, which is not easily visible and therefore it is more difficult to confirm that there is no residual stromal.

The main disadvantage is that future surgeries of glaucoma may be compromised.

Some experience in glaucoma surgery, especially in the performance of deep non perforating sclerectomy is required. The dissection of DM is not difficult, except in cases with adhesions, as in previous hydrops or deep leukomas.

★ CONCLUSION ★

Sclero-DALK is a novelty in surgical treatment of corneal surface opacities. It offers the same advantages than conventional DALK since it is also a non-penetrating extraocular technique. Better final visual acuities are expected with this technique in comparision with PK and the conventional DALK because less residual stroma can be remained since we acces directly to the predescemetic space.

More cases are required in order to standardize the technique and clearly establish its indications and limitations, since there are no publications on this new surgical approach.

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THE CASE OF THE SUCCESSFUL AMNIOTIC MEMBRANE TRANSPLANTATION FOR BILATERAL TOXIC KERATITIS AFTER ELECTRIC OPHTHALMIA

★ INTRODUCTION ★

Electric ophthalmia is an eye disorder caused by fairly long and intensive exposure to ultraviolet or other rays during electric or gas welding,motionpicture filming and so on. The most common form of radiation damage occurs when welding has been carried out without adequate shielding of the eye.

It is manifested by hyperemia and edema of the conjunctiva, tearing,

photophobia and blepharospasm. Involvement of the cornea gives rise to petechial infiltrates, for example, opacifications and superficial detachment of epithelium.

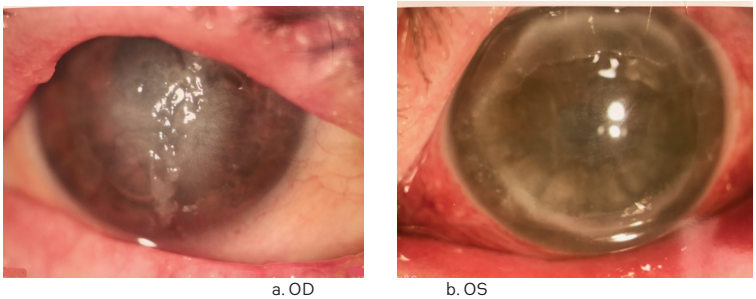
Treatment of electric ophthalmia includes anesthetics, antibiotics, nonsteroidal anti-inflammatory drugs and lubricants. Despite the treatment, corneal damage may progress, and eventually, perforation may occur. In such cases surgical intervention is required – conjunctival flap, tarsorrhaphy, application of glue or keratoplasty is performed.

More recently, in such progressive cases, amniotic membrane transplantation (AMT) has been considered in combination with medical treatment. Studies have shown that AMT promotes rapid epithelialization, reduce stromal inflammation and scarring[1, 2, 3,4] AMT has antimicrobial properties and acts as an effective drug delivery system[5,6,7].

★ CASE REPORT ★

A 63 year-old male was admitted to the corneal department of the SI «The Filatov Institute of eye diseases and tissue therapy NAMS of Ukraine» for 2,5 months of both eyes pain, photophobia, tearing, blepharospasm and decreased vision on February 2017. In December 2016 patient was welding without shielding of the eyes. He had a history of long term administration of topical anesthetic and nonsteroidal anti-inflammatory drugs for electric ophthalmia. Within two months the effect of the therapy was not observed.

On physical examination, our patient's best corrected visual acuities were 0,005 in the right eye and 0,02 in the left. Slit lamp examination of the both eyes showed inflamed, irritated and reddened eyelids, conjunctival injection, limb vascularization, bullous keratopathy, stromal edema and infiltration. Anterior chamber was deep and fundus ophthalmoscopy was difficult. Slit lamp examination of the left eye revealed subtotal corneal abrasion, positive for fluorescein staining (fig 1 a,b).



a. OD b. OS

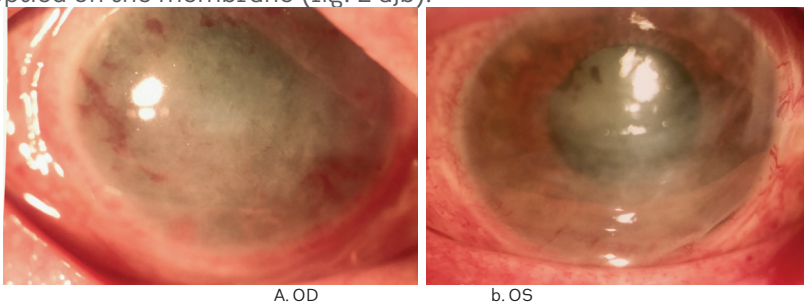
Figure 1. Toxic keratitis after electric ophthalmia

Corneal and conjuctival smears were obtained for microbiological examination. Initial cultures revealed Escherichia coli.

A diagnosis of toxic keratitis, bullous keratopathy, cataract after electric ophthalmia of both eyes was made. Patient stopped all medications, particularly topical anesthetic agents. He was treated with preservative-free 0,02% chlorhexidine and artificial tears with hyaluronic acid, antibiotic, mydriatic, dexpanthenol and wipes with hyaluronic acid and caprylic glycine were used for eyelids. The patient was given systemic nonsteroidal anti-inflammatory injections. By hospital staff it was discovered patient using alcaine secretly on the 2nd day of hospitalization.

Stabilization of the process was not achieved and it was decided to carry out the amniotic membrane transplantation with the aim to reduce the pain syndrome and vascularization, accelerate epithelization of the corneal surface.

17.03.2017 on the left eye and 28.03.2017 on the right eye amniotic membrane transplantation was performed with the use of biological covering technique. After conjunctiva removal and corneal de-epithelialization amniotic membrane was fixed by interrupted sutures 8/00 to episclera. A bandage contact lens was applied on the membrane (fig. 2 a,b).



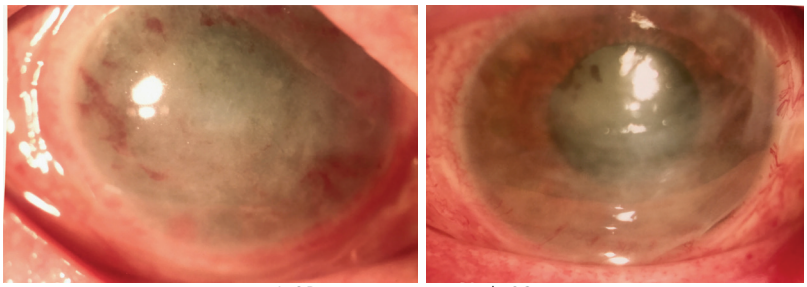
A. OD b. OS

Figure 2. One day after surgery.

During the operation cryopresereved by new technique amniotic membrane was used. The Institute of Cellular Therapy in Kiev has developed a new method of cryopreservation of the human amniotic membrane with 10% dimethylsulfoxide (DMSO) by slow conventional freezing protocol with automatic controlled seeding. This cryopreservation technology provides for the survival of the amniotic cells after its thawing, which reduces the loss of membrane properties to a minimum.

At the time of discharge from hospital in two weeks after surgery best corrected visual acuities were 0,03 in the right eye and 0,07 in the left. Slit lamp examination of the both eyes showed mild conjunctival injection, limb vascularization, safe amniotic membrane, covering the corneal surface and bandage contact lens applied on it. Anterior chamber was deep and fundus ophthalmoscopy was difficult.

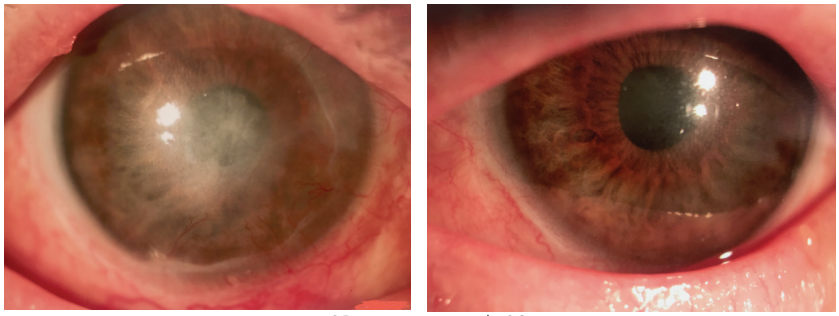
In one month after surgery the patient marked no pain syndrome and photophobia. Visual acuities were 0,03 in the right eye and 0,07 in the left. Slit lamp examination of the both eyes showed mild conjunctival injection, limb vascularization, safe amniotic membrane, covering the corneal surface and bandage contact lens applied on it. Anterior chamber was deep and fundus ophthalmoscopy was difficult. Repeated microbiological culture showed no growth (fig 3 a,b).



A. OD b. OS

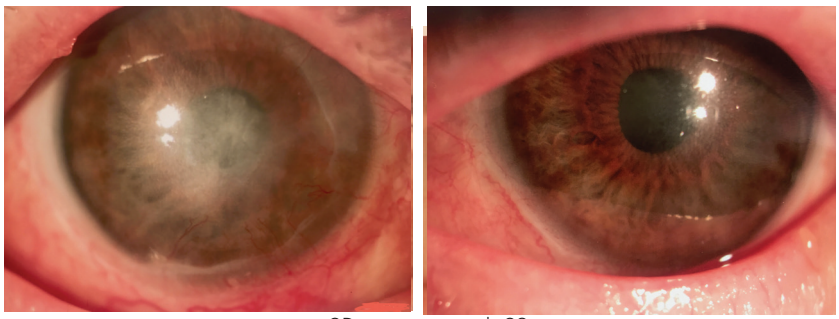
Figure 3. One month after surgery

In two months after surgery visual acuities were 0,08 in the right eye and 0,3 in the left. Slit lamp examination of the both eyes showed normal conjunctiva, decreased limbal vascularization, corneal opacity (˚ D˚ ˚ S) and complete epithelization of corneal surface. Amniotic membrane was partially safe on the right eye (fig 4 a,b).



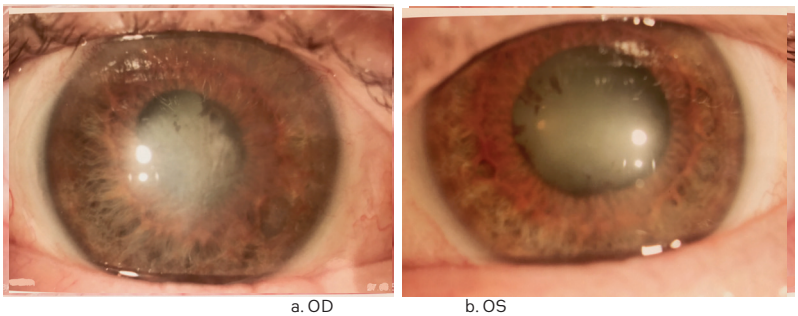
a. OD b. OS
Figure 4. Two months after surgery.

In three months after surgery visual acuities were 0,12 in the right eye and 0,35 in the left. Slit lamp examination of the both eyes showed marked supression of limbal vascularization, nebular corneal opacity, more pronounced on the right eye and epithelization of corneal surface, cataract (fig 5 a,b).



a. OD b. OS
Figure 5. Three months after surgery.

In five months after surgery best corrected visual acuities were 0,3 in the right eye and 0,6 in the left. Slit lamp examination of the both eyes showed nebular corneal opacity and complete epithelization of corneal surface, cataract (fig 6 a,b).



a. OD b. OS
Figure 6. Five months after surgery

★ DISCUSSION ★

The ocular toxicity secondary to topical medications is common after use of anti-glaucoma medications, topical anesthetics and to lesser extent topical antibiotics [8,9,10]. Nonsteroidal anti-inflammatory drugs (NSAID) also can cause severe ocular surface complications[9].

Vingesh et al. (2015) reported a case of corneal edema after use of moxifloxacin drops used to treat conjunctivitis[10].

NSAID can cause upregulations of corneal matrix metalloproteases (MMPs) which will interfere with the corneal epithelial defects healing[11].

Systemic medications can cause ocular depositions and toxicity, and one of them is the Amiodarone which can reach the eye through the tear film and limbal vessels and results in powder like deposition of different colors in the corneal basal epithelial and stromal cells[12].

Our case had corneal toxicity in the form of delayed healing of the epithelial defect and pain syndrome after long term administration of topical anesthetic for electric ophthalmia. Moreover, the patient continued to instill anesthetics secretly on the 2nd day of hospitalization.

The cessation of topical anesthetic use is the first step of the treatment of toxic keratopathy. Given that preservatives can increase toxicity, it is crucial to use preservative free agents in the treatment.

The prognosis in patients with toxic keratitis varies according to how long and how often topical anesthetic agents have been used. Even though satisfactory outcomes have been reported with medical treatment in some patients in the literature[13], in some cases, keratoplasty was performed to preserve the integrity of the globe[14], or enucleation was performed because of treatment failure[15].

There are several reports of the successful use of the amniotic membrane in patients with toxic keratitis[16, 17].

This report shows that AMT is an effective method for treatment of toxic keratitis after electric ophthalmia keratitis, where other strategies have failed. AMT was performed in two weeks after hospitalization to reduce pain and vascularization, accelerate epithelization of the corneal surface.

Studies show, that AM serves as a "basement membrane", produces various growth factors and promotes the corneal healing[18]. In our case we noted complete epithelialization after the first month.

AM contains anti-inflammatory mediators. It was found that AM suppresses the expression of inflammatory cytokines. In addition, polymorphonuclear

cells adhered to its stromal side and underwent rapid apoptosis[14]. In our case we noted the suppression of inflammation on the second week after operation.

Siu G.D. et al showed that majority of eyes (94 %) with bullous keratopathy experienced pain reduction after amniotic membrane transplantation and had pain free period for 39.0 ± 36.3 months[19].

In our case patient noticed marked pain relief on the second day after surgery.

Conclusions. Amniotic membrane transplantation is effective method of treatment of toxic keratitis after electric ophthalmia and promotes persistent epithelization of the corneal surface, decreased inflammation, corneal haze and neovascularization, as well as increased visual acuity.

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SEVERE OCULAR SURFACE DISEASE IN CHILDHOOD

★ INTRODUCTION ★

Vitamin A deficiency can cause a range of ocular manifestations, including conjunctival and corneal xerosis, Bitot's spots (keratinization of the conjunctival epithelium in typical triangular shape), keratomalacia and night blindness.[1, 2] It is an important cause of preventable blindness. Although it usually is a result of malnutrition, it can also be due to a malabsorption syndrome.[3, 4]

Vitamin A is an essential fat-soluble vitamin which exists in three forms: retinoid acid, retinaldehyde and retinol. It must be delivered by food from either animal-derived products or synthetic vitamin A analogues. Different causes of vitamin A deficiency include malnutrition, malabsorption or impaired vitamin A metabolism.

Although vitamin A has many important roles in the body, it is essential for ocular metabolism, including maintenance of the corneal and conjunctival epithelial surfaces as well as for the retinal phototransduction and retinal pigment epithelial viability.[2]

★ CASE REPORT ★

A 3-year-old boy was brought to the children's department of our eye hospital by his parents for the first time. His mother told us that he was reacting very sensitively to light and that he was very insecure when moving in the dark. They had consulted another eye doctor a few months ago complaining about the same symptoms. They were told that everything was within normal limits.

The past medical history included premature birth (29+2 weeks) with status post laparoschisis with multiple surgeries due to necrosis of the small intestine which demanded bowel resection in the course of the disease. No other abnormalities were reported, no medications were taken on a regular basis.

The clinical examination demonstrated a slightly reduced uncorrected visual acuity in both eyes tested via LEA-test: right eye 20/40 OD and 20/25 OS. The objective refraction disclosed a hyperopia of 2 diopters in both eyes which is within normal limits for this age group. No astigmatism was seen. Retinoscopy in miosis as well as the swinging-flashlight-test were unremarkable. Pupillary reaction, ocular motility and external lid structures appeared normal in both eyes. Slit-lamp examination showed severe pancorneal staining in both eyes (Fig. 1) as well as diffuse conjunctival xerosis with Bitot's spots in the temporal and nasal limbal area. (Fig. 2).

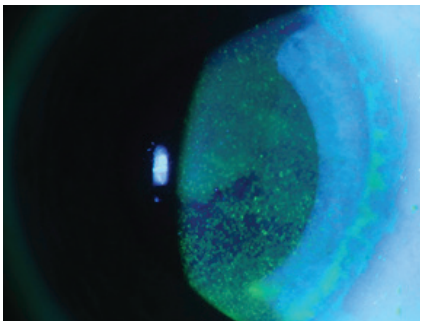

Fig. 1: Diffuse punctate keratitis

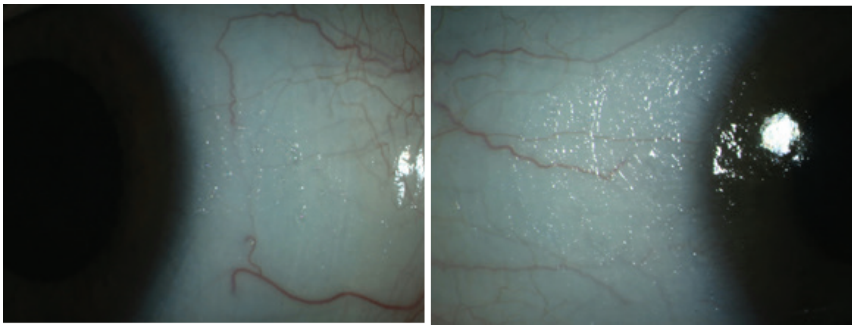

Fig. 2: Bitot's spots (hyperkeratinization of the conjuncitival epithelium

Testing the corneal sensitivity by using Cochet-Bonnet-Corneal esthesiometry showed a markedly reduced score of 2 out of 6 suggesting severe neurotrophic keratopathy. Schirmer tests with and without anesthesia were within normal limits.

The anterior chamber, iris and the crystalline lens appeared without any abnormal findings in both eyes. A dilated fundus examination showed normal findings of the optic disc, macula, vessels and peripheral retina. All the ocular findings put together suggested substantial vitamin A deficiency.

We therefore started therapy with preservative-free artificial tears every hour and vitamin-A-ointment for nighttime use. In collaboration with the paediatrician we also substituted vitamin A systemically as the serum vitamin-A level were reduced.

16 weeks later the boy and his mother returned for follow-up. They reported a marked reduction in symptoms under the prescribed medication that they have applied as recommended. Visual acuity had returned to 20/20 tested via LEA-test. Slit-lamp examinations showed resolution of the ocular surface staining as well as the Bitot's spots (Fig. 3) in both eyes. Corneal sensitivity testing using the Cochet-Bonnet esthesiometer had returned to normal values (6/6). We recommended to continue with the topical and systemic medication.

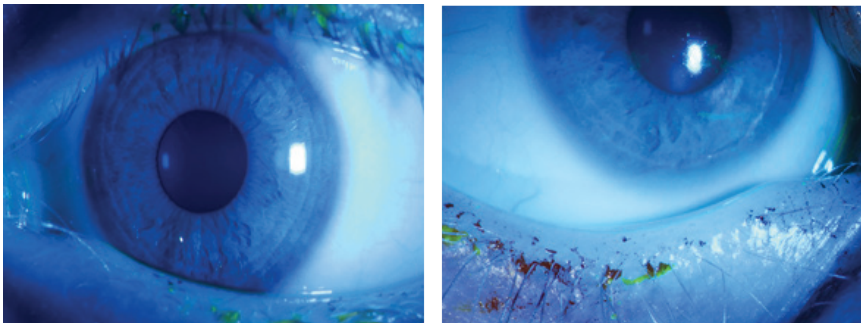

Fig. 3: Normalization of the cornea and the conjunctiva after treatment for 16 weeks

★ DISCUSSION ★

Vitamin A deficiency is estimated to affect approximately one third of children under the age of five in the world and has an impact on approximately 670.000 children under the age of five every year. (5, 6) Around 250.000 – 500.000 children in developing countries loose vision every single year owing to hypovitaminosis A. It is believed to be the leading cause of preventable childhood blindness. (7, 8) Typical ocular symptoms of a vitamin-A deficiency are night blindness, xerophthalmia, Bitot's spots, keratitis and keratomalacia. (7, 9)

There are different pre-forms of vitamin A which are absorbed in the small intestine: Retinol and Carotenes are converted to fat-soluble vitamin A in the small intestine and then transported to the liver and accumulates there. (8)

A vitamin A deficiency is defined as a serum retinol level < 0,3mg/l or 0,7µM. (3) Vitamin A deficiency can occur as either primary or secondary deficiency. The primary deficiency affects children and adults who do not consume the correct amount of pro-vitamin A carotenoids from animal and dairy products. However, the recommended amount of vitamin A intake depends on the age, sex and the environment (average daily consumption of an adult: 0,8 – 1,0mg/d). (3)

Secondary vitamin A deficiency is related to food deprivation associated with malabsorption syndrome mostly due to poverty and/or chronic diseases. Typical medical reasons leading to hypovitaminosis A are low food intake, malabsorption syndrome, intestinal parasitosis and diets containing low amounts of vitamin A. (10) The classical cause is food deprivation – which is very common in developing countries in South Asia, Latin America and Africa. In addition to the above mentioned ocular symptoms, multiple systemic problems can occur due to vitamin-A deficiency such as retarded growth, congenital malformations, infertility, infections and early mortality. (2)

The most common cause of a secondary hypovitaminosis A in industrial countries is a malabsorption syndrome due to different reasons as seen in the case presented here. (4, 11) Treatment always consists of systemic substitution of vitamin A which allows a majority of patients to live a normal life with an increased life expectancy.

However, it is very important to monitor serum levels of vitamin A closely in patients with hypovitaminosis A as many of them may develop xerophthalmia which may progress and cause severe ocular damage. On the other hand, an excessive intake of vitamin A can lead to nausea, headache and many other symptoms.

★ CONCLUSION ★

In industrialized countries, vitamin-A deficiency is rare but should be considered by ophthalmologists in daily clinical practice, in patients who are complaining about nyctalopia or photophobia. This may be a sign of retinal and/or corneal disease associated with reduced vitamin A levels including neurotrophic keratopathy. In patients with ocular surface disease as described above and a past medical history or living conditions suggesting malabsorption or reduced food intake, Vitamin A deficiency should always be ruled out.

The major goal of treatment is monitoring and restoring systemic vitamin A levels.

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COMPLEX TREATMENT OF CORNEAL DAMAGE IN THYROID EYE DISEASE

★ INTRODUCTION ★

Thyroid eye disease (TED) is a progressing inflammatory orbital disease involving extraocular muscles and orbital fat. The disease is associated with thyroid disfunction and characterized by chronic course and sometimes unfavorable visual and cosmetic outcome.

Corneal damage and optic neuropathy are the most severe vision threatening complications of TED. Corneal ulcer without appropriate treatment may result in corneal melting and perforation that in 1,8% lead to endophthalmitis. Treatment of corneal damage in TED is often challenging becuase standart approaches in these cases turn to be ineffective. This is due to the multifactorial nature of corneal involvement in these patients including orbital inflammation activity, exophthalmos, lagophthalmos, palpebral fissure opening, lid retraction, dry eye syndrome and reduced corneal sensitivity [1 - 7].

★ CASE REPORT ★

We present a clinical case of severe corneal involvement in patient with TED.

A white 44 years old male was administered to clinic with complaints of visual impairment OS, red eyes, proptosis and retroocular pain OU.

HISTORY

Proptosis on the left eye appeared 6 months before. One month later the patient felt paraesthesias and weakness in low extremities. Patient did not have history of alchohol or drug abuse. Due to deterioration of general state the patient was admitted to narcological department with diagnosis of predelirious state. Three days later he was transferred to intensive care unit because of precomatous state. During 20 days the patient was comatous and had undergone tracheostomy. During this period septicemia, viral hepatitis B and C were revealed, elbow contractures developed. A prominent exophthalmos OU was observed. Thyrotoxicosis was diagnosed and mercazolilum 15 mg daily was administered. In complex treatment high doses of systemic glucocorticoids were used (total dose unknown). In 2 months the patient was discharged with the following diagnosis: diffuse toxic goiter, thyrotoxicosis, thyroid eye disease, elbow ankylosis, chronic viral hepatitis B and C. Oral prednisone 30 mg daily was administered with dose tapering during 1.5 months (total dose 832.5 mg).

Initial best corrected visual acuity (BCVA) was 1.0 OD and 0.7 OS, ocular hypertension, exophthalmos 24 mm OD and 28 mm OS, significant periorbital edema. OD: lagophthalmos 2 mm, red chemosis, crescent - shaped erosion in the lower part of the cornea (Fig. 1). OS: lagophthalmos 5 mm, red chemosis, opacity in the lower half of the cornea extending to the optic zone (Fig. 2).

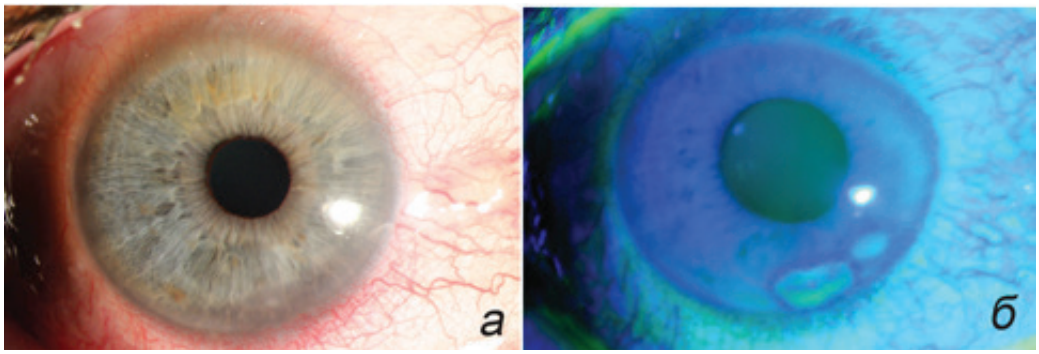

Fig. 1. Right eye. Corneal erosion.

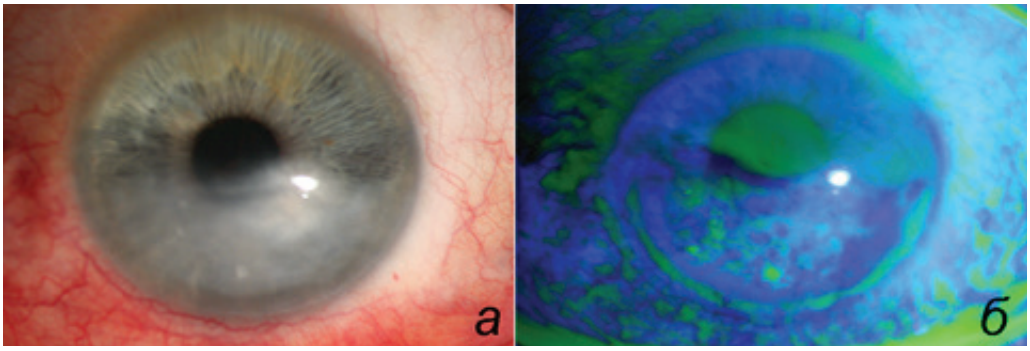

Fig. 2. Left eye. Corneal opacity and erosion.

Temporal tarsorhaphy was performed on the left eye as an emergent procedure. Within few days progression of exophthalmos and chemosis was observed, tarsorhaphy sutures cheese-wired. BCVA OD decreased to 0.6, OS – to 0.1. Exopthalmos increased by 2 mm both sides, ocular motility was significantly restricted on the right and absent on the left, eyelid retraction was observed, lagophthalmos OD was 6mm, OS 9 mm, severe chemosis (Fig. 3). Corneal ulcer was revealed on both eyes, more prominent on the left.

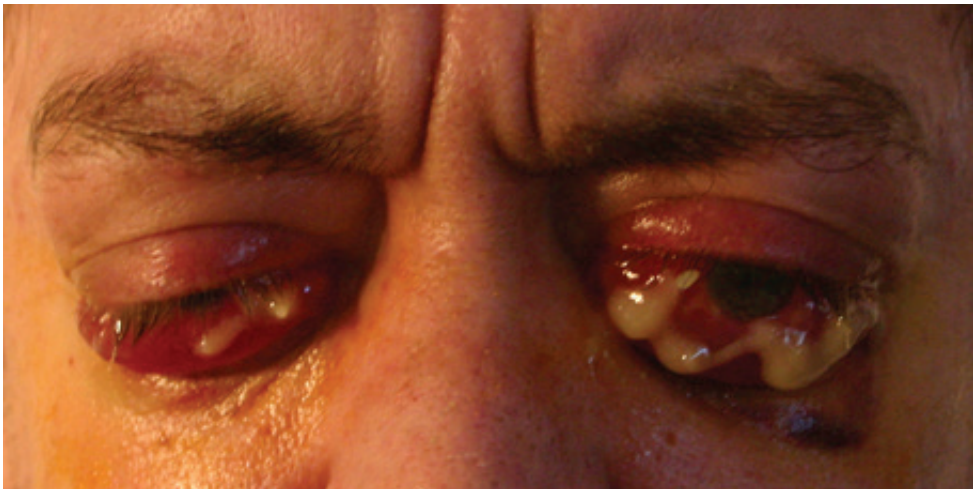

Fig. 3. Prominent active orbital inflammation, significant chemosis. Ointment on conjunctiva.

Pulse-therapy with 1000 mg methylprednisone №5 was administered, positive results were achieved. Surgical treatment included orbital fat decompression and temporal tarsorhaphy both sides, epikeratoplasty on the left and autoconjunctival corneal plasty on the right eye. The patient was discharged with significant improvement on both eyes.

In two months orbital inflammation and left corneal ulcer recurred. BCVA OD was 1.0, OS 0.1, exophthalmos 23 on the right and 24 on the left eye,

periorbital edema and ocular motility restriction. Lagophthalmos 2 mm and corneal erosion were revealed on the right eye. Lagophthalmos OS was 4 mm, corneal epitransplant lysis and corneal vascularization were observed.

Surgical treatment was performed. Retraction of both upper eyelids was corrected via lengthening of levator using homologous sclera. Besides surgery intravenous cyclophosphamide was administered. As a result of this treatment reduction of palpebral fissure opening and lagophthalmos were achieved. Peripheral corneal haze formed on OD. Stabilization of orbital inflammation was achieved.

In two months a new relapse of orbital inflammation developed that resulted in optic neuropathy and lysis of epicorneal transplant on the left eye. BCVA OD 1.0, OS 0.01. Exophthalmos 24 mm OD and 26 mm OS, severe periorbital edema (Fig. 4). Lagophthalmos 2 mm, chemosis and corneal conjunctivization in the lower ⅓ were revealed on the right eye (Fig. 5). Lagophthalmos OS was 8 mm, severe chemosis and lysis of epicorneal transplant and corneal vascularization were present (Fig. 6). Amnion transplantation and permanent tarsorhaphy were performed (Fig. 7). Pulse-therapy was initiated again. Treatment resulted in significant improvement. Periorbital edema, pain and chemosis reduced, ocular motility improved, exophthalmos OD decreased by 2.5 mm, lagophthalmos by 1 mm. Total steroid dose was about 6000 mg including oral intake.

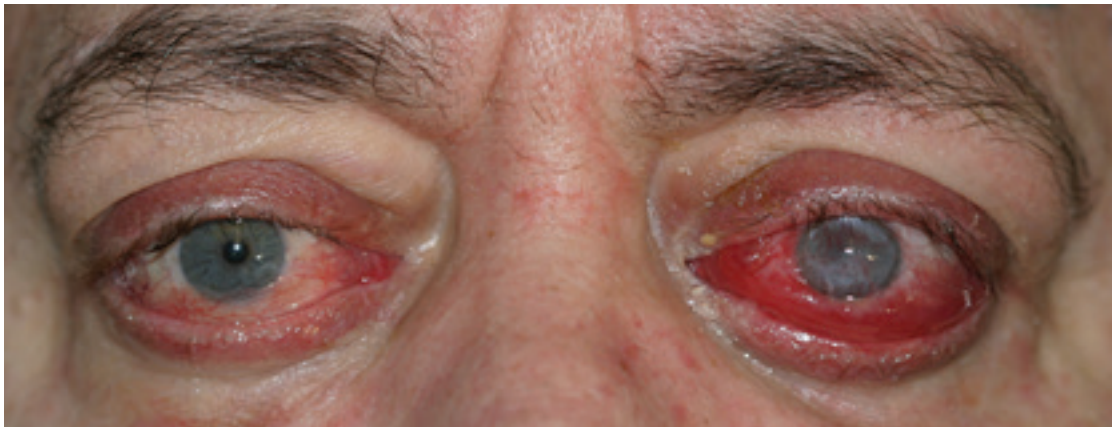

Fig. 4. Appearance of the patient: significant exophthalmos, chemosis

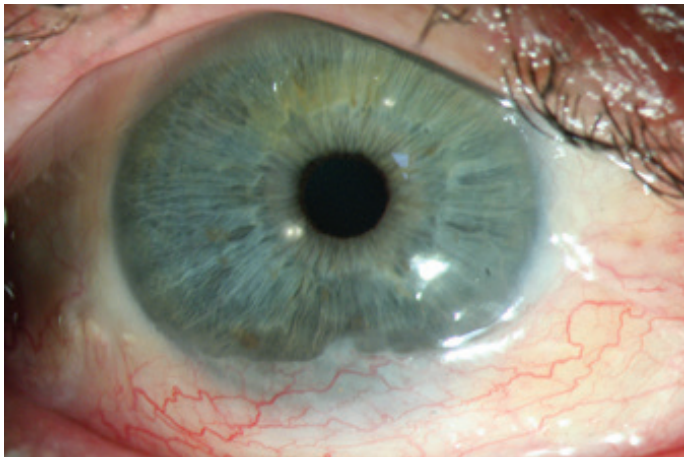

Fig. 5. Right eye. Corneal conjunctivization in the lower 1/3.

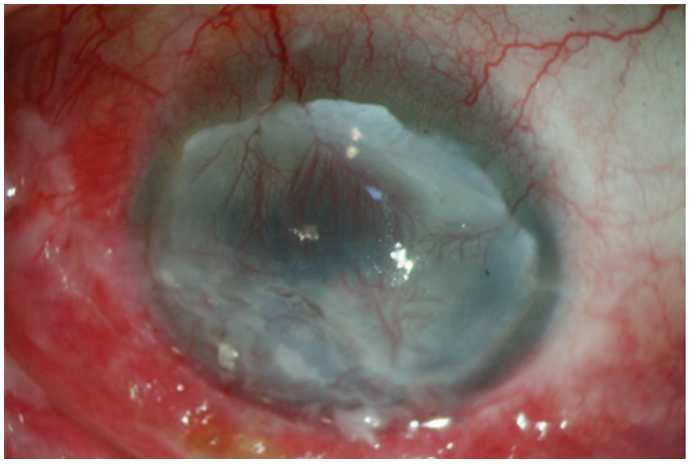

Fig. 6. Left eye. Левый глаз. Lysis of epicorneal transplant.

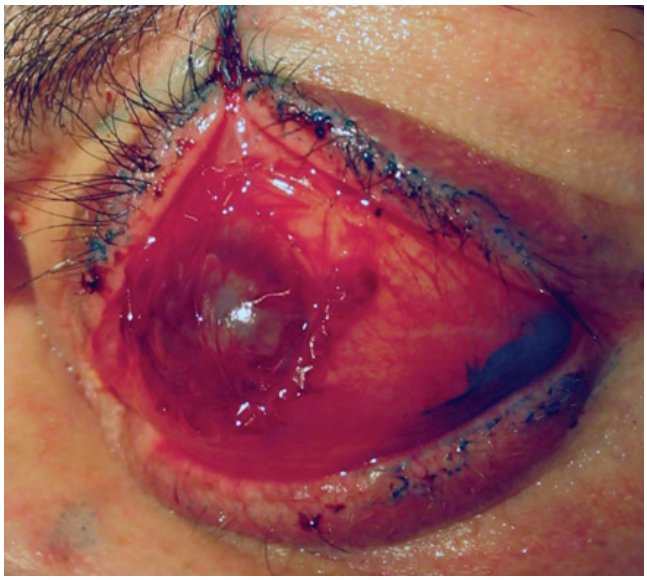

Fig. 7. Intraoperative photo of amnion transplantation.

In two months a course of radiotherapy was conducted. Thyroid gland was removed and hormone replacement therapy was initiated.

As a result long-term stabilization was achieved (Fig. 8). In one year BCVA OD was 1.0. exophthalmos 19 mm, slight abduction restriction, lagophthalmos 1 mm, peripheral corneal haze. Left palpebral fissure was closed in lateral 2/3, visible cornea was vascularized, central haze. BCVA OS was 0.1, exophthalmos approximately 21 mm. The patient was suggested to open left palpebral fissure but he refused.

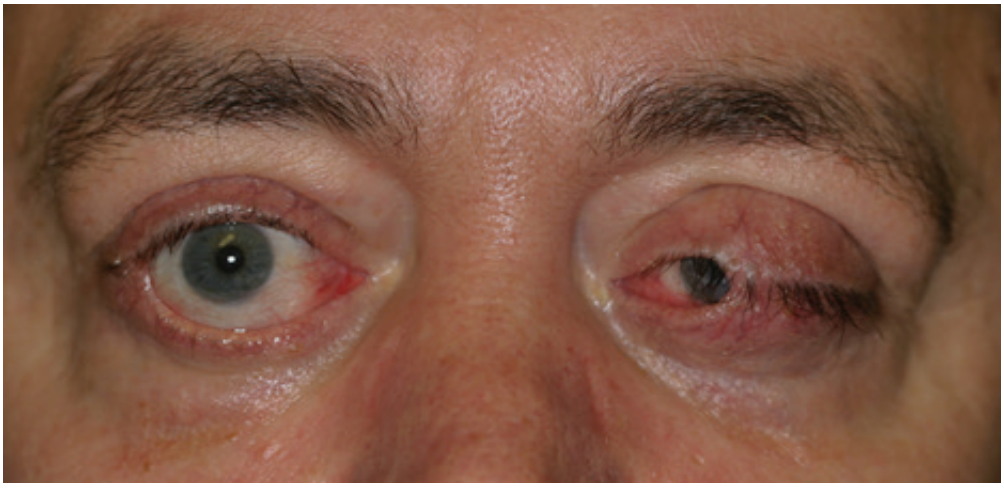

Fig. 8. Appearance after 12 months of remission.

★ DISCUSSION ★

Treatment of corneal damage in patients with TED is always difficult especially if orbital inflammation is severe. It should include ethiological, pathogenical and symptomatic approaches.

This clinical case is of interest because medical treatment (high doses of intravenous methylprednisone, cyclophosphamide) and surgery (orbital decompression, eyelid and corneal surgery) in a patient with severe TED allowed to achieve only short-term improvement. Only combination of long-term glucocorticoid treatment, including oral intake, and radiation therapy led to long-term stabilization of orbital inflammation and guaranteed success of surgical interventions. Literature data confirm reasonability of this combination in treatment of severe TED [7,8]. Temporal tarsorhaphy on the left eye failed because of progression of orbital inflammation that resulted in increase of exophthalmos, eyelid retraction and chemosis. In cases like this effective corneal protection may be provided only by combination of orbital decompression, eyelid surgery (permanent tarsorhphy, levator lengthening) and pathogenic treatment of orbital inflammation [9].

★ CONCLUSION ★

Thus this clinical case demonstrates necessity of complex treatment of corneal damage in TED, including pulse-therapy with subsequent long-term steroid intake, orbital radiation and surgery.

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SUCCESSFUL TREATMENT OF ACANTHAMOEBA SCLEROKERATITIS WITH INTRAVENOUS PENTAMIDINE FOLLOWED BY THERAPEUTIC KERATOPLASTY

★ INTRODUCTION ★

Acanthamoeba spp. are a rare and severe cause of keratitis, with predisposing factors including soft contact lens wear and poor lens hygiene.[1,2] Acanthamoeba sclerokeratitis (ASK) occurs as an uncommon and devastating complication of Acanthamoeba keratitis (AK) and may lead to the loss of an eye, despite maximal treatment.[3] Therapy for ASK has not been standardized, and includes medical and surgical approaches.[4] Most common medical therapy plans contain multiple agents, such as propamidine isethionate (Brolene, Sanofi-Aventis, Auckland, New Zealand), polyhexamethylene biguanide (PHMB), and chlorhexidine 0.02%. Other antiamebic and antifungal medications, such as voriconazole, are often included as part of treatment as well.[5] Surgical therapy, such as penetrating keratoplasty (PKP), is usually considered only after medical therapy has failed, and involves a high recurrence rate.

Intravenous pentamidine (IVP) represents another treatment option that has been demonstrated to be amebicidal against Acanthamoeba spp. in vitro and in vivo.[6,7] To the best of our knowledge, this is the first report on the successful treatment of ASK with the use of IVP before therapeutic keratoplasty.

★ CASE REPORT ★

A 68-year-old man presented with redness, constant pain, photophobia, and mild blurred vision in the left eye, ongoing for six weeks. He had worn soft contact lenses intermittently for over 5 years, with good lens hygiene. At presentation, his corrected visual acuity was 20/25 in the right eye, and his uncorrected visual acuity was 20/200 in the left eye. Slit-lamp examination revealed conjunctival hyperemia and moderate injection superiorly from 9-2 o'clock, no scleral nodules or necrosis, superior corneal haze, possible pseudo-dendrites, and mild anterior chamber reaction. The patient was already being treated with hourly prednisolone acetate 1% beginning a week before presentation. Additionally, oral valacyclovir 1g three times daily, and ibuprofen 600 mg were added for suspected Herpes Simplex Virus, and scleritis. At a one week follow-up, the patient presented a decrease in uncorrected visual acuity (counting fingers at 2 feet), and examination revealed a superonasal 1.0 mm x 4.9 mm epithelial defect, a peripheral infiltrate adjacent to the limbus, and stromal edema (Fig. 1A). Oral doxycicline 100 mg twice daily, topical moxifloxacin every 2 hours, topical defomedene 0.1% and chlorhexidine 0.02% hourly were added to the treatment regimen. The patient also reported kayaking in mountain streams and was submerged under water, indicating a high probability of acanthamoeba exposure. Eleven days after presentation, corneal culture revealed amoebic cysts by histopathological evaluation. In vivo confocal microscopy (IVCM) was performed, confirming the presence of acanthamoeba trophozoites in the corneal epithelium, as well as clusters and chains of the organism in cystic form in the stroma (Fig. 1D). Epithelial debridement was performed, prednisolone acetate 1% was stopped and topical polyhexamethylene biguanide 0.02% (PHMB) hourly and oral voriconazole 200 mg twice daily were prescribed.

Twenty-one days after presentation, IVCM was repeated and images showed amoeba cysts from limbus to limbus nasally and temporally, and indicated presence of acanthamoeba in the peripheral cornea (Fig 1E). Triple topical therapy and oral voriconazole were continued and valacyclovir and doxycycline stopped.

In spite of the intense treatment and maximal medical therapy, the eye pain increased, and vision decreased to hand motion. Slit-lamp examination demonstrated a total epithelial defect, stromal haze superiorly, moderate anterior chamber reaction, corneal endothelial inflammatory debris, and a 2.2 mm plaque inferiorly, as well as cataract formation (Fig. 1B). IVCM images suggested persistent cysts. Despite intracameral and intrastromal injections of voriconazole and chlorehexadine, conditions worsened and the patient developed a complete hyphema. The patient stopped defomedene 0.1% after 3 months usage due to severe burning sensation. Topical PHMB, chlorhexidine, moxifloxacin, cyclosporine 2% and oral voriconazole were continued. The hyphema was unresolved for a period of three weeks. Anterior chamber was washed out, and intrastromal and subconjunctival injections of voriconazole and chlorhexidine were performed. In addition, cryotherapy of the sclera was performed. Injections and cryotherapy diminished cysts by half in IVCM examination, but could not achieve a complete resolution (Fig. 1F).

By 150 days after presentation, the patient started a 14-day-course of intravenous pentamidine at a dose of 300 mg/day over 2 hours. Initially, a 28-day course was planned, but during pentamidine infusion the patient experienced episodes of nausea. After the treatment, he underwent therapeutic extracapsular cataract extraction combined with a penetrating keratoplasty. Histopathology of the removed cornea showed acanthamoeba cysts in the stroma (Fig. 1G and 1H). Postoperatively, topical moxifloxacin, prednisolone, and cyclosporine 2% were prescribed 4 times daily, and oral voriconazole was continued. One month postoperatively, the graft was clear and sutures were intact, but IOP was low. B-scan showed a choroidal effusion and the patient underwent pars plana vitrectomy, choroidal drainage, and gas infusion in his left eye. Nine months after pentamidine treatment followed by PKP vision remains stable, and the graft is clear (Fig. 1C), and IVCM has revealed no evidence of acanthamoeba cysts or trophozoites.

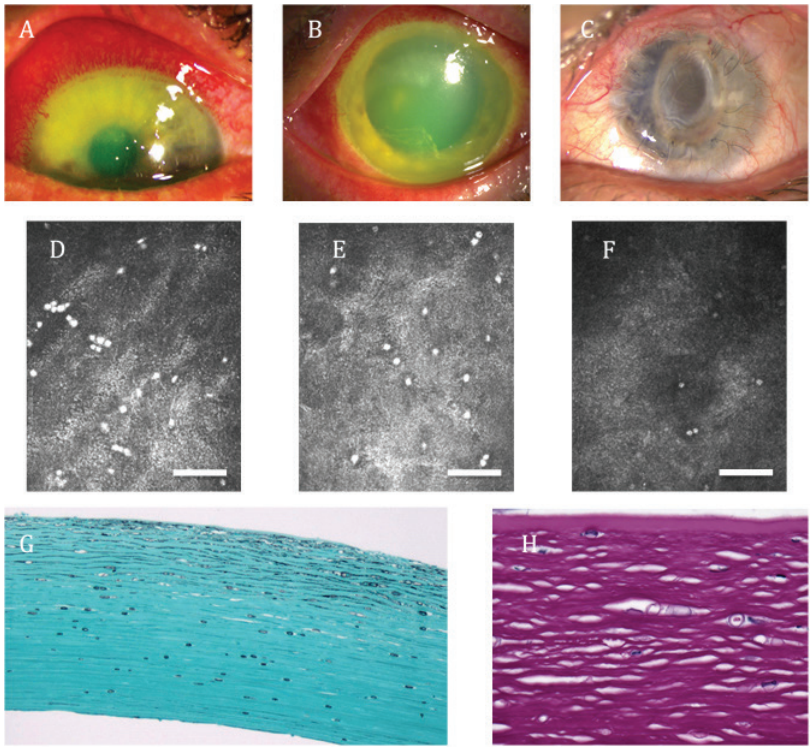

Figure 1. Slit lamp examination in pre-treatment and post-treatment with intravenous pentamidine in acanthamoeba sclerokeratitis; follow up IVCM images and corneal button histopathology. (A) Slit-lamp examination demonstrates a conjunctival hyperemia and moderate injection superiorly from 9-2 o'clock, no scleral nodules or necrosis, superonasal 1.0 mm x 4.9 mm epithelial defect, a peripheral infiltrate adjacent to the limbus, stromal edema and mild anterior chamber reaction. (B) Slit-lamp examination reveals a total epithelial defect, stromal haze superiorly, moderate anterior chamber reaction, corneal endothelial inflammatory debris, and 2.2 mm plaque inferiorly. (C) Slit-lamp examination post-treatment with intravenous pentamidine followed by penetrating keratoplasty, showing a clear graft.

(D) At presentation, IVCM in the affected eye shows acanthamoeba cysts in deep stroma, arranged in clusters and chains. Scale bar 100 m. (E) IVCM was repeated and images revealed amoeba cysts in peripheral cornea, from limbus to limbus nasally and temporally. Scale bar 100 m. (F) Injections and cryotherapy diminished cysts by half according to IVCM examination, but could not achieve a complete resolution. Scale bar 100 m. (G) Gomori-Grocott methenamine stain shows a great density of acanthamoeba cysts, x10. (H) Periodic acid-Schiff stain highlights the acanthamoeba cysts, x40.

★ DISCUSSION ★

The treatment of Acanthamoeba sclerokeratitis is challenging.3,7 The early signs of AK are highly inconstant and usually include epitheliopathy and dendritiform lesions, while stromal and/or endothelial inflammation may be present. The early similarities to herpes simplex keratitis often leads to the use of topical corticosteroid, delaying the diagnosis of AK.[8] In addition, it is hard to distinguish between secondary scleritis and the presence of acanthamoebal infection in the sclera. IVCM has been demonstrated to be an important adjunct tool to evaluate amoeba cysts and trophozoite elements on the ocular surface. Although our patient received intense care, maximal topical and oral medication, and close follow-up with serial IVCM, amoeba cysts were observed for 5 months, until intravenous pentamidine followed by PKP was performed.

Intravenous pentamidine (IVP), has been shown to have both in vitro and in vivo amoebicidal activity, but there are no established protocols regarding dosage or duration of therapy, or the interval between fulfillment of IVP therapy and surgical intervention.6,7 Sacher et al. showed that the median daily dose of IVP was 300 mg/day, and there was a median treatment duration of 14 days for Acanthamoeba keratitis patients. Our patient completed a 14-day-course of intravenous pentamidine at a dose of 300 mg/day. Although our patient did not report any major side effects, he complained of mild nausea and did not complete the originally planned 28-day-course. Sacher et al. also demonstrated a mean time of 3.1 months after presentation to the first dose of IVP for acanthamoeba keratitis cases, with 5.8 months as the longest period between presentation and IVP therapy. Our patient received the first IVP dose almost 6 months from his initial presentation.

Kuennen et al. reported a case of IVP therapy in conjunction with surgery that resulted in eventual enucleation 6 months after apparent cure.3 Enucleation in this case was prompted by presentation of pain and the presence of a mass in the anterior chamber that demonstrated Acantahmoeba like structures by IVCM, which were confirmed by pathology after removal. 3 Our patient showed no signs of inflammation at slit lamp examination at a 9 months-period follow up visit post-treatment, and the graft remains clear.

Limitations of this study include use of multiple forms of therapy before IVP, which may have contributed to the efficacy of treatment.

★ CONCLUSION ★

To the best of our knowledge, this is the first case report to describe a successful treatment of acanthamoeba sclerokeratitis (ASK) with intravenous pentamidine. The severe ASK patient in our report, who was refractory to maximal topical, oral, intracameral, and intrastromal medications, showed significant improvement in symptoms with no evidence of acanthamoeba cysts or trophozoites via IVCM nine months after pentamidine treatment.

In conclusion, this case report indicates that the adjunctive use of IVP before PKP may serve as an effective treatment for refractory and severe cases of acanthamoeba sclerokeratitis. In cases of acanthamoeba sclerokeratitis, where traditional therapy fails to eradicate the organisms, an earlier use of this therapy should be considered.

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CORNEAL, SCLERAL AND CONJUNCTIVAL EXCISION WITH LAMELLAR KERATO-SCLERAL GRAFTING AS A SURGICAL TREATMENT OF JUXTALIMBAL CARCINOMA "IN SITU" WITH CORNEAL INVOLVEMENT

★ INTRODUCTION ★

The Ocular Surface Squamous Neoplasia (OSSN) is a collective term referring to diseases from benign dysplasia, carcinoma „in situ" to invasive squamous cell carcinoma. The clinical presentation and virulence of these lesions depend on the extent and degree of the pathologic involvement.[1] The symptoms predominantly occur in older men as an unilateral eye irritation with a slowly progressive gelatinous mass with superficial vessels. The most common localization is juxtalimbal conjunctiva within the interpalpebral fissure.[1-3] Advanced lesions may invade the adjacent limbus and cornea or extend intraocularly with the eventuality of metastases although systemic spread is extremely rare.[1-3]

The predisposing factors of OSSN include ultraviolet B irradiation, human papilloma virus or human immunodeficiency virus infection, smoking, vitamin A deficiency, ocular surface injuries, xeroderma pigmentosum. The incidence of OSSN vary depending on the latitude with higher prevalence in tropical climates [1-3].

The diagnostics of OSSN is based on clinical examination, including presence of conjunctival lesion of juxtalimbal location. In clinically uncertain cases an excision biopsy should be performed to determine the histopathological features of the lesion.[1,2] Other less invasive methods include exfoliative cytology, impression cytology or fine-needle biopsy [1,2,5]. Ultra high-resolution OCT (UHR OCT) is a non-invasive technique to diagnose and provide follow-up for patients with OSSN[6].

★ CASE REPORT ★

A 68-year-old woman with a history of recurrent corneal erosions of the left eye and diagnosis of limbal stem cell deficiency was admitted to the department of ophthalmology. The patient's medical history comprised of recurrent incidents of severe pain and redness with significant deterioration of visual acuity, treated conventionally with topical antibiotics drops, dexpanthenol ophthalmic gel and hyaluronic acid solution with no improvement. Slit lamp examination revealed a partial corneal opacity with multifocal epithelial defect and heaped conjunctival lesion 5mm width in the inferonasal quadrant engaging the limbus (Fig.1). Best-corrected visual acuity of the affected eye was 4/50. The oncologic history and occurrence of OSSN risk factors were negative.

Due to uncertain clinical presentation, a biopsy was performed to determine the type of the conjunctival lesion. The examination revealed conjunctival carcinoma "in situ" G2 with centripetal invasion of cornea without epithelial membrane penetration. Taking into consideration the histopathological diagnosis and the fact of corneal involvement , the patient was qualified for surgical treatment. This comprised anterior lamellar keratoplasty and the resection of the conjunctival lesion with partial-thickness sclera resection followed by scleral grafting.

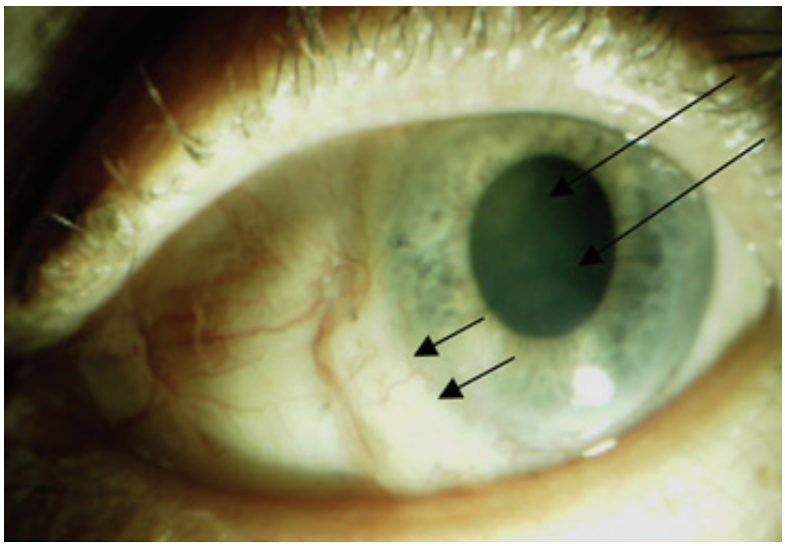

Fig.1 : Surface of the left eye with a heaped conjunctival gelatinous lesion in the inferonasal quadrant with surrounding widened blood vessels (small arrows) and corneal opacity extended to the central part of cornea (long arrows).

SURGICAL PROCEDURE

Donor`s corneal lamellar graft 200µm of thickness and 8,5mm of diameter with adjacent limbal and scleral flap was prepared. The conjunctival lesion of the recipient was meticulously excised maintaining a 2mm margin of the unaltered tissue. The superficial layer 200µm of depth of the recipient`s cornea was dissected manually followed by a partial-thickness trephination

of the sclera of 200μm depth and 5mm width with adjacent corneal limbus in the inferonasal area. The donors flap was then sutured. Eventually the scleral part of the graft was covered with mobilized peripheral conjunctiva. (Fig.2) Topical levofloxacin drops and a soft contact lens were applied.

The postoperative histopathologic examination of the resected tissues revealed preinvasive OSSN G2 with positive Ki index.

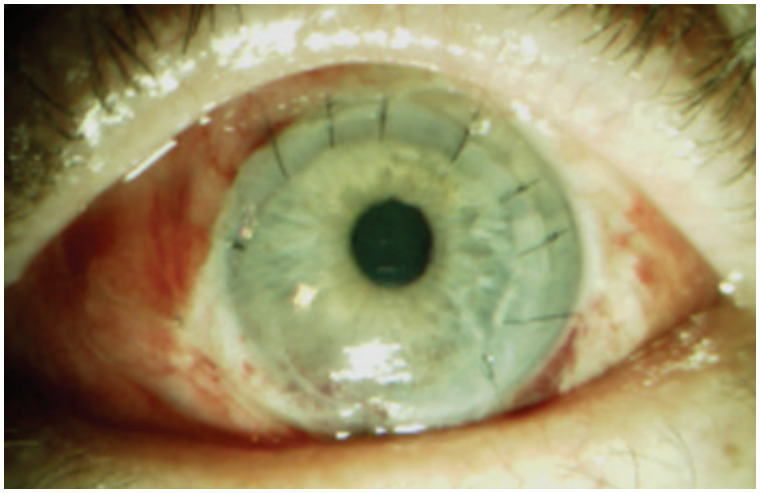

Fig.2: Ocular surface promptly after surgery. Corneoscleral lamellar graft is tightly sutured.

POST-OPERATIVE PERIOD

In the postoperative period intensive immunosuppressive therapy consisting of 100mg of oral cyclosporine and 0,1% topical dexamethasone drops and hyaluronic acid solution was administered. Proper healing with no graft rejection or failure was observed (Fig.3, 4). The incidental intraocular pressure spikes were controlled by topical 0,2% brimonidine. On examination performed 9 months after grafting, the patient obtained BCVA of 4/10, without evidence of graft rejection or OSSN recurrence.

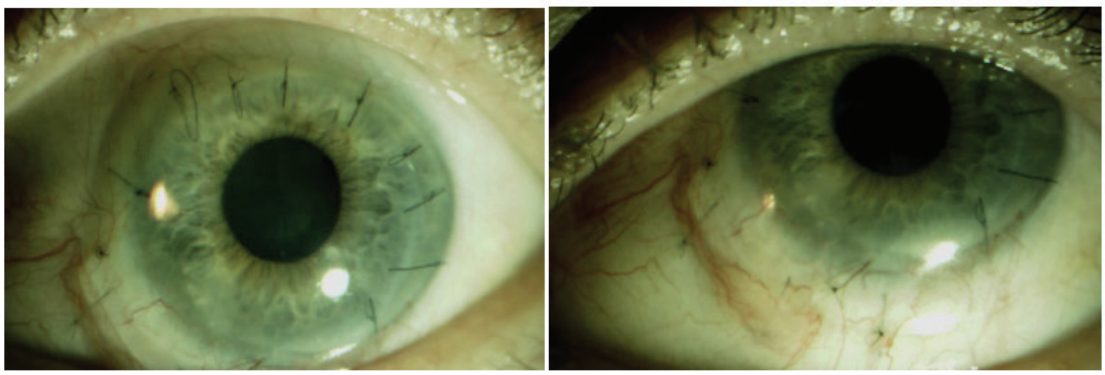

Fig.3: Ocular surface 4 months after surgery. Transparent corneal graft secured with interrupted sutures (left panel). Limbal and scleral part of the graft has normal appearance (right panel)

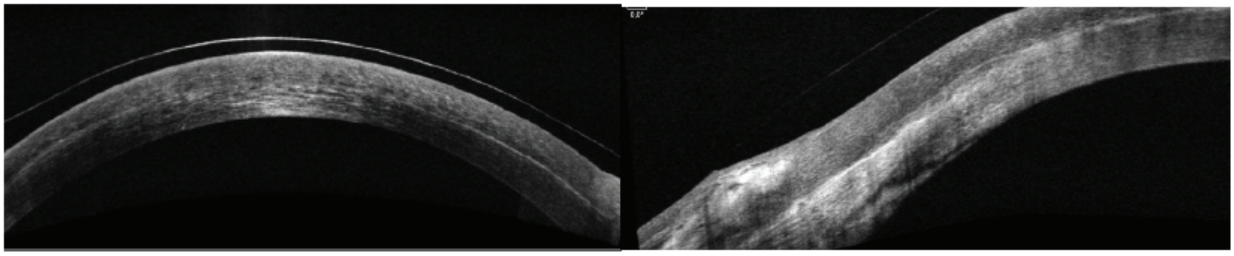

Fig.4. High-definition OCT scan of patient`s cornea (left panel) and sclera- corneal limbus (right panel) 4 months after surgery.

★ DISCUSSION ★

The OSSN is a relatively uncommon neoplastic lesion affecting conjunctiva/limbus and the corneal area of the eye surface.[1,2] Corneal invasion of OSSN may mimic primary limbal stem cell deficiency what was well observed in presented patient. The conjunctival biopsy and the histopathologic examination was essential to confirm the diagnosis of OSSN. Corneal spreading of the neoplastic lesion without morphological evidence of epithelial basement membrane penetration were the reasons for extensive lamellar tissue excision.[1] It is suggested that total resection of the OSSN lesion within the conjunctiva, adjacent limbus, cornea and sclera potentially guarantees avoidance of imperceptible neoplastic invasion and consequently OSSN recurrence.[1,2] On the other hand resection of the limbus may promote iatrogenic epithelium healing disruption.[7] Therefore combining the resection with lamellar corneal and limbal grafting seems to counteract limbal stem cell deficiency providing adequate functional results.

★ CONCLUSION ★

Conjunctival lesion resection combined with corneal, limbal and sclera's lamellar excision followed by donor grafting should be considered as an effective option of OSSN treatment with corneal invasion. Moreover this type of surgical procedure helps to prevent the patient from secondary limbal stem cell deficiency and allows rapid visual improvement.

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MANAGEMENT OF ASSOCIATION KERATOCONUS AND VERNAL KERATOCONJUNCTIVITIS OF YOUNG ADULT

★ INTRODUCTION ★

Ocular surface diseases (OSD) are a very diverse range of multifactorial disorders[1], where endogenous and/or exogenous, local and/or systemic factors can be associated and lead to chronic and progressive disease.

Vernal keratoconjunctivitis (VKC) is a chronic inflammatory disease, in extreme cases cornea may be involved leading to severe complications[2].

Keratoconus is a corneal disorder, closely related to ocular surface disease due to all the physio pathological pathways, environmental factors such as ocular friction and allergy on a predisposing genetic field, will impact on this pathology[3].

When these conditions "keratoconus and VKC "are associated it will lead to a therapeutical challenge where all management options intervenes on the ocular surface at all stages of the disease[4].

However, a well-led treatment based on a good analysis of each involved disease can help to preserve ocular surface homeostasis.

★ CASE REPORT ★

The case concerns a 26-year-old Caucasian male, miner, with history of rhinitis, presented with acute red, itchy and painful eyes and photophobia for 05 days; he also reported a progressive vision loss since 03 months, more significant in the right eye.

Clinical examination revealed : reduced visual acuity in both eyes with best corrected VA at 20/200, P28 OD and 20/70 P14 OS , an eccentric infero-temporal corneal protrusion, more apparent on profile, deforming the the curve of the lower eyelid in downgaze "Munson's sign " on both eyes.

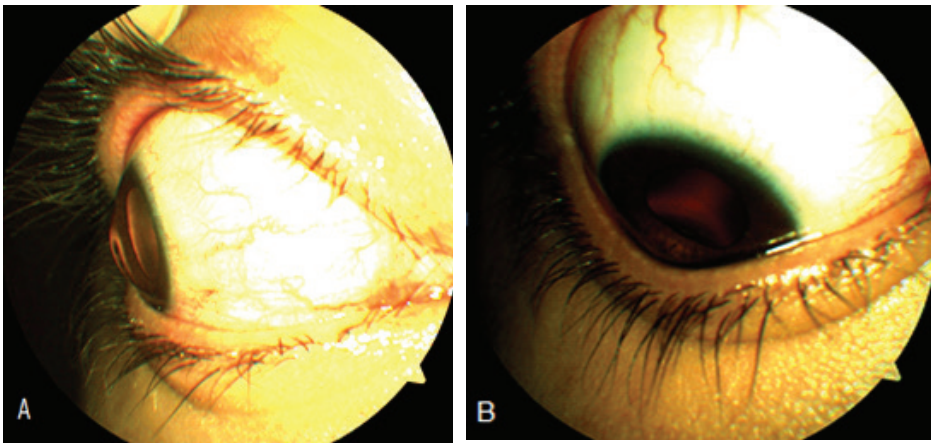


Figure1: (A) paracentral corneal ectasia (B) Munson's sign.

Upper lid eversion showed multiple conjunctival tarsal outgrowth, realizing the classic cobblestone or "paving stone" papillae appearance on both eyes.

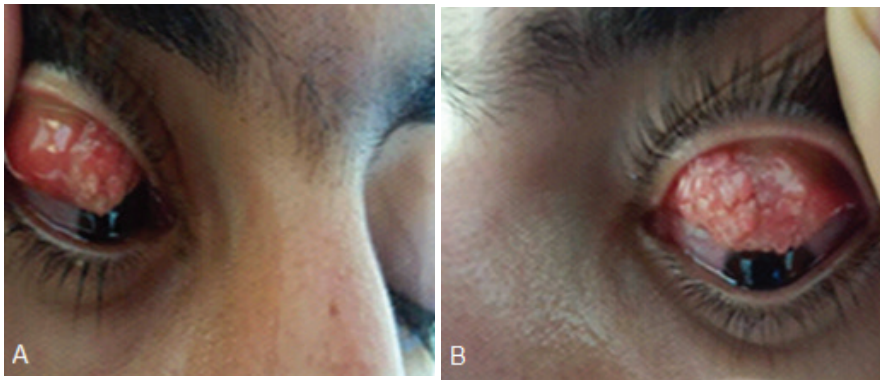


Figure 2 : a cobblestone appearance of tarsal conjunctiva (A)and(B).

Slit lamp exam of the right eye revealed a para central 2x4mm ovulary infero-temporal corneal ectasia ,with thinning of the apex, it also revealed a superficial reticular opacity of the anterior stroma disturbing the optical axis.

Slit lamp exam of the left eye also revealed a paracentral 2x3mm ovular infero-temporal corneal ectasia with thinning of the apex, without opacities.

Shirmer test is normal in both eyes (13 mm OU),Breack up time "BUT" is altered 06 mm on right eye , 7mm on left eye , assesses for evaporative dry eye .

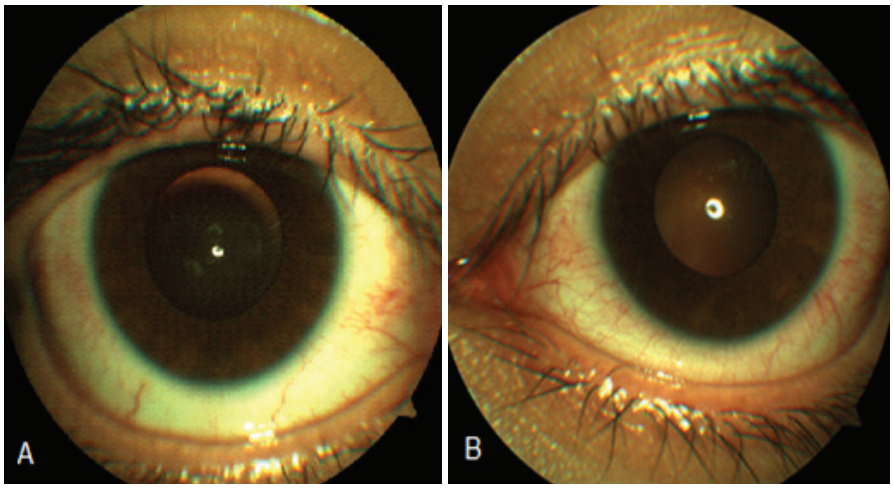


Figure 3: (A) corneal ectasia with central opacity OD /B) corneal ectasia without opacities OS

Corneal topography elevation map confirmed the presence of keratoconus, stage 4 in the right eye (figure 4a) and stage3 in the left eye (figure 4b) according to amsler krumeich classification. Minimum corneal Pachymatry:366 OD, 420 OS

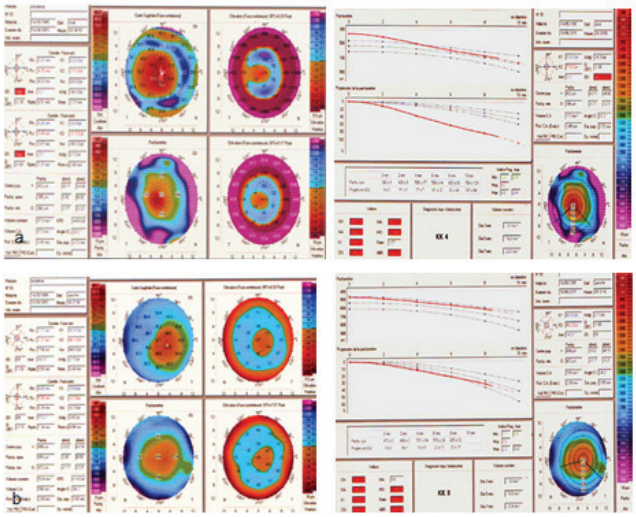


Figure 4: elevation corneal topography: (a) keratoconus stage 4 OD. (b) keratoconus stage 3 OS .

In collaboration with allergist; allergy review and tests were recommended, the results revealed an allergy to mites, which explains the sleeping disorders of the patient who uses a wool pillow.

A full blood panel revealed vitamin D deficiency.

Our therapeutic strategy aimed to cool VKC by proposing; a free preservative high pulse and short term topical corticosteroide "dexamethasone " ; mast cell stabilizers " N-acétyl-aspartyl-glutamate-acid" (NAAGA) , and free preservative artificial tears "carbomere" a long term, in addition of vitamin D supplementation.

After cooling the allergic episode, we opted for a deep anterior lamellar keratoplasty "DALK" (figure 5) on right eye in winter season which provide high visual outcome and long term graft survival.

Topical corticosteroids and antibiotics were administered postoperatively; the follow up was all good, the withdrawal of corneal stitches started after 6 months in regular rhythm.

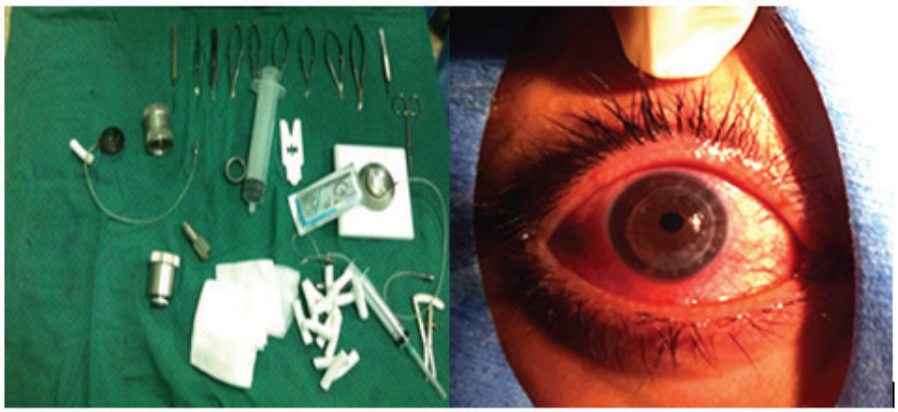


Figure 5: DALK OD.

For visual improvement and astigmatism management of the left eye, it was equipped with rigid gas permeable contact lenses.

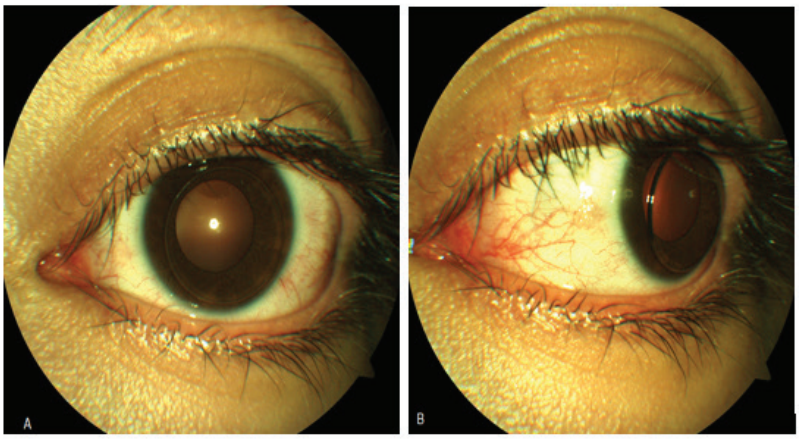


Figure 6: rigid gas permeable lens OS (A)(B).

Few weeks later , the patient presented with acute left eye redness , light sensitivity and mucoid discharge , ocular examination reveals blepharitis with collarettes , diffuse conjunctiva injection +++ and mild chemosis , multiple

peripheral corneal area of infiltrates .

Large spectrum antibiotics therapy was started immediately after scraping the cornea, samples of conjunctiva sac, contact lens, solution and box were sent to laboratory for investigation and culture.

48h later, the clinical presentation was the same, with negative test results. The infiltrates are probably a mechanical complication (CLARE:Contact Lens Acute Red Eye, IK:infiltrative karatitis)of the association contact lens and vernal keratoconjunctivitis We introduced high pulse topical corticosteroides , mast cell stabilizers NAAGA , free preservative artificial tear drops and macrolide with anti inflammatory action "azithromycine".

The patient returned one week later for follow-up with improved symptoms, the epithelial defects were fully closed.

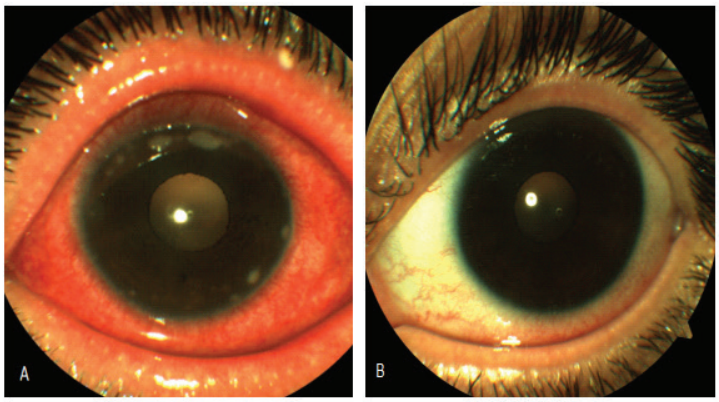
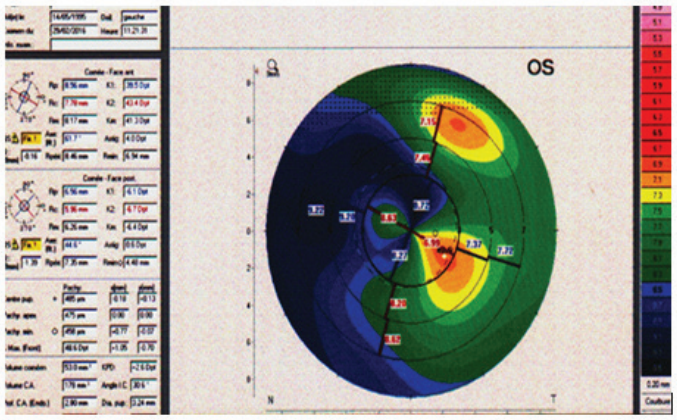


Figure 7: (A) Blepharokeratoconjunctivitis OS before treatment .
(B) OS after treatment

To evaluate the keratoconus course, a second elevation topography was performed 8 months later, which revealed astigmatism aggravation, and maximal keratometry plus 01 dioptrie (figure 8).



To stop the keratoconus course, we opted for a trans epithelial cross-linking flash mode collagen and intra corneal ring segments which aim to restore the cornea curvature and geometry (figure 9A and B).

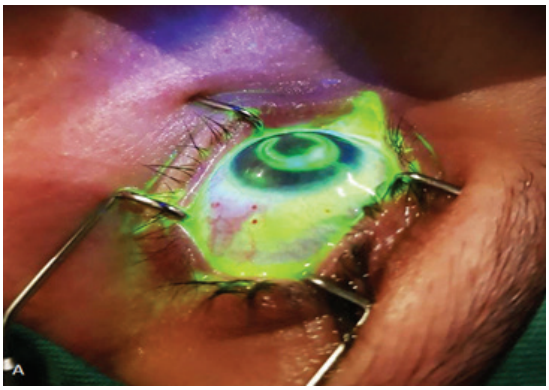


Figure 9A: crosslinking with intra corneal ring segments.

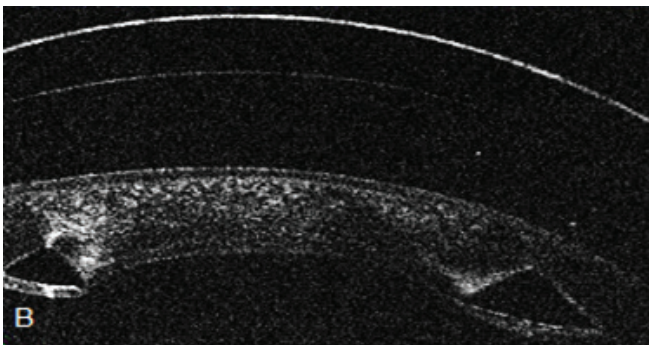


Figure 9B: OCT SA: intra corneal ring segments.

To overcome this rigid contact lens intolerance, second adaptation with scleral contact lens was proposed; the patient reported a significant improvement of visual acuity to 20/20 P2 (figure10A).

The right grafted eye was also equipped with scleral contact lens, as a result visual acuity 20/20 P2 (figure10B).

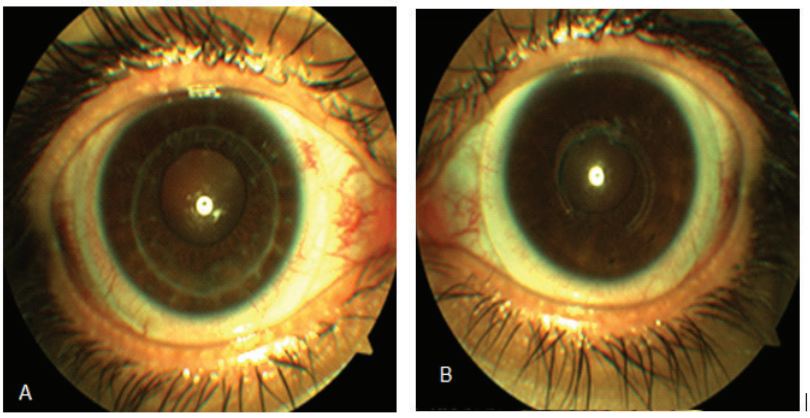


Figure 10: scleral contact lens OD (A) OS (B

★ DISCUSSION ★

It's classic to say that keratoconus is less epidemiologically associated with allergy, multiple studies [5] showed that prevalence of keratoconus in patients with vernal keratoconjunctivitis is about 27% (detected by placido topography).

The origin of this association is still unknown, the pathogenic role of repeated is possible but hypothetical[6], some sleeping positions with prolonged eye support[7] should be banned such as sleeping on the stomach , or laterally with face buried under the pillow.

Another hypothesis is about the interleukin and inflammatory proteases' (IL-6, TNF-a, and MMP-9) role; involved in vernal keratoconjunctivitis and may promote corneal fibroblasts and keratocysts apoptosis, eventually generating collagen damaging and leading to corneal thinning [8].

This association "keratoconus and vernal keratoconjunctivitis "makes the therapeutic approach even more challenging.

The management of VCK is based on high pulse corticosteroids drops for short-term treatment in addition of cool compresses and lid scrubs, free preservative artificial tears and antihistamine [9].

Two studies[10.11] showed a lower 25-OH-Vit D dosage in patients with VKC compared to normal, therefor vitamin D deficiency should be searched in patients with VKC , due to less solar exposure.

Rigid gas permeable lens are the first line treatment for mild and severe cases of keratoconus, as long as the cornea remains transparent [12].

Scleral lenses are used to adapt patients with hard to fit eyes, which are intolerant to the rigid lenses, due to their geometry where no contact with the cornea is needed; they can be used after cornea transplant and for people with severe dry eyes and OSD such as VKC [13].

A part from visual rehabilitation, keratoconus management is based on it course stabilization, the most effective method is the collagen cross-linking, which can be combined with visual rehabilitation techniques such as the intra corneal ring segments. And would reduce the need for corneal grafting [14].

After crosslinking, there is a majoration of cornea hypoesthesia, with gradual return to preoperative values in 03months [15].

Confocal microscopy showed immediate disappearance of corneal nerves after conventional cross-linking, which is much more different and controversial from the trans-epithelial cross-linking [16].

After crosslinking treatment, there is alteration of tears mediators in immediate post operatory; 06months later, there is correlation between tear mediators rate and corneal topography modifications, in contrast with trans-epithelial cross-linking which have no constant influence on dry eye syndrome[17].

★ CONCLUSION ★

It is important to highlight ocular surface problems associated to keratoconus, at either diagnosis, therapeutic care methods or research field in order to better identify the pathophysiology [18].

Indeed, preserving the ocular surface most probably intervenes favorably in this pathological association evolution.

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NEUROTROPHIC KERATITIS, WHEN LESS IS MORE - THE ROLE OF PRESERVATIVE-FREE ARTIFICIAL TEARS

★ INTRODUCTION ★

Neurotrophic keratitis is a degenerative corneal disease caused by impairment of corneal sensory innervation. It is characterized by decreased or absent corneal sensation, leading to epithelial breakdown, impairment of healing, and ultimately to the development of corneal ulceration, melting and perforation.

Ocular and systemic conditions associated with damage at any level of the fifth cranial nerve, from the Trigeminal nucleus to the corneal nerve endings may lead to the development of Neurotrophic keratitis. The most common causes include herpetic keratitis, chemical burns, long-term use of contact lenses, topical anesthetic abuse, corneal surgery, ablative procedures for trigeminal neuralgia, and surgical procedures for reduction of jaw fractures. Systemic diseases that may compromise trigeminal function like diabetes, multiple sclerosis and Leprosy may lead to this entity.

Neurotrophic keratitis is considered to be a rare disease with an estimated prevalence of less than 5/10,000. It is estimated that neurotrophic keratitis affects 6% of herpetic keratitis cases, 12.8% of Herpes zoster keratitis cases and 2.8% of patients who underwent surgical procedures for Trigeminal neuralgia.

Corneal nerves play an important role in maintaining corneal epithelial integrity, proliferation and wound healing. It has been postulated that corneal sensory nerve damage leads to marked changes in levels of neuromodulators, that cause impairment in epithelial cell vitality and metabolism. There is an associated reduction in lacrimation reflex with sensory nerve involvement, triggering a vicious circle in which tear film dysfunction worsens the prognosis. The resulting morphological and metabolic epithelial disturbances lead to the development of recurrent or persistent epithelial defects, which can progress to corneal ulceration, melting and perforation.

Patients with Neurotrophic keratitis rarely complain of symptoms, probably due to their lack of corneal sensation. Occasionally, however, they may present with redness and blurring of vision.

Neurotrophic keratitis can be classified into three stages according to the Mackie classification. Stage 1 is characterized by corneal epithelial changes with dry and cloudy corneal epithelium, the presence of superficial punctate keratopathy, and corneal edema. Stage 2 is characterized by recurrent and/or persistent epithelial defects with an oval or circular shape, most frequently localized at the superior half of the cornea. Stage 3 is characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation.

Antecedent episodes of redness and eye pain or the presence of cutaneous blistering or scarring suggest previous herpetic infections. A history of corneal trauma, surgery, chemical burns, long-term use of topical medications, neurosurgical procedures, or diabetes may be obtained.

The presence of systemic diseases (Diabetes Mellitus), medication use (Neuroleptics), and corneal causes must be evaluated. Clinical evaluation of different cranial nerve functions may help in localization of the site of the lesion. Associated seventh or eighth nerve palsy may be an indication of Acoustic neuroma or its surgical resection causing Trigeminal nerve damage. Associated third, fourth, and sixth nerve palsy may point to a Cavernous sinus pathology. Assessment of the cornea includes a quantitative evaluation of decreased corneal sensation using a Cochet-Bonnet or no-contact gas esthesiometer. Slit lamp examination can be of great help for identifying the characteristic corneal lesions and for sector iris atrophy, which is characteristic of herpetic infections. An ulcer, if seen, requires microbiological examination to rule out an infection. Dilated fundus examination may reveal pale or swollen optic disc in cases of intracranial tumors with trigeminal compression. The eyelids need to be examined, both for diagnostic and prognostic reasons.

Early diagnosis, treatment and careful monitoring of neurotrophic keratitis patients are mandatory to achieve epithelial healing and prevent progression of corneal damage.

Stage 1 neurotrophic keratitis is mainly managed with preservative-free artificial tears, stage 2 with conjunctival flap and partial tarsorrhaphy for the persistent epithelial defects, and stage 3 with therapeutic contact lenses and

amniotic membrane transplantation.

The use of preservative-free artificial tears may help improve the corneal surface at all stages of disease severity.

In the event of stromal melting, use of topical collagenase inhibitors, such as N-acetylcysteine, and systemic administration of tetracycline or medroxyprogesterone may be considered.

Use of topical antibiotic eye drops to prevent infection in eyes with neurotrophic keratitis at stages 2 and 3 are recommended.

Topical nerve growth factor (NGF) and autologous serum eye drops are considered as promising treatments of neurotrophic keratopathy.

Surgical treatments are reserved for refractory cases. They include partial or total tarsorrhaphy, amniotic membrane transplantation, conjunctival flap, and Botulinum A toxin injection of the eyelid elevator muscle

Corneal perforations may be managed with cyanoacrylate glue application, conjunctival flap or lamellar/penetrating keratoplasty.

★ CASE REPORT ★

A 73 year old female, previously healthy, with no ocular history, underwent left eye cataract surgery on May 2016. Two months after, on June 2016, recur in an ophthalmologic emergency service with left eye reddeness , accompanied by pain and photophobia. An Herpetic Keratouveitis episode was diagnosed and treated with a 4 week combination of Ganciclovir ophthalmic gel 1.5mg/g 5id, plus Tobramycin ophthalmic solution 0.3% 5id associated with the non-steroid anti-inflammatory Nepafenac ophthalmic suspension 0.1% 3id.

After a good initial clinical response, she came back on the same emergency service on August 2016 complaining about red eye plus diminished visual acuity this time. At this moment, the whole situation had evolved and a Geographic ulcer was inferred.

Patient was then referenced to Ophthalmology department, Centro Hospitalar e Universitário do Porto (CHUP).

On admission in our service, the patient had ocular discomfort accompanied with photophobia, with an uncorrected visual acuity (UCVA) of counting fingers (CF). On slit lamp examination cornea had an extensive central ovalized ulcer with stromal edema and Descemet folds; anterior chamber had Tyndall 1+ and fine keratic precipitates (KP's); in addition we found posterior capsule opacification (PCO). Intraocular pression measured was 14mmHg. Fundus observation was normal, besides difficulties due to media opacification.

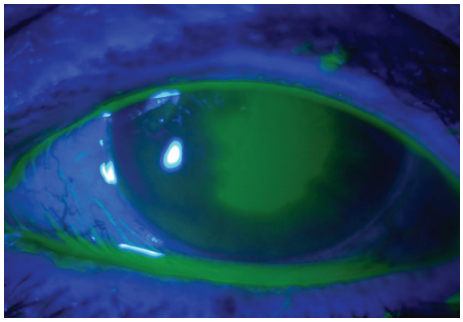

Figure 1. First evaluation

The post-herpetic keratitis state plus long topical aggressive treatment in addition with this clinical picture, made us suspect of Neurotrophic keratitis, with ulceration.

Was then decided to stop all 3 medications and initiate a new treatment approach based on a preservative-free tear drop – Sodium Hialuronate0.15% & Trehalose3% - hourly, accompanied by an infectious prophylaxis with Ofloxacin 3mg/ml unidosis qid plus Oral Valaciclovir 500mg tid.

Right after 4 days the patient experimented rapid clinical improvement. On slit lamp examination only a diffuse superficial punctate keratitis (SPK) persisted and less corneal edema with only a few Descemet folds; anterior chamber had cells 1+ and maintained fine KP's. Intraocular pression remains stable: 14mmHg. A better fundus examination was made this time, with the certainty of a normal exam.

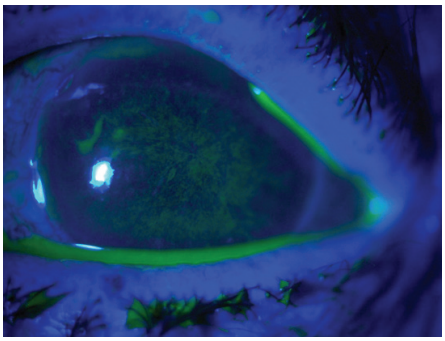

Figure 2. Second evaluation

Ofloxacin was stopped with the maintenance of the Sodium Hialuronate0.15% & Trehalose3% hourly-based scheme plus Oral Valaciclovir tid. To combat the mild residual inflammatory state, Fluorometholone ophthalmic suspension 0.1% qid was initiated.

Patient was evaluated 10 days after. No symptoms were noted and UCVA increased to 20/100. Slit lamp examination showed SPK focalization with mild corneal haze and no associated edema; anterior chamber maintained only mild fine KP´s with no cells. Even so, media opacification was still given by PCO. Intraocular pressure remained stable -13mmHg- and fundus examination normal.

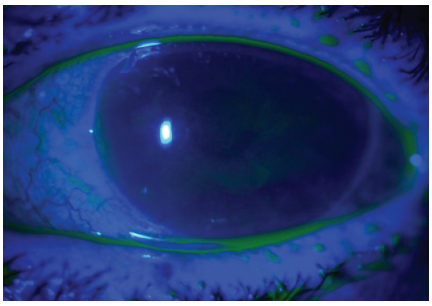

Figure 3. Third evaluation

Figure 4. Third evaluation

At this time, we decreased Sodium Hialuronate0.15% & Trehalose3% frequency to qid and Oral valaciclovir 500mg was reduced to prophylaxis dosis of id. Fluorometholone ophthalmic suspension 0.1% qid was maintained.

A new outpatient visit occurred 20 days after. Clinical stabilization was achieved, with no symptoms reported and a BCVA of 20/40 – refraction +1.25*170°. The only signs on slit lamp examination were a slight corneal haze and the posterior capsule opacification. Then we decide to maintain Oral valaciclovir 500mg id and taper Sodium Hialuronate0.15% & Trehalose3% and Fluorometholone ophthalmic suspension 0.1% to tid.

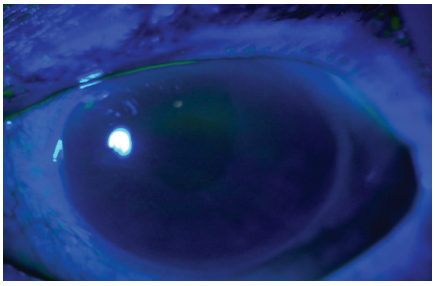

Figure 5. Fourth evaluation

After four months, corneal transparency is maintained, with BVCA of 20/40

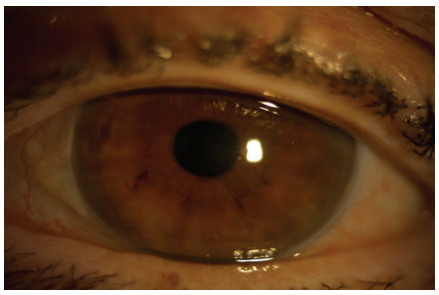

Figure 6. Fifth evaluation

★ DISCUSSION ★

Neurotrophic ulcers are more common among patients who underwent herpetic ulcer.

Sometimes differential diagnosis between them is difficult.

This patient underwent aggressive and prolonged topical treatment for a refractory herpetic ulcer with anti-infectious and anti-inflammatory drugs that can lead to various forms of corneal pathology.

In fact, Ganciclovir ophthalmic gel 1,5mg/g, Nepafenac ophthalmic suspension 0,1% and Tobramycin 3 mg/ml are very effective and safe drugs widely used nowadays, of which epithelial toxicity have been reported in literature, including neurotrophic keratitis.

With high clinical suspicion on a neurotrophic ulcer stage 2/3, we decided to take a "less is more" approach. Instead of perform an invasive procedure, like an amniotic membrane graft, we stop all 3 medications and initiate a new treatment approach based on a preservative-free tear drop – Sodium Hialuronate0.15% & Trehalose3%, accompanied by an infectious prophylaxis with Ofloxacin 3mg/ml unidosis plus Oral Valaciclovir 500mg tid.

In just a few days, the refractory ulcer closed. With a careful monitoring, we tapered and maintained the preservative-free tear drop, and viral prophylaxis and added a corticosteroid to combat residual inflammation.

We achieved complete rapid clinical response of a prolonged refractory ulcer wrongly handled as a herpetic ulcer only by suspending potentially toxic medications and monitoring natural corneal healing.

All the current therapeutic approaches focus on preventing the disease progression, but there are none to improve the corneal sensation and visual acuity. However, use of topical nerve growth factor derivatives and an Ergoline derivative, called Nicergoline are promising approaches in improving corneal sensation and thus extremely beneficial in patients who fail to respond to conventional therapy.

★ CONCLUSION ★

Although uncommon, topical ocular drugs may cause corneal toxicity, including neurotrophic ulcers, more commonly when several classes are added during long cycles in fragile corneas, as in the case of herpetic keratitis. It is important to consider this differential diagnosis in cases of prolonged non-responding ulcers.

In cases of mild and moderate ulcers, is important to stop all aggressions and not forget that an intense preservative-free lubrification regimen with tight monitoring can be enough and save the eye from invasive procedures.

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BILATERAL AND SIMULTANEOUS FUNGAL KERATITIS WITHOUT PREDISPOSING FACTORS

★ INTRODUCTION ★

Fungal keratitis (FK) constitute an important cause of corneal infection. It is reported in one-third of all cases of suppurative keratitis in tropical parts of the world[1]. The infection with FK can be more virulent and damaging compared to that of a bacterial origin[2].

Simultaneously occurring bilateral fungal keratitis, without predisposing factors is rarely reported. Generally, the bilateral keratits, occurs in certain predisposed individuals[3]. These include ocular trauma, contact lens use, ocular surface disease ,topical corticosteroid use, and history of prior corneal surgery[1,3].

We report the case of a 50 year-old- male without any obvious predisposing factors who had simultaneous bilateral fungal keratitis.

★ CASE REPORT ★

A 50-year-old male presented to our ophthalmology department with redness, pain, photophobia, and defective vision since 08 days in the right eye and since 05 days in the left eye (figure1).There was no previous ocular history, trauma, contact lens wear, systemic illness. However, the patient used corticosteroid eye drops twice a day prior to consultation, purchased at a local pharmacy.

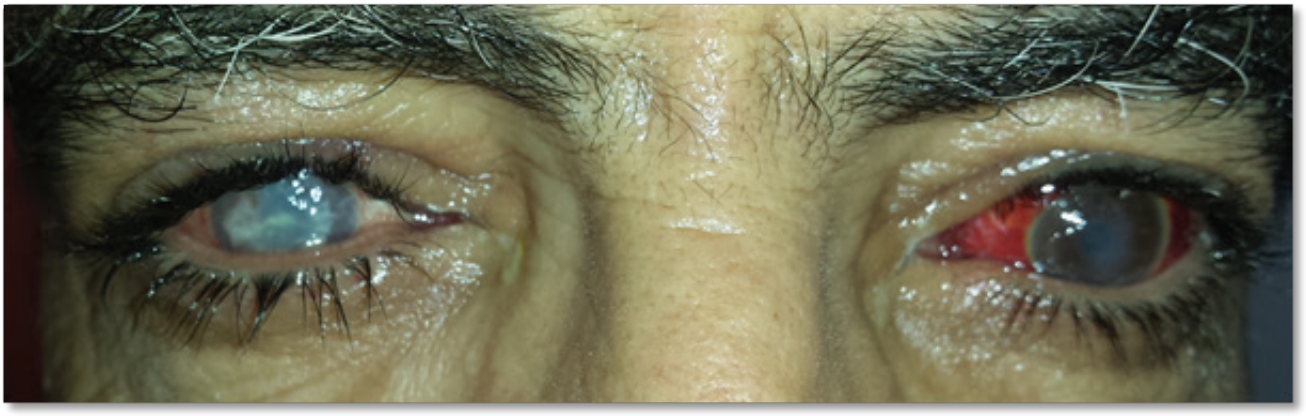

Figure1: clinical evocative presentation of a fungal keratits, in the both eye

Examination of the eyes revealed visual acuity of hand movements close to face in the right eye and finger counting at two metres in the left eye. On slit lamp biomicroscopy, he had in the right eye, a deep stromal infiltration with peripheral satellite micro abscess and a central ulcer; its diameter was 8mm / 6.5mm without hypopion [figures2]. In the left eye, the patient had an anterior stromal infiltration and an ulcer measuring 2,8 mm/1,2 mm without hypopion [figures3].The fundus examination of both eyes was difficult. However, B-scan ultrasonography showed no vitreoretinal pathology.

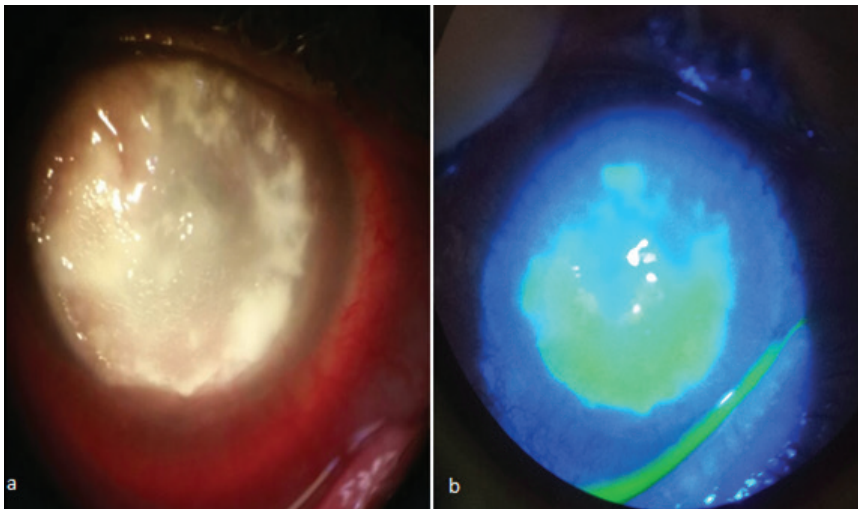

Figure2: Clinical picture of the right eye at initial presentation. There is marked deep stromal infiltration with peripheral satellite micro abscess[a] and a central ulcer[b].

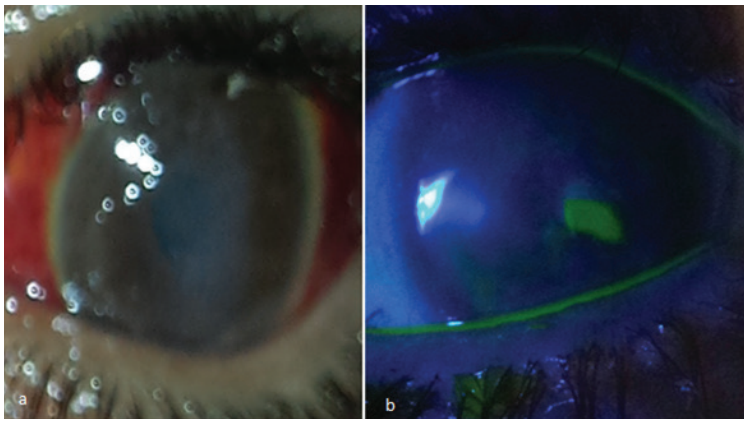

Figure3: anterior stromal infiltration [a] and a central ulcer[b] in the left eye at initial presentation.

In view of the unusual presentation, we performed an investigation of immunosuppression and any systemic focus of infection. Human immunodeficiency virus serology and blood cultures were negative. Blood counts, liver,function tests, renal function tests and blood sugar levels were all within normal limits.

Based on the clinical evocative presentation of a fungal abcess, the patient was treated with antifungal including topical voriconazol 1% at hourly intervals for the initial seven days, thereafter at two-hour intervals and oral fluconazol 200mg twice a day. A local treatment with artificial tears was associated. Corneal scrapings and a conjunctival swab from both eye confirmed the presence of Candida.

One week after initiating medication, the evolution was marked by regression of the redness, disappearance of the ulcer at both eyes, the corneal infiltration was reducing in the left eye but not in the right eye.

After 15 Days , the corneal infiltration in the left eye continue its regression [figure4] but still the same in the right eye. We decide to perform an intrastromal injection of voriconazole in adjunction to the topical antifungal therapy.

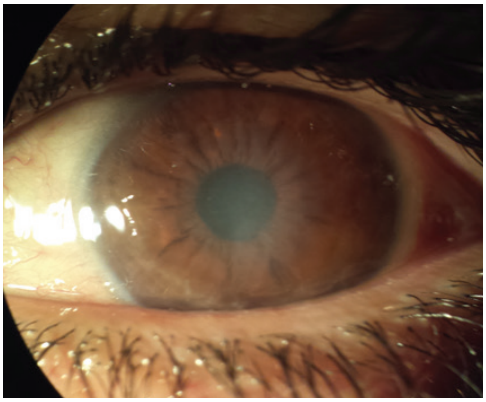

Figure 4: Clinical picture of the left eye 15 days after topical and oral antifungal therapy. Infection resolved completely.

The infiltration in the right eye decreased gradually after one week of the injection and completely disappear one month later [figure5].

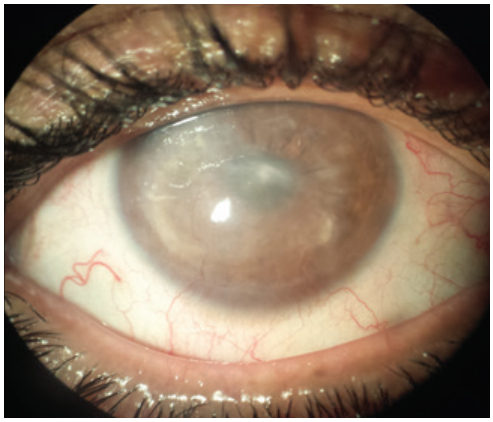

Figure 5: Clinical picture of the right eye one month after intrastromal injection of Voriconazol. Infection resolved completely.

Finally the visual acuity of the left eye improved to 8/10 but in the right eye the patient retained a scarred opacity with superficial neovascularisation and a visual acuity that remaind at finger couting at five metres, for which a corneal graft is programmed [figure6].

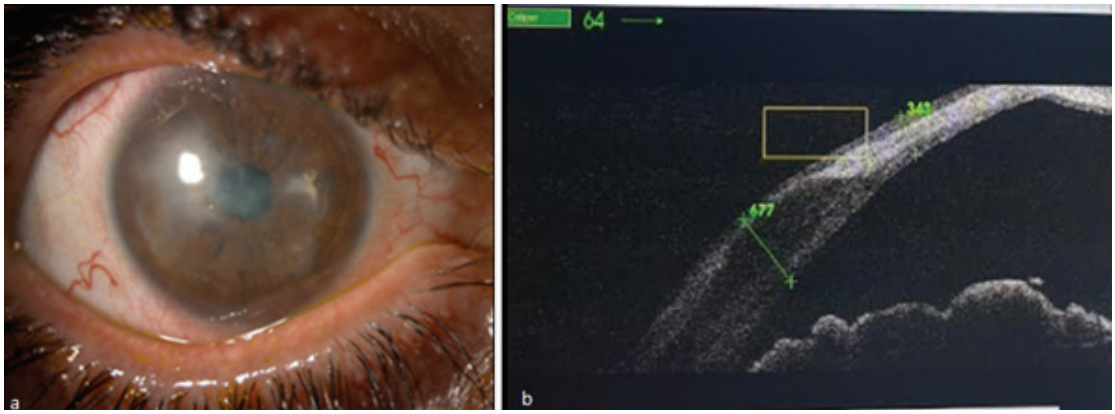

Figure 6: a:Clinical picture of the right eye 5 months after treatement: corneal opacity with superficial neovascularizationon.
b: the junction between the normal cornea and corneal opacity on AS-OCT

★ DISCUSSION ★

Bilateral fungal keratitis usually occurs in individuals with apparent risk factors[1]. These include ocular trauma, contact lens use, ocular surface disease, topical corticosteroid use, and history of prior corneal surgery. In addition to that, people who have diabetes, weakened immune system[1,2,4,5]. There has only one report of bilateral keratitis caused by Pseudomonas aeruginosa developed in the absence of any obvious predisposing factor[4].

Simultaneous occurrence of bilateral fungal keratitis after LASIK is extremely rare[6]. Predisposing factors include history of corneal surgery, break in the epithelial barrier, intraoperative contamination, excessive surgical manipulation, delayed postoperative reepithelialization of the cornea, and use of topical steroids[7]. It may be difficult in some cases to distinguish between infective infiltrates and postoperative inflammatory response.

Another predisposing factor of bilateral fungal keratitis is contact lense use. Infections secondary to the use of contact lenses are most often related to bacterial pathogens[8]. Although less frequent, fungal keratitis, is a recognize risk of contact lenses users. Recently, fungal infections due to an epidemic of Fusarium keratitis combined a brand of contact lens solution, create an increased interest. Generally contact lens solutions are more effective against bacteria rather than fungi[9]

Our patient had none of the usual predisposing factors for bilateral fungal keratitis. what could explain bilaterality of the infection? To respond to this question, we performed a biological investigation of immnusuppression ,wish proved negative.

Filamentous fungi, such as Fusarium and Aspergillus, and yeast-like fungi, such as Candida, are most commonly associated with keratitis[2]. In our case, the Microbiological examination of a corneal scraping confirmed the presence of Candida in both eyes. In fact, Candida Albicans and related fungi are implicated in keratitis, and specially when systemic illness such as immunosupression or diabetes mellitus, or such as complicated chronic ocular surface are present as factors . The simultaneous occurrence of bilateral fungal keratitis, caused by two different fungi has been reported in one case. One eye was affected by Aspergillus and the fellow eye was affected by Curvularia[12].

Therapy of fungal infections, can be difficult and prolonged. Our patient has been treated by topical and oral Voriconazol. The choice of voriconazol in first intention is based on its high bioavailability and its broad spectrum of activity[13]. In the right eye, our patient has deep fungal keratits wich it didn't responds to topical antifungal therapy , but when received intrastromal injections as adjunctive therapy, the resolution of infection was complete. This proves that intrastromal injection is more effective than topical drops in treatment of resistant fungal keratitis especially that with deep infiltrations.

Solaiman et al concluded that Voriconazole eye drops might be effective for treatment of deep and/or resistant fungal keratitis[14]. Adding intrastromal injection to topical drops provides maximum concentration of the drug at the target site and this increases its killing effect.

★CONCLUSION ★

To our knowledge, this is the first reported case of bilateral fungal kiratits developed in the absence of any obvious predisposing factor. In this situation, the diagnosis must be rapid to ensure prompt treatment and save such eyes.

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PERFORATED CORNEAL ULCERATION ASSOCIATED WITH RHEUMATOID ARTHRITIS

★ INTRODUCTION ★

Rheumatoid arthritis (RA), a chronic systemic autoimmune inflammatory entity, is considered one of the most common collagen vascular diseases. 3-5% of the adult population is affected, more frequently women than men with an average age of onset 35-40 years.[1] It is characterized as an erosive, symmetric synovitis with multiple extra-articular manifestations.
The eye occupies a special place since RA can affect the anterior segment causing keratoconjunctivitis sicca, punctate keratopathy, keratitis, episcleritis and scleritis, the extraocular muscles, and even the posterior segment (choroid, retina or optic nerve)[1]. An overwhelming number of 90% of patients with RA suffer from dry eye syndrome especially keratoconjunctivitis sicca[2] and there seems to be a correlation between a disease course longer than 10 years and the presence of dry eye syndrome.
Regarding corneal involvement many types of keratitis have been described such as peripheral limbal furrow, peripheral or paracentral ulcerative keratitis, keratolysis, acute stromal keratitis or sclerosing keratitis.

The pathophysiology of rheumatoid-associated corneal ulceration is far from being fully elucidated. It seems to be an imbalance between metallo-proteinases(MMP) such as MMP-2 in the corneal stroma and MMP-9 in the lacrimal glands and tissues inhibitors metallo-proteinases (TIMP-1)[1]. Reduced levels of TIMP-1 are responsable of high collagenase activity that leads to a keratolytic sterile process[2]. A resulting altered epithelial barrier facilitates the entrance of inflammatory mediators in the stroma such as monocytes and macrophages that subsequently determines the activation is T-cells, leading to production of antibodies and formation of immune complexes. There seems

to be a significant HLA-DR expression by stromal keratocytes and epithelium determined by interferon-° realesed by TH2 lymphocites[1]. Local cytokines such as Interleukin-1 and tumour necrosis factor-alpha induce production of collagenase and protease3. The paracentral ulcerative keratitis develops in patients with severe dry eye but without marked conjunctival inflammation.

Dealing with a rheumatoid-associated perforated corneal ulceration is a difficult task. Of utmost importance is treatment or just prophylaxis of infection, and in the meantime reducing the inflamation and promoting the repair.[1] Probably the systemic immunosuppression must be revised.

★ CASE REPORT ★

A 73-year-old female patient with a 13 year history of rheumatoid arthritis presented intense pain in her left eye (LE), red eye and the sensation of a hot leakage on her cheek approximately 12 hours before hospital admission. In the last 3 weeks she was treated with gentamicine drops and indomethacin drops for a previously diagnosed corneal ulceration LE.

Her general medication at presentation was immunosuppressive therapy (methotrexate 2.5 mg 3 times a week) and NSAID (as needed) and topically free-preservatives lubricants for her dry eye syndrome.

On examination her visual acuity was 20/32 RE and 20/630 LE. The slit lamp examination reavealed RE subtle conjunctival congestion with stromal opacities (Figure 1) and LE ciliary injection, a perforated paracentral corneal ulceration of approximately 1mm with a dense perilesional infiltrate, with stromal melting, a few corneal new vessels and stromal opacities around (Figure 2). The pupil was peaked but reactive and the iris was plugging the perforation.

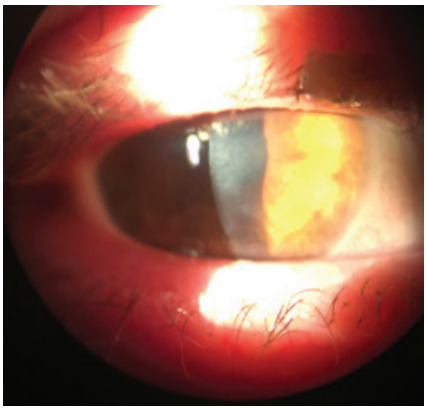

Figure 1.Slit lamp RE: stromal opacities

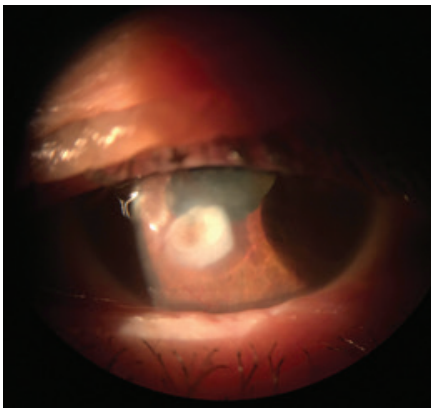

Figure 2.Slit lamp LE: paracentral corneal ulceration

A shallow almost flat anterior chamber with a clear aqueous humour was found (Figure 3). No abnormality was noted in the fundus examination of the both eyes. We performed an anterior segment OCT(Heidelberg Spectralis) which pointed out the inclavated iris in the ulceration zone and a thin cornea. (Figure 4).

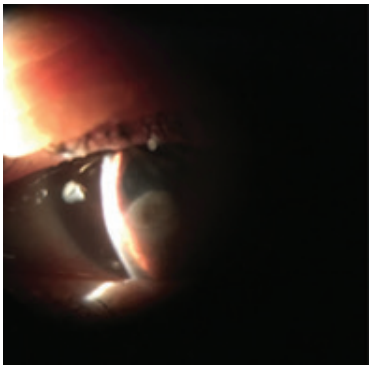

Figure 3.Shallow anterior chamber

Figure 4. Anterior segment OCT showing the iris plugging the perforation and the thin cornea

Ophthalmology evaluation was consistent with a corneal paracentral perforation secondary to severe dry eye attributed to rheumatoid arthritis.

General treatment with Ceftriaxone was initiated 1 g every 12 hours, and topical medication was modified to tobramycine hourly, dilatation with tropicamide and phenylephrine 5 times a day, lubricants and occlusive patch.

Evolution under treatment was stationary without signs of improvement. 5 days after admission cyclosporine 1mg/ml was added to the topical treatment and it was administered 1 drop a day in the evening. The treatment with Methotrexate 7.5 mg/week was continued. Meanwhile LE visual acuity started to improve to 20/63, the perilesional infiltrate decreased in size and depth, the iris was liberated from the perforation and the corneal transparency was improving. (Figure 5)

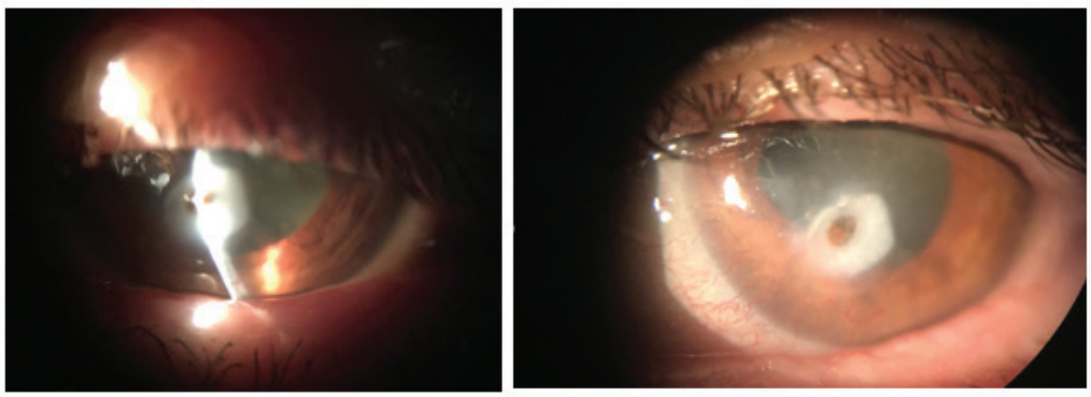

Figure 5.Slit lamp LE after 5 days of topical cyclosporine.
a)AC depth increased, iris was liberated
b) perilesionl infiltrate decreased and a diminished corneal oedema

Anterior segment OCT revealed an impending 100µm minimal corneal thickness at the site of perforation.(Figure 6)

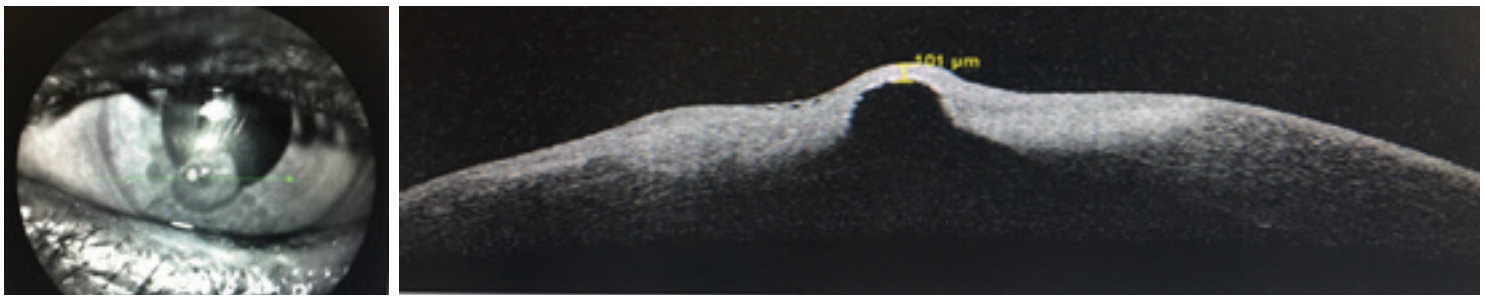

Figure 6.Anterior segment OCT LE: 101µm minimal corneal thickness

The danger of this sight-threatening situation required rheumatologist expertise. Taking into account the lack of general symptoms and the normal values of C reactive Protein and ESR, neither pulse theraphy with metilprednisolone, nor ciclophosphamide addition were considered necessary.

Fortunately, the aspect of the ulceration improved and the infiltration gradually diminished. At discharge her visual acuity LE was 20/25 and the patient was free of symptoms (Figure 7). We performed a Schirmer test without anesthesia RE and the result was 1mm at 5 minutes.

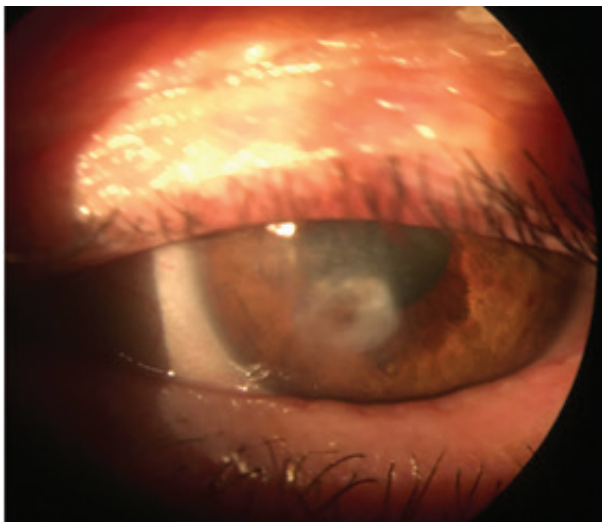

Figure 7.Slit lamp LE aspect: closed ulceration with a diminished perilesional infiltrate

We performed another anterior segment OCT which surprisingly showed an increased minimal corneal thickness from 100µm to 250 µm.

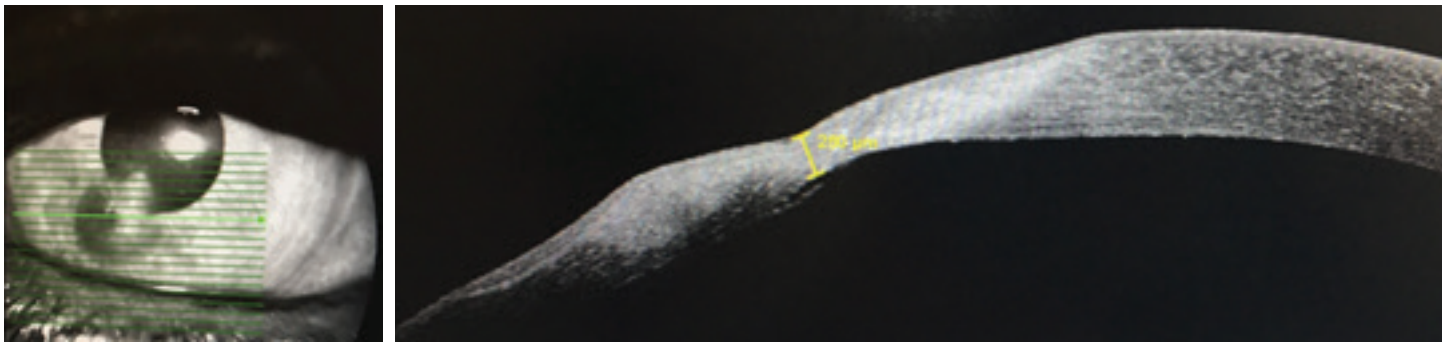

Figure 8. Anterior segment OCT LE: increased minimal corneal thickness 250 μm.

After beeing discharged the patient continued topical treatment with tobramycine 3 times/day and cyclosporine 1mg/ml 1 drop/day every evening and free preservatives lubricants.

★ DISCUSSION ★

We brought into discussion a complex case of perforated corneal ulceration secondary to Rheumatoid arthritis which we managed to treat satisfactorily by medical approach. The previously diagnosed dry eye syndrome in the context of RA, even under treatment with free-preservative lubricants, favored the ulceration development. There are studies showing that the corneal central thickness and stromal thickness in patients with RA were statistically significantly lower than in the control group[4]. Additionally, there is evidence of proteolytic degradation in both corneas of patients ranging from early xerophthalmia to ulcerating xerophthalmia.[5]

The use of NSAIDs in our case, both systemically and topically, is questionable. There have been case reports with patients taking NSAIDs who developed corneal perforation that healed after discontinuation.6 Moreover, it has been proved that topical NSAIDs determine corneal hypoesthesia and can cause corneal perforation.[1,2]

A difficulty in addressing the case was understanding its etiology. Were we dealing with an ulcerative sterile keratitis, a ulcerative keratitis with a secondary infection or an infective keratitis alone?7. Considering the outcome after topical cyclosporine, the inflammatory component could not be excluded. On the other sider, treating the condition purely as a autoimmunity corneal melt without antibiotic coverage can result in a potentially blinding condition.

For logistical reasons we did not have the possibility to perform corneal scraping and therefore we choosed a broad-spectrum antibiotics topically and systemically.

The initiation of topical cyclosporine therapy was the mainstay given the fact it arrested the keratolysis and determined re-epithelization of the ulcer4. There are several reports that recomand topical cyclosporin in corneal ulcer associated with rheumatoid disease8, as it may enable epithelial healing while reducing cell-mediated immune reactions in the cornea.1 Regarding the systemic chemotherapy in rheumatoid corneal perforations there are no clear guidelines, but a strong collaboration between ophthalmologists and rheumatologists is mandatory to asses the systemic disease status and to decide the need to change or readjust the immunosuppression therapy .

Although the patient was on immunosuppressive treatment and free of systemic symptoms, she developed corneal ulceration, highlighting the fact that there are several events that initiate the corneal modifications and others perpetuating them, such as infection that accelerates the corneal melting.9

In cases with perforation, the application of cyanocryalate adhesive, lamellar grafting or tarsorraphy are indicated, depending on ulceration size. In our case, the presence of the iris in the ulceration played the role of a self-adhesive substance.

Nevertheless photographies of the lesion were helpful in evaluating regression. Anterior segment OCT images were particulary important, highlighting the anatomical improvement.

★ CONCLUSION ★

Corneal perforated ulceration is a rare complication secondary to RA. This case signals and demonstrates the importance of effective control of the underlying disease and properly treatment of dry eye syndrome in RA patients. In the event of a perforated corneal ulceration, NSAIDs administered topically may cause negative effects, but cyclosporine associated with antibiotics administered topically and systemically have great chances to determine good visual outcome.

Anterior segment OCT has demonstrated its valuable role in monitoring the disease from an anatomical point of view.

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AGE AND GLAUCOMA MEDICATION RELATED OCULAR SURFACE DISEASE

★ INTRODUCTION ★

Ocular surface disease is combination of insufficient and improper lubrication of ocular surfaces and chronic inflammation in the ocular surface organs. Their appearance increases with age. Every eye drop is potential irritator, including glaucoma drops. Glaucoma is chronic disease and glaucoma drops are used every day for dozens of years. Many glaucoma patient suffers from ocular surface problems and this weakens their commitment to treatment. My presentation is quite typical of that kind of case.

★ CASE REPORT ★

81-year old lady with arterial hypertension. Glaucoma since 2010. Patients dad and uncle also had a glaucoma.

2010 - In the beginning

Initial IOP was 25-29/21-29, and visual field in right eye was moderately affected, while left eye was in normal limits. Right optic nerve head was moderately damaged. Visus 0.8/0.8. Bimatoprost once a day started before diagnosis and continued after diagnosis.

2011-2013 - "Let's try another medication..."

Due to ocular surface problems many medication exchanges:

- Bimatoprost
- Travoprost + dorzolamide
- Tafluprost + brinzolamide

2014 - Laser year

Selective laser trabeculoplasty I/2014.

2015 - Holy lump, progression!

I/2015 visual field progression, IOP 18/16 (tafluprost + brinzolamide), preservative allergy. Drug exchange to bimatoprost + timolol preservative free combination. BCVA 0.4/0.8.

IV/2015 o.dx phaco + IOL.

VI/2015 BCVA 1.0/0.63. TA 12/14, visual field better than before cataract surgery, but still desired for lower IOP => Laser trabeculoplasty VII/2015.

IX/2015 TA 12/11. BCVA 1.0/0.63. Trichiasis on both side, severe chronic conjunctivitis. Drug exchange to tafluprost + timolol.

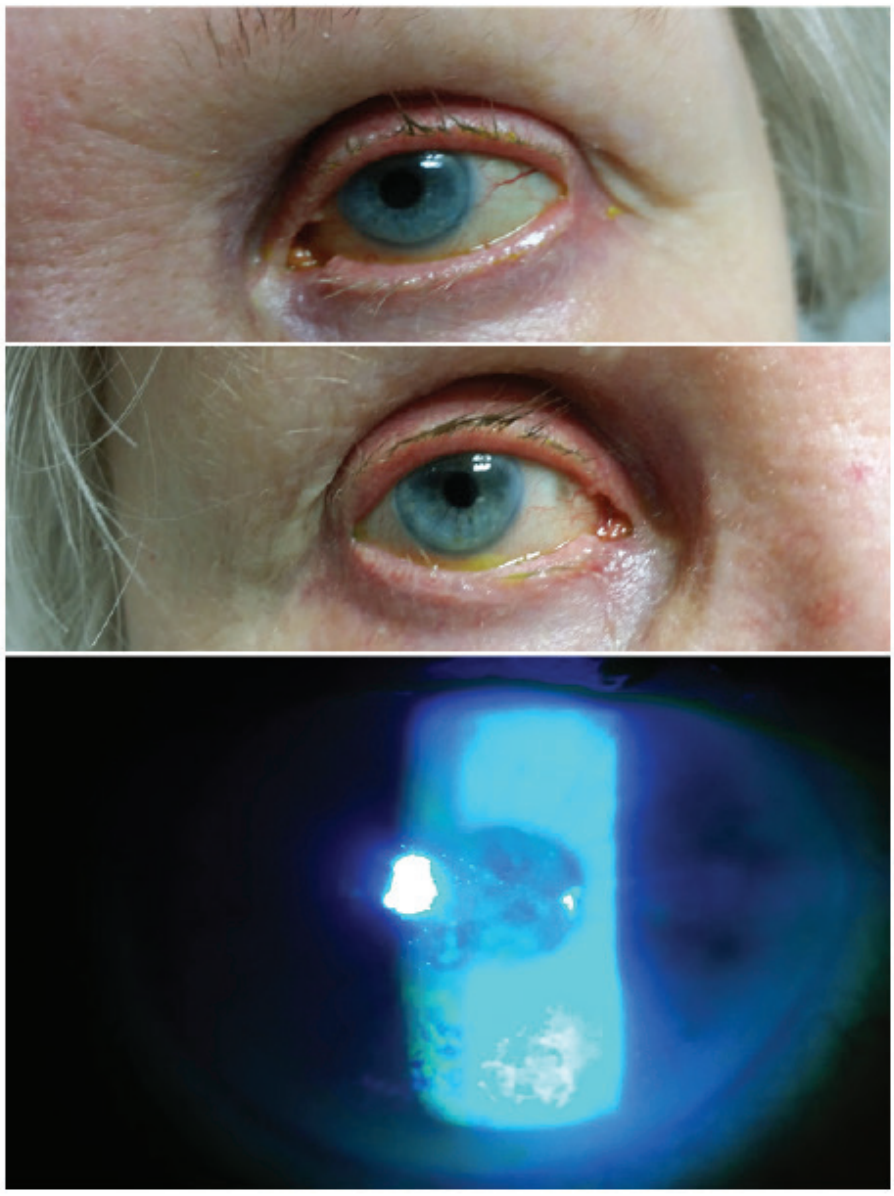
2016 - Hard balls on fire

I/2016 TA 14/14. Due to insufficient IOP lowering effect and because the effect to ocular surface didn't impress, medication exchanged back to bimatoprost + timolol.

2017 - "My optic nerve is useless, if I wanted to dig my eyes on me?"

VIII/2017 BCVA 1.0/0.8. TA 11/12. Severe blepharitis, trichiasis. Chronic conjunctivitis. BUT < 5s. Visual fields: no progression. Removed turned eyelashes. Removed bimatoprost + timolol -combination from treatment and changed to preservative free latanoprost. Planning to add preservative free

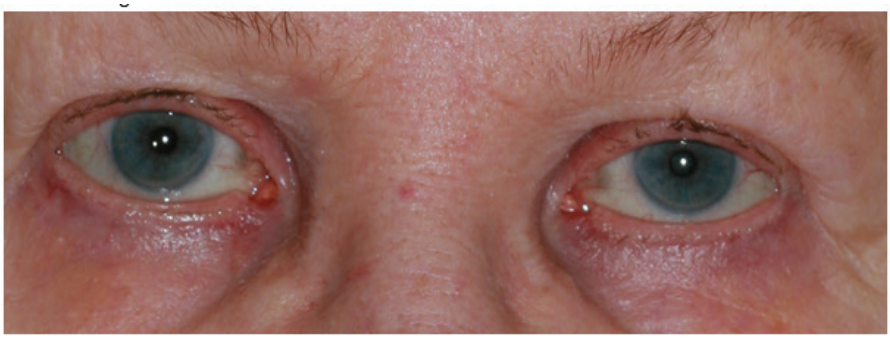
timolol or timolol + CAI -combination when ocular surfaces are better. Also described azithromycin 1x2 six days to both eyes to decrease inflammation.



X/2017 - "I saw the gates of heaven, then I turned back..."

Still had reddness in the eyes, but discomfort had gone away. Sadly, when one one-month-pack of Monoprost was used, patient decided to use Ganfort instead, because "I didn't know I should use it longer".

TA 12/12, BCVA 1.0/0.8. BUT was significantly better than one month before, but redness was unchanged.



★ DISCUSSION ★

Patients adherence to long term treatment is important. Side effects of the drug doesn't help the compliance. It's important to select as gentle treatment as possible. Preservative eye drops can be considered as old-fashioned choice for glaucoma treatment. Preservative-free glaucoma drops are investment to the future for glaucoma patients.

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