TROPHY CONTEST

THEA INTERNATIONAL CONTEST OF CLINICAL CASES IN PATHOLOGIES OF THE EYE

EDITION 2016 - 2017

NON-SURGICAL TREATMENT OF CORNEAL DISORDERS

CLINICAL CASES

WWW.THEA-TROPHY.COM

Thea
Driving innovation

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 Théa has sponsored the European Meeting of Young Ophthalmologists (EMYO) since their first meeting in 2014, and is also a close partner of the European Board of Ophthalmology (EBO) and the European association for Vision and Eye Research (EVER).

In 2012, Théa launched "TROPHY", the "Théa euRopean 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. Due to its success, the contest has been opened to countries outside Europe and has now become "inteRnational". Since the creation of the contest in 2012, we have had 15 winners from 8 countries.

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

Each year, more and more participants are competing for the chance to submit their latest research and present their cases during this international symposium. In the first year, only 26 cases were submitted. However, in the most recent competition we received more than 110, which is an incredible growth in just 5 years.

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

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 2017-2018 TROPHY edition is "Novel management of ocular surface disease".

PREFACE

Prof. HARMINDER S. DUA

Harminder S. DUA
University of Nottingham | Notts · School of Clinical Sciences
MBBS, DO, DO (Lond), MS, MNAMS, FRCS, FRCOphth, FEBO, MD, PhD , FRCP (Edin) and FCOptom.
Specialist in; Cornea, Ocular Surface, Anterior Segment, Cataract, Refractive Laser & Lens Surgery

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 5th edition of TROPHY, which covered a specific topic of personal interest to me: "NON-SURGICAL TREATMENT OF CORNEAL DISORDERS".

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 THE AWARD CEREMONY DURING THE ARVO 2017 MEETING

Théa gave 3 applicants the opportunity to present an unpublished clinical case to an international audience during the Théa symposium at the 2017 ARVO meeting.

From left to right: Laura Vermuso, 1st place, Jean-Frédéric Chibret, President of Laboratoires Théa, Eduardo Sebastian Arellano Arias, 2nd place, Maria Poimenidou, 3rd place, Prof. Harminder DUA.


TROPHY

TOP 3 CLINICAL CASES

EDITION 2016 - 2017

REFRACTORY CHILDHOOD OCULAR ROSACEA TREATED BY INFLIXIMAB

P.14

Laura VERMUSO
University Hospital of Rouen, Rouen – FRANCE

SQUAMOUS CELL CARCINOMA: AN ATYPICAL PRESENTATION

P.22

Eduardo Sebastian ARELLANO ARIAS
Fundación Hospital Nuestra Señora de la Luz, IAP, Mexico D.F. – MEXICO

CORNEAL MELT: A PARADOXICAL ADVERSE EVENT TO INTERLEUKIN-6 RECEPTOR BLOCKAGE?

P.28

Maria POIMENIDOU
CHIEMSEE AUGEN TAGESKLINIK, PRIEN – GERMANY

BEST NATIONAL CASES

A CONJUNCTIVITIS HARD AS WOOD P.40

Damien GUINDOLET
Pierre & Marie Curie Medical School (Paris 6), Paris – **FRANCE**

INVASIVE SQUAMOUS CELL CARCINOMA OF THE CORNEA TREATED WITH MITOMYCIN EYE DROPS P.46

Bennis AHMED
CHU Hassan II, Fès – **MOROCCO**

CHALLENGES IN THE MANAGEMENT OF SEVERE *FUSARIUM* KERATITIS: A ROLE FOR INTRASTROMAL VORICONAZOLE P.52

Peter John MORGAN-WARREN
Health Education West Midlands – **UNITED KINGDOM**

A RARE CAUSE OF KERATITIS: MICROSPORIDIUM P.62

Dilaų OZEK
Ophthalmologist, Numune Research & Training State Hospital, Ankara – **TURKEY**

RGTA TREATMENT EFFECTIVENESS IN AN ELDERLY PATIENT BILATERAL MOOREN´S ULCERATION P.68

Jose Vicente DABAD MORENO
Hospital Universitario La Paz, Madrid – **SPAIN**

MEDICAL MANAGEMENT OF BULLOUS KERATOPATHY COMPLICATING AN IRIDO-CORNEAL ENDOTHELIAL SYNDROME P.76

Naïrouz ZINE EL ABIDINE
Mohamed Lamine Debaghine - Bab el Oued Universitų Hospital in Algiers – **ALGERIA**

BEST NATIONAL CASES

NICERGOLINE®: A NOVEL TREATMENT FOR PERSISTENT CORNEAL EPITHELIAL DEFECT P.88

Valeria OLIVA BIÉNZOBAS
Hospital Central de Mendoza, Argentina – **MEXICO**

PERSISTENT CORNEAL ULCER IN A PATIENT WITH GLAUCOMA P.92

Anna-Maria LAINE
Turku University Hospital , Turku – **FINLAND**

THE USE OF MATRIX THERAPY IN PERSISTENT EPITHELIAL DEFECTS RELATED TO BACTERIAL KERATITIS P.96

Elke KREPS
Ghent University Hospital, Ghen – **BELGIUM**

PARAPROTEINEMIC KERATOPATHY: 14 YEARS OF FOLLOW-UP P.106

Pavlina SKALICKA
Charles University Hospital, Prague – **CZECH REPUBLIC**

SUCCESSFUL TREATMENT OF SPONTANEOUS CORNEAL PERFORATION RELATED TO UNDERDIAGNOSED SJÖGREN'S SYNDROME USING POLYCARBOXYMETHYLGLUCOSE SULFATE AND AUTOLOGOUS SERUM EYE DROPS P.110

Argyrios TZAMALIS
Papageorgiou General Hospital, Thessaloniki – **GREECE**

TOPICAL ASCORBATE ADMINISTRATION IN SEVERE OCULAR BURN P.118

Tim ENZ
University Hospital Basel – **SWITZERLAND**

BEST NATIONAL CASES

NEUTROPHIC ULCER SECONDARY TO HERPETIC KERATITIS P.124

Francesca URBAN, Claudio GORLA, Giuseppe SCARPA
UCO Ophthalmology, Ospedale Ca' Foncello, Treviso – **ITALY**

BILATERAL LINEAR ENDOTHELIITIS IN THE CONTEXT OF LEPTOSPIROSIS: FROM A CUTANEOUS RASH TO A NEW CLINICAL ENTITY? P.128

José Guilherme NERI MIRANDA PIRES
Centro Hospitalar de Lisboa Central – **PORTUGAL**

RGTA MATRIX THERAPY IN THE TREATMENT OF ALKALIRELATED OCULAR BURN P.134

Marlena KONKOL
Copernicus Hospital, Gdańsk – **POLAND**

CASE OF SUCCESSFUL TREATMENT OF BILATERAL ACANTHAMOEBA KERATITIS P.140

Kateryna SEREDA
State Institution «Filatov Institute of Eye Diseases and Tissue Therapy NAMS of Ukraine», Odessa – **UKRAINE**

EFFICACY OF THEALOZ-DUO FOR THE TREATMENT OF DRY EYE DISEASE IN COMPUTER USERS P.146

Alexandra-Maria JURCA
Municipal Clinical Hospital Timisoara – **ROMANIA**

SUCCESSFUL TREATMENT OF A CORNEAL HERPETIC ULCER USING CACICOL P.152

Karine DAVTYAN
Privat clinic "Sfera"– **RUSSIA**

1

Laura VERMUSO

University Hospital of Rouen, Rouen – **FRANCE**

Laura Vermuso was born in France. She studied at the University of Bobigny in France in the field of the state examination for human medicine.

She is currently resident in ophtalmology in the University of Rouen.

REFRACTORY CHILDHOOD OCULAR ROSACEA TREATED BY INFLIXIMAB

★ INTRODUCTION ★

Childhood ocular rosacea is a rare and often misdiagnosed disorder associated with chronic blepharitis, and in many cases, chalazia and phlyctenular keratoconjunctivitis [1]. It is also known as blepharokeratoconjunctivitis [2, 3].

Childhood ocular rosacea is believed to be the consequence of chronic meibomian gland dysfunction, which is responsible for chronic inflammation of the ocular surface. Stagnation of the meibum, due to an increase in its liquefaction temperature, encourages secondary bacterial infection. In addition, the bacterial lipases affecting the meibum increase its viscosity. A cell-mediated delayed hypersensitivity reaction to bacterial exotoxins and to bacterial parietals is at the origin of phlyctenular keratoconjunctivitis [4].

Childhood blepharokeratoconjunctivitis is known to be a rare condition whose diagnosis is often delayed. It is commonly asymmetrical without any associated cutaneous signs [5], making diagnosis even more challenging. Its clinical spectrum is polymorphous including conjunctival hyperemia, superficial punctate keratitis, anterior blepharitis, recurrent chalazia, phlyctenular keratoconjunctivitis and corneal infiltrates [2, 6].

Populations of India, Pakistan and the Middle East have been shown to be more seriously affected by this disease. There is an added risk of neovascularization and corneal perforation in its most severe forms [7]. In young patients, we must also consider the amblyogenic potential of the pathology, particularly irregular astigmatism linked to corneal scarring [8]. Thus, stepladder management must be advocated, including eyelid hygiene, warm compresses, a combination of oral and topical antibiotics, topical steroids, and steroid sparing strategies such as topical cyclosporine A, which may be necessary depending on the severity of the disease [9]. Appropriate and sometimes more aggressive treatments of this chronic condition are essential to avoid amblyopia, blinding corneal scars and other complications [10].

Biologic agents have revolutionized the care management of many autoimmune diseases. Infliximab is a chimeric monoclonal antibody biologic systemic drug targeting tumor necrosis factor alpha (TNF-α). It has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis.

We report a case of refractory childhood ocular rosacea, which required an increased course of treatments leading to biologics.

★ CASE REPORT ★

The case concerns an 11-year-old girl referred in 2009 for bilateral keratoconjunctivitis and recurrent chalazia with a history of facial dermatitis. Clinical investigation revealed a previous history of acne rosacea in the patient's mother and atopy in the patient's sister. The initial clinical findings showed large limbal phlyctenules in both eyes (Figure 1). Best-corrected visual acuity was measured at 20/32 in both eyes. There was no sign of ocular allergy such as giant papillary conjunctivitis or Trantas dots.

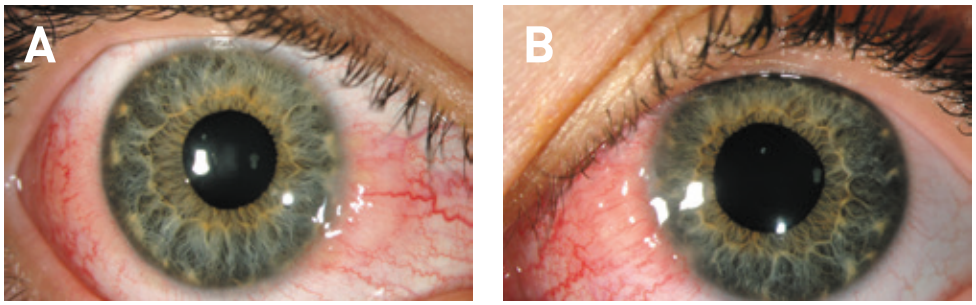


Figure 1: Right eye (A) and left eye (B). Initial slit lamp images demonstrating large bilateral limbal phlyctenules.

Blepharokeratoconjunctivitis associated with rosacea was suspected. Cutaneous rosacea was confirmed by histological analyses of cutaneous biopsy showing numerous non-necrotizing epithelioid granulomas with giant cells sometimes centered on hair follicles in keeping with granular rosacea.

Sarcoidosis, the main differential diagnosis as regards histological analyses was ruled out by performing a chest abdomen pelvis computed tomography scan, by angiotensin converting enzyme dosing and respiratory functions tests looking for a restrictive syndrome. Lupus was also ruled out by performing a biological check-up. Clinical cutaneous signs were not compatible with psoriasis or atopic dermatitis.

Despite systemic treatment combining doxycycline 100 mg per day, local corticosteroid therapy with topical dexamethasone 6 drops per day, topical azithromycin 1.5%, topical cyclosporine A 2% (2 drops per day) and regular eyelid hygiene, this young girl remained steroid dependent. Therefore, the

symptoms recurred when the local corticosteroid therapy dexamethasone was decreased to 2 drops per day (Figure 2). On the contrary, the cutaneous inflammation regressed with doxycycline treatment alone.

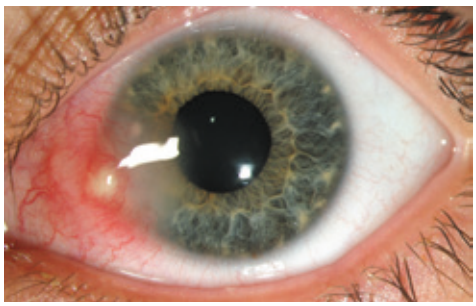


Figure 2 : Large limbal phlyctenule recurrence in the left eye despite doxycycline treatment, topical dexamethasone 2 drops per day and topical cyclosporine A 2% (2 drops per day).

In April 2011, at the age of 13 years, given the potential involvement of a sight-threatening corneal disease, systemic corticosteroid therapy was started at 0.5 mg/kg of prednisone per day without success. The symptoms recurred when the local corticosteroid therapy dexamethasone was decreased to 3 drops per day and prednisone 10 mg a day (Figure 3). Then, azathioprine (125 mg per day) was added. Unfortunately, this did not prevent the worsening of the condition in the right eye, which until then had been less affected (Figure 4). Visual acuity in her right eye was limited to counting fingers and to 20/200 in her left eye.

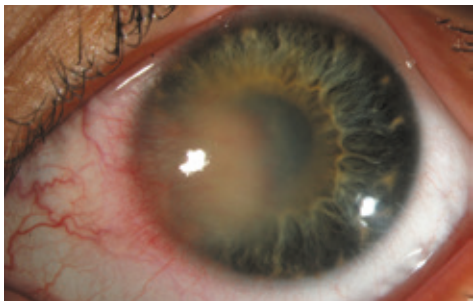


Figure 3: Recurrence of corneal involvement in the left eye despite doxycycline treatment, topical dexamethasone 3 drops per day, topical cyclosporine A 2% (2 drops per day) and prednisone 10 mg a day.

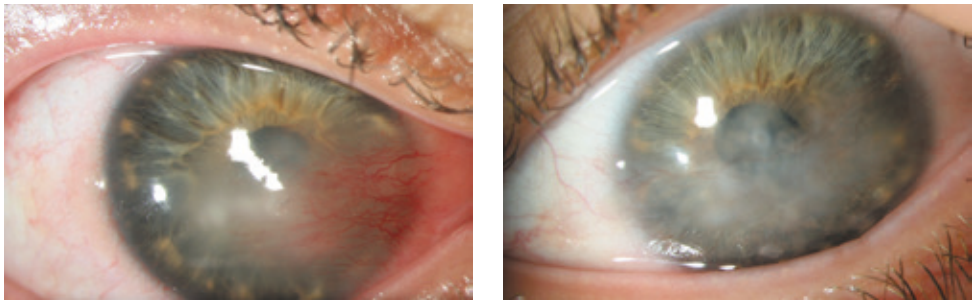


Figure 4: Right eye (a) and left eye (b). Corneal involvement worsening in both eyes despite doxycycline treatment, topical dexamethasone 8 drops per day, topical cyclosporine A 2% (2 drops per day), prednisone 15 mg a day and azathioprine 125 mg per day.

The case of our young patient with sight-threatening ocular surface disease thought to be an exceptionally severe case of childhood ocular rosacea was presented in multidisciplinary meeting. In July 2013, intravenous treatment by anti TNFα (infliximab, 5 mg/kg every 8 weeks) and weekly 12.5 mg methotrexate were introduced, in combination with steroid therapy increased to 1 mg/kg of prednisone per day. This treatment provided complete remission with weaning off steroid therapy. However, best-corrected visual acuity remained limited to 20/63 in the left eye due to corneal opacity but increased to 20/25 in the right eye (Figure 5).

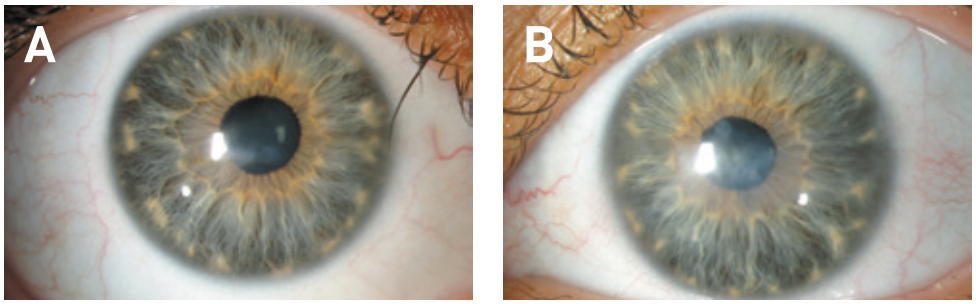


Figure 5: Right eye (A) and left eye (B). Slit lamp images demonstrating complete remission in both eyes 4 months after treatment introduction including intravenous infliximab, weekly oral methotrexate and prednisone 10 mg.

In July 2015, infliximab was stopped after two years of treatment. Three months later, the ocular surface inflammation recurred with reappearance of corneal neovascularization (Figure 6). The patient was still treated with oral doxycycline and methotrexate. Infliximab was started again providing complete regression of symptoms (figure 7) and withdrawal of local and systemic corticosteroids. The patient remained in steroid-free remission.

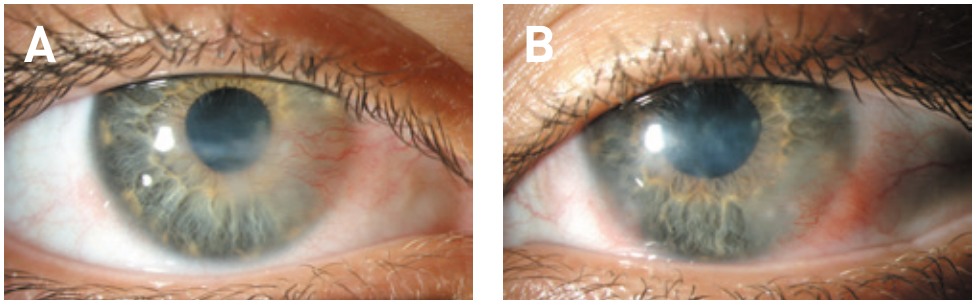


Figure 6: Right eye (A) and left eye (B). Recurrence of corneal involvement in September 2015 after withdrawal of infliximab.

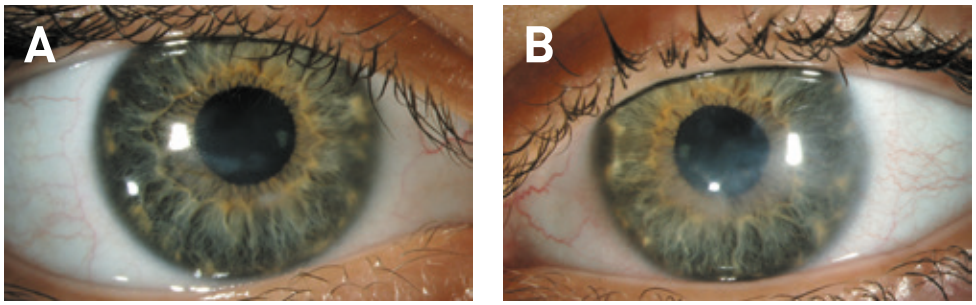


Figure 7: Right eye (A) and left eye (B). Remission in both eyes after infliximab reintroduction.

★ DISCUSSION ★

The treatment of childhood ocular rosacea is based on its presumed physiopathogenic mechanisms and relies on lid hygiene and antibiotics to control bacterial proliferation and to improve meibomian gland function. Oral cyclines may induce the reduction of lipases produced by the commensal staphylococci diminishing the liberation of toxic fatty acids produced by the hydrolysis of meibomian lipids [7]. This treatment is authorized for children over eight years of age due to risk of tooth staining [11]. For children under eight years of age, antibiotic treatment by macrolide (erythromycin or josamycin) might be suggested. However, these last two antibiotic treatments have now been replaced by local azithromycin, whose simplified therapeutic approach encourages observance in children [3]. Corticosteroid eye drops [12] or cyclosporine A eye drops as corticosteroid-sparing agent are associated in the most severe forms of disease [9].

Although ocular manifestations usually respond well to antibiotic therapy and local therapy, systemic immunosuppressive therapy is required in extreme cases, as reported here. In particular, a more severe form of the disease, with a greater likelihood of developing corneal vascularization, marginal corneal ulceration, and corneal phlyctenules has been reported in Asian and Middle Eastern children [7, 13]. Among fifty-one Asian patients, diagnosed with pediatric blepharokeratoconjunctivitis, one patient had severe inflammatory disease that required systemic control with oral prednisolone and five patients required surgical treatment. Among these five patients, three required deep lamellar keratoplasty (2 tectonic and 1 optical), and two had cornea gluing alone [13]. However, destructive phenotype has been described in white children, which may require systemic immunosuppression. Indeed, due to persistent active disease, three among ten white European adolescents with an aggressive condition, were started on systemic immunomodulatory treatments (azathioprine, mycophenolate mofetil or prednisolone), despite ongoing treatment with local steroid therapy [14]. These treatments achieved disease remission within three months with no adverse events reported.

In the case reported here, corticosteroid use and the addition of azathioprine failed to control ocular surface inflammation because our patient remained steroid dependent. Therefore, treatment had to be intensified with biologics. The off-label use of infliximab, by analogy with treatments used for severe cases of mucous membrane pemphigoid [15], was started after multidisciplinary discussion with pediatricians and dermatologists. As far as we know, there have been no other reports in the literature of childhood ocular rosacea in children or in adults treated by biologics.

Corneal complications of rosacea, such as phlyctenules and corneal infiltrates are thought to be caused by means of an immunological specific T-cell response [3]. There is substantial evidence that TNFα has protective effects against T-cell-mediated autoimmunity, which may explain its efficacy here [16].

Nonetheless, a male patient with a granulomatous variant of cutaneous rosacea was treated with adalimumab for 3 months without any improvement on dermatological lesions [17]. Furthermore, the development of severe cutaneous rosacea in a patient treated with infliximab for ulcerative colitis was reported in 2009 [18]. Hence, studies are required to evaluate the efficacy and tolerance of anti-TNFα in the management of ocular and dermatological rosacea.

Lastly, topical anti-TNFα known as ESBA105, although not currently available commercially, could be a future option in the management of ocular complications of rosacea [19].

★ CONCLUSION ★

Severe forms of blepharokeratoconjunctivitis or childhood ocular rosacea are well known, though fortunately rare. This pediatric case of exceptionally serious blepharokeratoconjunctivitis underlines the importance of appropriate and sometimes aggressive treatments.

★ REFERENCES ★

1. Erzurum, S.A., R.S. Feder, and M.J. Greenwald. Acne rosacea with keratitis in childhood. Arch Ophthalmol 1993, 2, 111: 228-30.
2. Zaidman, G.W. and S.I. Brown. Orally administered tetracycline for phlyctenular keratoconjunctivitis. Am J Ophthalmol 1981, 2, 92: 178-82.
3. Doan, S., E. Gabison, F. Chiambaretta, et al. Efficacy of azithromycin 1.5% eye drops in childhood ocular rosacea with phlyctenular blepharokeratoconjunctivitis. J Ophthalmic Inflamm Infect 2013, 1, 3: 38.
4. Tiffany, J.M. The lipid secretion of the meibomian glands. Adv Lipid Res 198722: 1-62.
5. Chamaillard, M., B. Mortemousque, F. Boralevi, et al. Cutaneous and ocular signs of childhood rosacea. Arch Dermatol 2008, 2, 144: 167-71.
6. Gupta, N., A. Dhawan, S. Beri, et al. Clinical spectrum of pediatric blepharokeratoconjunctivitis. J AAPOS 2010, 6, 14: 527-9.
7. Viswalingam, M., S. Rauz, N. Morlet, et al. Blepharokeratoconjunctivitis in children: diagnosis and treatment. Br J Ophthalmol 2005, 4, 89: 400-3.
8. Doan, S., E.E. Gabison, S. Nghiem-Buffet, et al. Long-term visual outcome of childhood blepharokeratoconjunctivitis. Am J Ophthalmol 2007, 3, 143: 528-9.
9. Doan, S., E. Gabison, D. Gatinel, et al. Topical cyclosporine A in severe steroid-dependent childhood phlyctenular keratoconjunctivitis. Am J Ophthalmol 2006, 1, 141: 62-66.
10. Jones, S.M., J.M. Weinstein, P. Cumberland, et al. Visual outcome and corneal changes in children with chronic blepharokeratoconjunctivitis. Ophthalmology 2007, 12, 114: 2271-80.
11. Lacz, N.L. and R.A. Schwartz. Rosacea in the pediatric population. Cutis 2004, 2, 74: 99-103.
12. Donaldson, K.E., C.L. Karp, and M.T. Dunbar. Evaluation and treatment of children with ocular rosacea. Cornea 2007, 1, 26: 42-6.
13. Teo, L., J.S. Mehta, H.M. Htoon, et al. Severity of pediatric blepharokeratoconjunctivitis in Asian eyes. Am J Ophthalmol 2012, 3, 153: 564-70 e1.
14. Hamada, S., I. Khan, A.K. Denniston, et al. Childhood blepharokeratoconjunctivitis: characterising a severe phenotype in white adolescents. Br J Ophthalmol 2012, 7, 96: 949-55.
15. Heffernan, M.P. and D.D. Bentley. Successful treatment of mucous membrane pemphigoid with infliximab. Arch Dermatol 2006, 10, 142: 1268-70.
16. Suresh, M., A. Singh, and C. Fischer. Role of tumor necrosis factor receptors in regulating CD8 T-cell responses during acute lymphocytic choriomeningitis virus infection. J Virol 2005, 1, 79: 202-13.
17. Sand, F.L. and S.F. Thomsen. Off-label use of TNF-alpha inhibitors in a dermatological university department: retrospective evaluation of 118 patients. Dermatol Ther 2015, 3, 28: 158-65.
18. Kosmidou, M., G. Gaitanis, K. Nomikos, et al. Severe rosacea in a patient on infliximab for ulcerative colitis: pathophysiological considerations. Acta Derm Venereol 2009, 5, 89: 522-3.
19. Thiel, M.A., A. Wild, M.K. Schmid, et al. Penetration of a topically administered anti-tumor necrosis factor alpha antibody fragment into the anterior chamber of the human eye. Ophthalmology 2013, 7, 120: 1403-8.

2

Eduardo Sebastian ARELLANO ARIAS

Fundación Hospital Nuestra Señora de la Luz, IAP, Mexico D.F. – **MEXICO**

Eduardo Sebastián Arellano Arias was born december 4th, 1987 in Mexico D.F., Mexico.

He was graduated as a medical doctor from the Universidad Nacional Autónoma de México and in ophtalmology surgeon from the Fundación Hospital Nuestra Señora de la Luz, IAP. He is also teaching in the field of medical physiology in the Universidad Nacional Autónoma de México.

SQUAMOUS CELL CARCINOMA: AN ATYPICAL PRESENTATION

★ INTRODUCTION ★

Squamous cell or epidermal carcinoma is the most common ocular neoplasia[1] It can arise from cornea or conjunctiva and has the capacity to spread through local dissemination or, less commonly, by metastasis. It has a wide spectrum of histological presentation that goes from displasia (mild, moderate or severe) to conjunctival intraepithelial neoplasia (NIC) and invasive squamous cell carcinoma.[1,2,4]

These types of lesions are more frequent in males and tend to have a higher incidence in older people. The leading risk factor is ultraviolet exposure (sunlight). Other factors associated with this pathology are the presence of congenital genome repair anomaly, such as xeroderma pigmentosum, human papilloma virus (HPV) infection and any condition that produces immunodeficiency, such as HIV/AIDS. Squamous cell carcinoma has been associated with other ocular surface lesions, such as pterygium, cysts and nevi. [2,4]

Clinically, squamous cell carcinoma may present with a wide variety of manifestations. Lesions can be nodular, diffuse or placoid. The later can be further divided into gelatinous, papilliform, velvety and leukoplakic. Lesion can be completely avascular or have plenty of vascular supply. The presence of nutritious or sentinel vessels, tortuous or cork like vessels is highly suggestive of squamous cell carcinoma. Color may vary from transparent-unpolished glass to grey or pigmented lesions. The size of the neoplasia can also be quite variable, ranging from millimeters to a few centimeters in its mayor diameter.[2,4] Specifically talking about corneal disease, the lesion is usually pre-invasive and avascular, with tendency to arise from central cornea and have a centrifuge growth. Lesion is grayish- glassy and affects central vision due to pupil axis involvement.[3,4]

Patients may complain about "chronic conjunctivitis", fluctuating red eye, foreign body sensation, tenderness and irritation. They may also report visual acuity decrease due to affection of the visual axis by the lesion or induced refractive errors by irregular corneal curvature. [1,2]

Treatment of ocular surface squamous cell carcinoma has many variants. Surgical excision, cryotherapy and chemotherapy are some of the options and they can be used alone or combined. Among chemotherapeutic agents interferon α2b, mitomycin C (MMC) and 5- fluorouracil (5-FU). Success rates differ from series to series, and rates of recurrence go from 9% to 53% depending on the consulted literature. [3,5]

★ CASE PRESENTATION ★

A 77 year old male presented with a 10 month history of red eye and intermittent foreign body sensation and tenderness in the right eye. He reported diagnosis of systemic hypertension and type 2 diabetes mellitus of eight years of evolution, currently under pharmacological control. He was under topical treatment with acyclovir 3% (5 times a day) and sodium hyaluronate 0.4% (5 times a day).

His visual acuity was 20/1200 (1.9 logMAR) on the affected eye, with papillary reaction in the tarsal conjunctiva and Meibomian gland dysfunction. An epithelial defect of 7mm x 6mm was also found, with underlying stromal melting. Topical medication was modified and topical gancyclovir 1.5mg/g (q 5hrs) was initiated under the suspect of herpetic geographic ulcer. (Figure 1.)

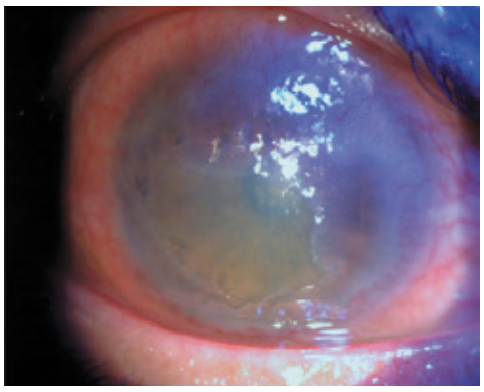


Figure 1: Corneal epithelial defect before treatment adjustment.

Even though the patient reported improvement of symptoms after 10 days of treatment, the epithelial defect increased to 8mm x 6mm. Perilimbal and stromal vascularization was found, some of them with cork appearance. Visual acuity remained stable. Due to lack of response to treatment, oral acyclovir was initiated (400mg po q4.5hrs)

One week later, patient remained with symptoms and epithelial defect persisted. At this point, diagnosis was questioned and therapeutic approach was modified. Treatment was established for a neurotrophic ulcer. Topical sodium hyaluronate 0.4% (q 2hrs) and dexpantenol 5% qid was initiated and occlusive patch was placed.

Two months later, patient reported no symptoms. Even though there was a clinical improvement, patient remained with same visual acuity (20/1200; 1.9 logMAR), hyperemic conjunctiva, perilimbic vessels with cork appearance and an irregular corneal epithelium, with stromal edema and loss of corneal transparency. (Figure 2.)

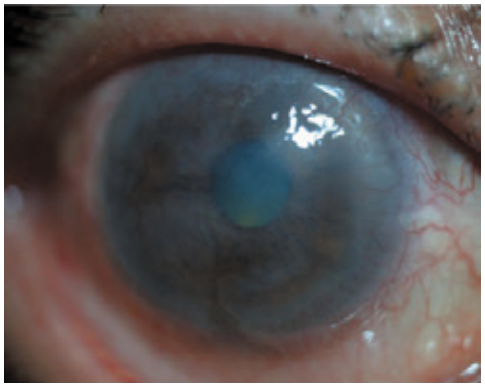


Figure 2: Persistent irregular epithelium with patchy stromal edema.

These new findings conducted to take an impression cytology of the perilimbic corneal epithelium, which reported neoplastic squamous epithelial cells, with loss of nucleus- cytoplasm relation, with big, pleomorphic nuclei and irregular cell membranes, thick granular chromatin and micronucleolus with scarce mitotic figures. Histological findings were compatible with squamous cell carcinoma with moderate differentiation (Figure 3). With this diagnosis, topical treatment was established with interferon α2b 1 million IU/ml qid.

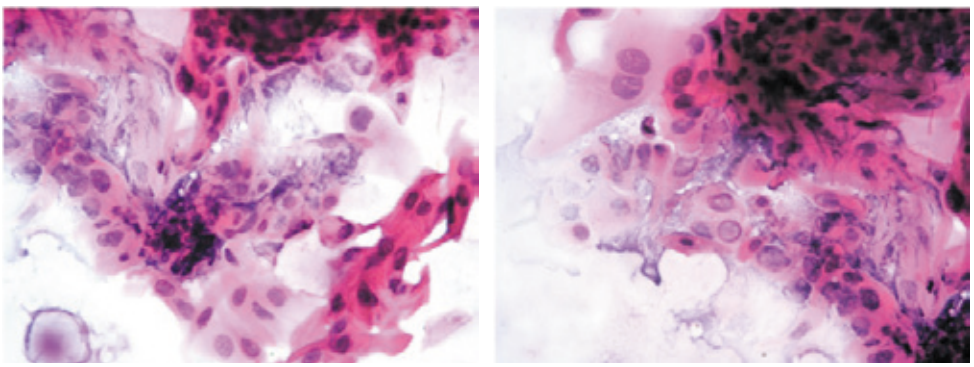


Figure 3: Squamous cell carcinoma with moderate differentiation

After two months of treatment, corneal transparency was recovered, corneal epithelium showed uniformity and perilimbic vessels showed discrete involution. Visual acuity after treatment was 20/80 (0.6 logMAR).

★ DISCUSSION ★

Squamous cell carcinoma is an uncommon diagnosis, even though is the most common ocular surface neoplasia. For a proper diagnosis, clinician has to have a high level of suspicion based on the characteristic findings of this pathology.

Most of the literature reports classic presentation of this kind of diseases (displasia, intraepithelial neoplasia and invasive carcinoma), but it may have an atypical presentation like the case of our patient, which presented a persistent epithelial defect. On first instance, it was managed as a herpetic ulcer, then as a neurotrophic ulcer and finally as a squamous cell carcinoma. Initial therapeutic approach was based on clinical findings and epidemiologic probability.

A key element to the proper diagnosis was the presence of abnormal vessels in the corneal periphery, which, according to the consulted bibliography, should always rise the suspicious of a malignant underlying process, especially if they have uncommon appearance, such as cork vessels. A second key element was the partial response to an adequate treatment to the original diagnosis, which forced to reanalyze the case and its evolution.

Although one of the first treatment lines for this disease is the surgical excision, topical treatment was elected due to lack of a defined lesion borders and the integrity of corneal structure. Fortunately, clinical response to chemotherapy was optimal, based on the described regimens for interferon α2b.

Of the available chemotherapeutics described to treat squamous cell carcinoma, interferon α2b has not been associated with limbal stem cell damage and has demonstrated efficacy as a single- agent treatment. It is a cytokine with antineoplastic and immune functions which action mechanism is though to be the modulation of enzymatic intracellular response, cell proliferation and increased cytotoxic response of leukocytes. [8,9]

Interferon α2b is usually prepared to 1 million IU/ml for topical use as eye drops and is recommended 4 to 6 times a day until clinical resolution of lesion is noted, which in average takes 8 to 10 weeks according to consulted literature. Some authors recommend continuation of treatment up to one month after resolution. Interferon α2b has also been described for subconjunctival use. [8,9]

★ CONCLUSION ★

The main lesson from this case is to always keep in mind that diseases may have erratic behavior. This case report should serve as a guide to those whose practice is centered on eye surface diseases, since there may be underdiagnosis of squamous cell carcinoma due to atypical presentations.

Unlike nodular, diffuse or plaque lesion (classic presentation), this patient's main findings were a persistent epithelial defect with stromal edema and abnormal perilimbal vessels. Once other more common causes of these findings are ruled out, complementary tests should be done if there is no conclusive diagnosis. When ocular surface squamous cell carcinoma is to be tested, impression cytology is a good alternative, since it is a noninvasive technique that can be easily done at practitioner's office.

The location of this type of neoplasia offers the possibility of different types of treatment. Besides surgery, topical treatment with antineoplastic medications has offered good results, being Interferon α2b a very good option with clinical response over few weeks of treatment in most cases.

★ REFERENCES ★

1. Yousef, Y, Finger, P. Squamous Carcinoma and Dysplasia of the Conjunctiva and Cornea. An analysis of 101 cases. Ophthalmology 2012; 119: 233-240.
2. Chauhan, S, Sen, S, Sharma, A et al. American Joint Committee on Cancer Staging and Clinicopathological High-Risk Predictors of Ocular Surface Squamous Neoplasia. Arch Pathol Lab Med Vol 138, November 2014.
3. Krishnaraj, J, Surya, S, Exhil, K. Ocular surface squamous neoplasia. Review Article. International Journal of Ocular Oncology and Oculoplasty, January- March 2016; 2(1): 19-30.
4. Honovar, S, Manjandavida, F. Tumors of the ocular surface: A review. Indian Journal of Ophthalmology Vol. 63, No. 3: 187-203.
5. Zarei- Ghanavati, S, Alizadeh, R, Deng, Sophie. Topical Interferon Alpha-2b for Treatment of Noninvasive Ocular Surface Squamous Neoplasia with 360° Limbal Involvement. J Ophthalmic Vis Res 2014; 9(4): 423-426
6. Padma, P, Padma, M. Ocular Surface Squamous Neoplasia (OSSN): A Retrospective Study. Journal of Clinical and Diagnostic Research. 2015 Nov, Vol 9 (11); NC10-NC13
7. Nguena, M, can den Tweel, J, Makupa, W et al. Diagnosing Ocular Surface Squamous Neoplasia in East Africa. Ophthalmology 2014; 121:484-491.
8. Ramberg, I, Heegard, S, Sjo, N. Squamous cell dysplasia and carcinoma of the conjunctiva. A nationwide, retrospective, epidemiological study of the Danish patients. Acta Ophthalmol 2015: 93 663-666
9. Huerva, V, Manges, I. Treatment of conjunctival squamous neoplasia with interferon alpha 2b. Journal Français d' Ophthalmologie 2008: Vol 31 No3; 317-325

3

Maria POIMENIDOU

Chiemsee Augen Tagesklinik, Prien – **GERMANY**

Maria Poimenidou studied during some years at the Institute of Eye Diseases of Russian Academy of Medical Sciences, Moscow, Russia as a post-graduate student. Then she works as a general practitioner, in Pyrgos, Greece. Today, she's resident at the Eye Center "Chiemsee Augen Tagesklinik", Prien am Chiemsee, Germany.

CORNEAL MELT: A PARADOXICAL ADVERSE EVENT TO INTERLEUKIN-6 RECEPTOR BLOCKAGE?

★ INTRODUCTION ★

In rheumatoid arthritis inflammatory involvement of the cornea and sclera is usually a sign of severe generalized rheumatic disease. Unless the disease is properly identified and intense systemic therapy is instituted promptly, the outcome for the afflicted eye and even the life of the patient is guarded. Intensive comanagement of the patient with rheumatologists using systemic and topical anti-inflammatory as well as immunomodulatory therapy is mandatory to ensure good visual and general outcome.

We describe a case of a 39 years old gentleman with known rheumatoid arthritis, who was well managed for his systemic disease by tocilizumab therapy since 12 months. However he was complaining of recent onset severe redness and pain in his eyes as well as reduced vision despite good general control of his disease.

★ CASE PRESENTATION ★

A 39 years old male of Egyptian descent was referred from the rheumatology service. He had been treated with methotrexate (MTX) 15mg/week and tocilizumab 500mg iv. every four weeks since 12 months for his rheumatoid arthritis, which had been diagnosed in 04/2005 and showed a marked involvement of shoulders, hands, knees and feet bilaterally.

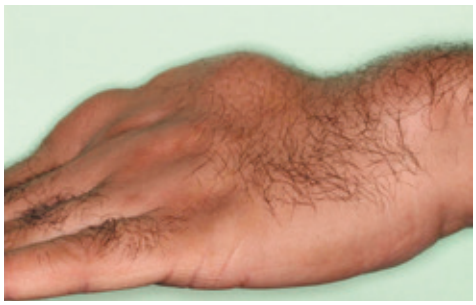


Figure 1: Markedly afflicted joints of the left hand.

With the therapy he had noticed marked improvement in joint pain and motion range. However since two months he noted increased redness of both eyes with marked pain, and sensitivity to light especially in his left eye. He was referred from the rheumatology service.

On initial presentation in 03/2011 he presented with a corrected visual acuity of 20/30 in his right eye (RE), 20/100 in his left eye (LE). His conjunctiva and sclera was heavily inflamed in both eyes (OU) with marked granulomatous, centrally ulcerated episcleral lesions more pronounced in the right eye superiorly (Fig. 2, 3).

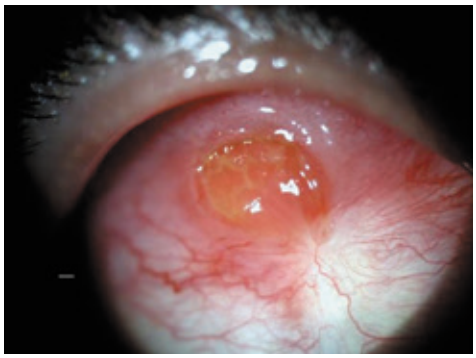


Figure 2: Granulomatous, ulcerated lesion RE.

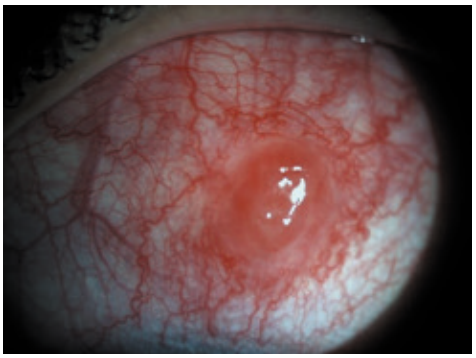


Figure 3: Granulomatous, ulcerated lesion LE

His right eye showed punctuate keratopathy, his left revealed a central, round, flat corneal erosion (Fig. 4). The anterior chambers were normal in both eyes. The fundus exam was unremarkable OU.

A conjunctival swab and blood work up was performed.
A biopsy was taken from the lesion of the right eye.

Figure 4. A central, round, flat corneal erosion left eye (arrow).

Topical therapy was started with prednisolone acetate eye drops 6 times/day, ofloxacin eye drops 4 times/day and copious use of non preserved hyaluronic acid artificial tears. Systemic prednisolone 60mg/die was added to the existing systemic therapy. His blood work up was unremarkable for inflammatory parameters as well as infectious diseases such as tuberculosis or syphilis. The conjunctival swab was negative for bacteria and chlamydia trachomatis. The biopsy revealed chronic granulomatous and active infiltrates characterized by eosinophil granulocytes, lymphocytes and plasma cells with some histiocyte aggregations.

Despite the systemic therapy of 60 mg prednisolone added to MTX and tocilizumab the granuloma in the right eye enlarged (Fig.5) and the corneal erosion in the left eye progressed to a central ulcer with beginning tissue melt in the ensuing 4 weeks.

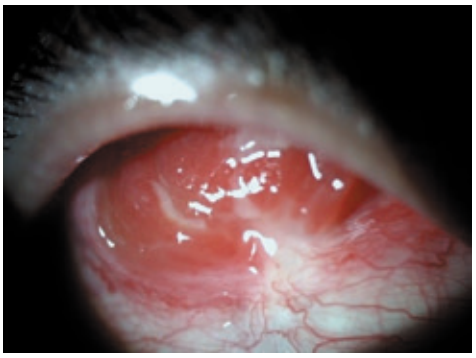


Figure 5: The enlarged progressing granuloma in the right eye.

Locally serum eye drops were added hourly and azithromycin eye drops 4 times /day were used instead of ofloxacin eye drops. Since the situation did not change and further loss of corneal tissue due to uncontrolled inflammation was feared, the decision was made to perform an amnion membrane transplant in the left eye (Fig.6).

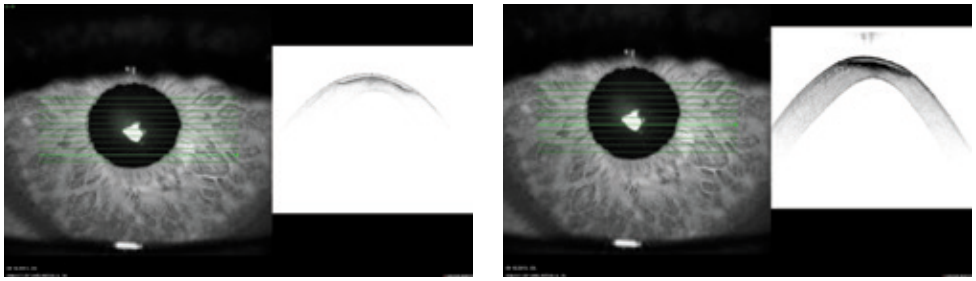


Figure 6: Anterior segment OCT of the left cornea after sandwich technique amnion membrane transplant, demonstrating corneal scar and central thinning with masking multilayered epithelium.

The sclera granulomas were unchanged. Together with the rheumatologists we decided six weeks after initial presentation to switch the systemic immunosuppressive therapy. The rheumatologists initiated a therapy with certolizumab pegol.

After two more weeks of intensified topical therapy with serum eye drops, prednisolone acetate eye drops 6 times /daily and moxifloxacin eye drops 4 times /daily as well as a therapeutic bandage contact lens the sclera granulomas slowly regressed (Fig.7) and the left cornea healed leaving a paracentral subepithelial scar.

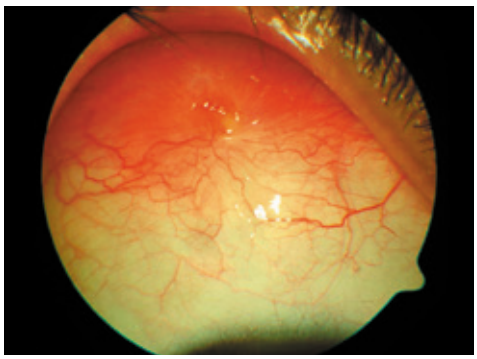


Figure 7: Granuloma right eye regressed after cessation of tocilizumab therapy.

From 7/11 to 9/14 the patient was treated by the rheumatologist with certolizumab pegol and by the ophthalmologists by frequent 0,3% non preserved hyaluronic acid eye drop application. Sometimes slight decompensation of the left corneal epithelium with corneal fluorescein punctate staining occurred which could be managed by contact lens application and dexamethasone unpreserved eye drops 2 times /daily, when flare ups occurred. His visual acuity remained stable at corrected 20/20 right eye and 20/50 left eye, with a beginning cataract in his left eye and the corneal subepithelial scar (Fig.8).

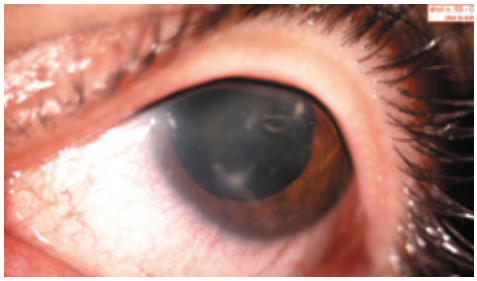


Figure 8. Residual corneal scarring in left eye after cessation of tocilizumab. Managed with artificial tears and rigid gas permeable contact lens.

In 10/14 the patient presents with increased sensitivity to light, beginning granulomatous episcleral lesions in both eyes (Fig.9) and a non healing central corneal erosion in his left eye. Additionally long strands of mucus were present in both eyes (Fig.10).

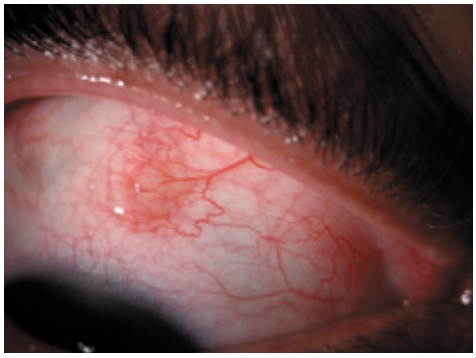


Figure 9: Recurrence of granuloma in right eye after reexposure to tocilizumab.

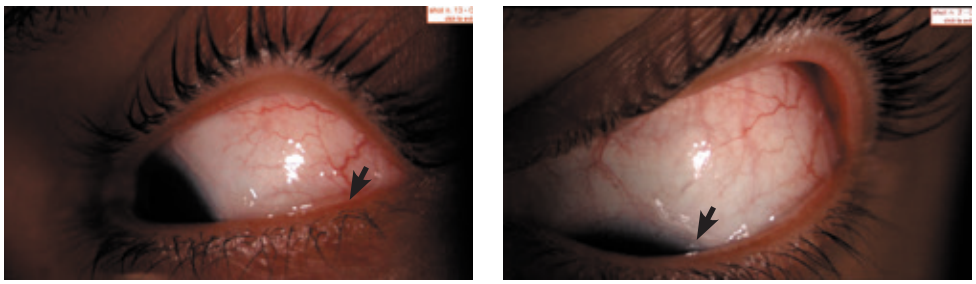


Figure 10: Left eye with bandage contact lens for non healing central erosion and pain management. Also note pathological mucus formation (arrow).

Topical therapy with bandage contact lens to the left eye and serum eye drops was started together with 6 x unpreserved dexamethasone eye drops OU. The situation slowly worsened over three weeks.

The patient then revealed that his new rheumatologist had started him on a new preparation of tocilizumab 162mg sc once a week since 3 months, thus reexposing him to the drug used in 2011 on initial presentation.

After consultation with the rheumatologist the systemic therapy was switched to abatacept 125mg sc plus methotrexate 15 mg every week and the granulomas slowly regressed over the ensuing 2 months.

The topical therapy was switched to 6 x hyaluronic acid OU and polycarboxy-methylglucose sulfate matrix eye drops every other day OU in order to expedite corneal healing.

The patient presented last in September 2016 with a systemic medication of abatacept 125mg sc plus methotrexate 15 mg every week for his rheumatoid arthritis with acceptable results. Visual acuity was 20/20 RE and 20/60 LE. The eye exam showed mildly injected conjunctiva OU, regular cornea in his right eye (Fig. 10 a), a subepithelial central scar in his left eye (Fig.10 b) and calm anterior chamber OU. The fundus is unremarkable OU.

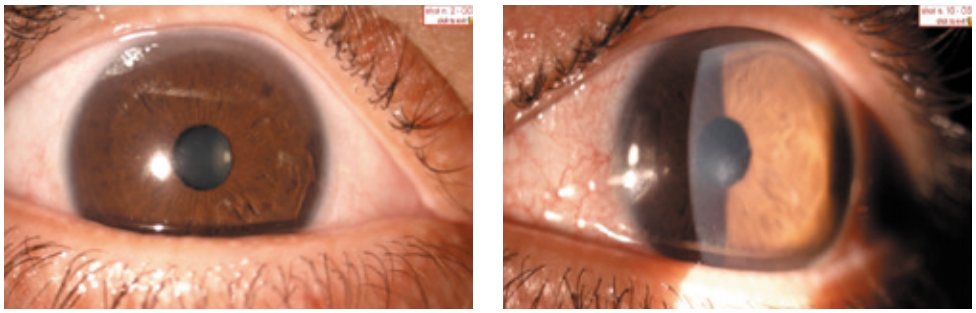


Figure 10a: RE with slightly dry eye symptoms but otherwise normal anterior segment.
10b: LE after cessation of reexposure to tocilizumab with subepithelial irregular scar causing irregular astigmatism.

Figure 11: Anterior segment OCT of LE after cessation of reexposure to tocilizumab. Demonstrating considerable corneal thinning, subepithelial irregular scar causing irregular astigmatism and bandage contact lens.

Local therapy with non preserved 0,3% hyaluronic acid eye drops every hour and eventual use of a bandage contact lens when necessary in the left eye is continued. The patient is content and able to work.

★ DISCUSSION ★

We present a case of a man who was exposed to tocilizumab treatment for his rheumatoid arthritis twice, first as i.v. infusion once a month and on the second occasion sc injection 162mg every week. Tocilizumab is a humanized monoclonal antibody against the IL6 receptor. It is an immunosuppressive drug mainly used in rheumatoid arthritis. It is however also used in severe inflammatory diseases of the eye such as scleritis[1] or uveitis[2].

On each exposition our patient presented with severe bilateral granulomatous scleritis and central keratitis more pronounced in his left eye. The effect of tocilizumab on his joints was good. Despite intensive topical anti-inflammatory treatment, the scleral and corneal situation only got better when the tocilizumab was discontinued by the rheumatologists and the systemic medication switched to another biologic agent.

The advent of biological agents has dramatically changed the therapeutic approach to a variety of systemic immune-mediated diseases, such as chronic inflammatory rheumatic diseases (rheumatoid arthritis and spondyloarthritis), plaque psoriasis and inflammatory bowel diseases (Crohn's disease and ulcerative colitis). Currently, five tumor necrosis factor α (TNF-α) blocking agents are available: three monoclonal antibodies (infliximab, adalimumab, golimumab), a p75 TNF-α soluble receptor (etanercept) and a Fab' fragment associated with a pegol molecule (certolizumab). With the improved understanding of the pathophysiology of immune-mediated diseases, new relevant therapeutic targets have been identified, leading to the development of new biological drugs. In this setting, anti-CD20 (rituximab), anti-interleukin (IL)-1 (anakinra), anti-IL-6 (tocilizumab) and a fusion protein inhibiting the costimulatory pathway (abatacept) have been developed for the treatment of rheumatoid arthritis.

Of course one would assume that these agents meant to treat the different sequelae of the disease would also positively affect the ocular involvements. So potentially two reasons could be the cause for the repeat granulomatous scleritis and non healing erosions leading to corneal melt in our patient.

First, the dosage of tocilizumab might be too low to influence the ocular involvement. This sometimes is the case in uveitis accompanying systemic inflammatory diseases. For example in uveitis patients treated with adalimumab, antibodies against adalimumab may form. This immunogenicity is more common in patients in whom uveitis is associated with a systemic disease[3]. Therefore clinicians sometimes recommend higher dosages of adalimumab for the ocular involvement than required for the treatment of e.g. joint involvement.

Open-label studies and post hoc analysis of randomised controlled trials in patients with SpA indicate that anti-TNF-α agents may reduce the frequency of uveitis flares. On the other hand, anecdotal reports have suggested that uveitis can occur during anti-TNF-α therapy which might be due to undertherapy[4].

Theoretically this could also have happened in the presented case, because after the switch to a more targeted and efficient therapy the scleral and corneal involvements resolved.

The second explanation is that, we might have seen a paradoxical adverse event. Paradoxical adverse events (PAE) are gaining more and more attention in rheumatology. If extraarticular tissue such as the eye is involved theses events are called borderline PAEs.

In general, PAEs are described as isolated events and they are mainly reported with anti-TNF-α agents. This may be explained by the long-term use of anti-TNF-α agents compared to more recently introduced biological drugs. Certain PAEs such as uveitis, Crohns disease or sarcoidosis occur more frequently with the TNF-α soluble receptor (namely etanercept) as compared to monoclonal antibodies, suggesting the involvement of the differential immunological properties of these two classes of anti-TNF-α

agents. Conversely, etanercept is used for more than 15 years compared to the more recently available anti-TNF-α monoclonal antibodies. The pre-existing condition that requires TNF-α inhibition is in general well controlled, indicating that the TNF-α agent is given at an adequate dosage or interval. However, some PAEs correspond to conditions that usually require a high dose regimen compared to the standard dose given for inflammatory rheumatic disease. For instance, adalimumab treatment in Crohns disease requires a loading dose at initiation. This could potentially explain certain PAEs observed with standard dose anti-TNF-α. The hypothesis of an imbalance in the cytokine milieu is advanced for most PAEs, especially for psoriasis, as well as a shift towards a Th1 cytokine profile or unopposed production of IFN-α[4].

IL-6 is a macrophage/monocyte-derived cytokine and plays a role in the promotion and maintenance of granulomatous inflammation through the activation of CD4+ T cells[5]. In patients with sarcoidosis, IL-6 is increased in bronchoalveolar fluid[6] and in urine from patients with acute renal failure[7]. IL-6 blockers should have a protective role in sarcoidosis. However PAE have been described with tocilizumab in sarcoidosis[8]. Other possible induced events have been reported with tocilizumab, such as eye inflammation including uveitis[9], onset of psoriasis[10], and immune complex-mediated glomerulonephritis[11].

Whether the biological agent associated with PAE onset should be maintained or not is a challenging issue that depends on a number of factors, namely: the type of PAE and its severity, the preexisting condition that initially required the biological agent, and the existence of alternative therapeutic options for the underlying disease.

In our case the successful therapy consisted in taking the patient off the tocilizumab which was suspected to produce the PAE plus local anti-inflammatory as well as surface reconstitution eye drops. Because of a switch in the person of the treating rheumatologist the exposure happened to the patient twice. Up to date he could be sufficiently managed with systemic abatacept.

The non healing corneal erosion and melt and the granulomas responded very well to topical therapy with tear substitutes, dexamethasone eye drops and polycarboxymethylglucose sulfate matrix eye drops once the tocilizumab was halted.

This case illustrates once more that close comanagement and communication between treating rheumatologist and ophthalmologist is important for the management of the patient.

★ CONCLUSION ★

Patients suffering from systemic inflammatory disease may present with various ocular involvement. The disease itself as well as side effects of the necessary systemic medication may progress during the course of the disease. In order to treat the patients adequately close cooperation between rheumatologist and ophthalmologists is mandatory. This is the case especially in patients with severe disease and those receiving relatively new therapies, for which not all side effects might be known yet. This was the case in our patient who was exposed twice to the IL-6 receptor antagonist tocilizumab and on both occasions experienced scleral granulomas, non healing corneal erosions and corneal melt, a condition which has not yet been described. After cessation of the tocilizumab the lesions healed with subepithelial corneal scar formation with the help of topical dexamethasone, hyaluronic acid, polycaboxymethyl-glucose sulfate matrix eye drops and a bandage contact lens.

★ REFERENCES ★

1. J.Tode, R. Zeuner, M. Saeger, J. Roider and B. Nölle. Tocilizumab and steroid boli for treatment-resistant anterior necrotizing scleritis. ActaOphthalmologica.2015: 93:683–684.

2. S. Silpa-Archa, M. Oray, JM. Preble, CS. Foster. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. Ophthalmol. 2016; 94:400-6.

3. M. Cordero-Coma, S. Calleja-Antolín, I. Carzo-Garcia et al. Adalimumab for Treatment of Noninfectious Uveitis: Immunogenicity and Clinical Relevance of Measuring Serum Drug Levels and Antidrug Antibodies. Ophthalmology.2016:16:0161-6420.

4. É.Toussirot, F.Aubin. Paradoxical reactions under TNF-α blocking agents and other biological agents given for chronic immune-mediated diseases: an analytical and comprehensive overview. RMD Open. 2016;2:000239.

5. T. Urbankowski,G. Hoser, Domagala-Kulawik.Th1/Th2/Th17 related cytokines in the bronchoalveolarlavage fluid of patients with sarcoidosis: association with smoking. Pol Arch Med Wewn 2012;122:320–5.

6. Ishioka S., Saito T, Hiyama K, Haruta Y, Maeda A, Hozawa S, et al. Increased expression of tumor necrosis factor-alpha, interleukin-6, platelet-derived growth factor-B and granulocyte-macrophage colony-stimulating factor mRNA in cells of bronchoalveolarlavage fluids from patients with sarcoidosis. SarcoidosisVasc Diffuse Lung Disease.1996;13:139–45.

7. Maniwa K, Ogushi F, Haku T, Sone S, OhmotoY. Sarcoidosis associated with acute renal failure and increased levels of interleukin-6 in urine. Intern Med.1998;37:757–61.

8. A. Nutz, C.Pernet, B. Combe, J-D. Cohen. Sarcoidosis Induced by Tocilizumab: A Paradoxical Event? The Journal of Rheumatology.2013:10:1773-1774.

9. D. Wendling, E. Dernis, C. Prati, E. Frisch, B. Delbosc. Onset of inflammatory eye disease under tocilizumab treatment for rheumatologic conditions: a paradoxical effect?.J Rheumatol 2011;38:2284.

10. D. Wendling, H. Letho-Gyselinck, X. Guillot , C. Prati. Psoriasis onset with tocilizumab treatment for rheumatoid arthritis. J Rheumatol.2012;39:657.

11. Y. Matsuo, F. Mizoguchi, H. Kohsaka, E. Ito, Y. Eishi, N. Miyasaka. Tocilizumab-induced immune complex glomerulonephritis in a patient with rheumatoid arthritis. Rheumatology. 2013:52(7):1341-3.

BEST NATIONAL CASES

Damien GUINDOLET
Pierre & Marie Curie Medical School (Paris 6), Paris
FRANCE

A CONJUNCTIVITIS HARD AS WOOD

★ INTRODUCTION ★

Ligneous conjunctivitis is a rare cause of chronic conjunctivitis starting at any age from birth to 85 years of age[1] with a median age ranging from 3.5 to 5.5 years. Duration of the disease could range from few months to several decades[1]. It is characterized by the formation of recurrent fibrinous pseudomembrane above the palpebral conjunctiva, triggered by infection, inflammation, traumatism or surgery. It is the most frequent manifestation of a systemic disorder related to a quantitative deficit of plasminogen (prevalence 1.6:1,000,000[2]) impairing fibrin clearance. Cases were reported worldwide[2]. Normally, plasminogen is activated by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA) to form plasmin that is responsible of fibrinolysis (Figure 1).

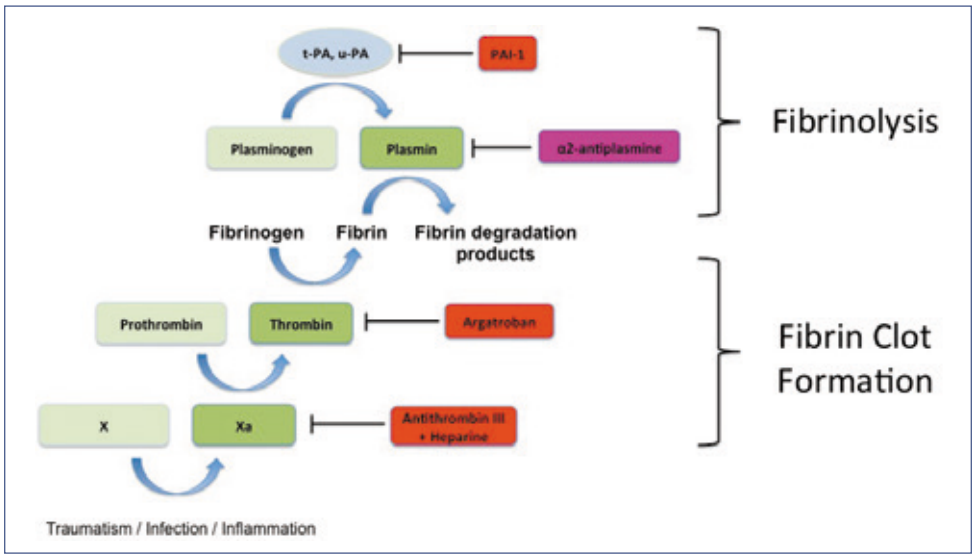


Figure 1: Schematic pathways of fibrin clot formation and fibrinolysis.
t-PA: tissue-type plasminogen activator; u-PA: urokinase-type plasminogene activator; X: factor X or Stuart–Prower factor; Xa: activated factor X; PAI-1: Plasminogen activator inhibitor-1.

Aside from fibrin degradation, plasminogen is also involved in pericellular proteolysis and wound healing[2]. Fibrin clearance deficiency is not associated with vascular thrombosis[3] and is limited to the extravascular tissues; fibrin formation is mainly located on mucosa, i.e. on the conjunctiva and to a lesser extent gingiva, nasopharyngeal or pulmonary tract, brain's ventricular system, genito-urinary or gastrointestinal tract. Local production of plasminogen and u-PA in tears during wound healing process[4] could evoke a major role of fibrinolysis process on ocular surface in comparison to other mucosa and could explain the predominant involvement of the ocular surface. The pseudomembrane is an accumulation of fibrin, epithelial and inflammatory cells[1]. Chronic inflammation and irritation of the ocular surface related to pseudomembrane could lead to blindness secondary to corneal damages (limbal stem cells deficiency, corneal scar and neovascularization).

Several genetic mutations were identified on the gene coding for plasminogen (located on 6q26); the inheritance is autosomal recessive.

Several treatments were used and described in the literature. Available treatments either inhibit fibrin clot formation (heparin[5], argatroban[6]) or activate de fibrinolysis (eyedrops[7,8] or systemic[9] administration of human plasminogen, fresh frozen plasma[10,11], fibrinolysin[12]). Local (corticosteroids or cyclosporin[13] A) or systemic (azathioprine[14]) anti-inflammatory drugs were also used; these treatments target ocular surface inflammation that induces fibrin formation. Few authors also reported the use of hyaluronidase, alpha-chromotipsine and mitomycin C[15], or amniotic membrane graft[16]. Several associations of aforementioned treatments were reported. Human plasminogen was recently reported and seamed efficient; nevertheless no

recombinant plasminogen is available and plasminogen is a product derived from human blood; its production is not possible in every country of the world and it implies complex and expansive manufacturing practices to guaranty the stability and the safety of the product.

We report a severe case of ligneous conjunctivitis treated with argatroban, a direct thrombin inhibitor.

★ CASE REPORT ★

A 2 years old girl was referred for the management of a ligneous conjunctivitis. She was Algerian and her parents were blood related (second-degree). She had a plasminogegen deficiency type 1 with a plasminogen activity level of 17%. The family refused genetic screening. Work-up demonstrated a moderate obstructive hydrocephalus. Her brother was also affected by plasminogen deficiency and died at one year of age of complications related to occlusive hydrocephalus.

She had bilateral pseudomembrane severely limiting eye opening (Fig. 2-A) that were associated to severe and painful diffuse punctate keratitis. She had no treatment or previous surgical removal of pseudomembrane. We introduced a treatment with sodium heparinate eye drops (5000UI/mL), 6 drops daily, associated to topical corticosteroids (fluorometholone, 4 drops daily), without success after 1 month of treatment. Therefore, we planed a surgical removal of pseudomembrane and to intensify postoperative local treatment. Under general anesthesia, fibrinous pseudomembrane were removed (Fig. 2-B,C,D). Removed pseudomembrane had a typical yellowish aspect and wood-like consistency. A subconjunctival injection of fresh frozen plasma was done at the end of the intervention (Fig. 2-E). After the surgery, sodium heparinate eye drops were continued hourly and we introduced argatroban eye drops with the same regimen in association with topical corticosteroids (rimexolone, 3 times daily). Two months after the surgery, she could keep her eyes wide open without pain or photophobia; the palpebral conjunctiva was not inflamed with mild deposits of fibrin (Fig. 2-F,G,H) that are part of normal conjunctival wound healing process. Argatroban enabled to avoid recurrence of severe fibrinous pseudomembrane after surgical removal. Local treatments were progressively tapered, nevertheless they should be continued and doses should then be adapted.

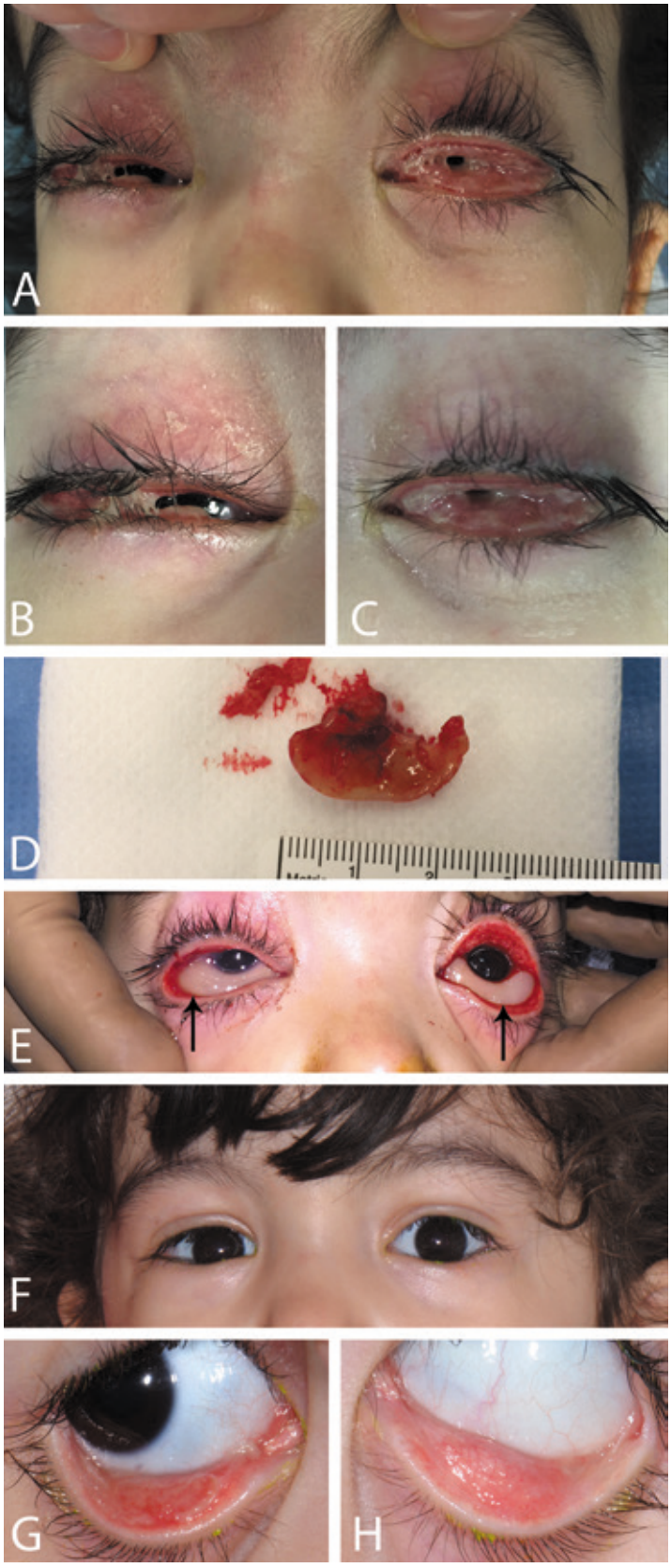


Figure 2: Patient's evolution before and after the surgery associated to the treatment with Argatroban.

A. Aspect before the surgery, after a one-month treatment with topical heparin and corticosteroids. Eyes are closed because of fibrinous pseudomembrane. B & C. Magnified aspect are displayed in B (right eye) and C (left eye). D. Aspect of the removed pseudomembrane (scale in centimeter). E. Immediate postoperative aspect after bilateral removal of fibrinous pseudomembrane and subconjonctival injection of fresh frozen plasma (arrows). F. Two month after the surgery, the girld could keep her eyes wide open. G & H. Aspect of the conjunctiva of the right (G) and the left (H) eye 2 months after the surgery.

★ DISCUSSION ★

Argotroban was used with success in conjunction to topical heparin and corticosteroids to avoid recurrence of pseudomembrane after surgical removal.

There are no studies to compare the efficiency of treatments reported in the literature. Several drawbacks of plasminogen substitute and fresh frozen plasma can be listed: human origin with potential transmission of infectious agents, specific conservation conditions with potential infection of the product and their commercial unavailability. Our choice was limited to commercially available treatments as product derived from human blood would not be available in her country. Argatroban was used considering the initial severity of the ocular involvement and also regarding reported frequent failure of the association topical heparin and corticosteroids. Argatroban is direct thrombin inhibitor; thrombin is a proteolytic enzyme that converts fibrinogen into fibrin that results in a clot formation after polymerization. Heparin acts indirectly, inhibiting factor Xa that cleaves prothrombin (yielding to the active thrombin), or by increasing antithrombin III activity that inactivate thrombin. The effect of argatroban combined to heparin could be synergistic[17]. Only two reported cases were treated with argatroban[17]. It should be emphasized that surgical removal of pseudomembrane should be performed in association with the appropriate medical treatment of the disease, and should not be considered as the main treatment; surgical procedure alone will fail and could result in worsen lesions[1].

★ CONCLUSION ★

Topical argatroban is efficient in association to topical heparin and corticosteroids to prevent recurrence of ligneous conjunctivitis related to plasminogen deficiency. This association could be used when blood derived products are not available.

★ REFERENCES ★

1. Hidayat, A. A. & Riddle, P. J. Ligneous conjunctivitis. A clinicopathologic study of 17 cases. Ophthalmology 94, 949–959 (1987).

2. Schuster, V. & Seregard, S. Ligneous conjunctivitis. Surv. Ophthalmol. 48, 369–388 (2003).

3. Shigekiyo, T. et al. Type I congenital plasminogen deficiency is not a risk factor for thrombosis. Thromb. Haemost. 67, 189–192 (1992).

4. Berta, A., Tözsér, J. & Holly, F. J. Determination of plasminogen activator activities in normal and pathological human tears. The significance of tear plasminogen activators in the inflammatory and traumatic lesions of the cornea and the conjunctiva. Acta Ophthalmol. (Copenh.) 68, 508–514 (1990).

5. De Cock, R., Ficker, L. A., Dart, J. G., Garner, A. & Wright, P. Topical heparin in the treatment of ligneous conjunctivitis. Ophthalmology 102, 1654–1659 (1995).

6. Suzuki, T., Ikewaki, J., Iwata, H., Ohashi, Y. & Ichinose, A. The first two Japanese cases of severe type I congenital plasminogen deficiency with ligneous conjunctivitis: successful treatment with direct thrombin inhibitor and fresh plasma. Am. J. Hematol. 84, 363–365 (2009).

7. Conforti, F. M. et al. Novel plasminogen and hyaluronate sodium eye drop formulation for a patient with ligneous conjunctivitis. Am. J. Health-Syst. Pharm. AJHP Off. J. Am. Soc. Health-Syst. Pharm. 73, 556–561 (2016).

8. Schott, D. et al. Therapy with a purified plasminogen concentrate in an infant with ligneous conjunctivitis and homozygous plasminogen deficiency. N. Engl. J. Med. 339, 1679–1686 (1998).

9. Pergantou, H. et al. Management of ligneous conjunctivitis in a child with plasminogen deficiency. Eur. J. Pediatr. 170, 1333–1336 (2011).

10. Tunay, Z. Ö., Özdemir, Ö., Acar, D., Gül, E. & Akbay, S. Successful treatment of ligneous conjunctivitis with topical fresh frozen plasma in an infant. Arq. Bras. Oftalmol. 78, 318–319 (2015).

11. Tabbara, K. F. Prevention of ligneous conjunctivitis by topical and subconjunctival fresh frozen plasma. Am. J. Ophthalmol. 138, 299–300 (2004).

12. Melikian, H. E. Treatment of ligneous conjunctivitis. Ann. Ophthalmol. 17, 763–765 (1985).

13. Holland, E. J. et al. Immunohistologic findings and results of treatment with cyclosporine in ligneous conjunctivitis. Am. J. Ophthalmol. 107, 160–166 (1989).

14. Cohen Tervaert, D., Cruysberg, J. R., Deutman, A. F. & Manschot, W. A. Ligneous conjunctivitis. Doc. Ophthalmol. Adv. Ophthalmol. 64, 5–11 (1986).

15. Meire, F. M., Claerhout, I. & Kestelyn, P. H. Use of mitomycin C and r-tPA for the management of conjunctival membrane and cataracts in a child with conjunctivitis lignosa. Br. J. Ophthalmol. 84, 1204–1205 (2000).

16. Tok, O. Y., Kocaoglu, F. A., Tok, L., Burcu, A. & Ornek, F. Treatment of ligneous conjunctivitis with amniotic membrane transplantation and topical cyclosporine. Indian J. Ophthalmol. 60, 563–566 (2012).

17. Tanaka, K. A. et al. The effects of argatroban on thrombin generation and hemostatic activation *in vitro*. Anesth. Analg. 99, 1283–1289; table of contents (2004).

Bennis AHMED
CHU Hassan II, Fès
MOROCCO

INVASIVE SQUAMOUS CELL CARCINOMA OF THE CORNEA TREATED WITH MITOMYCIN EYE DROPS

★ INTRODUCTION ★

Squamous cell carcinoma of the cornea represent a particular clinical form of squamous neoplasia of the ocular surface, this rare lesion affect more frequently conjunctiva and the limbus, but there are pure corneal forms without conjunctival or limbic invasion [1].

That invasive tumor is more frequent in elderly and male patients [2], it stems from the epithelial cells of the ocular surface, and its evolution is slowly progressive [1].

These malignancies can in a few years of change (five to nine years in most literature series), invade the epithelial basement membrane to become invasive carcinoma [1].

Exposure to UV.B [3], infection with the human papillomavirus (HPV 16,18) [4] or immunosuppression [5] are the main aetiopathogenic factors usually involved in this type of neoplasia.

Complete surgical excision for squamous cell cacinoma of the ocular surface with 4mm margin clearance without touching the tumour dubbed the « no touch technique » is the treatment of choice [6,7,8]. But the recurrence rate is important, for this reason different therapeutic alternatives were develloped specially topical therapies which offer a non-surgical method for treatment of the entire surface, without defining tumor limits [9].

The purpose of this report is to discuss the use of topical 4% mitomycin c as a sole therapy for invasive and extensive corneal squamous cell carcinoma without surgical excision.

★ CASE PRESENTATION WITH ILLUSTRATIONS ★

A 57 year old man, without previously ocular history, worked as a security guard, exposed to strong sun rays more than 8 hours a day. He presented to our department with reduced vision in the left eye started 2 years earlier.

His best corrected visual acuity was 20/20 in the right eye, without anterior or posterior segment alterations. On left eye visual acuity was limited to count of fingers at a distance of less than a meter, at the slit lamp we found a limited pinkish richly vascularized sessile lesion which is slightly raised and ending with prominent blood vessels giving a raspberry aspect.

With this clinical aspect suggesting malignancy, patient had a biopsy of the tumor with a moderately differentiated invasive squamous cell carcinoma (figure 1) as a result.

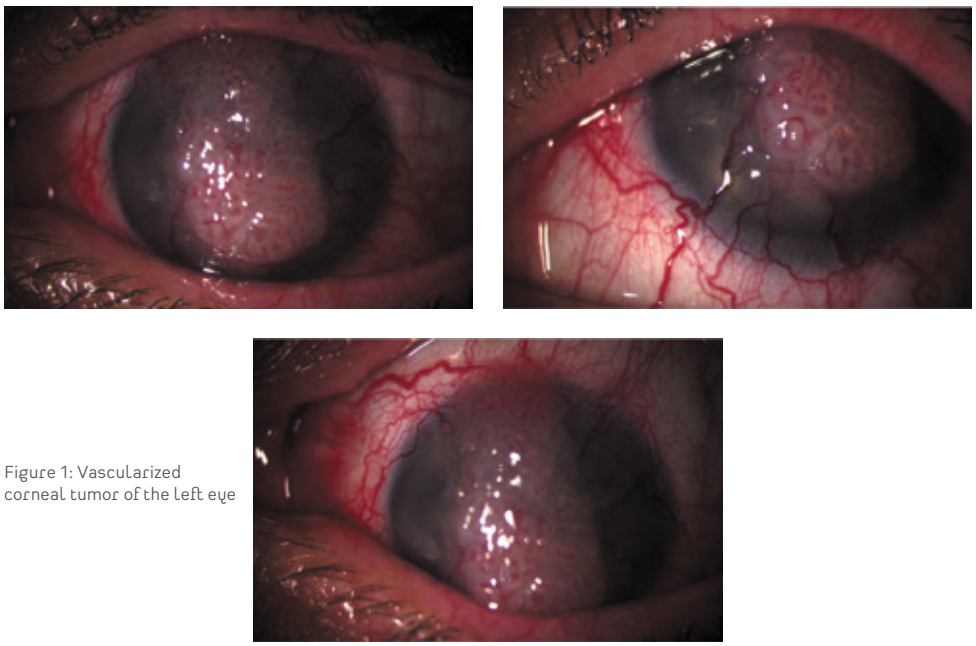


Figure 1: Vascularized corneal tumor of the left eye

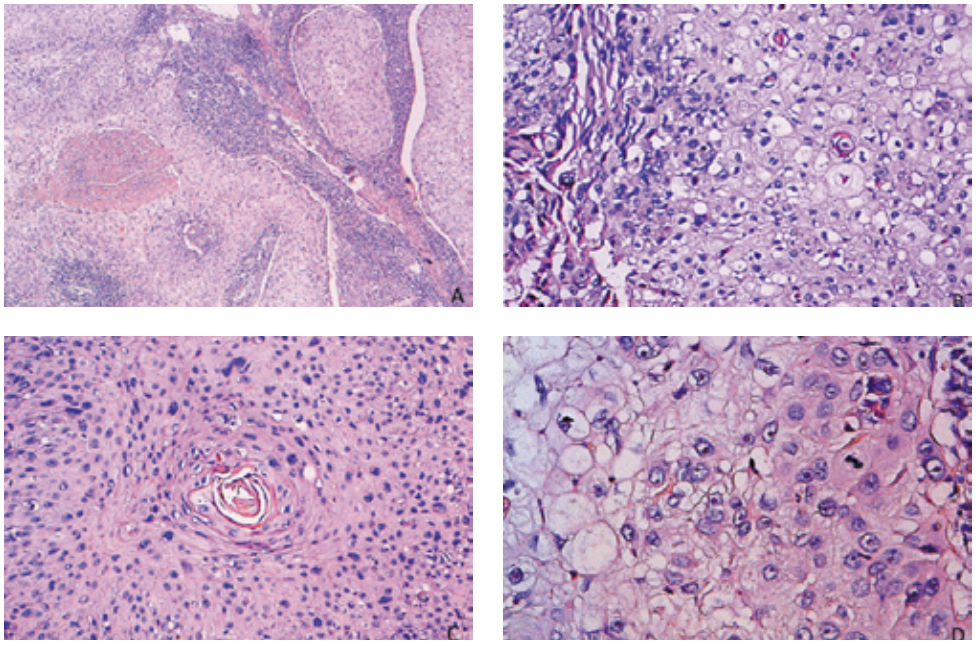


Figure 2: invasif Squamous Cell Carcinoma (A : HES*50, B : HES*100 , C :HES*200, D :HES*400)

★ TREATMENT ★

Since radical treatments were refused by the patient, we opted for the alternative of using Mitomycin C eye drops (4 percent for four cure periods), explaining to the patient the higher probability risk of further tumor spreading.

★ EVOLUTION ★

Evolution was marked by a complete disappearance of the tumor (Figures 3, 4, 5, 6) and no sign of recidivism was found even after a two years follow up.

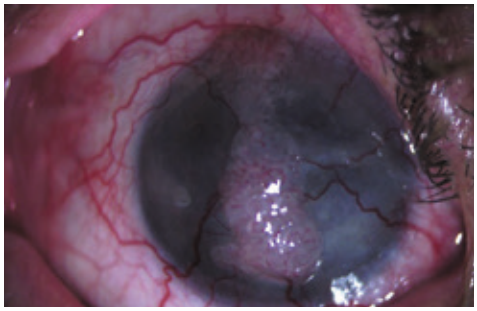
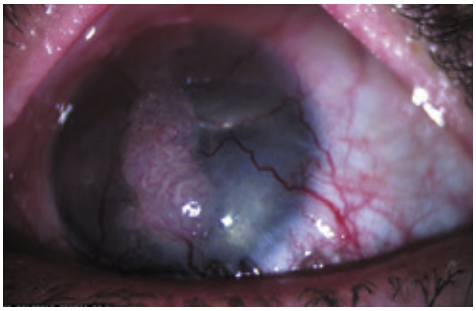



Figure 3: After the First cure, with one week of 4 percent of mitomycin eye drops

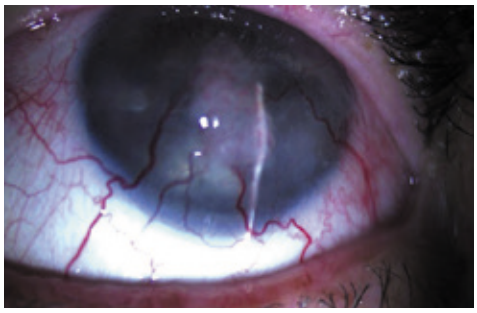
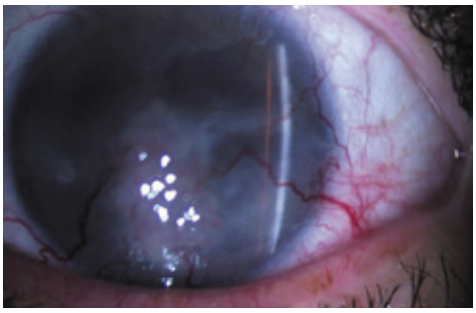



Figure 4: After the second cure

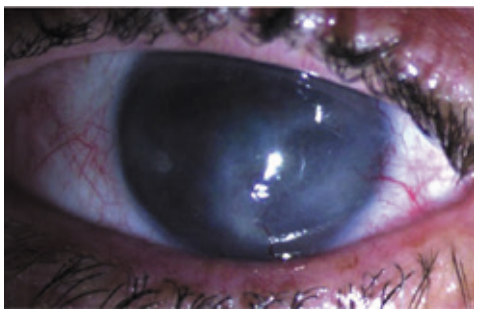
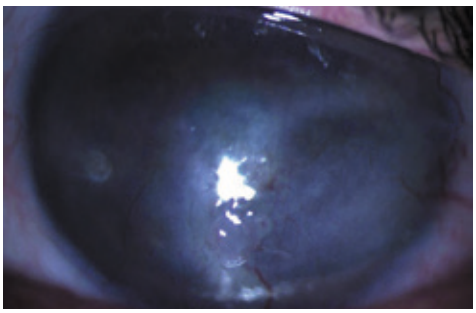



Figure 5: After the third cure

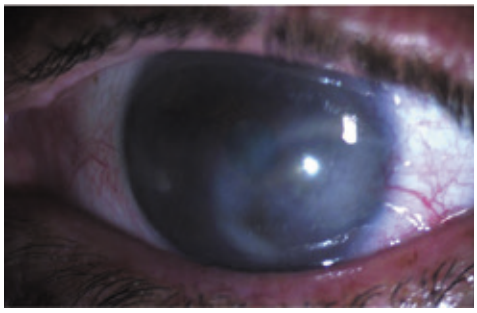
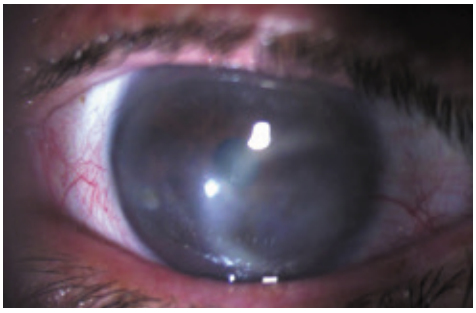



Figure 6: 1 month after 4 cures of mitomycin eye drops 4percent

Figure 7: 6 months after treatment

★ DISCUSSION ★

Squamous cell carcinoma is an extremely rare cause of progressive corneal opacification and neovascularization, and a delayed diagnosis may lead to unsuccessful treatment and loss of the eyeball [2].

Wide surgical excision has been considered the treatment of choice for OSSN lesions and specialized techniques for decreasing recurrence rates have been described [10,11]. Despite adjunctive cryotherapy, intraoperative application of alcohol, and other precautions, recurrence rates for OSSN following excision range between 15% and 52% [10,12]. Incomplete excision with positive surgical margins has been identified as a major risk factor for recurrence [10].

according to the literature the use of mitomycin C is recommended as adjuvant therapy to surgical excision to reduce tumor size before surgery or control of the tumor margins and prevent recurrence, but in case of large tumor with invasion of the underlying structures radical treatment still the only choice[10].

The treatment of this extenive tumor should be enucleation of this eye, but given the patient's refusing, treatment with Miomycin was started without real conviction of the team especially when taking into consideration the excessive size of tumor.

To our knowledge this is the first report in the literature and we are unaware of previous reports of this peculiar tumor covering the majority of the surface of the cornea treated with topical 4 % mitomycin C with a complete disappearance of the tumor and could find no reference to it in a computer search using MEDLINE.

★ CONCLUSION ★

This case highlights the possibility of conservative treatment despite extencive tumor at the surface and at depth of the cornea when the choice should be made for a radical surgery, topical MMC can be used as a surgical adjunct for invasive tumors, both preoperatively to decrease the size of diffuse lesions before surgical excision and postoperatively to risk of decrease recurrences.

★ REFERENCES ★

1. G. Bonnaų , M. Saleh , A. Sauer , D. Gaucher , C. Speeg-Schatz , T. Bourcier Carcinomes in situ de la cornée Corneal intraepithelial neoplasia j.jfo.2011.03.020

2. P. Rodríguez-Ausína,*, C. Hita-Antóna, C. Míguez-Garciaa, D. Antolín-Garciaa, J. Suárez-Aguado b. A new OCT sign of invasive squamous cell carcinoma of the cornea ar ch soc e s p of talmol . 2 0 1 6;91(2):90–93

3. Hug H D. Mcgowa N, M.D., Frc Sc La néoplasie squameuse conjonctivale: nouvelle classification TNM de l'American Joint Committee on Cancer (AJCC) Ophtalmologie Conférences scientifiques JANVIER/FÉVRIER 2009 Volume 7, numéro 1

4. Mcdonnel J.M, Mayr A.J., Martin W.J DNA of human papilloma virus type 16 indysplasic and malignant lesions of the conjunctiva and cornea. New Engl. J.Med., 1989, 320, 1142-1146

5. Lee G.A., Hirst L.W, Ocular surface squamous neoplasia. Surg ophtalmol, 1995, 39, 429-450

6. Shields CL, Shields JA. Tumours of the conjunctiva and cornea.Surv Ophthalmol. 2004;49:3–24

7. Mauriello JA, Napolitano J, Mclean I. Actinic keratosis and dysplasia of the conjunctiva: A clinicopathological study of 45 cases. Can J Ophthalmol. 1995;30:312–16.

8. Shields Ja, Shields Cl, De Potter P. Surgical management of conjunctival tumours. The 1994 Lynn B. McMahan Lecture. Arch Ophthalmol. 1997;115:808–15.

9. Padma Prabha Dandala, Padma Malladi, and Kavitha Ocular Surface Squamous Neoplasia (OSSN): A Retrospective Study J Clin Diagn Res. 2015 Nov; 9(11): NC10–NC13.

10. Jonathan W Kim and David H Abramson Topical treatment options for conjunctival neoplasms Clin Ophthalmol. 2008 Sep; 2(3): 503–515.

11. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture.Arch Ophthalmol. 1997;115:808–15

12. Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol. 1995;39:429–50.

Peter John MORGAN-WARREN
Health Education West Midlands
UNITED KINGDOM

CHALLENGES IN THE MANAGEMENT OF SEVERE *FUSARIUM* KERATITIS: A ROLE FOR INTRASTROMAL VORICONAZOLE

★ INTRODUCTION ★

Fungal keratitis is a serious ocular infection with potential for catastrophic visual outcomes. Often diagnosed late, and commonly resistant to treatment, fungal keratitis may progress to deep corneal involvement, corneal descemtocoele, corneal perforation or endophthalmitis[1,2]. We report a case of severe *Fusarium* keratitis that highlights many important aspects of fungal corneal disease, including delay in diagnosis and challenges with effective clinical management, and report our experience with intrastromal antifungal therapy, an emerging clinical therapeutic option aimed at reducing the need for surgical intervention.

★ CASE REPORT ★

A 50 year old contact lens wearer was referred by a local unit to our Eye Casualty clinic with an eight-week history of a large right eye corneal ulcer that was not responding to therapy. He had presented approximately 6 weeks previously to the referring unit with a 2-week history of ocular discomfort and reduced vision OD (BCVA 6/15 Snellen, approximately logMAR 0.4) and was noted to have a corneal ulcer measuring 3 x 4 mm in size. Corneal scrapes were taken at presentation and he was commenced on intensive topical treatment with cefuroxime 5%, ciprofloxacin 0.3%, ganciclovir 0.15% and oral acyclovir 800mg five times daily. The clinical diagnosis at this stage was herpetic keratitis with secondary microbial keratitis. The patient had no history of herpetic eye disease and viral swabs were not taken prior to antiviral treatment. One week later there had been some clinical response, and the treatment was continued. Six weeks after his initial presentation BCVA was 6/48 (approx. 0.9 logMAR) with a 3.5 x 3.5mm corneal ulcer. The initial corneal scrapes isolated *Fusarium oxysporum* and scanty growth of *Candida* species, but no bacterial growth. Definitive anti-fungal therapy was unavailable at the referring unit, and the patient was referred to our clinic for ongoing management.

On presentation to our unit, BCVA was counting fingers (CF) in the right eye and 6/4 Snellen (approximately logMAR -0.2) in the fellow eye. Clinical examination demonstrated a large, purulent corneal ulcer OD, with a 3.1 x 3mm epithelial defect and infiltrate on the temporal cornea, with some small deep satellite lesions superiorly, and feathery endothelial opacity. There was a 1.1mm hypopyon and B-scan ultrasonography confirmed the absence of vitreal inflammation (Figure 1). Corneal sensation was normal. The clinical appearance was highly suggestive of fungal keratitis, supported by the positive microbiological isolate reported at the referring unit. The initial management was to temporarily stop all the concurrent treatment and undertake a new set of corneal scrapes for microbiological investigation, including gram stain, blood agar, chocolate agar, sabaroud media, acanthamoeba plate (non-nutrient agar overlaid with E.coli). As his treatment regime had been consistent for a significant period of time, a minimum of 12 hours was left after stopping all treatment before samples were taken. He was admitted and commenced on intensive topical treatment, comprising voriconazole preservative free (PF) and natamycin PF (hourly day and night), levofloxacin PF 6 times daily, atropine 1% PF bd, and oral voriconazole 200mg bd. The hypopyon initially increased to 1.9mm on the first day, but the clinical picture improved significantly over 5 days of admission, with the hypopyon measuring <0.2mm and a smaller ulcer. The patient did not wish to remain an inpatient, and was discharged on natamycin and voriconazole, each 6 times daily, and oral voriconazole. On review three days later, the patient reported increased pain and further reduced vision, with a recurrence of the hypopyon (now 1.6mm) (Figure 2). The admission corneal scrapes confirmed *Fusarium oxysporum* as the isolated pathogen, and PCR demonstrated the presence of *Fusarium* 18s RNA. The patient was re-admitted for intensive topical antifun-

gals day and night, although the ulcer failed to respond adequately to treatment. Six days after the re-admission, the patient underwent corneal intrastromal injection of voriconazole (0.3ml of 1mg/ml solution), combined with intracameral voriconazole (0.1ml of 0.5mg/ml) and cefuroxime (1mg), in a dedicated clean room in the eye clinic. After 2 days, the ulcer had reduced in size to 1.5 x 1.5mm, with a 0.8mm hypopyon, and the patient was discharged home on hourly topical voriconazole and natamycin, levofloxacin qds and oral voriconazole 200mg bd. Clinic review a week later showed an improvement in the ulcer appearance, with BCVA improved to 6/24 (0.6 logMAR). Intensive topical antifungals were continued, with the addition of the topical lubricant sodium hyaluronate and ciclosporin 0.1%. Unfortunately, over the following week the patient experienced an increase in ocular pain, and an impending corneal perforation was noted at the base of the residual ulcer. He reported that he had stopped using topical voriconazole a few days prior as it was causing irritation symptoms. Corneal glue was applied to the perforation at the slit lamp, and a bandage CL placed (Figure 3).

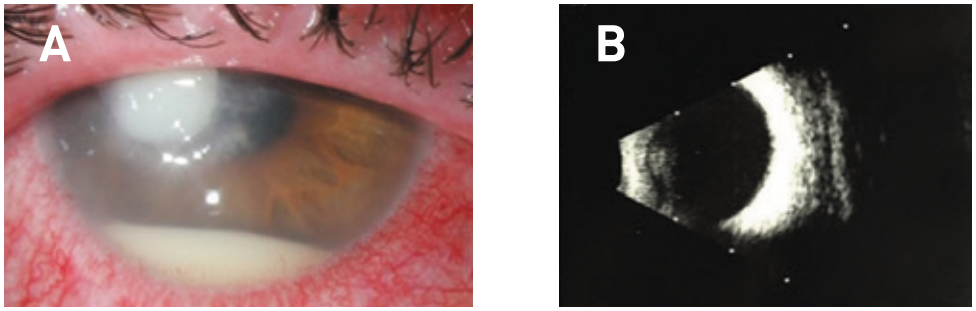


Figure 1: Clinical appearance on presentation to our Eye Clinic. (A) Large corneal epithelial defect and infiltrate, with endothelial plaque and hypopyon. (B) B-scan ultrasonography demonstrating absence of vitreal inflammation.

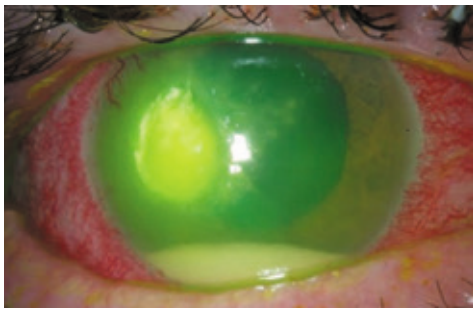


Figure 2: Clinical appearance on readmission, 10 days after commencement on antifungal therapy. The large infiltrate, epithelial defect and hypopyon had improved after initial treatment, but deteriorated after a reduction in the intensity of topical treatment at home. Note that topical fluorescein had been instilled shortly before this photograph as taken.

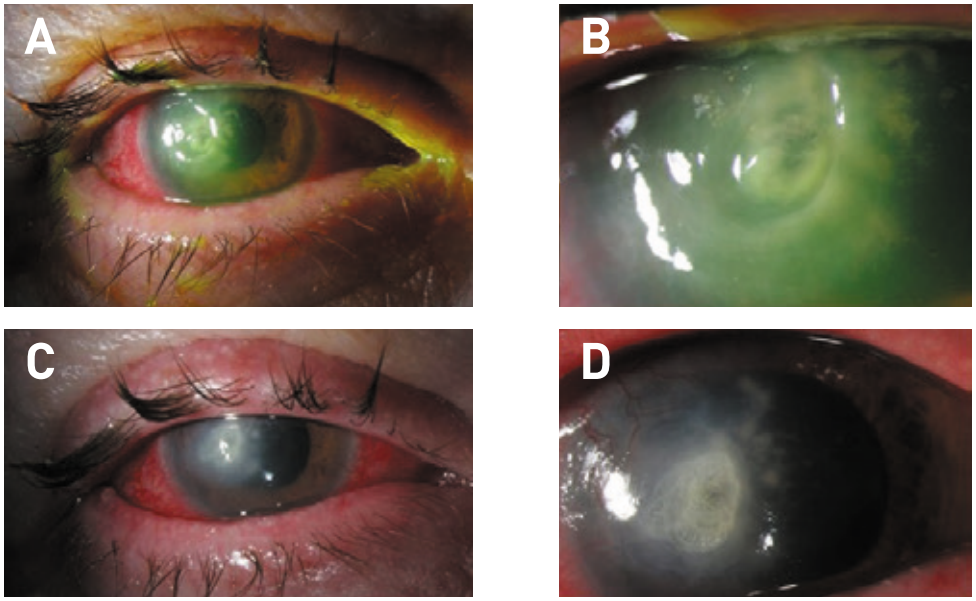


Figure 3: (A, B) Two weeks after intrastromal voriconazole, the infiltrate was resolving and the hypopyon had cleared, but an impending corneal perforation was apparent at the base of the residual ulcer, requiring application of cyanoacrylate glue to restore corneal integrity. (C, D) One week after corneal gluing.

Within 3 weeks the patient had a significant clinical improvement with the BCVA improving to 6/24 and with pinhole up to 6/12. The area of corneal thinning eventually recovered with scarring and the cyanoacrylate glue detached and bandage contact lens was no longer necessary. There are 2 main reasons why the descemetocele appeared; due to necrotic cell death following treatment with intense antifungal, or an inflammatory melt-like process from chronic inflammation. Intrastromal voriconazole may have also accelerated this process due to direct effect on the fungal infiltrate.

The decision to gradually reduce antifungal treatment was based on the improving clinical picture, but due to increasing neovascularisation despite ciclosporin drops and reducing infiltrate size, the decision was made 4 months after initiation of antifungal treatment to introduce prednisolone 0.5% minims twice a day. Despite rapid clinical improvement within the first ten days (the patient reported he could see much better and the redness had almost disappeared), he re-presented 2 weeks later with an increasingly painful eye and 1mm hypopyon. He had a recurrence of the fungal infection from one of the endothelial satellite lesions with no external epithelial defect evident. The steroid was stopped and natamycin increased to 1 hourly day and night with oral voriconazole recommenced. Two weeks after this regimen he returned to the stage just prior to starting steroid drops. The decision was made to avoid any steroid drops until all endothelial signs disappear, and continue natamycin drops qds and oral voriconazole with the only anti-inflammatory drop being ciclosporin as it also has antifungal properties. At the time of writing, the clinical appearance is improving, with BCVA 6/12.

★ DISCUSSION ★

Fungal keratitis accounts for approximately 1-44% of cases of microbial keratitis, with the incidence varying markedly depending on geographical location[3]. Traditionally associated with tropical and subtropical areas, the most common risk factor is agricultural trauma with vegetable matter or soil contamination, accounting for up to 40-50% of all corneal infections in some countries, such as India[3, 4]. Fungal keratitis is becoming increasingly common in developed countries, with use of contact lenses and their solutions emerging as a crucial risk factor in recent years. One large series of fungal keratitis cases from 10 tertiary centres in the United States identified CL wear as the presumed risk factor in 37%, with ocular trauma accounting for 25%[3]. Ocular surface disease is also an important risk factor, especially for infections with yeast, such as *Candida*[5,6].

Awareness of fungal keratitis associated with CL use has increased significantly since an outbreak of *Fusarium* keratitis in the United States and Singapore in 2004-2006[7]. Outbreaks were subsequently also reported in other countries, including France[8] and Switzerland[9], and studies found a new contact lens care solution, ReNu with MoistureLoc (Bausch & Lomb) was likely responsible for a majority of cases, possibly due to loss of fungistatic activity of the lens care solution with failure to regulate storage and transport temperatures[10]. Our patient was a long-term user of monthly soft contact lenses, and as such was at risk of developing corneal infection. Although the culprit lens care solution in the previously documented worldwide outbreaks has been withdrawn, and we cannot directly attribute our case to the lens care solution, it does correlate with epidemiological evidence of increasing cases of *Fusarium* keratitis associated with CL wear[11], and highlight the fact that clinicians should have a high index of suspicion for fungal keratitis in a CL wearers presenting with corneal infections.

As demonstrated in our case, there can often be a considerable delay between the onset of symptoms and the confirmation of diagnosis of fungal keratitis. Early fungal keratitis may be clinically indistinguishable from other causes of microbial keratitis, and our patient was managed for several weeks by the referring unit as a presumed case of viral and bacterial keratitis until *Fusarium oxysporum* was isolated on microbiological sample. Upon presentation to our department the case had many classic features of fungal keratitis, including deep-seated ulceration, feathery borders, endothelial plaque and hypopyon (Figures 1 & 2), and further confirmation of the diagnosis was provided by PCR. Severe features at presentation, such as the presence of hypopyon, are indicative of a poor prognosis and many will need early surgical input.

Conventional methods for diagnosis of fungal keratitis include Gram stain, Giemsa stain and 10% potassium hydroxide (KOH) wet mount, the latter being one of the most common direct microscopy procedures for detection of fungal elements as it is inexpensive and rapid, although its sensitivity is limited.4 Sabouraud dextrose agar is a commonly used culture medium for isolating fungi, although may take several days for a positive culture.

Although relatively expensive and not widely available, PCR has emerged as a highly sensitive and specific diagnostic test, with results available in hours, rather than days[12, 13]. Technical limitations of PCR include artefactual amplification of non-pathogenic organisms and DNA, potentially leading to over-diagnosis, and so PCR as a stand-alone diagnostic method for fungal keratitis is not recommended[12, 13]. However, the rapid detection of fungal DNA in corneal scrape material may allow anti-fungal therapy to be commenced at an earlier stage of keratitis, particularly where there is a lack of classic clinical features. Our case may have benefited from a less protracted clinical course had PCR been utilised earlier in his management.

Medical Management

Timely commencement of appropriate antifungal agents is important in the management of fungal keratitis in order to increase the potential for better clinical outcomes. Although keratitis due to any fungal infection is serious and may require surgical intervention for definitive treatment, infection with *Fusarium* species can be especially problematic, due both to specific pathogenic mechanisms and also to the relative resistance of *Fusarium* to antifungal treatment. It has been demonstrated that formation of biofilms is a key pathogenicity determinant of *Fusarium*, resulting in higher minimum inhibitory concentration (MIC) values for commonly used antifungal medications[14]. Several studies have investigated the preferred antifungal regimes for fungal keratitis, providing reliable evidence that natamycin is the preferred agent, especially for *Fusarium* infections. The Mycotic Ulcer Treatment Trial compared topical natamycin versus voriconazole in 368 cases of *Fusarium*, *Aspergillus* and other filamentous fungal keratitis[15]. It found significantly better 3-month visual acuity and reduced likelihood of corneal perforation compared to voriconazole, especially in *Fusarium* cases, thus favouring natamycin as the agent of choice against *Fusarium*. Sharma et al reported a prospective, double-masked, randomised controlled trial comparing the efficacy of topical voriconazole versus natamycin for the treatment of fungal keratitis in 118 patients, demonstrating more patients with healing ulcers and significantly greater improvements in visual acuity in eyes treated with natamycin, and a significantly better response to natamycin in *Fusarium* keratitis than *Aspergillus*[16]. Furthermore, two systematic reviews have concluded that topical natamycin 5% is more effective than topical voriconazole 1% in the treatment of *Fusarium* keratitis, and therefore this should be the topical agent of choice where available[17, 18]. In practice, antifungal susceptibility testing is not routinely carried out and therefore patients are likely to be treated with a combination of agents. Our patient was managed with both natamycin and voriconazole, an approach supported by *in vitro* data which has demonstrated synergism between these two agents against many *Fusarium* strains[19].

A role for intrastromal voriconazole

In common with many cases of fungal keratitis, our case failed to adequately respond to intensive topical therapy and oral antifungals. We therefore undertook intrastromal injection of voriconazole in an attempt to halt the clinical deterioration and help control the disease process. The combination of limited spectrum of activity, poor ocular penetration and ocular surface toxicity associated with topical antifungal treatments has led to increasing research into more targeted drug delivery, and in recent years there have been several reports of advocating an advantageous therapeutic effect of intrastromal injection of antifungal agents. Such an approach overcomes the poor bioavailability of antifungal agents, provides a depot of antifungal agent close to the ulcerated area, from where it is released into the adjacent infected tissue[2], and may prevent the need for more invasive surgical intervention, such as keratoplasty (Figure 4).

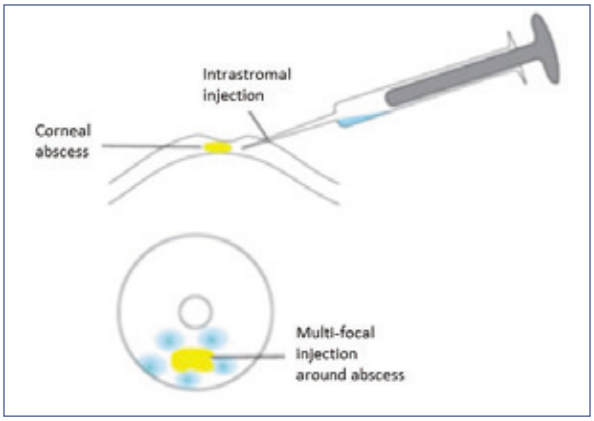


Figure 4: Schematic representation of method of corneal intrastromal injection

In a laboratory study evaluating the effect of intrastromal voriconazole against *Fusarium solani* keratitis in a rabbit model, there was a significant reduction in clinical score (area/density of corneal opacity and surface irregularity), fungal colony forming units, signs of chronic inflammation and anterior corneal vascularisation compared to topical voriconazole treatment[20]. In the clinical setting, Prakash and colleagues described complete resolution of corneal ulcers in three patients with recalcitrant fungal keratitis resistant to topical antifungals[21], and Siatiri et al reported a dramatic therapeutic response with reduction in infiltrate size and control of infection in two patients with *Fusarium* keratitis[22]. A case series of 12 eyes with microbiologically proven fungal corneal ulcer, which did not respond to topical and systemic voriconazole were treated with intrastromal injections of 50µg/0.1ml voriconazole, and enabled complete ulcer resolution in 10 (83%) cases[23]. A majority of these cases, however, required two or three injections at 72 hour intervals for adequate clinical response. Kalaiselvi et al reported a large series of 25 eyes of fungal keratitis refractory to topical natamycin and voriconazole, including 13 eyes with *Fusarium* isolates, reported resolution of ulcer in 18 (72%) patients[24]. Twelve of these cases responded to a single injection, 2 required

one repeat injection and 2 underwent a total of three intrastromal injections. A further two cases, similar to our case, had impending corneal perforation during follow-up and were successfully managed with cyanoacrylate glue and bandage contact lens. Intrastromal voriconazole has also been shown to be a useful therapy in cases of *Alternaria* keratitis[25], recalcitrant *Acremonium* fungal keratitis[26], interface infection in late-onset infectious keratitis after DSAEK[27], cataract surgery tunnel *Aspergillus* infection[28], and post-photorefractive keratectomy fungal keratitis[29].

Despite the relatively broad antifungal spectrum of action of voriconazole[30], there are some conflicting results in the literature, including possible species-specific variation in susceptibility and response to intrastromal administration. One randomised study found no significant benefit in the addition of intrastromal voriconazole over topical agents in 40 cases of unresponsive fungal keratitis[31]. Niki and colleagues reported rapid clinical resolution of four case of fungal keratitis caused by *Candida* after intrastromal voriconazole, but recurrences in cases of keratitis due to filamentous fungi (*Fusarium* and *Aspergillus*), which required adjuvant treatment with topical and systemic antifungals and progression to keratoplasty[32]. Moreover, out of seven treatment failures in the large case series of Kalaiselvi et al described above, *Fusarium* species were responsible for six (86%), and only 7/13 cases of *Fusarium* keratitis in the series responded to intrastromal voriconazole[24], illustrating the fact that *Fusarium* may be a particularly resistant group of organisms. Amongst this genus, *F solani* is the most resistant and, along with *F oxysporum* (isolated in our case), is amongst the most common isolate in fungal keratitis[33].

As mentioned previously, there is good evidence that natamycin is a more effective therapeutic choice in the treatment of fungal keratitis. There are currently no clinical reports of intrastromal delivery of natamycin in the treatment of fungal keratitis, but intrastromal natamycin 5% has been investigated in a rabbit model of *Fusarium solani* keratitis, and failed to show significant benefit over topical therapy alone[34]. Thus, whilst there is some promise for the use of intrastromal antifungal treatment in resistant cases of fungal keratitis, current evidence suggests it should be restricted to voriconazole. Moreover, intracameral voriconazole may be beneficial for localised delivery of antifungal treatment, particularly in the presence of endothelial exudates that are too deep to respond to topical/intrastromal injection[35]. Further work is required to ascertain the optimum treatment regime, although it appears worth considering intrastromal delivery in cases of fungal keratitis that are unresponsive to topical and systemic administration, before opting for surgical intervention.

Future directions

There are many exciting advances which may become standard of care for fungal keratitis in the future. DNA sequencing methods are likely to be more widely employed in rapid, specific diagnosis of fungal pathogens. Genotyping may identify species-specific antifungal susceptibility profiles[36], thus yielding important prognostic information to guide appropriate therapy.

Advances in medical management include both the development of newer antifungal agents and optimised delivery methods. Posaconazole is a new triazole antifungal, a synthetic analogue of the widely used itraconazole, that interferes with fungal cell wall ergosterol synthesis[37]. Both *in vitro* and *in vivo* studies suggest a broad spectrum of activity against *Candida, Cryptococcus* and *Aspergillus* species and there is emerging case report evidence of rapid resolution of resistant *Fusarium* ulcers with systemic posaconazole, alone or in combination with topical therapy[2]. Echinocandins are a newer class of antifungals, acting via inhibition of 1,3-β-d-glucan synthesis, leading to increased fungal cell wall permeability and cell lysis[2]. There are limited data on the use of this class of antifungals in keratitis, although case reports have shown success of micafungin and caspofungin in treating fungal ulcers resistant to conventional therapy[38,39]. Naturally occurring antimicrobial peptides, such as defensins, human cationic antimicrobial protein (CAP), lysozyme, lactoferrin and mucins have significant potential for use as therapeutic agents for ocular infections, with potential advantages including broad-spectrum activity, low risk of resistance and synergy with conventional antibiotics[40]. There is increasing laboratory data supporting efficacy of antimicrobial peptides against fungal pathogens, but at present there is no clinical evidence to support their use. Finally, there has been much interest in the potential role of corneal collagen cross linking (CXL) in infectious keratitis, and the term photoactivated chromophore for infectious keratitis (PACK)-CXL has been adopted to distinguish its use from CXL in kerectasia[41,42]. PACK-CXL may have both a direct antimycotic effect and halt corneal melting in response to fungal infection, thus potentially reducing the need for surgical keratoplasty. Antifungal activity has been shown against *Candida*, *Fusarium* and *Aspergillus* species, but at present the results of clinical use are contradictory. There are reports that PACK-CXL is useful in the management of fungal keratitis[43,44], but other studies that demonstrated no significant advantage against standard therapy[45], and concerns about a higher rate of corneal perforation with PACK-CXL[46].

★ CONCLUSION ★

In summary, we have reported a case of severe fungal keratitis in a contact lens wearer, with a delayed diagnosis and protracted clinical course. Management included use of intra-stromal voriconazole, an intervention with increasing evidence of clinical efficacy in patients resistant to conventional antifungal therapy. This case highlights important challenges in the clinical management of fungal keratitis, including the importance of early suspicion of fungal disease to avoid delay in appropriate therapy, close monitoring of clinical course to enable tailored treatment based on evolution of clinical symptoms and signs. The judicious and timely use of antifungal therapy, including the use of intrastromal voriconazole in selected patients with infection who are poorly responsive to topical treatment, may contribute to a successful visual outcome without the need for surgical intervention. Complete eradication of fungal infection before considering topical steroid anti-inflammatory is important to prevent recurrence. Advances in diagnostics and clinical therapy show promise for improving prognosis in cases of fungal keratitis in the future.

★ REFERENCES ★

1. Gao Y, Chen N, Dong XG, et al. Int J Ophthalmol 2016; 9(6):848-53
2. Maharana P, Sharma N, Nagpal R, et al. Indian J Ophthalmol 2016; 64(5):346-357
3. Gower EW, Keay LJ, Oeschler RA, et al. Ophthalmology 2010; 117:2263-7
4. Garg P. Eye (Lond) 2012; 26:245-51
5. Keay LJ, Gower EW, Iovieno A, et al. Ophthalmology 2011; 118:920-6
6. Nielson SE, Nielson E, Julian HO, et al. Acta Ophthalmol 2015; 93:54-8
7. Tu EY, Joslin CE. Am J Ophthalmol 2010; 150: 602-8
8. Gaujoux T, Chatel MA, Chaumeil C, et al. Cornea 2008; 27:1018-21
9. Kaufmann C, Frueh BE, Messerli J, et al. Klin Monbl Augenheilkd 2008; 225:419-21
10. Bullock JD, Warwar RE, Elder BL, Northern WI. Trans Am Ophthalmol Soc 2008; 106:117-26
11. Ong HS, Fung SS, Macleod D, et al. Am J Opthalmol 2016;168:227-36
12. Thomas PA, Teresa PA, Theodore J, et al. Expert Rev Mol Diagn 2012; 12:703-18
13. Vengayil S, Panda A, Satpathy G, et al. Invest Ophth Vis Sci 2009; 50:152-6
14. Mukherjee PK, Chandra J, Sun Y, et al. Invest Ophthalmol Vis Sci 2012; 53:4450-7
15. Prajna NV, Krishnan T, Mascarenhas J, et al. JAMA Ophthalmol 2013; 131:422-9
16. Sharma S, Das S, Virdi A, et al. Br J Ophthalmol 2015; 99:1190-5
17. Qiu S, Zhao GQ, Wang X, et al. Int J Ophtalmol 2015; 8:597-602
18. FlorCruz NV, Evans JR. Cochrane Database Syst Rev 2015; CD004241
19. Al-Hatmi AM, Meletiadis J, Curfs-Breuker I, et al. J Antimicrob Chemother 2016; 71:953-5
20. Nejabat M, Yaqubi N, Khosravi A, et al. J Ophthlamol 2016; 8692830
21. Prakash G, Sharma N, Goel M, et al. Am J Ophthalmol 2008; 146:56-59
22. Siatiri H, Daneshgar F, Siatiri N, Khodabande A. Cornea 2011; 30:872-5
23. Sharma N, Agarwal P, Sinha R, et al. Br J Ophthalmol 2011; 95:1735-7
24. Kalaiselvi G, Narayana S, Krishnan T, Sengupta S. Br J Ophthalmol 2015; 99:195-198
25. Tu EY. Cornea 2009; 28:116-9
26. Haddad R, El-Mollayess GM. Middle East Afr J Ophthalmol 2012; 19:265-8
27. Tu EY, Hou J. Cornea 2014; 33:990-3
28. Jain V, Borse N, Shorne D, et al. Int Ophthalmol 2010; 30:723-5
29. Cavallini GM, Ducange P, Volante V, et al. Indian J Ophthalmol 2013; 61:669-71
30. Marangon FB, Miller D, Giaconi JA, Alfonso EC. Am J Ophthalmol 2004; 137:820-5
31. Sharma N, Chacko J, Velpandian T, et al. Ophthalmology 2013; 120:677-81
32. Niki M, Eguchi H, Hayashi Y, et al. Clin Ophthalmol 2014; 8:1075-9
33. Alastrucy-Izquierdo A, Cuenca-Estrella M, Menzon A, et al. J Antimicrob Chemother 2008; 61:805-9
34. Mimouni M, Tam G, Paitan Y, et al. J Ocul Pharmacol Ther 2014; 30:543-7
35. Lekhanont K, Nonpassopon M, Nimvorapun N, et al. Medicine (Baltimore) 2015; 94:e541
36. Wang X, Xiao M, Kong F, Chen S, et al. J Clin Microbiol 2011; 49:1890-8
37. Torres HA, Hachem RY, Chemaly RF, et al. Lancet Infect Dis 2005; 5:775-85
38. Hurtado-Sarrio M, Duch-Samper A, Cisneros-Lanuza A, et al. Arch Ophthalmol 2010; 128;941-2
39. Matsumoto Y, Dogru M, Goto E, et al. Cornea 2005; 24:748-53
40. Brandt CR. J Ocul Ther Pharmacol Ther 2014; 30:691-9
41. Said DG, Elalfy MS, Gatzioufas Z, et al. Ophthalmology 2014; 121:1377-82
42. Shetty R, Nagaraja H, Jayadev C, et al. Br J Ophthalmol 2014; 98:1033-5
43. Li Z, Jhanji V, Tao X, et al. Br J Ophthamol 2013; 97:669-71
44. Saglk A, Ucakhan OO, Kanpolat A. Eye Contact Lens 2013; 39:413-5
45. Vajpayee RB, Shafi SN, Maharana PK, et al. Clin Experiment Ophthalmol 2015; 43:103-7
46. Uddaraju M, Mascarenhas J, Das MR, et al. Am J Ophthalmol 2015; 161:131-4

Dilay OZEK
Ophthalmologist, Numune Research & Training State Hospital, Ankara
TURKEY

A RARE CAUSE OF KERATITIS: MICROSPORIDIUM

A 40-year-old male, without any systemic disease, visited our clinic with pain, stinging, visual impairment and redness in his right eye. His complaints started five days after splash of water from an aquarium. Slit-lamp examination showed conjunctival hyperemia, anterior stromal infiltration on a few spots at central cornea and widespread punctate epithelial erosions (PEE) upon staining with fluorescein. Microsporidia were spotted after Gram and Giemsa staining corneal scraping specimen. After confirming the presence of microsporidia, oral Albendazole 2x1, topical Voriconazole 12x1, propamidin isetiyonat %0,1 (brolene) 6x1 and artificial tears 8x1 were started for microsporidial keratoconjunctivitis. After one month, minimal corneal haze remained at corneal infiltration area and visual acuity increased to 1.0 from 0.7 in the effected eye.

★ DISCUSSION ★

Rarely encountered parasites, such as microsporidia, may be the underlying reason for keratitis, which does not respond to standard antibacterial and antiviral treatments for a long period of time. Although confocal microscopy is an efficient method to determine the cause of keratitis, microbiological inspection of specimens, obtained by corneal scraping, plays an important role in spotting such rare parasites.

★ INTRODUCTION ★

Microsporidia are small eukaryotic, spore forming obligate intracellular parasites and opportunistic pathogens causing gastrointestinal, sinus, pulmonary, muscular, renal, and ocular diseases [1].

Predisposing conditions include immunodeficiency, use of contact lenses, topical or systemic corticosteroids, trauma, and exposure to contaminated water [4].

We encountered a case of microsporidial keratitis in our clinic. The case was presented with histopathologic diagnosis and managed by medical therapy.

★ CASE ★

A 40-year-old male, without any systemic disease, was referred to our clinic. He complained pain, stinging, visual impairment and redness in his right eye, lasting for five days after splash of water from aquarium. He had already consulted by other clinics but his condition did not improve. He had been using moxifloxacin 4x1 (Vigamox), oral acyclovir 5x1 400 mg pills.

His best visual acuity was 0.7 on the right eye and 1.0 on left. Biomicroscopic inspection revealed hyperemic conjunctiva and few punctate epithelial keratitis spots at central cornea. Upon staining with fluorescein, the cornea showed widespread PEE (Fig. 1 a, b, and c).

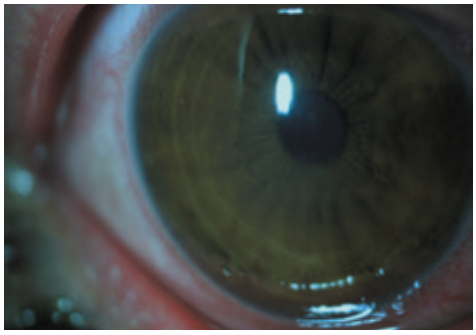


Figure 1a: Central corneal infiltration at first visit to our clinic

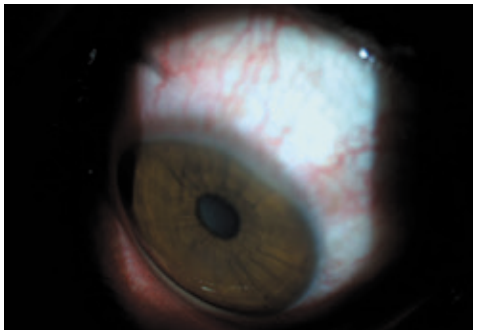


Figure 1b: Conjunctival hyperemia

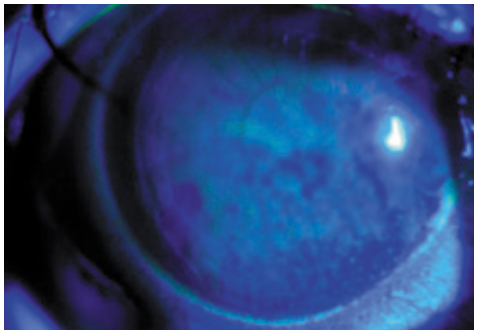


Fig 1c: Widespread PEE

All medications were stopped and a specimen was collected by corneal scraping for microbiological examination. Microsporidia were observed in Gram and Giemsa stained specimens (Fig. 2 a, b). No parasite was observed on confocal microscopy.

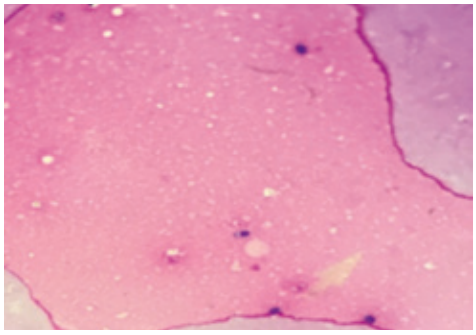


Figure 2a: Microsporidia Cyst with Giemsa Staining. Polar Tubules are demostrated painted dark in oval shape spore.

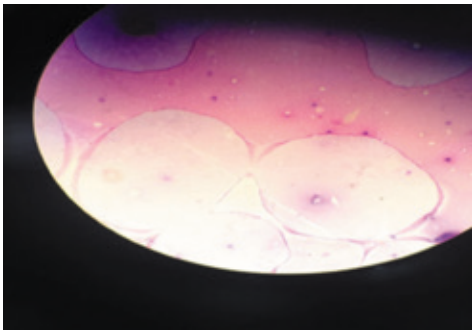


Figure 2b: Microsporidia Cyst with Gram Staining

After the microbiological inspection, oral Albendazole 2x1, topical Voriconazole 12x1, propamidin isetiyonat %0,1 (brolene) 6x1 and artificial tears 8x1 were started for microsporidial keratoconjunctivitis. After one week of the treatment, PEE were considerably reduced but keratic precipitate (KP) was still there (Fig. 3 a, b). Loteprednol 4x1 was incorporated to the treatment. The treatment was continued with oral Albendazole 2x1, topical Voriconazole 6x1, propamidin isetiyonat 6x1, and artificial tears 6x1.

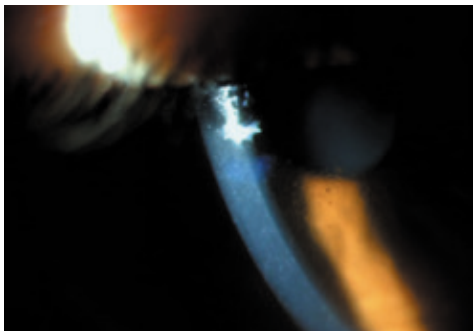


Figure 3a: Widespread KP on central cornea at week 1 follow up

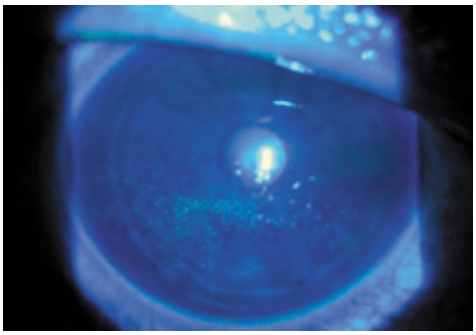


Figure 3b: Retreated PEE

At one month, KPs and PEE were resolved completely; however, minimal corneal haze remained at corneal infiltration area (Fig 3a, b). Visual acuity increased to 1.0 on the right eye. Medication was continued as Brolene 4x1 and loteprednol 4x1 for the following month. After two months, all medications were stopped. Corneal haze that does not decrease the visual acuity remained to a certain degree.

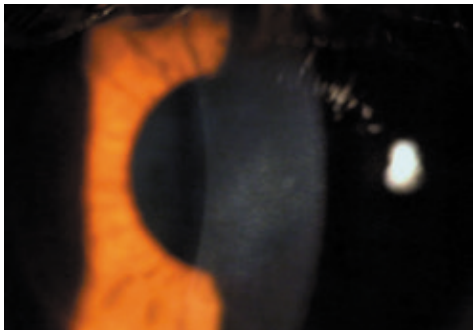


Figure 3a: Central corneal haze at month one follow-up

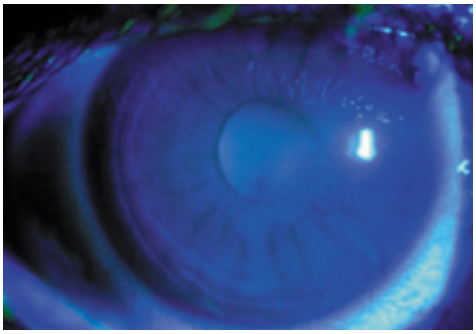


Figure 3b: No PEE observed

★ DISCUSSION ★

Microsporidial keratitis is an emerging opportunistic clinical condition caused by parasite belonging to the genus *Microspora* [2]. Ocular microsporidial infection occurs in two forms: first one is keratoconjunctivitis, which is the most common primary ocular infection in individuals with acquired immunodeficiency syndrome (AIDS), and the second one is stromal keratitis, seen in immunocompetent individuals [3]. Keratoconjunctivitis form is similar to acute adenoviral keratoconjunctivitis or herpes simplex (HSV) keratoconjunctivitis [4]. It is generally a self-limited condition, especially in immune competent persons. Clinically, the stromal form presents with mid to deep stromal infiltration that mimics stromal HSV keratitis. Stromal microsporidial keratitis progresses from stromal infiltration to the thinning with descemetocele formation [2]. A study reported a case of stromal microsporidial keratitis with the presence of an intact Descemet's membrane (DM) and demonstrable microsporidial spores in the AC exudates [5]. There have been reports on intraocular microsporidiosis causing endophthalmitis [6,7] or sclerouveitis with retinal detachment [8]. However, in these reports, the mechanism of spread was presumed to be systemic and none of the patients had corneal involvement.

A variety of drugs have been used for keratoconjunctivitis treatments, including fumagillin, propamidine, isethionate, and polyhexamethylene biguanide (PHMB), or antifungal agents such as natamycin with or without systemic therapy with albendazole or itraconazole [10,11]. Stromal keratitis has also been reported in immunocompetent contact lens wearers [9]. There is no definitive medical treatment for microsporidial stromal keratitis. Current literature suggests that the definitive treatment is the excision of the infected tissue and replacement with corneal tissue [4].

★ CONCLUSION ★

Microsporidia should be considered in the differential diagnosis of stromal keratitis, secondary to the presumed herpetic eye disease and in the keratitis cases that do not respond to treatment for a long period of time. Microsporidia are fastidious organisms and are difficult to culture. A microscopic examination of the tissue with appropriate staining can help to diagnose the disease. In our case, confocal microscopy failed to detect microsporidia and diagnosis was reached by microbiological inspection of stained corneal scraping and culture. Microsporidium can cause infection in the cornea even with minor trauma like splash of aquarium water. It is important to take detailed history from the patient, to have high index of suspicion and careful work up to diagnose a rare cause of keratitis, like Microsporidium.

★ REFERENCES ★

1. Weber R, Bryan RT, Schwartz DA, et al. Human microsporidial infections. Clin Microbiol Rev.1994;7(4):426–61.

2. Vemuganti GK, Garg P, Sharma S, Joseph J, Gopinathan U, Singh S. Is microsporidial keratitis an emerging cause of stromal keratitis? A case series study. BMC Ophthalmol. 2005;5:19.

3. Friedberg DN, Stenson SM, Orenstein JM, et al. Microsporidial keratoconjunctivitis in acquired immunodeficiency syndrome. Arch Ophthalmol. 1990;108(4):504–8.

4. Garg P. Microsporidia infection of the cornea—a unique and challenging disease. Cornea. 2013;32(Suppl 1):S33–8.

5. Somasheila I, Murthy, Vishram A. Varsha M. Rathi. Microsporidial Spores can Cross the Intact Descemet Membrane in Deep Stromal Infection. Middle East Afr J Ophthalmol. 2013 Jan-Mar; 20(1): 80–82.

6. Das S, Sharma S, Sahu S, Vemuganti GK. Intraocular invasion by micorsporidial spores in case of stromal keratitis. Arch Ophthalmol. 2011;129:513–51.

7. Kodjikian L, Garweg JG, Nguyen M, Schaffner T, Deplazese P, Zimmerli S. Intraocular microsporidiosis due to Encephalitozoon cuniculi in a patient with idiopathic CD4+ T-lymphocytopenia. Int J Med Microbiol. 2005;294:529–33.

8. Mietz H, Franzen C, Hoppe T, Bartz-Schmidt KU. Microsporidia-induced sclerouveitis with retinal detachment. Arch Ophthalmol. 2002;120:864–5.

9. Fogla R, Padmanabhan P, Therese KL, et al. Chronic microsporidial stromal keratitis in an immunocompetent, non-contact lens wearer. Indian J Ophthalmol. 2005;53(2):123–5.

10. Diesenhouse MC, Wilson LA, Corrent GF, et al. Treatment of microsporidial keratoconjunctivitis with topical fumagillin. Am J Ophthalmol. 1993;115(3):293–8.

11. Khandelwal SS, Woodward MA, Hall T, et al. Treatment of microsporidia keratitis with topical voriconazole monotherapy. Arch Ophthalmol. 2011;129(4):509–10.

Jose Vicente DABAD MORENO
Hospital Universitario La Paz, Madrid
SPAIN

RGTA TREATMENT EFFECTIVENESS IN AN ELDERLY PATIENT BILATERAL MOOREN´S ULCERATION

★ INTRODUCTION ★

Mooren's ulcer is a rare progressive chronic inflammatory process of the marginal cornea. It can be either unilateral or bilateral (50%)[1]. It affects the connective-scleral-corneal limbus, and presents with pain, photophobia, ocular redness, tearing and complaint of decreased visual acuity. The disease is strictly a peripheral ulcerative keratitis (PUK), with no associated scleritis. It´s an idiopathic disease occurring in complete absence of any diagnosable systemic disorder. The pathogenesis of Mooren's ulcer remains uncertain, it´s usually multifactorial, being triggers physical, chemical or surgical trauma, infectious or inflammatory processes, but the causal mechanism is immunologic[2].

Clinical evolution begins as a crescent-shaped gray-white infiltrate in the peripheral cornea, followed by epithelial breakdown and stromal melting. Developing into a characteristic chronic crescent-shaped peripheral ulcer. The adjacent conjunctiva is usually inflamed and hyperemic. As it progresses, it creates an overhanging edge at it´s central border. It begins peripherally and progresses circumferentially and centrally and may cover the entire cornea, reaching perforation. Behind the advancing edge of the ulcer, healing may take place as epithelialization and vascularization. The healed area remains clouded.

Therapeutic behaviors are multiple, but the current treatment base is the immunomodulation[3], reserving surgery for imminent risk of perforation, perforation or acute corneal necrosis[11].

We report here the case of a patient suffering from bilateral Mooren's ulcer with severe thinning who were successfully treated with ReGeneraTing Agents therapy (RGTA) and bandage contact lenses (BCL).

★ CASE PRESENTATION ★

A 97-year-old female presented to the emergency department with 1 week of mild pain, itching in both eyes and decreased visual acuity (VA), with little ocular discharge. She was diagnosed with ulcerative perifherical keratitis (PUK) and sent to our Cornea department for urgent study. Meanwhile, she was treated with topical ofloxacin 4 times a day, artificial tears 4-5 times a day and oral doxycycline 100 mg, 1 tablet with lunch.

Her personal history included a brain-ischemic accident 16 years ago and she was treated with acenocoumarol since then; hyperuricemia and osteoarthritis. Her ophthalmologic history included lachrymal surgery, she underwent cataracts surgery in both eyes without complications and she was currently being treated with topical dorzolamide and timolol, every 12 hours for Chronic Simple Glaucoma in both eyes.

We performed an ophthalmologic study. The baseline visual acuity of the patient was 0.05 in the right eye and left eye 0.13. Schirmer test was 4 mm right eye and 11 mm in left eye. Corneal sensitivity was preserved in both eyes. In the slit lamp study, we found mild mixed conjunctival hyperemia greater in higher sector, conjunctivochalasis and normal sack backgrounds. Circumferential superior from 3h to 9h extension up to 50% peripheral corneal thinning with epithelial defect F(+) was observed in both eyes, and mild inferior peripheral corneal thinning. Open anterior chamber and pseudophakic in both eyes, without Tyndall sign. Intraocular pressure was 16 and 15 mmHg, respectively. Conjunctival smear and corneal scraping were taken. Analytical and serology were requested. We performed interconsultation to Rheumatology service for systemic evaluation.

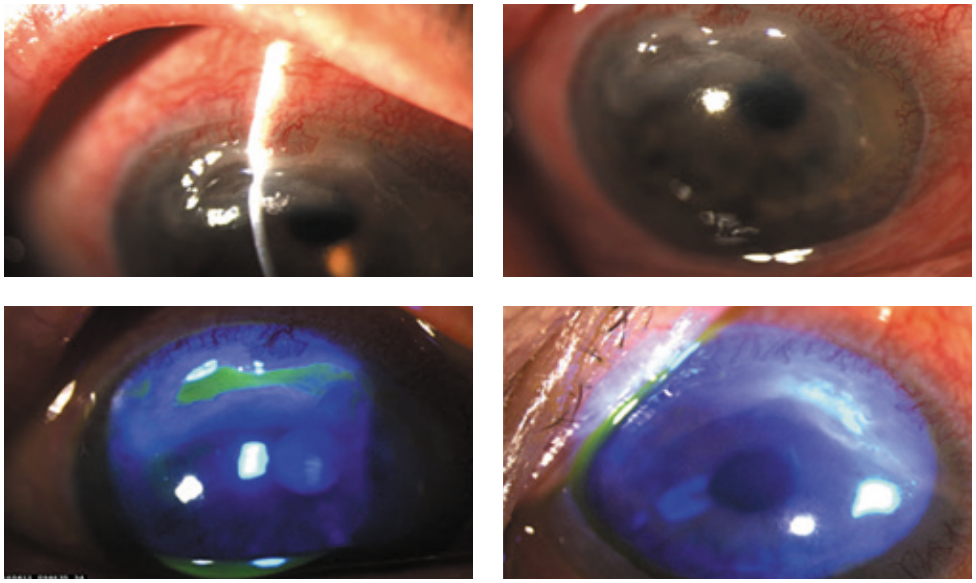


Figure 1: IM900 Haag Streit. Photography of ocular surface: A) See above right eye deep corneal thinning. B) See circumferential extension of right eye Mooren's ulcer. C) See upper epithelial defect F (+) right eye. D) Upper epithelial defect F (+) left eye.

Empirical treatment was completed with fortified vancomycin (10mg/0,1cc) and ceftazidime (2.5mg/0.1cc) eye drops, with applications 5 times a day. Topical dexamethasone and atropine twice a day and oxytetracycline ointment for night application. Ganciclovir gel 5 times a day and oral famciclovir 750mg a day were added. Oral doxycycline and artificial tears were maintained. Topical dorzolamide and timolol were suspended in both eyes.

The patient was reviewed in 48 hours, she presented mild conjunctival hyperemia mixed mayor in the upper sector, up to 50% of peripheral corneal thinning and circumferential epithelial defect with an area of 1,5x5,2mm in right eye and 1x2,6mm in left eye and mild lower peripheral thinning in both eyes, without vascular invasion neither infiltration. The analytical results showed serum urate of 6.4 mg / dL, elevated acute phase reactants (Sedimentation rate 57 mm / h and CRP 8.12 mg / L) and a high IgA 825 mg / dl. Immunology study presented negative antibodies. Serology was negative for syphilis, HBV, HCV and HIV. PCR corneal scraping was negative for herpes virus group. Bandage contact lenses were put in both eyes. Polysulfate carboximetilglucosa (RGTA) 1 application every 48 hours and vitamin A 2 tablets a day were added to treatment. Ganciclovir gel and oral famciclovir tablets were stopped.

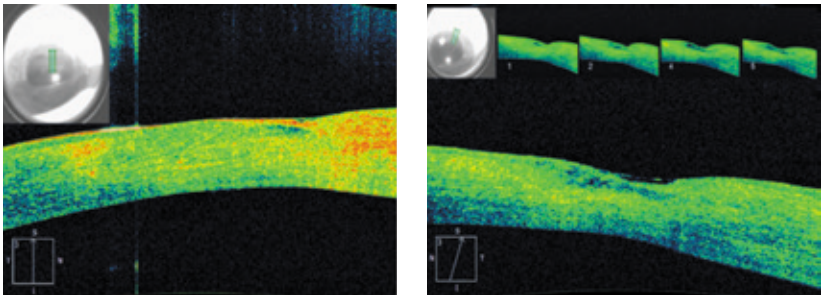


Figure 2: Zeiss OCT. Anterior chamber captures at 10 days follow-up: Longitudinal upper sections A) right eye cornea - B) left eye cornea

Five days later the patient was revealuated. In biomicroscopy she showed similar conjunctival hyperemia, peripheral corneal thinning up to 50% in right eye and 30% in left eye, decrease of the epithelial defect and corneal toxicity with punctate keratopathy in both eye. The patient referred a gout attack that was controlled with NSAIDs. The culture was sterile corneal for fungi, bacteria and parasites. We change treatment with fortified antibiotic eye drops to topical moxifloxacin 5 times a day to reduce toxicity and topical cyclosporine 0.5% twice a day was added.

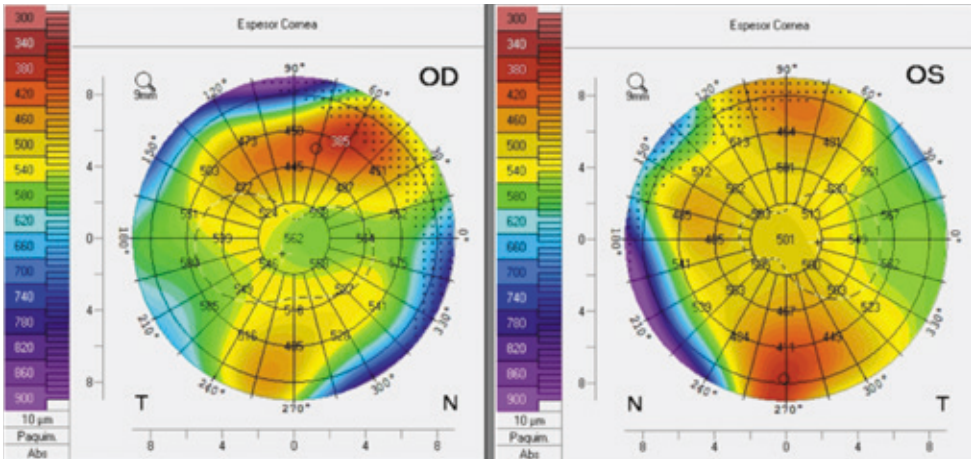


Figure 3: OCULUS PENTACAM: corneal thinning in upper corneal in both eyes after 8 days of starting with RGTA.

After 10 days from starting treatment, there was a subjective and objective improvement of the patient. In biomicroscopy, conjunctival hyperemia dissapeared, peripheral corneal thinning stabilized in right eye and decreased in left eye to 30%. Healing took place in the form of corneal epithelialization and vascularization.

One week later, the patient had no symptons, visual acuity without correction was 0.16 in both eyes. In the slit lamp study, she showed peripheral corneal thinning less than 30%, with intact epithelium, irregular corneal staining and superior pannus in both eyes.

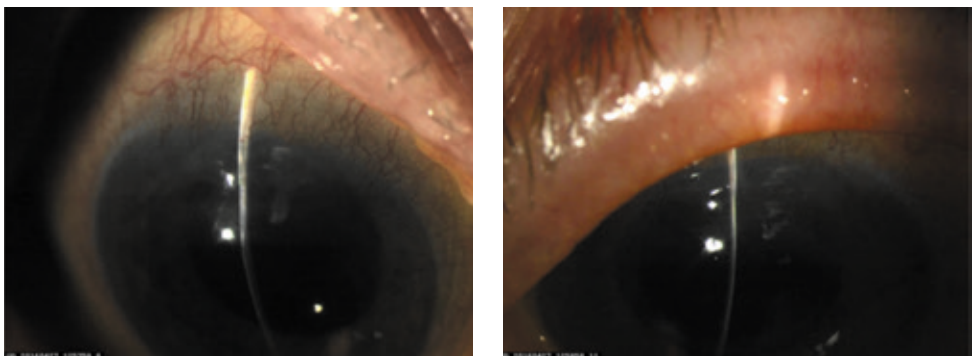


Figure 4: IM900 Haag Streit. Photography of ocular surface: See above recovery of corneal thickness: right eye (A) and left eye (B).

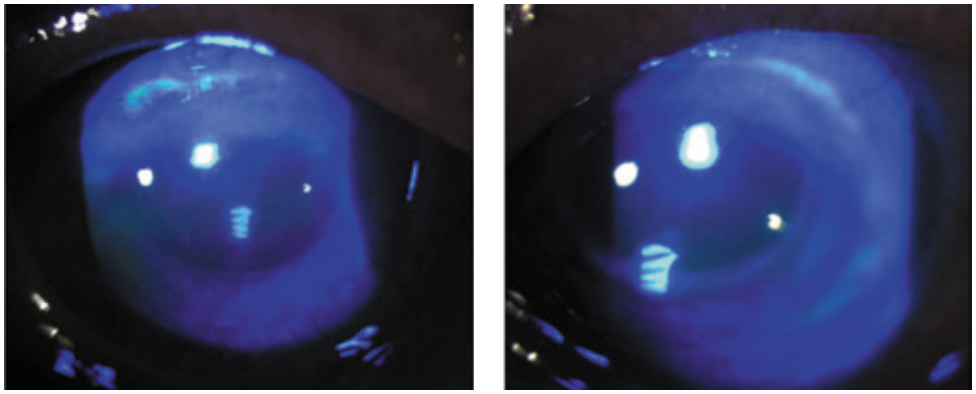


Figure 5: IM900 Haag Streit. Photography of ocular surface staining with fluorescein: See retention thinning area, but no epithelial defect in right eye (A) and left eye (B).

Given the satisfactory progress of patient, contact lenses, RGTA, moxifloxacine and atropine were removed. Treatment was maintained with vitamin A 2 tablets daily, oral doxycycline 100mg 1 tablet daily, topical cyclosporine 0.5% twice a day, topical dexamethasone once a day and artificial tears 4-5 times a day. Glaucoma treatment was started with carteolol eye drops once a day.

In one month control, the patient referred pain and visual accuity lost since 1 week. She had suspended cyclosporine treatment due to itching about 3 weeks ago. In slit lamp examination, there was a lower infiltrated ulcer and up to 50% thinning with melting in temporal peripheria from 5h to 9h, with the rest of ephitelium intact in right eye. Left eye had no ulcer. There were added to treatment RGTA 1 eye drop every 48h, tobramicine twice a day and cyclosporine 0,5% twice a day during a week, with a good response. Posterior evolution of the patient was satisfactory with local immunomosupressants with topical dexamethasone and cyclosporine.

★ DISCUSSION ★

Treatment in Mooren´s ulcer should be firstly with immunosuppressants and, nevertheless, it can evolve to perforation[11]. In that case, surgical procedures should be neccesary. The goals are to stop the ulcerative process and allow reepithelialization of the cornea. We should use adjuvant treatments as lubricating eye drops, collagenase synthetase inhibitors, RGTA, BCL, oral tab ascorbic acid ororal doxycycline, improving the reepithelialization process and extracellular matrix remodelation.

RGTA include a family of biodegradable glucose-based polymers engineered to replace heparan sulfates[5]. RGTA mimic the action of destroyed heparan sulfate molecules and binds to matrix proteins to protect them from proteolysis; the extracellular matrix microenvironment protection improves the production of signals and growth factors needed for tissue healing [5,6]. RGTA treatment

seemed to be effective in reducing the clinical signs of inflammation, enhancing reepithelialization, and improving histological patterns such as edema, fibrosis, neovascularization, and inflammation[7].

In patients, RGTA was tested for the first time for treating corneal ulcers and severe dystrophies resistant to standard therapies[13].RGTA in significant reduction in pain, improvement of keratitis and healing of the majority of corneal ulcers. Several case reports using RGTA in cases of neurotrophic keratopathy and corneal ulcers since then have indicated a positive effect of the treatment. The effectiveness of RGTA in corneal neurotrophic ulcers of various primary etiologies was also examined in a larger study with 11 patients, where RGTA treatment resulted in complete corneal healing in eight patients, with the remaining patients presenting the most severe cases (Aifa et al. 2012[12]. More recently, the combination of RGTA with a bandage contact lens in three patients with persistent epithelial defects promoted complete corneal epithelial healing in 4 to 21 days (Kymionis et al. 2015)[4].

Bandage contact lenses has been successfully used in the reepithelialization process for enhancement of corneal healing[6], Kymionis et al.[4] reported a new approach of combined RGTA (Polysulfate carboximetilglucosa) with a BCL for treatment of persistent epithelial defect that we can use in our case. All patients after topical daily instillation of an RGTA (Polysulfate carboximetilglucosa) combined with a BCL improved their clinical condition (complete corneal epithelial healing at 4–21 days) in their study[4].

We decided as they did to combine this agent (Polysulfate carboximetilglucosa) with aergel BCL because the BCL protects the cornea from additional mechanical injury, whereas the RGTA enhances epithelial healing. RGTA improves the reepithelialization process and enhances extracellular matrix remodeling, optimizing wound healing[12]. The combined therapeutic approach of an RGTA with BCL was successfully used in all 3 patients to achieve tissue reconstruction and homeostasis restoration[4].

We also want to notice the existance of hyperuricemia in this case. Making screening of possible systemic associations, we didn´t found nothing in the patient that it´s related with Mooren´s ulcer, not even hyperuricemia[8]. But we had another case of Mooren´s ulcer at our hospital long time ago and the unique systemic disease was hyperuricemia. We found in literature a poster that establishes a relationship between hyperuricemia and PUK[10]. Since Dr. Hutchinson's lecture[9], over 130 years ago, ocular manifestations related with gout and hyperuricemia have been reported infrequently. These include descriptions of tophaceous deposits in different locations of the eye as the cornea[8]. In his lecture, he described various presentations of ocular diseases in different locations of the eye and their relation to gout. According to him, the paroxysmal character of the ocular attacks resembled gouty attacks in their sudden development, great pain, and rapid resolution. Cases of gout with involvement of ocular structures, such as the cornea (causing keratitis and band keratopathy) were described as well[9].

★ CONCLUSION ★

To summarize, Mooren's ulcer is a corneal condition with an immune component that requires immunomosupressive therapy, topical treatments as cyclosporine are useful, they must be maintained in time to avoid relapses. A RGTA matrix therapy agent can be used for the treatment of ocular surface disorders as peripherical ulcerative keratitis.The combination of RGTA with a bandage contact lens seems to be an effective alternative therapeutic approach for the treatment of Mooren´s ulcer and severe corneal thinning, which increases effectiveness of both together outside the already known and established separate treatment effects, because they perform in diferent and summation ways optimizing wound healing.

Also put hyperuricemia forward as a risk factor for Mooren's ulcer and other periferical ulcerative keratitis. However, further studies with a larger number of patients are needed to evaluate this pathogenesis relationship.

★ REFERENCES ★

1. Srinivasan M, Zegans ME, Zelefsky JR, Kundu A, Lietman T, Whitcher JP, et al. Clinical characteristics of Mooren's ulcer in South India. Br J Ophthalmol. 2007;91:570–5.

2. Kafkala C, Choi J, Zafirakis P, Baltatzis S, Livir-Rallatos C, Rojas B, et al. Mooren ulcer: An immunopathologic study. Cornea. 2006;25:667–73.

3. Ashar JN, Mathur A, Sangwan VS. Immunosuppression for Mooren's ulcer: Evaluation of the stepladder approach–topical, oral and intravenous immunosuppressive agents. Br J Ophthalmol. 2013;97:1391–4.

4. Kymionis GD1, Liakopoulos DA, Grentzelos MA, Diakonis VF, Klados NE, Tsoulnaras KI, Tsilimbaris MK, Pallikaris IG. Combined topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. Cornea. 2014 Aug;33(8):868-72.

5. Barritault D, Caruelle JP. Regenerating agents (RGTAs): a new therapeutic approach [in French]. Ann Pharm Fr. 2006;64:135–144.

6. Rouet V, Meddahi-Pellé A, Miao HQ, et al.. Heparin-like synthetic polymers, named RGTAs, mimic biological effects of heparin in vitro. J Biomed Mater Res A. 2006;78:792–797.

7. Brignole-Baudouin F, Warnet JM, Barritault D, et al.. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. J Fr Ophtalmol. 2013;36:740–747.

8. Sharon Y, Schlesinger N. Beyond Joints: a Review of Ocular Abnormalities in Gout and Hyperuricemia. Curr Rheumatol Rep. 2016 Jun;18(6):37.

9. Hutchinson J. The Bowman lecture on the relation of certain diseases of the eye to gout. Br Med J. 1884;2:995–1000.

10. S.Martin-Nalda, A.Segura, J.Puig-Galy, M.Calatayud, et al.. A rare case of peripheric ulcerative keratitis (PUK) and corneal perforation associated with hyperuricemia as only systemic disease. Poster XXXIII Congress of the ESCRS. 2015.

11. Vilaplana F, Temprano J, Riquelme JL, Nadal J, Barraquer J. Mooren's ulcer: 30 years of follow-up. Arch Soc Esp Oftalmol. 2016 Jul;91(7):337-40.

12. Aifa A, Gueudry J, Portmann A, et al.. Topical treatment with a new matrix therapy agent (RGTA) for the treatment of corneal neurotrophic ulcers. Invest Ophthalmol Vis Sci. 2012;53:8181–8185.

13. Chebbi CK, Kichenin K, Amar N, Nourry H, Warnet JM, Barritault D & Baudouin C (2008): [Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment- resistant corneal ulcers and corneal dystrophy]. J Fr Ophthalmol 31: 465–471.
De Monchy I, Labbe A, Pogorzalek N, Gendron G, M' Garrech M, Kaswin G & Labetoulle M (2012): Management of herpes zoster neurotrophic ulcer using a new matrix therapy agent (RGTA): a case report. J Fr Ophthalmol 35: 187.

14. 14. Mateo A, Abadía B, Calvo P, Minguez E, Pablo L & Benitez del Castillo JM (2015): Treatment of Acanthamoeba neurotrophic corneal ulcer with topical matrix therapy. J Ophthalmic Inflamm Infect 5: 18.
Pison A, Feumi C & Bourges JL (2014): Healing of a resistant neurotrophic corneal ulcer using a new matrix therapy agent. J Fr Ophthalmol 37: 101–104.

Naïrouz ZINE EL ABIDINE
Mohamed Lamine Debaghine - Bab el Oued University Hospital in Algiers
ALGERIA

MEDICAL MANAGEMENT OF BULLOUS KERATOPATHY COMPLICATING AN IRIDO-CORNEAL ENDOTHELIAL SYNDROME

★ INTRODUCTION ★

- **"Bullous Keratopathy"** results from the endothelial pump failure to maintain the normally dehydrated state of the cornea leading to chronic edema of stroma and epithelium, subepithelial bullae, pain, eventually diffuse scarring and reduced vision.

- This situation is observed in several contexts, most frequently in Fuchs corneal endothelial dystrophy and corneal endothelial trauma[1]. A less common cause of bullous keratopathy is **the Irido-Corneal Endothelial [ICE] syndrome.**

- ICE syndrome encompasses a **group of rare ocular pathologies**, typically sharing similar characteristics : It occurs mainly in middle-aged women, are generally unilateral, with abnormalities of the cornea, anterior chamber angle, and iris. The relative importance of iris atrophy and corneal changes differentiates the classic three entities : Progressive essential iris atrophy, Chandler's syndrome, and Cogan-Reese's iris naevus syndrome [2].

- The pathogenic mechanisms behind the clinical alterations observed in ICE syndrome have been identified in an **abnormal proliferation of the corneal endothelial cells** that can migrate across the angle, occluding it, and on to the anterior iris surface, where contraction of a sheet of cells, or its subjacent abnormal Descemet's membrane, can distort the pupil, thin the iris, and pull holes in it [4].

- The consequences of these changes are **secondary closed-angle glaucoma and cornea decompensation** leading to severe and hardly controlled corneal edema. They represent the most frequent causes of visual function loss for patients with ICE syndrome if not properly treated [2].

- Thus, an early diagnosis is helpful to better manage them. Indeed, the clinical management is usually not linked to the exact diagnosis of the clinical subtype but to the degree of its complications [2].

- We present a rare case of a Bullous Keratopathy complicating an advanced form of an ICE syndrome, and its medical management. In correlation with pathophysiology,we will discuss the choice and the place of each option.

★ CASE PRESENTATION WITH ILLUSTRATIONS AND FIGURES ★

- A 54 years old woman, presented with several years history of a recurrent painful red eye with progressive decreased vision in the right one. She reported a perception of coloured haloes around lights occasionally, and pain increasing upon awakening. These symptomes were strictly unilateral , and treated periodically , only with lubrificant instillations.

- She never underwent any ophthalmologic surgery and had no general or another ophthalmologic history. No similar case was noticed in her family.

ON EXAMINATION OF THE RIGHT EYE (RE) :

A - Best Corrected Visual Acuity (BCVA)was collapsed to counting fingers at one meter.

B - The slit lamp exam revealed :

- **Irritative signs** : Blepharospasm, photophobia, conjunctival hyperemia, ciliary injection,and tearing without infection signs (figure 1).

- A diffuse and severe corneal edema with a "hammered-silver" appearance, epithelial and sub-epithelial bullae, ulcers , Superficial Punctate Keratitis (SPK), making typically a **Bullous Keratopathy (figures 2 – 3 – 4 – 5 - 6)**

Corneal Findings

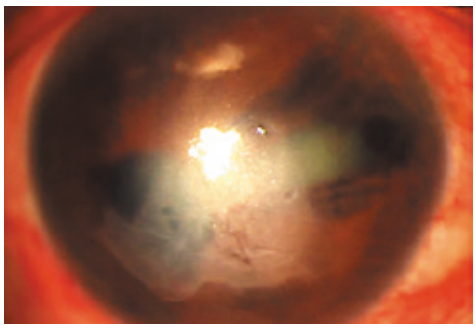


Figure 1: Edematous and thickned cornea with bullae on a red irritated Right Eye

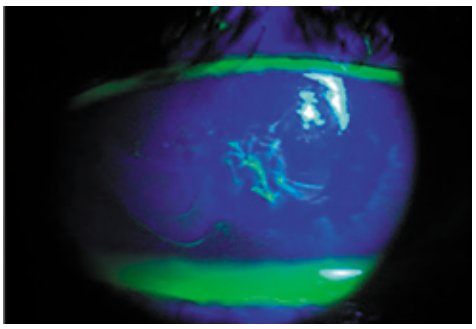


Figure 2: Epitelial bullae without fluorescein staining and irregular corneal surface

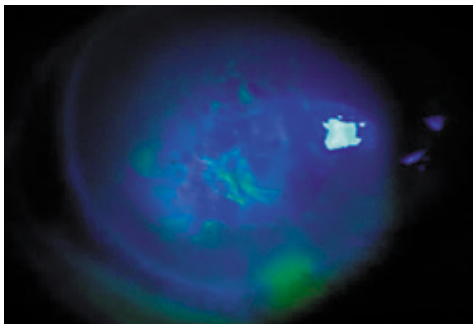


Figure 3: Fluorescein staining of SPK and ulcers

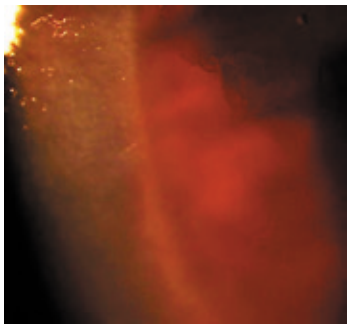


Figure 4: Magnified view of the swelling cornea with hammered silver appearance of endothelium on specular reflection

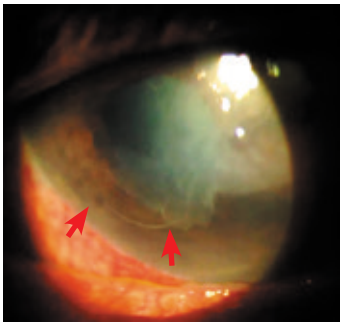


Figure 5: Distortion of the corneal surface with bullae (A blister imited with the 2 red arrows)

Figure 6: Optical section of the thicknked corneal stroma and epithelium crossing through the blister

- In the anterior chamber there was an aseptic hypopyon secondary to the chronic inflammation (figure 7).
- Corectopia : Pupillary distortion pulled to the inferior-temporal side, with an uveal ectropion (figure 8).
- Iris Abnormalities : 1 - An iris atrophy : stretch hole on the other side of pupillary distortion direction (figure 9) / 2 - Multiple brown iris nodules in the temporal half of the iris (figure 8).
- A dense Cataract (figures 8 and 9).

A mixed-form of an ICE Syndrome

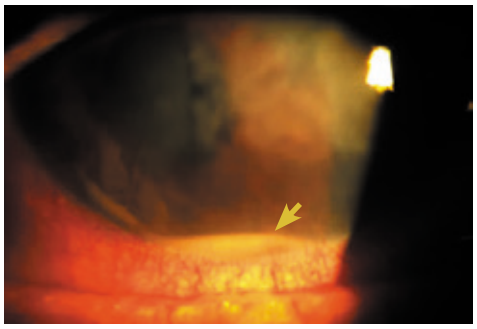


Figure 7: Aseptic Hypopyon

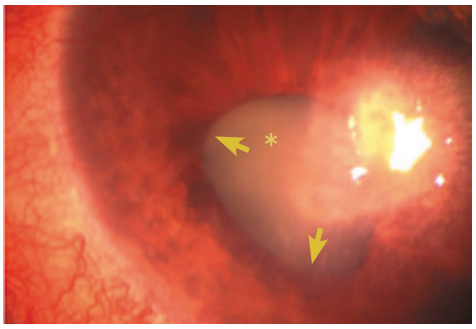


Figure 8: Corectopia pulled to the inferior temporal side + Uveal ectropion (limited by 2 yellow arrows) of a **Progressive essential iris atrophy** + Multiple Brown Nodules of a **Cogan Reese (Iris Neavus) syndrome** + Dense Cataract (*)

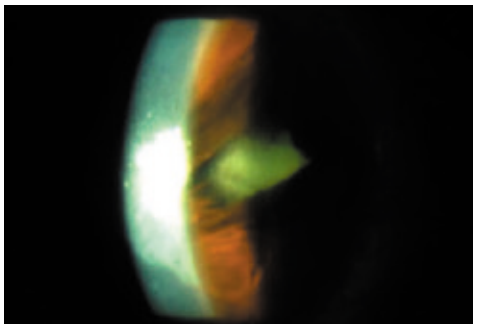


Figure 9 - Stretch hole in the opposite side (superior nasal) of the corectopia = Iris Atrophyof a **Progressive essential iris atrophy** + Dense Cataract seen through it.

C - The corneal swelling did not allow gonioscopic visualization. The Ultrasound Biomicroscopy (UBM) showed a totally closed angle with Peripheral Anterior Synechiae (PAS) (figures 10 - 11 - 12 - 13). The Optic Coherence Tomography (OCT) of the Angle magnified the extended endothelial membranE to the angle and its closure (figures 14 – 15 – 16).

D - The fundus examination was inaccessible too, because of the corneal sweling plus the dense cataract. A 10 MHz B-scan ultrasonography showed an anechoic vitreous, and a papillary excavation.

E - The Intra-Ocular Pressure (IOP) mesured with a non contact tonometer was high, reaching 34 mmgh.

Secondary Glaucoma explorations
UBM → Totally Angle Closure with PAS

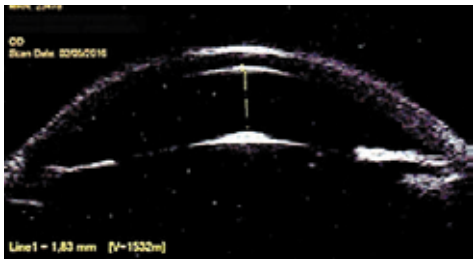


Figure 10

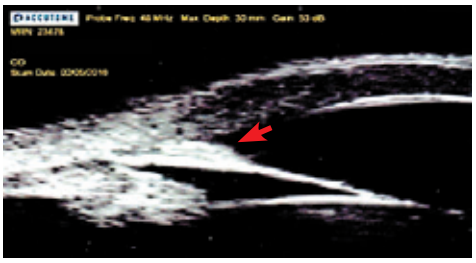


Figure 11: PAS (red arrow)

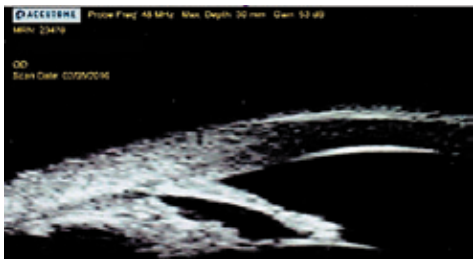


Figure 12

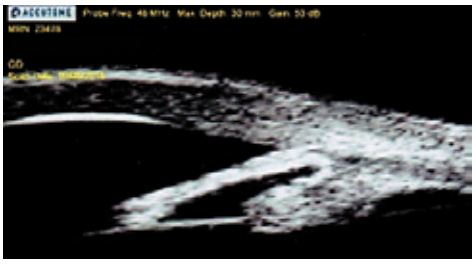


Figure 13

OCT of the irido-corneal angle

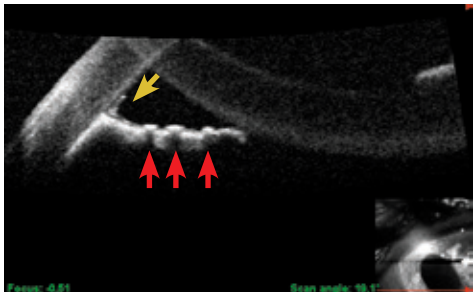


Figure 14: Crossing the iris nodules (3 red arrows) and showing the abnormal endothelial membrane occluding the angle = PAS (yellow arrow)

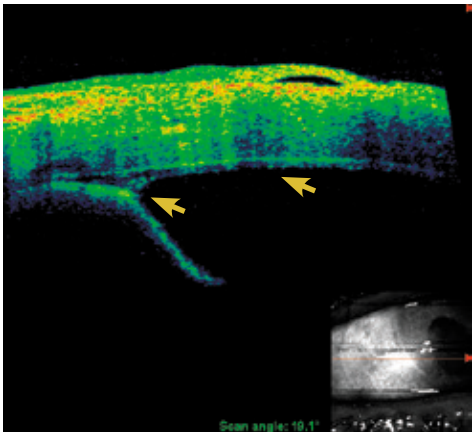


Figure 15: Abnormal endothelial membrane occluding the angle → PAS (yellow arrows)

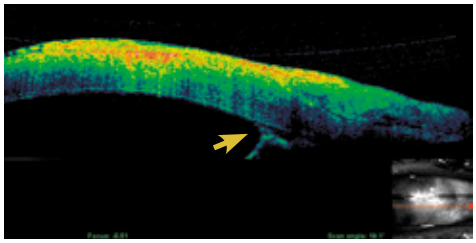


Figure 16: Abnormal endothelial membrane occluding the angle → PAS (yellow arrow)

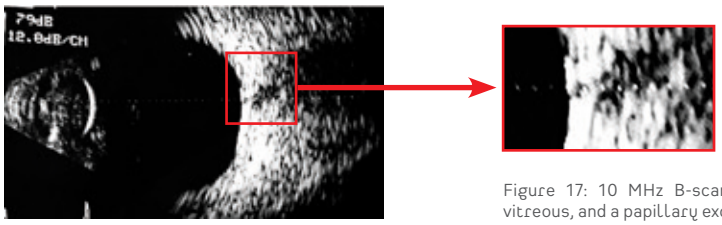


Figure 17: 10 MHz B-scan ultrasonography : anechoic vitreous, and a papillary excavation

The exploration of the cornea was completed by :

- **Specular microscopy** : Was inefficient because of the important corneal edema (figure 18).
- **Corneal OCT** : Showed the stromal and epithelial important swelling with bullae and the increased corneal thickness exceeding 600um.Furthermore, the abnormal endothelium was detected with the suspected abnormal membrane (figures 19 – 20 – 21 – 22).

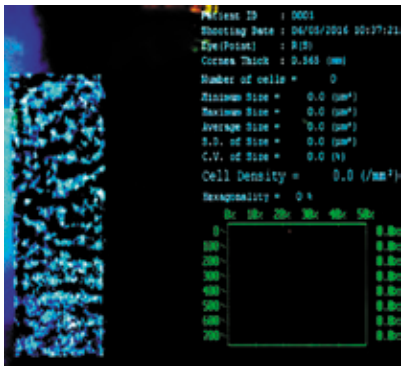


Figure 18: Specular microscopy

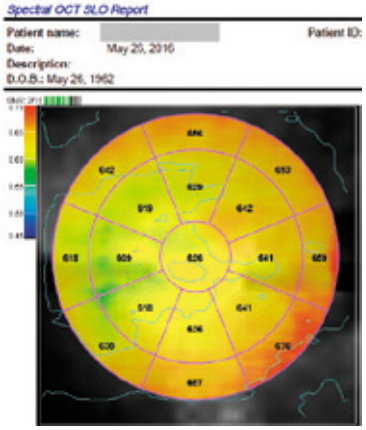


Figure 19: OCT non contact Pachymetry – Central Corneal Thikness= 626 um

Corneal OCT : Bullous Keratopathy

Irregular and abnormal endothelial layer, important increased stromal and epithelial thikness with bullae (Yellow arrows) between epithelium and Bowman's layer.

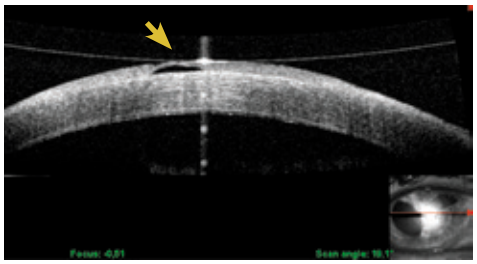


Figure 20: Horizontal section

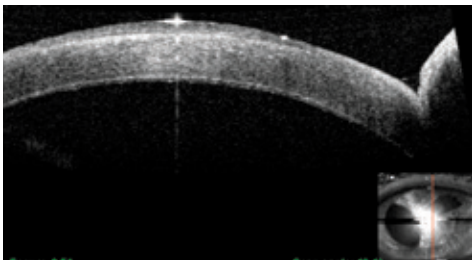


Figure 21: Vertical section

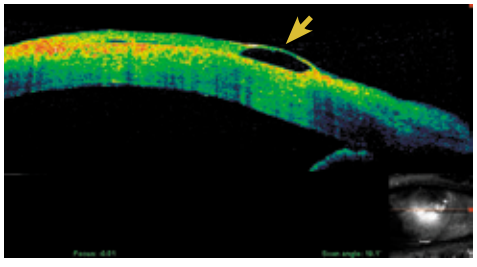


Figure 22: Bullous keratopathy with secondary angle closure

ON EXAMINATION OF THE LEFT EYE (LE) :

BCVA 20/20, Normal Anterior Segment (figure 23), an open angle in 4 quadrants, a normal fundus examen, without abnormal papillary excavation (figure 24). IOP=12 mmHg. A relative thin corneal thickness (figure 25), with normal endothelial parameters on specular microscopy.

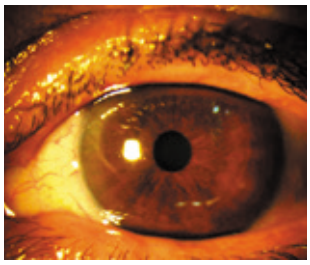


Figure 23: Normal AS

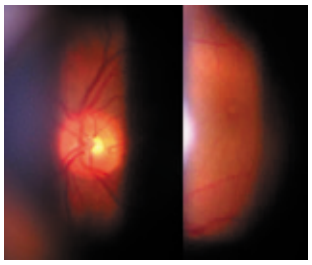


Figure 24: Normal Fundus

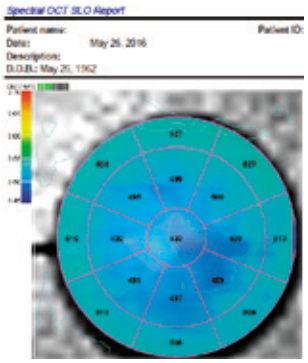


Figure 25: OCT non contact Pachymetry – Central Corneal Thikness = 483 um

THE POSITIVE DIAGNOSIS :

There was no doubt about the diagnostic of **a Bullous Keratopathy asoociated with secondary closed angle glaucoma complicating an advanced and severe mixed-form of an ICE syndrome,** typically unilateral of the **right eye**, sporadic, on a middle-aged woman.

MEDICAL MANAGEMENT & EVOLUTION OF BULLOUS KERATOPATHY [1] :

- The patient was immediatly treated medically by topical eyedrops , mostly non preserved , in order to :
  - Dehydrate the cornea : non-preserved hypertonic saline solution instilled 4 times per day.
  - Promote epithelial cicatrisation and reduce the inflammation : Vitamin A, Sodium hyaluronate and povidone (E12010) eye drops (3 drops per day each).
  - Reduce (IOP) : Bitherapy associating Beta-blocker (Timolol gel 0,1% LP unidose : one drop per day in the morning) and Carbonic Anhydrase Inhibitor (CAI) (Brinzolamide 2 drops per day).
- An Intravenous injection of 200 cc of Mannitol 20% was added for the first two days to contribute in reducing IOP.
- Mannitol and topical Beta-blocker were indicated after elimination of medical contraindication.
- The Treatment was well-tolerated without local or systemic side effects.

- The evolution at the first week : noted a slight IOP decrease of 7 to 8 mmHg, and of corneal swelling objectified by a better perception of the Anterior Segment details (figure 26 – 27).

- This same topical treatement was maintained for additionnal 5 days,after which we juged that it seemed insufficient, particullary for the the painful symptoms due to the persistant recurrent corneal erosions (figures 28-29).

CORNEAL FINDINGS AT 7 DAYS THEN AT 12 DAYS OF MEDICAL TREATMENT

Persistant bullae – Slight increased corneal transparency - better perception of the Anterior Segment details

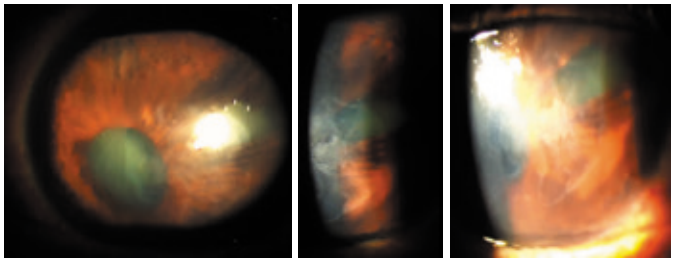


Figure 26

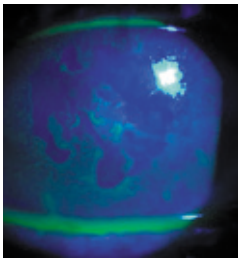


Figure 27

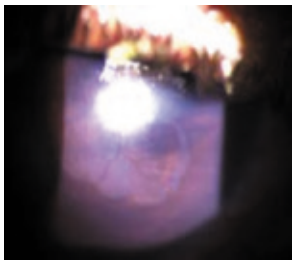


Figure 28

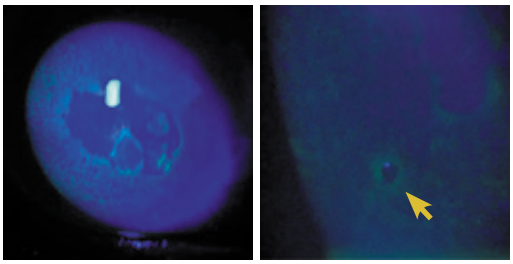


Figure 29

MEDICAL MANAGEMENT & EVOLUTION OF BULLOUS KERATOPATHY [2] :

- The decision went then for a Therapeutic Contact Lens (CL): Silicone-Hydrogel Soft CL, 14 mm diameter, Radius of Curvature = 8,40 , continuously worn (Day and night) and bimonthly changed, under close clinical monitoring (figure 30).

- Non preserved eyedrops were maintained as an adjuvant treatement instilled on the CL: Saline solution, Sodium hyaloronate, Povidone (2 drops a day each),and Betablocker (one drop a day in the morning). Preserved CAI eyedrops were replaced by acetazolamide at the posology of 1 tablet (250 mg) 2 times a day.

- One Month Later :
  - IOP were around 26-27 mmgh (evaluated by a non contact tonometer after removing the CL).
  - Corneal edema slightly reduce : Objectified by a better perception of the Anterior Segment details (Figure 31) and corneal OCT (Figures 32 - 33 – 34 -35).
  - The major benefice was the complete pain relief cheered by the patient since the first hours and the marked improvement of the irritative signs.

- Four months later : this treatement is still well tolerated , with the same outcomes and without any intolerance or complications.

The Clinical Evolution

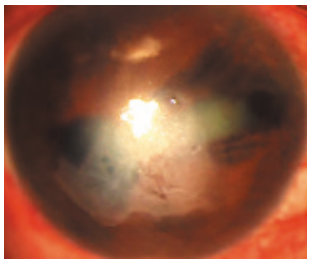


Figure 1: Bullous keratopathy at the fist day

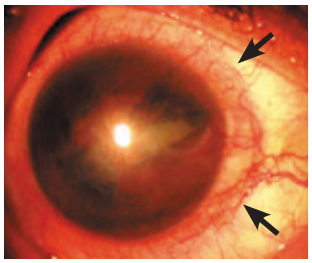


Figure 30: The cornea after 12 days of medical traetment and few minutes after wearing the CL (Black arrows)

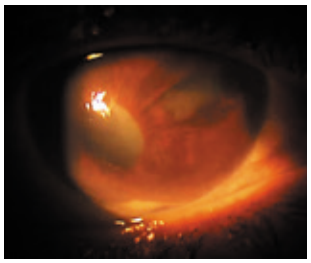


Figure 31: Day 30 - decrease irritative signes and a slight increase of corneal tranparency after CL removal to mesure IOP.

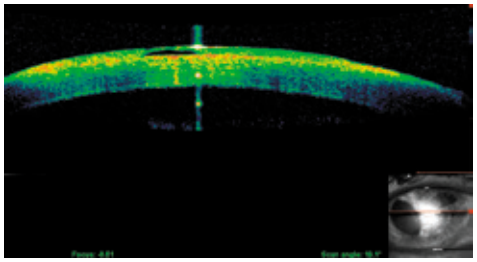


Figure 32: Before CL wear at day 12 of medical treatment

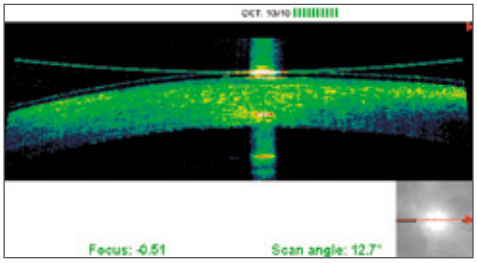


Figure 33: At day 30 of CL wear = desceased epithelial thikness and bullae

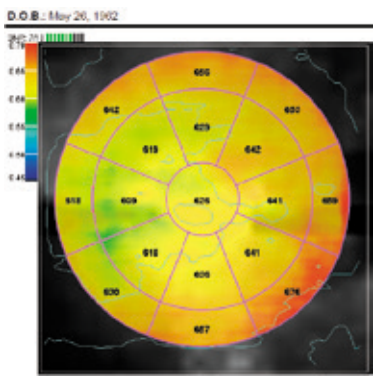


Figure 34: Before any treatment (CCT = 626um)

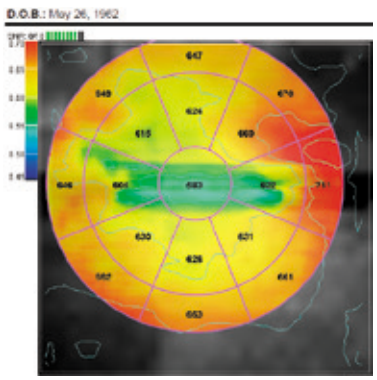


Figure 35: At day 30 of CL , after its removal (a slight decrease of the CCT = 583 um)

★ DISCUSSION ★

- ICE Syndrome is a very rare and unique ophthalmic disorder involving an irregular corneal endothelium that can lead to varying degrees of corneal edema, iris atrophy, and secondary closed-angle glaucoma[3]. Corneal edema, increased IOP, and glaucoma are the main therapeutic problems that even in the best hands, are extremely challenging to manage[5].

- The corneal edema found in ICE syndrome patients has a particular pathophysiology. It is felt to be secondary to both subnormal pump function from the altered corneal endothelial cells and the elevated IOP from secondary angle-closure[3].
  - Since corneal edema may benefit from the reduction of IOP, **antiglaucomatous medications** are usually indissociable to optimise the management of the corneal disorder :
    - Topical medication is the first line therapy, More specifically, aqueous suppressants (such as topical beta blockers, alpha agonists, and carbonic anhydrase inhibitors) are typically used, rather than medications that would target the aqueous drainage sites of the eye (e.g. miotics)[2,3].
    - The role of prostaglandin analogs, which reduce IOP by enhancing uveoscleral outflow, remains unclear ; plus -since the role of HSV in ICE syndromes has not been completely ruled out, this molecules should be used with caution as their use has been reported to stimulate recurrence of herpes simplex[2,3].
  - Inevitably, **topical hypertonic saline solutions** are used to improve corneal edema by dehydrating the cornea[4].
  - To preserve the corneal and ocular surface, **lubrificants** are used and **preservative-free eye drops** are always to favour.

- Bullous keratopathy appears when the edema becomes severe and reaches the corneal epithelium, causing it to separate from Bowman's layer. Clinically, this areas of seperations are called ''Bullae''. Epithelial blisters rupture causes pain, foreign body sensation, tearing, photophobia, and inflammation[6]. Eye drops may be insufficent especially for painful symptoms.

- Therapeutic contact lens is the ideal solution :
  - It facilitates corneal healing, reinforces the damaged tissues and protects the exposed nerve endings from the abrasive actions of the eyelids.
  - Their other advantage is the ability to continue to install topical medications and their role as vehicles for topical drug delivery[7].
  - The maximum relief of pain is obtained when they are used on an extended-wear basis, under a primordial condition of a close monitoring because of a higher risk of complications.
  - The silicone hydrogel material is decreasing hypoxia-related problems because of its heigh Dk/t values and increasing the safety of an extended wear, plus , the re-epithelialization is fast[8].

- As Bullous keratopathy becomes severe, corneal transpantation [Penetrating or endothelial keratoplasty] is the curative treatement. In this particular case of our patient, such an intervention is discussed and may not be recommanded if juged more risky than advantageous because of the limited visual potential, particullary of an untreated glaucoma, the multiple surgical procedures (Filtrating and cataract surgeries) that have to be combined to wish for an eventual functional recovery and their lower success rate in this specific context of an ICE Syndrome.

- Thus, the medical management chosen for our patient seems actually to be an adequate provisional preoperative or palliative solution,as long as the contact lens and the eye drops are well-tolerated and under the condition of a close and long-term follow-up of the cornea and the IOP.

★ CONCLUSION ★

Our observation highlights the undeniable place of the medical treatment in the management of a Bullous Keratopathy and the major role of IOP lowering and the therapeutic contact lens as a symptomatic temoprary or long term palliative solution for the corneal disorders in some particular contexts as this advanced ICE syndrome for which surgical management may be discussed and challanging.

★ REFERENCES ★

1. Melvin I. Roat, MD, FACS , Bullous Keratopathy , Last full review/revision September 2014 by Melvin I. Roat, MD, FACS. http://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/bullous-keratopathy

2. Marta Sacchetti,FlavioMantelli,MarcoMarenco,IlariaMacchi,Oriella Ambrosio,and Paolo Rama. Diagnosis and Management of Iridocorneal Endothelial Syndrome Hindawi Publishing Corporation BioMed Research International Volume 2015, Article ID 763093, 9 pages - http://dx.doi.org/10.1155/2015/763093

3. Gregory W.Oldham, MD and Sarwat Salim MD, FACS. Iridocorneal Endothelial Syndrome and Secondary Glaucoma . Review: Assigned status Up to Date by Sarwat Salim MD, FACS on May 7, 2015.

4. R J BUCKLEY. Pathogenesis of the ICE syndrome British_Journal ofOphthalmology 1994; 78: 595-597

5. Morris RW, Dunbar MT. Atypical presentation and review of the ICE syndrome. Optometry. 2004 Jan;75(1):13-25

6. Jimmy D. Bartlett,Siret D. Jaanus , Clinical Ocular Pharmacology , fifth edition 2008, Section III (ocular Drugs in clinical practice by Nicky R.Holdeman) ,Chapter 26 ,diseases of the cornea,page 493-494, Bullous Keratopathy.

7. Susan Gromacki, O.D., M.S., F.A.A.O. Review of Cornea and Contact Lenses (RCCL) .The Case for Bandage Soft Contact Lenses. A primer on the use of these therapeutic lenses to serve and protect the corneas of our patients, 1/25/2012.

8. GREGORY W. DENAEYER, O.D., Columbus, Ohio.Manage Anterior Segment Disorders.Use contact lenses to manage these six anterior segment disorders. Optometric Management, Issue: August 2008.

Valeria OLIVA BIÉNZOBAS
Hospital Central de Mendoza, Argentina
MEXICO

NICERGOLINE®: A NOVEL TREATMENT FOR PERSISTENT CORNEAL EPITHELIAL DEFECT

★ INTRODUCTION ★

Corneal transparency and visual acuity depends on normal corneal epithelium. Corneal epithelial defects activate healing and remodeling responses which are mediated by humoral and extracellular matrix proteins. An alternative mechanism of corneal healing response is mediated by the presence of neurotrophic factors. Nerve growth factor (NGF) is a neurotrophic factor with potential therapeutic use that promotes corneal wound healing. Nicergoline® is an ergoline derivative which induces expression of NGF in rats tear promoting migration of corneal epithelium.

★ CASE PRESENTATION ★

We present a 76 year-old female with history of vascular vein occlusion in the left eye and infectious keratitis in the right eye that was successfully treated with topical antibiotics. After resolution of the keratitis, a persistent epithelial defect was treated with oral Doxycicline and L-Ascorbic, and topical treatment based on antibiotics, steroids, artificial tears and eyepatch for three weeks without clinical improvement. Best corrected visual acuity (BCVA) was hand motions and no light perception in the right and left eye, respectively. Applanation tonometry was 10 mmHg in both eyes. Slit-lamp examination of the right eye revealed an epithelial defect measuring 8 x 5 mm involving the center associated with diffuse edema and a posterior stromal white plaque in the inferior cornea (figure 1).

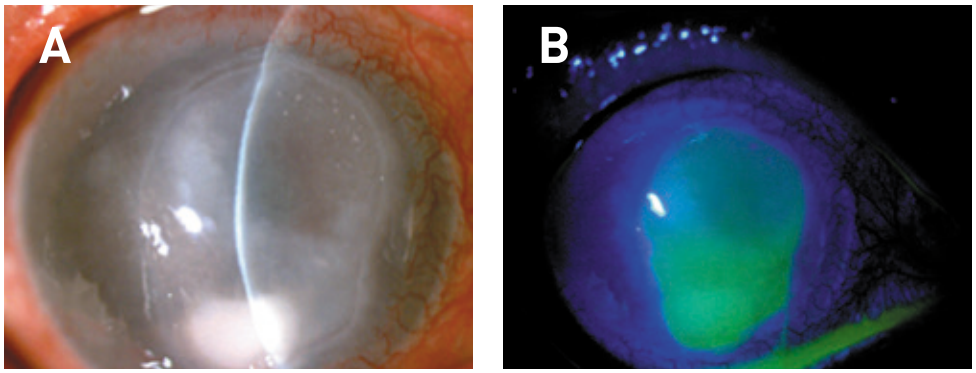


Figure 1: Slit-lamp examination of the anterior segment in a 76 year-old patient with persistent corneal epithelial defect (a). Cobalt blue-filter showing the extension of the corneal epithelial defect unresponsive to conventional treatment

We decided to add oral Nicergoline® 10mg TID for one week as an initial phase. Afterwards, a lower Nicergoline® dose of 10mg BID until the resolution of the epithelial defect.

After thirteen days of oral Nicergoline® treatment, slit-lamp examination revealed a remarkable clinical improvement of the epithelial defect measuring 1.3 x 2.1 mm (figure 2). BCVA improved to 20/1000 in the right eye.

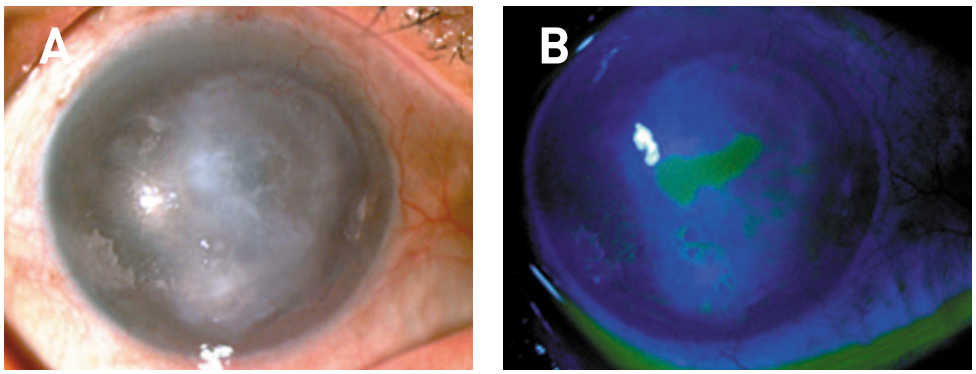


Figure 1: Slit-lamp examination thirteen days after treatment with oral Nicergoline® showing clinical improvement of the persistent epithelial defect (a). Cobalt blue-filter showing a small epithelial defect.

★ DISCUSSION ★

Recent evidence has shown NGF in cornea, tear, conjunctiva and lacrimal gland[2,5]. NGF promotes normal corneal healing and is essential for maintaining integrity of corneal epithelium. Kim et al. found that oral Nicergoline® for two weeks increased corneal wound healing in 50 rat corneas after photorefractive keratectomy[4]. The mechanism that promotes corneal wound healing process might be explained by increasing the expression of NGF in the rat corneas and lacrimal glands[1]. NGF might increase nerve regeneration by an unknown neurotrophic effect of Nicergoline® itself [1].

We are describing a patient with persistent epithelial defect unresponsive to conventional treatment that showed a remarkable clinical improvement after oral Nicergoline®. Proof of concept in animal models has shown that Nicergoline® promotes corneal wound healing and reepithelization[2,4]. Future clinical trials need to be conducted to determine the potential therapeutic benefit of Nicergoline® in patients with persistent epithelial defects.

★ CONCLUSION ★

Nicergoline® represents a potential therapeutic option in patients with abnormal corneal healing responses. Further studies and clinical trials need to be conducted to prove safety and efficacy as a treatment for persistent corneal epithelium defects in humans.

★ REFERENCES ★

1. Kim SY, Choi JS, Joo CK. Effects of nicergoline® on corneal epithelial wound healing in rat eyes. Invest Ophthalmol Vis Sci. 2009;50:621–625.

2. Lambiase A, Rama P, Bonini S, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 1998;338:1174–1180.

3. Bonini S, Lambiase A, Rama P, et al. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology. 2000;107:1347–1351.

4. Kim SY, Yang J, Lee YC. The effects of nicergoline® on corneal nerve regeneration in rat corneas after photorefractive keratectomy. Curr Eye Res. 2011;36:29–33.

5. Abdelkader H, Patel, et al. New therapeutic approaches in the treatment of diabetic keratopathy: a review. Clinical and Experimental Ophthalmology 2011; 39: 259–270.

Anna-Maria LAINE
Turku University Hospital , Turku
FINLAND

PERSISTENT CORNEAL ULCER IN A PATIENT WITH GLAUCOMA

★ INTRODUCTION ★

A healthy clear cornea is an essential part of good quality image and patient's wellbeing. All topical medications, except non-preserved artificial tear drops, are a potential threat for a cornea. Glaucoma as a progressive optic neuropathy may lead to visual impairment and blindness. The treatment is usually started with topical medication and most of the patients remain on it the rest of their life.[1, 2]

Topical glaucoma medication has been shown to be associated with numerous ocular surface changes.[3] The patients are more likely to have irritation and dry eye symptoms, suggesting significant ocular surface disease. Discomfort and problems with vision affect quality of life. Symptoms and signs are more prevalent if drops include preservatives or the dry eye symptoms have been present before glaucoma medication.[4,5,6] Preservatives can also cause toxicity and inflammation.[7, 8]

Corneal ulcer is a local epithelial defect with degradation or inflammation of underlying tissue and ocular surface disease is one of its main risk factors. The treatment of a corneal ulcer consists of topical antibiotics and artificial tear drops. Also, topical corticosteroids may have a beneficial effect. When epithelium heals and cornea stops thinning, the situation stabilizes.[9,10]

We now present a case report of a glaucoma patient with a severe corneal ulcer in her only seeing eye.

★ CLINICAL CASE ★

Our case is a 64-year-old woman with a history of dry eyes and angle-closure glaucoma in both eyes. She did not have any other diseases or systemic medications. The vision of her right eye was lost because of glaucoma and the left eye was her only seeing eye. That eye was red and it had blurry vision, secretion, and sensitivity to light. The sensitivity of her corneas was decreased. After initial IOP reduction she continued with bimatoprost and timolol (as a combination drug) as well as artificial tear gel for both eyes. Because of severe dry eyes symptoms she had also had occasional topical corticosteroid treatments.

Her dry eye symptoms got worse after 9 months use of glaucoma medication. In the right eye there was only mild corneal epithelial staining which was controlled with artificial tear gel and short topical corticosteroid treatment. In her left eye, a corneal ulcer was discovered. (Fig 1. and 2.) When the glaucoma treatment was started, her best corrected visual acuity (BCVA) in the left eye was 20/32 and now it had decreased to 20/200. There was redness in the conjunctiva, the cornea had epithelial surface defect which stained with fluorescein and the defect was surrounded by white stromal cloudiness. Topical levofloxacin was started. Glaucoma medication and artificial tear gel several times per day were continued. Herpes simplex virus sample turned out negative and the use of therapeutic contact lenses did not benefit.

Figure 1: Left eye approximately 2 months before starting Cacicol

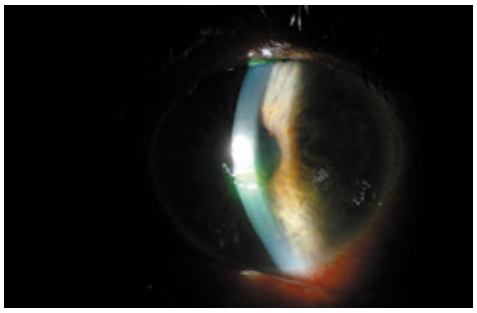


Figure 2: Left eye approximately 2 months before starting Cacicol

During treatment BCVA of the left eye fluctuated between 20/200 and 20/125. The stromal haziness increased and only the superior part of the cornea remained clear. The size of the ulcer increased significantly. Glaucoma medication was changed to preservative-free latanoprost and timolol. Topical dexametasone-chloramphenicol treatment and white vaseline ointment for night were started, and artificial tear gel several times a day was continued. The use of levofloxacin was discontinued. Redness of the eye started to resolve but the size of the ulcer and stromal haziness remained unchanged. BCVA was 20/125.

Cacicol was started three months after the ulcer was first seen. Two drops once a week was applied to the left eye. Glaucoma medication was continued as preservative-free, topical corticosteroid was discontinued and topical levofloxacin was restarted. After ten days use of Cacicol, corneal epithelium was sealed and after two more weeks stromal haziness started to clear out. BCVA was now 20/63. Because of signs of dry eye, topical fluorometholone was started. Week by week the situation came better. (Fig 3. and 4.) After four months, the use of Cacicol was stopped and the BCVA was 20/32-20/25.

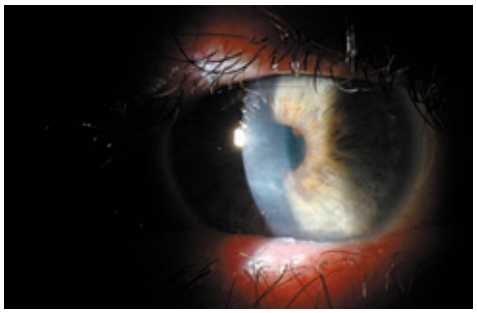


Figure 3: The left eye 3 weeks after Cacicol treatment was started

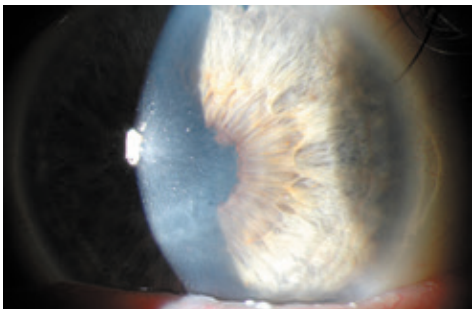


Figure 4: The left eye 7 weeks after Cacicol treatment was started

★ DISCUSSION ★

In this clinical case, the development of the corneal ulcer was probably connected with dry eyes and long-term use of glaucoma medication. Situation got severe and even though glaucoma medication was changed to preservative-free products no healing of the wound was seen.

Controlling infection with topical antibiotics and inflammation with topical corticosteroids and artificial tears is sometimes not enough. Cacicol is a topical regenerating agent (RGTA) and it works by restoring the corneal matrix architecture thus helping communication between cells. These effects allow the normal healing process to take place. [11,12,13]

Our patient had a persistent corneal ulcer causing significant decrease in vision in her only seeing eye. Once topical RGTA was started the healing process began and visual acuity gradually improved. As stated in literature, topical RGTAs seem to be a promising tool when treating persistent, treatment resistant corneal ulcers. [14]

★ CONCLUSION ★

Long-term use of topical glaucoma medication frequently causes ocular surface inflammation and damage. These together with dry eyes can significantly affect vision, ability to work, and quality-of-life.

Prolonged damage to ocular surface may lead to corneal ulceration and the healing process may be slow if the inflammation process continues. It has been shown that RGTAs can significantly help the healing process and it seems to be a useful and powerful tool for clinicians.

★ REFERENCES ★

1. Weinreb RN, Leung CK, Crowston JG, Medeiros FA, Friedman DS, Wiggs JL, Martin KR. Primary open-angle glaucoma. Nat Rev Dis Primers. 2016 Sep 22

2. Gupta D, Chen PP. Glaucoma. Am Fam Physician. 2016 Apr 15; 93 (8): 668-74.

3. Labbé A, Baudouin C. Treatment of glaucoma in patients with dry eye syndrome. J Fr Ophtalmol. 2010 Apr;33(4):285-90

4. Pillunat LE, Eschstruth P, Häsemeyer S, Thelen U, Foja C, Leaback R, Pfennigsdorf S. Preservative-free bimatoprost 0.03% in patients with primary open-angle glaucoma or ocular hypertension in clinical practice. Clin Ophthalmol. 2016 Sep 12; 10: 1759-65.

5. Lee SY, Wong TT, Chua J, Boo C, Soh YF, Tong L. Effect of chronic anti-glaucoma medications and trabeculectomy on tear osmolarity. Eye (Lond). 2013 Oct;27 (10): 1142-50.

6. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002 Apr; 86 (4): 418-23.

7. Aguayo Bonniard A, Yeung JY, Chan CC, Birt CM. Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK). Expert Opin Drug Metab Toxicol. 2016 Jul 18: 1-11.

8. Rasmussen CA, Kaufman PL, Kiland JA. Benzalkonium chloride and glaucoma. J Ocul Pharmacol Ther. 2014 Mar-Apr; 30 (2-3): 163-9.

9. Joseph I. Maguire; Ann P. Murchison; Edward A. Jaeger. Wills Eye Institute 5-Minute Ophthalmology Consult. ISBN-10: 1608316653, ISBN-13: 978-1608316656. 2010.

10. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. Am J Ophthalmol. 2003 Oct; 136 (4): 593-602.

11. Helin-Toiviainen M, Rönkkö S, Puustjärvi T, Rekonen P, Ollikainen M, Uusitalo H. Conjunctival matrix metalloproteinases and their inhibitors in glaucoma patients. Acta Ophthalmol. 2015 Mar; 93 (2): 165-71.

12. Mateo A, Abadía B, Calvo P, Minguez E, Pablo L, Del Castillo JM. Treatment of Acanthamoeba neurotrophic corneal ulcer with topical matrix therapy. J Ophthalmic Inflamm Infect. 2015 Jun 21; 5: 18. 2015.

13. Cacicol internetsite, accessed 10 October 2016 <http://cacicol.net/pro>

14. Brignole-Baudouin F, Warnet JM, Barritault D, Baudouin C. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. J Fr Ophtalmol. 2013 Nov; 36 (9): 740-7.

Elke KREPS
Ghent University Hospital, Ghen
BELGIUM

THE USE OF MATRIX THERAPY IN PERSISTENT EPITHELIAL DEFECTS RELATED TO BACTERIAL KERATITIS

★ INTRODUCTION ★

Bacterial keratitis is a potentially sight-threatening condition and constitutes the most common cause of suppurative corneal ulceration. It rarely occurs in a normal eye because of the natural resistance to infection, but predisposing factors including contact lens wear, trauma, corneal surgery, ocular surface disease, systemic inflammatory diseases and immunosuppression alter corneal defense mechanisms and render it susceptible to microbial infection[1].

The protocol for management of severe presumed bacterial keratitis involves collection of corneal scraping material for smear and culture and starting empirical antimicrobial therapy until culture and antibiotic sensitivity reports are available. Several studies have reported on similar clinical outcomes with the use of fourth-generation fluoroquinolones versus fortified antibiotics[1-4]. Severe ulcers are still frequently treated with a cephalosporin and an aminoglycoside used together to cover the maximum spectrum of bacteria, while awaiting culture results and clinical response. However, frequent dosing of multiple fortified antibiotics simultaneously results in increased toxicity and damage to the ocular surface epithelium.

Herein we describe our experience with the use of a matrix regenerating agent (RGTA, available under the trademark Cacicol®) in the nonsurgical approach of postinfectious persistent epithelial defects (PED). The case outlined below

mirrors our clinical experience with similar cases, clearly demonstrating the added value of Cacicol in handling PED following bacterial keratitis.

★ CASE PRESENTATION WITH ILLUSTRATIONS AND FIGURES ★

A 64-year-old female was referred to our department with a 4-day history of ocular redness and pain of the right eye. She had no history of contact lens wear, but reported blunt trauma to the right eye one week prior to presentation. On examination, she had hand motions vision in the right eye. Slit-lamp examination showed a central corneal ulcer (3x6mm) with a dense stromal infiltrate and a 1 mm hypopion (Figure 1).

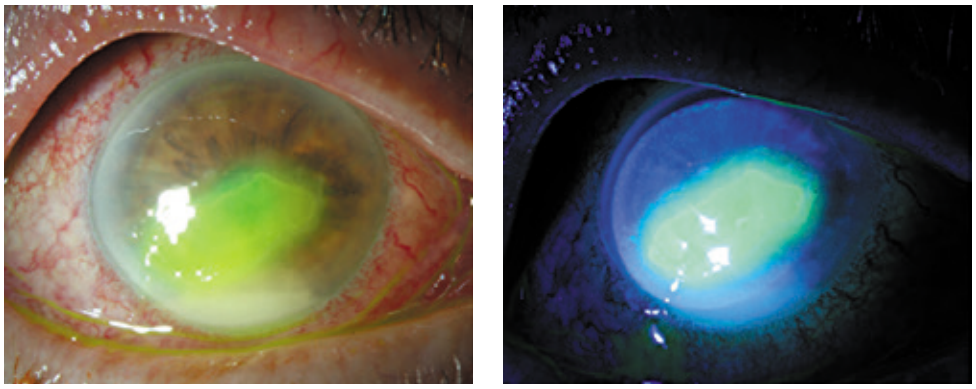


Figure 1: Slit-lamp examination of the right eye at presentation demonstrates ciliary injection and a large central corneal infiltrate (right panel). Fluorescein staining (left panel) indicates an extensive epithelial defect.

A corneal scraping was performed and she was admitted for hourly fortified drops (cefazoline 5% and tobramycin 1.4%). Gram staining and culture of the corneal scraping could not demonstrate an etiologic agent. Follow-up showed a good clinical response to the initiated antibiotic treatment, which clinically confirmed our preliminary diagnosis of bacterial keratitis. She was continued on hourly fortified drops for one week, until the corneal infection was sufficiently controlled to allow reducing of the antibiotic treatment. Fortified drops were then given three times a day for three days, before switching to a commercial preservative-free antibiotic (moxifloxacin). The corneal epithelial defect at that stage measured 5.5 mm (height) x 3 mm (width). Hourly autologous serum (AS) drops were initiated in order to facilitate epithelial healing. Despite hourly AS drops, lubricating ointment at night and a further decrease of the antibiotic drops, no change in diameter of the abrasion was observed following intensive 2-week treatment. Slit-lamp examination showed progressive thickening of the edges, impeding epithelial growth across the defect (Figure 2).

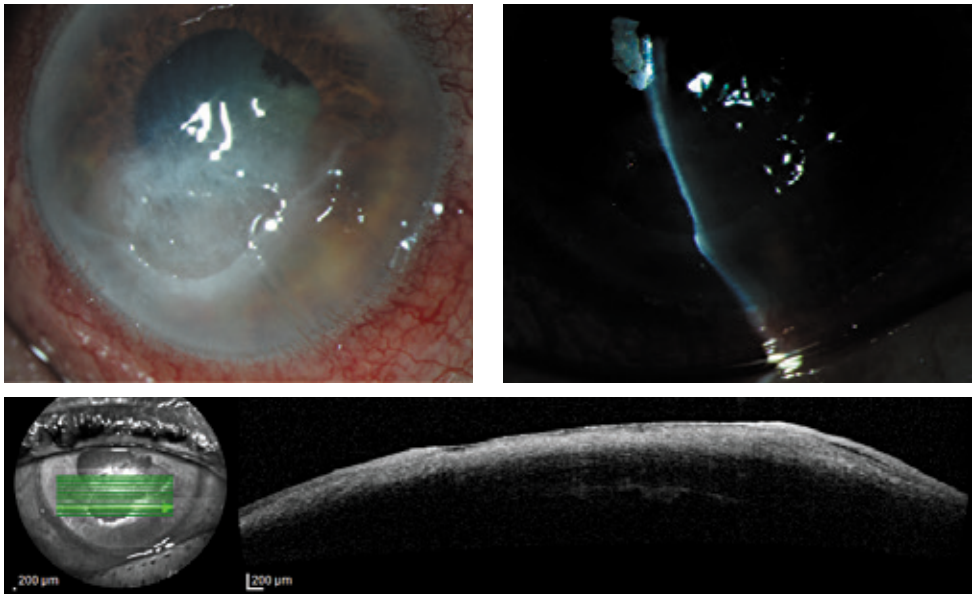


Figure 2: Status of the right cornea following a two-week course of hourly AS drops. A paracentral epithelial defect persists (upper left panel and anterior segment OCT image on lower panel) with thickened edges (upper right panel). At this stage, Cacicol treatment was initiated.

Because of the non-response to 2-week monotherapy of AS drops, matrix regenerating treatment (Cacicol) was initiated, one drop every other day, for a total of 5 applications alongside continued AS treatment. No local or systemic side effects were noticed and no discomfort during drop instillation was remarked. We observed progressive repair of the epithelial defect upon initiation of Cacicol treatment (Figure 3-4). Complete healing of the corneal epithelium was observed two weeks later (Figure 5). AS drop were gradually decreased in the following weeks without recurrence of the epithelial defect.

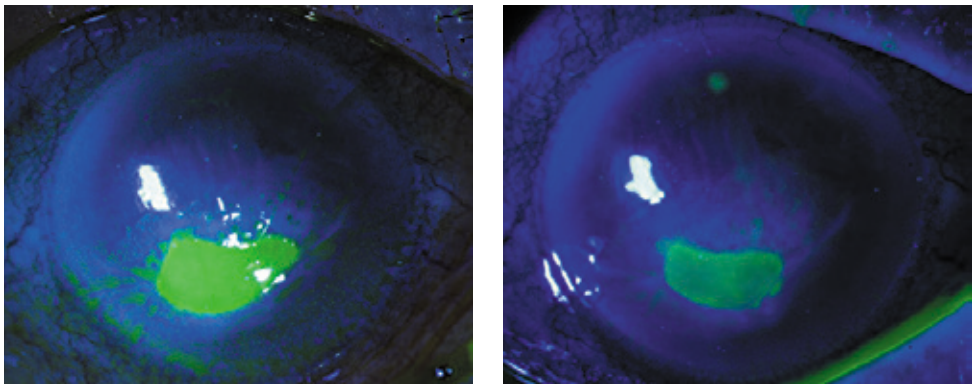


Figure 3: Resolution of the corneal epithelial defect following initiation of Cacicol treatment: the left panel shows the abrasion on the day of the first Cacicol application, the right panel on day 3.

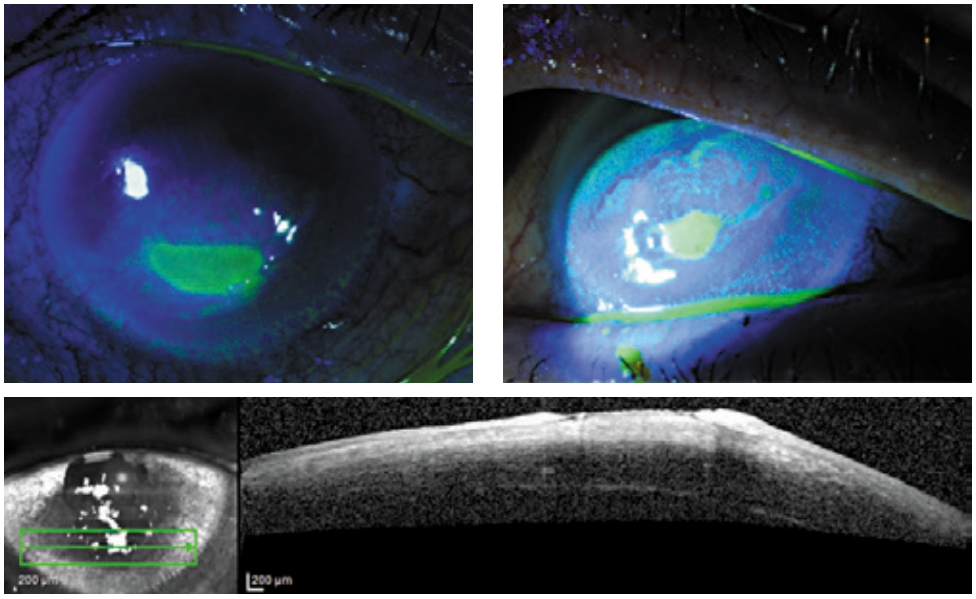


Figure 4: In the following days, a gradual epithelial migration is seen (day 5 on the upper right panel, day 10 on the upper left panel). The lower panel demonstrates the progressive epithelial growth across the defect (day 5).

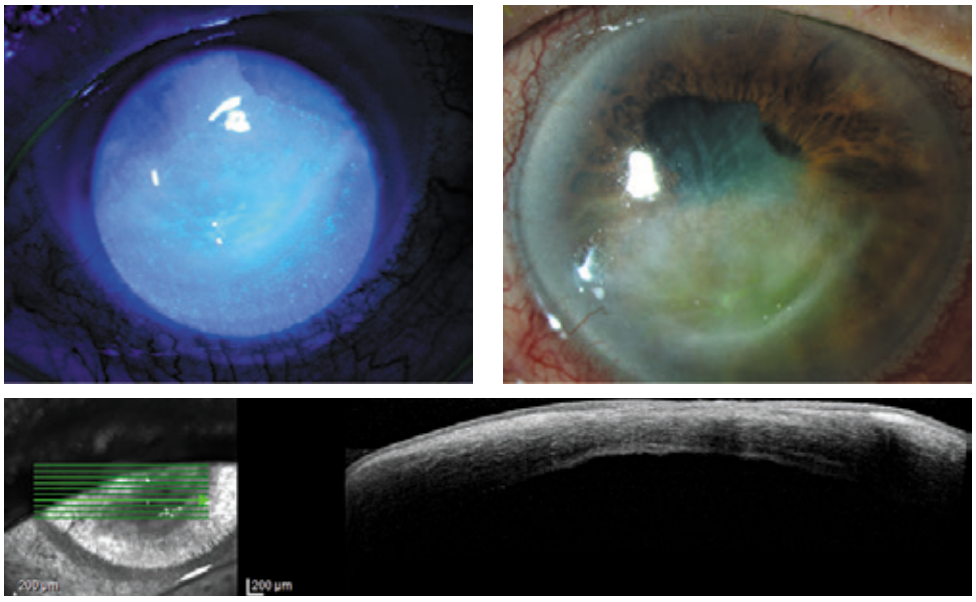


Figure 5: Complete epithelial healing is achieved 2 weeks following Cacicol treatment.

★ DISCUSSION ★

To our knowledge, we report on the first patient treated with Cacicol combined with AS drops in the setting of a PED following bacterial keratitis. The efficacy of matrix regenerating treatment in these cases is highly relevant, as it offers an easy, well-tolerated, nonsurgical approach to a vexing problem. The longer a PED is left unhealed, the longer it takes to heal and thus the higher the risk of complications[5]. The etiology of the PED in this patient was twofold: toxicity of the fortified antibiotics and the bacterial infection and associated inflammatory state of the cornea itself. Antimicrobial drugs exert their effects by one of two mechanisms of action. They either disrupt the cell wall or membrane structure to trigger osmotic or metabolic abnormalities or they inhibit intracellular processes that are necessary for the survival or replication of the organism[6]. Ocular surface toxicity is classically encountered in the latter, as these antibiotics impair metabolic processes which are shared by human cells. These include aminoglycosides such as tobramycin. In vitro models of corneal epithelial wound healing have demonstrated that 5% cefazolin has little retardation effect, whereas 0.3% tobramycin was among the most toxic[6]. We regularly use 1.4% tobramycin as a fortified antibiotic, a highly effective antimicrobial agent albeit at the cost of increased epitheliotoxicity. The negative culture results and slow clinical response prohibited earlier lessening of the fortified drops in this case.

Clinical approach to persistent epithelial defects

Persistent epithelial defects (PED) following bacterial keratitis pose a challenging problem. As a general rule, PED can be defined as a loss of integrity of the corneal surface and/or an epithelial defect caused by injury or disease, which does not heal within the usual time-frame of several days up to 2 weeks[7]. There is no universally accepted approach to managing PED. Possible etiologies are very heterogeneous and include keratoconjunctivitis sicca, limbal stem cell deficiency, diabetes, postherpetic ulcers, chemical burns, graft-versus-host disease and neurotrophic ulcers[8]. Even within each subcategory, the state of the corneas can be very different. For this reason, it is highly challenging to design randomised controlled clinical trials to test efficacy of compounds to heal PED[5]. Traditional treatments may include: high frequency application of preservative-free artificial tears, punctal occlusion, patching, soft contact lenses, AS tears, amniotic membrane (AM) application and tarsorrhaphy[9,10]. Artificial tears improve tear volume and dynamics but have limited efficacy in healing a PED as they do not replace essential tear components[11].

Autologous serum drops

Fox et al, in 1984, first described the successful use of AS as an eye drop in keratoconjunctivitis sicca, topical tears formulated from a patient's own centrifuged serum[12]. Studies on the management of ocular surface disease

- including cases with recurrent corneal erosions, PED, superior limbal keratoconjunctivitis, neurotrophic keratopathy and dry eyes - report favourably on the overall efficacy of AS drops[13,14]. PED recalcitrant to standard therapies have been shown to close in 47-83% of cases within four weeks of initiating AS treatment[8,13]. In vitro models also show significantly faster rates of cell migration with AS drops[8]. Combined use of AS drops and silicone hydrogel bandage contact lenses in 12 patients with postinfectious PED showed complete healing within 2 weeks[15]. The beneficial effects of AS are thought to arise from high concentration of various key components involved in epithelial proliferation and migration. These nutrients exist in normal tears and AS drops but are not present in artificial tears: vitamin A, vitamin E, epidermal growth factor, transforming growth factor-β (TGF-β), platelet-derived growth factor, fibroblast growth factor, fibronectin, substance P, insulin-like growth factor, and nerve growth factor[13]. Furthermore, AS drops have no potentially toxic preservatives.

The optimal concentration of AS drops remains to be confirmed. The 20% concentration - as used in our patient - is commonly administered and empirically based on adequate viscosity and the dilution of TGF-β to that which is the normal level in tears: TGF-β levels in serum are approximately 5 times higher than that in tears[13]. Higher levels of TGF-β are thought to be deleterious to wound healing because of its potential profibrogenic effects. AS drops have some shortcomings: they cannot be produced on a large scale, are difficult to manufacture without bacterial contamination and are not approved by all regulatory bodies[11]. Patients in poor general health or those with diseases whereby excess pro-inflammatory cytokines may be present in the serum, such as in graft-versus-host disease or Sjögren syndrome, are also poor candidates for AS treatment.

Amniotic membrane patching

Patching of an amniotic membrane (AM), the innermost layer of the placenta, is often used as the primary surgical approach to treat PED. It contains a thick basement membrane and a stromal matrix, which promotes epithelial differentiation[14]. As a source of vital components such as growth factor proteins, anti-inflammatory cytokines and proteinase inhibitors, it both helps to reconstitute an intact basal membrane and decrease inflammation and scarring of the cornea [13,16,17]. Drawbacks of AM patching include the need for surgical intervention, risk of postoperative infection, dislocation of the AM due to loosening of the sutures, submembrane haemorrhage and early disintegration of the membrane[7]. Interestingly, a 2016 study that compared post-photorefractive keratectomy eyes given AM versus standard bandage contact lens and lubrication showed a longer healing time and more discomfort in the AM group[18]. This clearly demonstrates the differential mechanisms of corneal surface healing in a healthy eye as opposed to PED. Findings of epithelial healing in healthy eyes are therefore not necessarily representative of healing in PED.

Experimental compounds

Isolated, small-scale reports have shown encouraging results in treating PED with platelet-rich plasma tears and topical fibronectin, one of the most important components in cell migration [9,19,20]. The PROSE system (prosthetic replacement of the ocular surface ecosystem; BostonSight, Needham, MA, USA), a fluid-ventilated, gas-permeable scleral device, has also been used in the setting of PED[9,10]. It creates a protected, hydrated microenvironment by vaulting over the entire cornea. Mixed results in regard to epithelial defect resolution have been reported with PROSE, as well as a significant incidence of microbial keratitis[9,10]. Overall, clinical experience with these components remains limited and its availability is restricted.

Matrix regenerating treatment

Facilitating the healing of PED helps to minimise recovery time, reduce the length of stay and decrease the risk of chronic epithelial defect-related complications, such as corneal haze, infectious and sterile keratitis, stromal melting, irregular astigmatism and loss of vision[10,21]. Our case demonstrates the efficacy of Cacicol treatment in postinfectious PED and the synergistic effect with AS drops.

To heal an epithelial defect, the bordering epithelium must replicate and migrate to fill the defect[6]. The extracellular matrix both has a structural role in providing a framework for cells and a biochemical role in cell-cell communication[22]. It is composed of fibrous proteins (primarily collagens) and glycoproteins, which include proteoglycans, fibronectins and laminins[22]. Proteoglycans consist of several glycosaminoglycans (GAG, long polysaccharides) attached to a core protein[22]. In the setting of bacterial keratitis, proteases, glycanases and inflammatory peptides are released, which destroy the extracellular matrix[22]. Research has identified a central role for heparan sulphates, a subclass of sulphated GAG, in regulating tissue homeostasis[23]. Matrix ReGeneraTing Agents (RGTA) consist of polysaccharides derived from dextran, designed to replace degraded heparan sulphates in injured tissues. As such, they protect extracellular matrix proteins and growth factors from enzymatic degradation. RGTAs are resistant to degradation by glycanases, in contrast to natural heparan sulphate. A formulation of RGTA eyedrops (Cacicol®, Laboratoires Théa), composed of polycarboxymethyl glucose sulphate, dextran 40, sodium chloride and purified water, has been approved for the use in PED in Europe.

Increasing evidence points to accelerated healing of chronic ulcers with the use of RGTA. Safety and effectiveness in treating PED has been demonstrated in corneal dystrophies, resistant corneal ulcers and herpetic keratitis, chemical burns and perforating keratitis, with mean wound healing ranging from 4 to 9 weeks[16,17,24,25]. Recently, the use of Cacicol in acanthamoeba keratitis has been described, as well as combined Cacicol with a bandage contact lens in 3 cases with PED[26,27]. Two recent reports on epithelial healing following epi-off crosslinking used alternate day application and showed significantly faster recovery than the placebo-group[28,29]. It should be added that the control

group in the trial of Bata et al was only given hyaluronic acid drops instilled every other day without bandage contact lens, which is not the common practice. Recommendations on instillation frequency of Cacicol vary from one to two weekly up to daily application. Empirically, too frequent application is best avoided as sites for heparan binding available in healing tissue are limited. Healing may become compromised by competing with heparan-binding growth factors. Given the properties of Cacicol, continuation of treatment after complete re-epithelialisation does not seem useful[16].

Cacicol has primarily been used in neurotrophic ulcers. Patients with resolving bacterial keratitis have also been shown to have a significantly lower nerve density[30]. We used Cacicol combined with AS drops in order to provide rapid resolution of PED following severe bacterial keratitis. The beneficial effect of AS drops is mainly thought to arise from its growth factors and related natural components. In inflamed corneas, enzymatic degradation of the extracellular matrix inhibits the effect of AS drops, as demonstrated in our case. By adding Cacicol to the treatment strategy, one can render the environment more conducive to epithelial closure and thus break the negative repair-destruction cycle. We opt to use AS in conjunction with Cacicol because of its synergistic effect and low infection risk: Cacicol provides the extracellular matrix support required to obtain a solid surface and the AS drops contain the growth factors necessary to speed up epithelial replication and migration.

★ CONCLUSION ★

In summary, our case demonstrates the added value of Cacicol in healing persistent epithelial defects following severe bacterial keratitis – a clinical indication not previously reported. The combined use of AS drops and Cacicol is also an interesting empirical approach to speed up recovery time of PED.

★ REFERENCES ★

1. McDonald EM, Ram FS, Patel DV, McGhee CN. Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials. Br J Ophthalmol 2014;98(11):1470-1477.

2. Gangopadhyay N, Daniell M, Weih L, Taylor HR. Fluoroquinolone and fortified antibiotics for treating bacterial corneal ulcers. Br J Ophthalmol 2000;84(4):378-384.

3. Rosenberg JB, Gritz DC. Monotherapy versus fortified antibiotics for bacterial keratitis. Cornea 2011;30(9):1066.

4. Sharma N, Goel M, Bansal S, Agarwal P, Titiyal JS, Upadhyaya AD, Vajpayee RB. Evaluation of moxifloxacin 0.5% in treatment of nonperforated bacterial corneal ulcers: a randomized controlled trial. Ophthalmology 2013;120:1173-1178.

5. Jeng BH. Abrasions, Planned defects, and Persistent Epithelial Defects in Corneal Epithelial Wound Healing. JAMA Ophthalmol 2016 Sep 1 [Epub ahead of print]

6. Stern GA, Killingsworth DW. Complications of topical antimicrobial agents. Int Ophthalmol Clin 1989;29(3):137-142.

7. Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel Therapy to Treat Corneal Epithelial Defects: A Hypothesis with Growth Hormone. Ocul Surf 2015;13(3):204-212

8. Tsubota K, Goto E, Shimmura S, Shimazaki J. Treatment of persistent corneal epithelial defect by autologous serum application. Ophthalmology 1999;106(10):1984-1989.

9. Ciralsky JB, Chapman KO, Rosenblatt MI, Sood P, Fernandez AG, Lee MN, Sippel KC. Treatment of refractory persistent corneal epithelial defects: a standardized approach using continuous wear PROSE therapy. Ocul Immunol Inflamm 2015;23(3):219-224.

10. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of Persistent Corneal Epithelial Defect With Overnight Wear of a Prosthetic Device for the Ocular Surface. Am J Ophthalmol 2013;156(6): 1095–1101

11. Watson SL, Geerling G, Dart JKG. Clinical study of therapeutic ocular surface medium for persistent epithelial defect. Ophthalmic Res 2015;51(2):82-87.

12. Fox RI, Chan R, Michelson JB, Belmont JB, Michelson PE. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum 1984;27(4):459-461.

13. Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol 2014;28(3):168-172.

14. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. Am J Ophthalmol 1997;124(6):765-774.

15. Wang WY, Lee YK, Tsai SH, Lin YC, Chen YM. Autologous serum eye drops combined with silicone hydrogel lenses for the treatment of postinfectious corneal persistent epithelial defects. Eye Contact Lens 2016 Mar 9. [Epub ahead of print]

16. Aifa A, Gueudry J, Portmann A, Delcampe A, Muraine M. Topical treatment with a new matrix therapy agent (RGTA) for treatment of corneal neurotrophic ulcers. Invest Ophthalmol Vis Sci 2012;53(13):8181-8185.

17. Brignole-Baudouin F, Warnet JM, Barritault D, Baudouin C. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. J Fr Ophthalmol 2013;36(9):740-747.

18. Vlasov A, Sia RK, Ryan DS et al. Sutureless cryopreserved amniotic membrane graft and wound healing after photorefractive keratectomy. J Cataract Refract Surg 2016;42(3):435-443.

19. Kim KM, Shin YT, Kin HK. Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis. Jpn J Ophthalmol 2012;56(6):544–550.

20. Yamada N, Morishige N, Yanai R, Morita Y, Kimura K, Chikama T, Nomizu M, Sonoda KH, Nishida T. Open clinical study of eye drops containing the fibronectin-derived peptide PHSRN for treatment of persistent corneal epithelial defects. Cornea 2012;31(12):1408-1413.

21. Lekhanont K, Jongkhajornpong P, Choubtum L, Chuckpaiwong V. Topical 100% Serum Eye Drops for Treating Corneal Epithelial Defect after Ocular Surgery. Biomed Res Int 2013;2013:521315. [Epub 2013 Jul 30]

22. Barritault D, Desgranges P, Meddahi-Pellé A, Denoix JM, Saffar JL. RGTA-based matrix therapy – A new branch of regenerative medicine in locomotion. Joint Bone Spine 2016 Sep 20. [Epub ahead of print]

23. Rouet V, Meddahi-Pelle A, Miao HQ, Vlodavsky I, Caruelle JP, Barritault D. Heparin-like synthetic polymers, named RGTAs, mimic biological effects of heparin in vitro. J Biomed Mater Res A, Sep 15 2006, 78(4), 792-797

24. Chebbi CK, Kichenin K, Amar N, Nourry H, Warnet JM, Barritault D, et al. [Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy]. J Fr Ophtalmol, May 2008, 31(5), 465-471.

25. De Monchy I, Labbe A, Pogorzalek N, Gendron G, M'garrech M, Kaswin G, et al. [Management of herpes zoster neurotrophic ulcer using a new matrix therapy agent (RGTA): A case report]. J Fr Ophtalmol, Mar 2012, 35(3), 187.e181-186.

26. Mateo A, Abadia B, Calvo P, Minguez E, Pablo L, Del Castillo JM. Treatment of Acanthamoeba neurotrophic corneal ulcer with topical matrix therapy. J Ophthalmic Inflamm Infect 2015;5:18.

27. Kymionis GD, Liakopoulos DA, Grentzelos MA, Diakonis VF, Klados NE, Tsoulnaras KI, Tsilimbaris MK, Pallikaris IG. Combined topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. Cornea 2014;33(8):868-872.

28. Kymionis GD, Liakopoulos DA, Grentzelos MA, Tsoulnaras KI, Detorakis ET, Cochener B, Tsilimbaris MK. Effect of the Regenerative Agent Poly(Carboxymethylglucose Sulfate) on Corneal Wound Healing After Corneal Cross-linking for Keratoconus. Cornea 2015;34(8):928-931.

29. Bata AM, Witkowska KJ, Wozniak PA, Fondi K, Schmidinger G, Pircher N, Szegedi S, Aranha Dos Santos V, Pantalon A, Werkmeister RM, Garhofer G, Schmetterer L, Schmidl D. Effect of a Matrix Therapy Agent on Corneal Epithelial Healing After Standard Collagen Cross-linking in Patients with Keratoconus: A Randomized Clinical Trial. JAMA Ophthalmol 2016 Sep 1. [Epub ahead of print]

30. Muller RT, Abedi F, Cruzat A, Witkin D, Baniasadi N, Cavalcanti BM, Jamali A, Chodosh J, Dana R, Pavan-Langston D, Hamrah P. Degeneration and regeneration of subbasal corneal nerves after infectious keratitis: a longitudinal in vivo confocal microscopy study. Ophthalmology 2015;122(11):2200-2209.

Pavlina SKALICKA
Charles University Hospital, Prague
CZECH REPUBLIC

PARAPROTEINEMIC KERATOPATHY: 14 YEARS OF FOLLOW-UP

★ INTRODUCTION ★

Monoclonal gammopathy of undetermined significance (MGUS) is from a hematologic point of view a benign condition not requiring any treatment, in which the clonal mass has not reached a malignant state, but it is a precursor to multiple myeloma or lymphoma at a rate of ~1% per year. MGUS is generally regarded to be a disease of elderly, increasing with age from 1.7% in individuals 50-59 to 6.6% in those over 80 years old [1,2].

However, organ damage secondary to the presence of monoclonal gammopathy can occur. Well recognized are now nephropathies, oculopathies and dermopathies, while autoimmune diseases and coagulopathies are found less commonly. Systemic involvement of multiple organs has also been observed[3].

Monoclonal gammopathy related to ocular disease has been reported as keratopathy, crystal-storing histiocytosis involving conjunctiva, orbital and extraocular muscles, maculopathy and uveal effusion [3]. Corneal involvement has been estimated to be present only in approximately 1% of patients with monoclonal gammopathy [4]. Two recent case series have greatly raised awareness and recognition of paraproteinemic keratopathy as a result of immunoglobulin light chain deposition within cells in the epithelial and stromal layers. The pattern of these corneal changes is variable, most often crystalline-like deposition in the corneal stroma can be found, followed by nummular epithelial lesions, lattice-like and diffuse stromal deposits or peripheral epithelial and stromal bands, granular-like or patch-like lesions[5-7].

In one female copper deposition at the level of Descement membrane was also seen [8]. Visual acuity is typically not affected and only few patients suffer from visual loss due to stromal haze necessitating corneal grafting with a high chance of disease recurrence [5].

In this study we describe a case with paraproteinemic keratopathy and thus further aid to the range of clinical spectrum associated with monoclonal gammopathy.

★ CASE REPORT ★

The 26-year-old male patient with no family history of corneal disease was referred to the Department of Ophthalmology with a diagnosis of bilateral lattice corneal dystrophy (Figure 1A). The patient did not have any subjective symptoms and his corneal disease was first noted at the age of 24 years during a random ophthalmological check-up.

When first examined in our department his Snellen best corrected visual acuity (BCVA) was 6/6 with -3.5 dioptres (D) and -1.75 D with in the right and left eye, respectively. The diagnosis of lattice corneal dystrophy was confirmed and venous blood sample taken for DNA extraction after signing informed consent. Coding sequences of *TGFBI* (OMIM *601692), the only gene known to be implicated in lattice corneal dystrophy, were Sanger sequenced as previously described [9]. No possibly disease-causing mutations were identified. Slit-lamp examination of both parents and a sister of the proband did not show any corneal pathology.

The patient was re-examined at the age of 40 years. Since 26 years of age his BCVA decreased to 6/12 and 6/36 in the right and left eye, respectively. Observed bilateral corneal deposits resembled lattice lines with blurry edges. In addition, there was also diffuse haze of the intervening stroma and few epithelial nummular lesions (Figure 1B, C, D, E). Spectral domain optical coherence tomography (SD/OCT; Spectral OCT/SLO (OTI Ophthalmic Technologies Inc., Toronto, Canada) confirmed the localization of deposits in throughout the whole stroma (Figure F, G) Central corneal thickness as measured by SD-OCT was 530 µm in both eyes. The rest of the ocular examination including fundus biomicroscopy in dilation, retinal nerve fibre layer, axial length, anterior chamber depth and keratometry measurements were bilaterally within normal limits.

As the corneal deposits were relatively symmetric and no *TGFBI* mutations were found, we have suspected the presence of monoclonal gammopathy which was subsequently confirmed. Paraprotein produced in excess of clonal proliferation was detected by serum protein electrophoresis (M-spike of 6.0 g/dL) and identified by immunofixation as IgG kappa light chain. Systemic examination did not indicate involvement of any other organs.

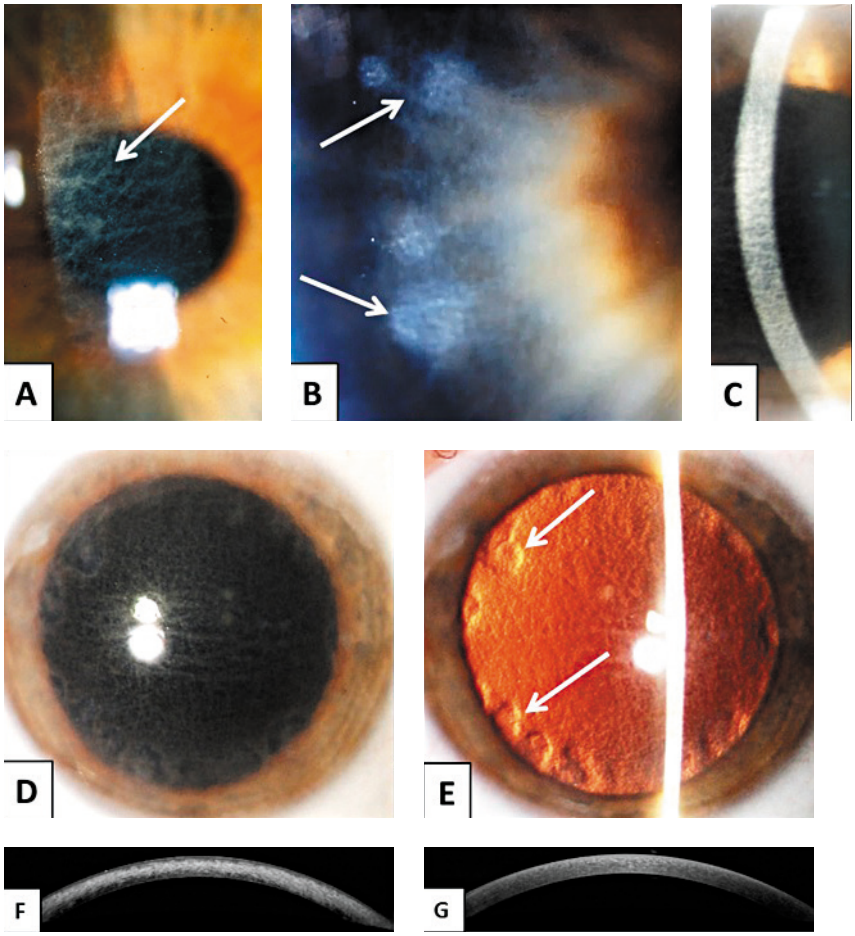


Figure 1: Clinical findings in a case with paraproteinemic keratopathy misdiagnosed as lattice corneal dystrophy.

Slit-lamp photographs of the right eye (A) showing stromal lattice-like lesions at the age of 26 years (arrow); slit-lamp photographs taken at the age of 40 years (B) peripheral nummular epithelial deposits (arrows) (C) narrow beam demonstrating dense opacification of the corneal stroma (D) corneal lesion as observed in dilation (E) and in in retroillumination (arrows indicate nummular peripheral lesions). SD-OCT imaging showing diffuse stromal haze (F) compared to normal cornea (G).

★ DISCUSSION ★

Herein we report on a case with monoclonocal gammopathy and corneal deposits followed for 14-years. The patient was noticed to have paraproteinemic keratopathy already at the age of 24 years which is to the best of our knowledge is the earliest corneal manifestation described.

The pattern of paraproteinemic keratopathy observed in our patient with lattice-like lines resembled a case described by Milman et al. [5]. Although mild

BCVA decrease has been noted bilaterally during the 14 years of follow-up we think that there is currently no need to pursue systemic treatment. We shall however closely monitor clinical ocular findings in our case.

With gene-based therapies on the horizon it is becoming essential that phenocopies of genetically determined disorders are correctly recognized. Awareness of relationship between clinical findings in monoclonal gammopathy mimicking corneal dystrophies is important to ensure that patients are screened for paraproteins and the diagnosis is not delayed. Once the diagnosis of paraproteinemic keratopathy is established and monoclonal gammopathy confirmed, there are several implications for the patient. Because the cumulative probability of progression to malignancy is 12% in 10 years increasing up to 30% at 25 years [2] regular systemic follow-up is need to ensure timely treatment. Also in case of significant progressive visual loss ophthalmologists may intervene and request treatment initiation before the damage is advanced.

★ CONCLUSION ★

In summary corneal opacity that has an unexplained etiology may be the first clinical symptom of monoclonal gammopathy even at a younger age. Ophthalmologists need to be aware of this and initiate multidisciplinary investigation to exclude malignacy and/or involvement of other organs.

★ REFERENCES ★

1. Kyle, R.A., et al., Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med, 2006. 354(13): p. 1362-9.

2. Kyle, R.A., et al., A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med, 2002. 346(8): p. 564-9.

3. Glavey, S.V. and N. Leung, Monoclonal gammopathy: The good, the bad and the ugly. Blood Rev, 2016. 30(3): p. 223-31.

4. Nagendran, S.T., et al., Crystalline keratopathy associated with monoclonal gammopathy of undetermined significance. Br J Haematol, 2012. 159(3): p. 258.

5. Milman, T., et al., Paraproteinemic Keratopathy: The Expanding Diversity of Clinical and Pathologic Manifestations. Ophthalmology, 2015. 122(9): p. 1748-56.

6. Hall, R.B., et al., A series of 4 cases of distinct keratopathy secondary to dysproteinemia: immunotactoid keratopathy. Can J Ophthalmol, 2014. 49(4): p. 388-91.

7. Lisch, W., et al., Chameleon-like appearance of immunotactoid keratopathy. Cornea, 2012. 31(1): p. 55-8.

8. Hawkins, A.S., et al., Ocular deposition of copper associated with multiple myeloma. Am J Ophthalmol, 2001. 131(2): p. 257-9.

9. Liskova, P., et al., Phenotype associated with the H626P mutation and other changes in the TGFBI gene in Czech families. Ophthalmic Res, 2008. 40(2): p. 105-8.

Argyrios TZAMALIS
Papageorgiou General Hospital, Thessaloniki
GREECE

SUCCESSFUL TREATMENT OF SPONTANEOUS CORNEAL PERFORATION RELATED TO UNDERDIAGNOSED SJÖGREN'S SYNDROME USING POLY-CARBOXYMETHYLGLUCOSE SULFATE AND AUTOLOGOUS SERUM EYE DROPS

★ INTRODUCTION ★

Sterile corneal melting (SCM) or keratolysis is a non-infectious corneal disorder and may often be an indication of systemic disease [1]. Corneal melting is a common prelude to the development of corneal perforation, which may even lead to blindness, when left untreated [2]. SCM is most frequently associated with preexisting tear-film abnormalities due to keratoconjunctivitis sicca (KCS), Sjögren's syndrome (SS), or collagen vascular diseases such as rheumatoid arthritis [1,3].

Sjögren's syndrome is a chronic inflammatory disorder characterized by exocrine gland dysfunction and a variable systemic course. Lymphocytic infiltration of the lacrimal and salivary glands results in the classic sicca complex characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS may occur alone (primary) or in association with other autoimmune diseases (secondary) [4].

Although extremely rare, corneal melting may be the initial presentation of primary Sjögren's syndrome [5]. When spontaneous perforation occurs, as a consequence of corneal melting, an ocular emergency is raised. Several therapeutic interventions have been proposed including bandage contact lens placement, cyanoacrylate glue, amniotic membrane, conjunctival grafts and partial- or full-thickness keratoplasty procedures [6-9].

Tears have lubricating and mechanical properties, but also epitheliotrophic and antimicrobial effects. A reduction of epitheliotrophic factors compromises the integrity of the surface epithelia [1,10]. In cases of sterile keratolysis, adequate lubrication with preservative-free tear and ointment supplements is very important. However, none of the commercially available artificial tear products includes all the essential tear components such as growth factors, vitamins, and immunoglobulins.

Autologous serum eye drops and regenerating agents (RGTAs) such as poly-carboxymethylglucose sulfate have been recommended for the treatment of several ocular surface disorders, SS included, that may lead to epithelial disruption [11-13]. However, there are no reports of their use in severe corneal melting, which can result in perforation of the globe.

We, hereby, report an interesting case of a sterile corneal ulcer complicated with corneal melting and perforation, which was treated successfully with the use of autologous serum eye drops, regenerative agent (poly-carboxymethylglucose sulfate), steroids and systemic therapy in a patient with undiagnosed primary Sjögren's syndrome.

★ CASE REPORT ★

A 74-year-old female presented complaining of blurry vision and foreign body sensation in her left eye, gradually worsening over the last month. Ocular history spoke of a dry eye syndrome treated topically during the last 6 months with preservative-free lubricants (sodium hyaluronate 0.1%, dexpanthenol 2%). The patient had no history of ocular surgery, or any other known ocular pathology. Systemically, she was diagnosed with arterial hypertension, adequately controlled with medication in the last 8 years.

Ophthalmological examination showed an oval-shaped central descemetocele with maximal diameter of 3.2mm without any signs of infection (Figure 1). A mild conjunctival injection was noted, while anterior chamber was deep without flare or cells. Anterior segment optical coherence tomography (AS-OCT) showed the site of corneal melting giving a remarkable "rope-bridge" imaging sign, whereby both Bowman's and the Descemet's membranes were clearly and continuously depicted, while stroma was disappeared completely in between, showing an excessive corneal melting (Figure 2).

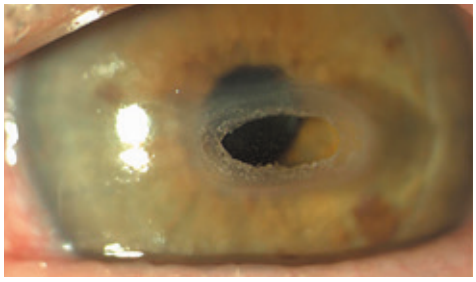


Figure 1: Anterior segment photograph of the left eye showing central descemetocele

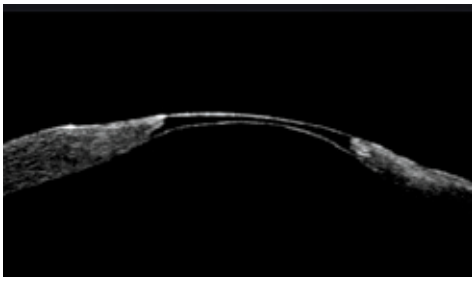


Figure 2: AS-OCT of the left eye at the site of descemetocele (horizontal axis 0-180°) showing excessive stromal melting but intact Bowman and Descemet layers ("rope-bridge" imaging sign)

Schirmer I test after 5 minutes was 6mm in her right (OD) and 4mm in her left eye (OS). Fluorescein instillation revealed a punctate epithelial lesions in both eyes (Grade 3, Oxford scale) and a positive staining at the site of corneal melting. Best corrected visual acuity (BCVA) was 0.15 logMAR (7/10 Snellen) OD and counting fingers at 50cm OS.

After a bandage contact lens was applied and intensive preservative-free ocular lubrication was prescribed, the patient was referred to a rheumatologist who confirmed the diagnosis of Sjögren's syndrome (positive anti-SSA/Ro antibodies, negative anti-SSB/La antibodies and rheumatoid factor) and set the patient on systemic steroids and hydroxychloroquine.

Two days after the initial assessment, the patient developed a perforation on the site of the descemetocele, presenting with a flat anterior chamber (Figure 3), while visual acuity decreased from counting fingers at 50cm to hand motion.

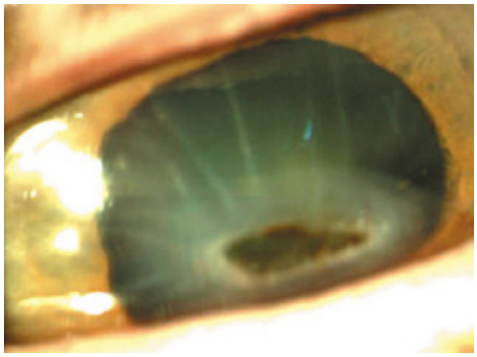


Figure 3: Anterior segment photograph of the left eye showing corneal perforation at the site of descemetocele with flat anterior chamber and Descemet folds expanding radially

The patient was admitted and scheduled for amniotic membrane graft transplantation, while topical dexamethasone 1% (qid), moxifloxacin 0.5% (qid) and autologous serum eye drops 20% (every 2 hours) were administered. On the next day, the anterior segment evaluation revealed a significant reforming of the anterior chamber and minimal inflammatory reaction. Thus the surgical procedure was postponed (Figure 4).

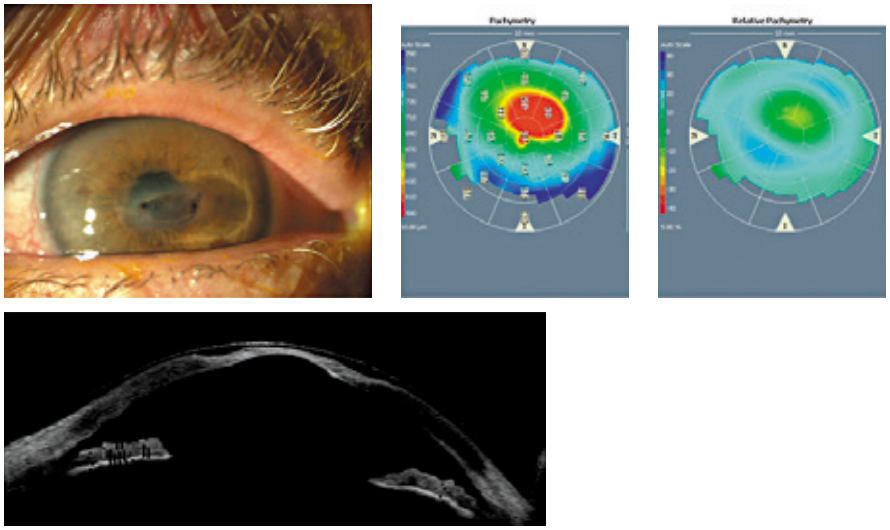


Figure 4: Anterior segment photograph (top left), pachymetry map (top right) and AS-OCT (bottom) of the left eye on the 1st day after spontaneous perforation. (CTmin=213μm)

Anterior segment optical coherence tomography showed a central anterior chamber depth of 2.7mm and a regeneration of the corneal stroma. In order to promote further corneal healing poly-carboxymethylglucose sulfate RGTA eye drops were prescribed (one drop every 2 days) and applied over the next month, tapering off dexamethasone antibiotic eye drops. The patient was monitored closely over the following week, showing clinical improvement (Figure 5) and, topical treatment was continued. Corneal thickness gradually increased and inflammation signs subsided during a course of one month (Figure 6).

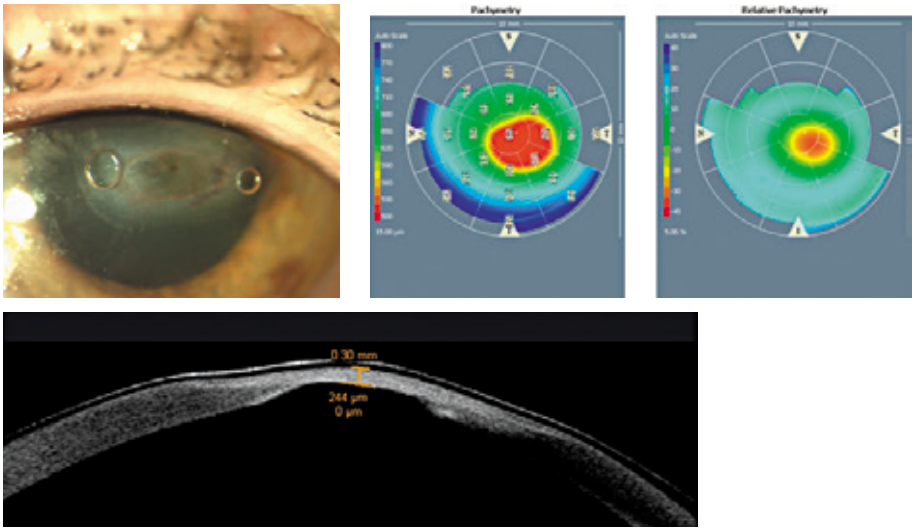


Figure 5: Anterior segment photograph (top left), pachymetry map (top right) and AS-OCT (bottom) of the left eye one week after spontaneous perforation. (CTmin=244μm)

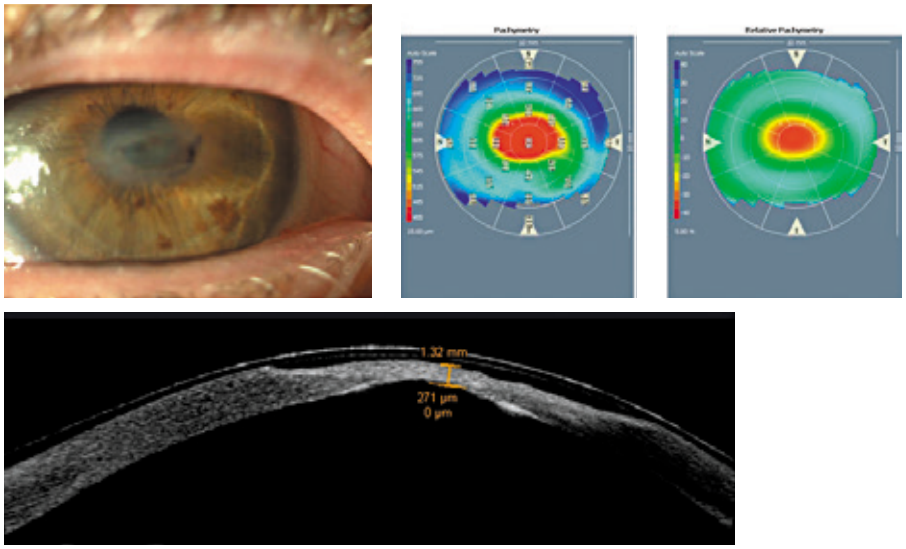


Figure 6: Anterior segment photograph (top left), pachymetry map (top right) and AS-OCT (bottom) of the left eye 1 month after spontaneous perforation. (CTmin=271µm)

In both eyes, KCS was treated with the use of preservative-free artificial tears and occlusion of the inferior lacrimal puncta with insertion of silicone punctum plugs.

Topical (artificial tears with hydroxypropyl guar, polyethylene glycol 400 0.4%, propylene glycol 0.3%, qid) and systemic therapy (hydroxychloroquine 400 mg/day) were continued for 6 months and a further improvement, in terms of corneal thickness, was noted. Visual acuity increased to counting fingers at 2m without any severe infection or other side effects (Figure 7). The patient was offered a penetrating keratoplasty but insisted on continuing with medication. At the 18-months follow-up the cornea showed a partially dissolved central scar raising BCVA to 0.7 logMAR (2/10 Snellen).

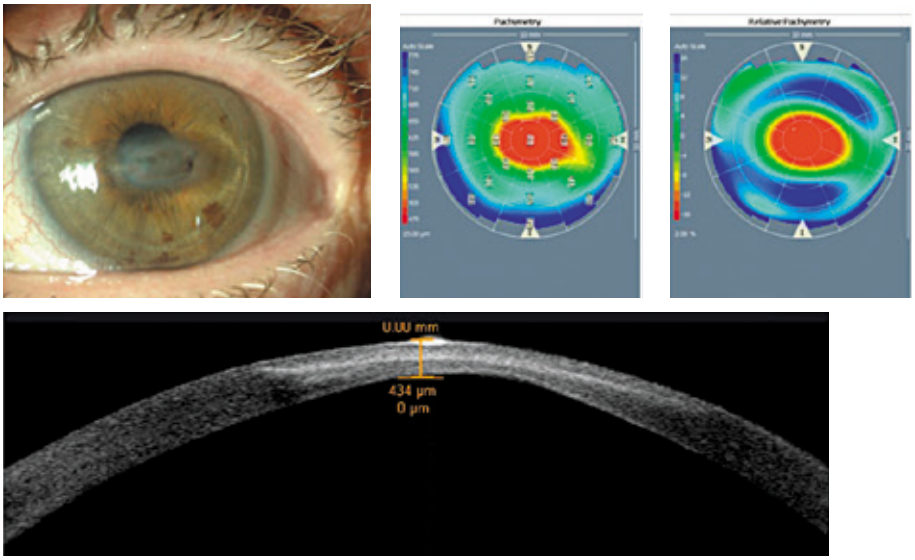


Figure 7: Anterior segment photograph (top left), pachymetry map (top right) and AS-OCT (bottom) of the left eye 6 months after spontaneous perforation. (CTmin=434µm)

★ DISCUSSION ★

Sterile corneal melting is a rare cornea pathology, that may lead to perforation with devastating consequences [1,2]. Several systemic disorders, including Sjögren's syndrome, rheumatoid arthritis and other collagen vascular diseases have been suggested as possible predisposing factors [3-5]. Prompt diagnosis of these diseases is essential, since early management may lessen morbidity. Systemic treatment of the underlying condition and intensive topical medical treatment can prevent the progression of corneal melting to perforation. When the latter occurs, surgical management using tectonic corneal grafts, amniotic membrane transplantation with or without the use of tissue adhesive seem to be inevitable [6-9].

Primary SS occurs in the absence of other underlying rheumatic disorders. First symptoms of primary SS include those related to KCS. These symptoms can easily be overlooked or misinterpreted and consequently diagnosis may be missed for several years [4]. Hallmarks of dry eye in Sjögren's syndrome include increased corneal staining, goblet cell loss and low tear volume [14]. Although extremely uncommon, primary SS may also originally present with corneal melting and impending corneal perforation [5].

In this paper, we present a very rare case of corneal melting, as the initial manifestation in a patient with undiagnosed primary SS, leading eventually to perforation, which was successfully managed medically without any surgical intervention. To the best of our knowledge, this is the first report in the literature describing conservative management of a sterile corneal perforation in SS by means of autologous serum eye drops and a RGTA.

Human serum eye drops and regenerating agents have already been tested in several cases of aseptic ulcers with promising results [4,11-14]. Human serum contains various substances including epidermal growth factor, vitamin A, transforming growth factor-β, fibronectin, and cytokines normally found in tears. These factors are important for maintaining a healthy corneal and conjunctival epithelium [11].

Moreover, many studies show that regenerating agents (RGTAs), may act as survival and protective agents in several pathological tissue injuries, mimicking the action of destroyed heparan sulfate (HS) molecules, protecting the bioavailability of preexisting and newly synthesized growth factors, and recreating a matrix microenvironment in which cells can migrate and regenerate [12,13].

RGTAs represent promising therapeutic options for controlling ocular surface inflammation and promoting corneal healing [14]. Poly-carboxymethylglucose sulfate, which was used in our case, is a commercially available RGTA, which replaces and mimics endogenous GlycosAminoGlycans (GAGs), such as heparan sulfate, that have been degraded by enzymes. The heparan sulfate is associated with growth factors such as the fibroblasts growth factor and is therefore involved in many regenerative processes, especially in nerve regeneration [15].

The binding of GAGs to matrix proteins (collagen, elastin, fibronectin) results in a mechanical protection against degradation. Restoration of extracellular matrix scaffolding properties is then induced, and so is the communication between cells [12-14].

Furthermore, the improvement of corneal transparency, which is strongly related to prompt regeneration and healing process, is considered an important aspect among the therapeutic goals in such cases. Poly-carboxymethylglucose sulfate was found to imply a potential benefit at the time of recovering the levels of transparency of the cornea, as compared to treatment with other agents [16]. RGTA eye drops were used in our case upon beginning of cornea regeneration, one day after perforation occurred at the site of corneal melting. The initially sizable corneal scar partially dissolved and corneal thickness gradually improved.

Autologous serum eye drops and RGTAs as poly-carboxymethylglucose sulfate, which were used in our case, may represent a useful adjunct in the conservative treatment of corneal melting even in cases of corneal perforation. Further understanding of the molecular and cellular mechanisms involved in SS-associated corneal melting, would provide us with useful tools in developing more efficacious treatments.

★ CONCLUSION ★

This case report demonstrates the successful management of a spontaneous corneal perforation without surgical intervention in a patient with undiagnosed primary Sjögren's syndrome. In patients with chronic dry eye syndrome and signs of corneal melting, it is crucial to promptly diagnose an underlying Sjögren's syndrome and provide the appropriate topical and systemic treatment. Topical treatment with autologous serum and RGTAs as poly-carboxymethylglucose sulfate eye drops was effective in this case, healing corneal melting and perforation thus dramatically improving prognosis.

★ REFERENCES ★

1. Krachmer JH, Mannis MJ, Holland EJ. Cornea, (3rd Edition) Mosby Elsevier: Oxford, 2011.

2. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. Bull World Health Organ 2001; 79(3): 214–221.

3. Matsubara M, Zieske JD, Fini ME. Mechanism of basement membrane dissolution preceding corneal ulceration. Invest Ophthalmol Vis Sci 1991; 32(13): 3221–3237.

4. Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjogren's Syndrome-Associated Dry Eye An Evidence-Based Review. Ophthalmology. 2011 Jul. 118(7):1242-52.

5. Vivino FB, Minerva P, Huang CH, Orlin SE. Corneal melt as the initial presentation of primary Sjögren's syndrome. J Rheumatol. 2001 Feb;28(2):379-82

6. Vote BJ, Elder MJ. Cyanoacrylate glue for corneal perforations: a description of a surgical technique and a review of the literature. Clin Experiment Ophthalmol. 2000;28:437–442.

7. Duchesne B, Tahi H, Galand A. Use of human fibrin glue and amniotic membrane transplant in corneal perforation. Cornea. 2001;20: 230–232.

8. Rodriguez-Ares MT, Tourino R, Lopez-Valladares MJ, Gude F. Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 2004;23:577–583.

9. Soong HK, Farjo AA, Katz D, Meyer RF, Sugar A. Lamellar corneal patch grafts in the management of corneal melting. Cornea. 2000 Mar;19(2):126-34

10. Noble BA, Loh RS, MacLennan S, Pesudovs K, Reynolds A, Bridges LR, Burr J, Stewart O, Quereshi S. Comparison of autologous serum eye drops with conventional therapy in a randomized controlled crossover trial for ocular surface disease. Br J Ophthalmol. 2004;88(5):647-52.

11. Koffler BH. Autologous serum therapy of the ocular surface with novel delivery by platelet concentrate gel. Ocul Surf. 2006;4(4):188-95.

12. Laboratoires Thea. Efficacy and safety assessment of T4020 versus vehicule in patients with chronic neurotrophic keratitis or corneal ulcer. Available from: http://clinicaltrials.gov/ct2/show/NCT01794312. NLM identifier: NCT01794312. Accessed September 28, 2014.

13. Brignole-Baudouin F1, Warnet JM, Barritault D, Baudouin C. RGTA-based matrix therapy in severe experimental corneal lesions: safety and efficacy studies. J Fr Ophtalmol. 2013 Nov;36(9):740-7.

14. Cejkova J, Olmiere C, Cejka C, Trosan P, Holan V. The healing of alkali-injured cornea is stimulated by a novel matrix regenerating agent (RGTA, CACICOL20): a biopolymer mimicking heparan sulfates reducing proteolytic, oxidative and nitrosative damage. Histol Histopathol. 2014 Apr;29(4):457-78.

15. Furusho M, Dupree JL, Bryant M, Bansal R. Disruption of fibroblast growth factor receptor signaling in nonmyelinating Schwann cells causes sensory axonal neuropathy and impairment of thermal pain sensitivity. J Neurosci. 2009;29:1608–14.

16. Alcalde I, Íñigo-Portugués A, Carreño N, Riestra AC, Merayo-Lloves JM. Effects of new biomimetic regenerating agents on corneal wound healing in an experimental model of post-surgical corneal ulcers. Arch Soc Esp Oftalmol. 2015 Oct;90(10):467-74.

Tim ENZ
University Hospital Basel
SWITZERLAND

TOPICAL ASCORBATE ADMINISTRATION IN SEVERE OCULAR BURN

★ INTRODUCTION ★

Chemical ocular burns account for a significant part of ocular trauma, in terms of quantity as well as clinical impacts for patients. Up to 18% of traumatic injuries to the eye are associated with chemical and thermal burns.[1] Depending on the clinical signs ocular burns are graded using the well-known Roper Hall (grade 1-4) or Dua (grade 1-6) classification. While some of these injuries are trivial (Roper Hall grade 1-2) and do not cause any persistent limitations, others are followed by severe and lasting visual restrictions.[1,2] Especially in severe burns (Roper Hall grade 4) and special situations like bilateral injuries, monocle situations or in cases with impaired vision due to ocular comorbidities in the fellow eye, severe visual impairment can result and might make several subsequent surgeries restoring vision and appearance necessary.[3] Still, in some cases, lid mal-positions, severe ocular surface diseases, corneal blindness and enucleation unfortunately cannot be prevented.

Euphorbia is a plant family consisting of more than 2000 species growing all around the globe.[4] The sap of many Euphorbia plants is highly toxic and has been reported to cause severe inflamma-tory reaction on contact with skin or ocular surface.[5] Typical findings include pain, photophobia, diminished visual acuity as well as epithelial defects, stromal edema, Descemet's folds and anteri-or uveitis, whereas the extent of the damage and the clinical course may vary depending on the type of plant and the amount of exposure.[4] While many patients fully

recover within 1-2 weeks[10], neglection of proper treatment can lead to severe keratouveitis, corneal scarring and subsequently to permanent blindness.[4,6]

Once a chemical eye burn has occurred, many of the unfavorable consequences could be pre-vented or minimized with adequate primary treatment.[2] It is essential to not only be aware of the adequate treatment modalities, but also ensure their availability. Eye rinsing is the undisputable primary therapeutic measure that has to be carried out instantaneously after chemical eye burn, as intraocular penetration of the toxic agent can occur within minutes.[7,8] A number of different buff-ering solutions are effectively available and widely used. Also, anti-inflammatory treatment and antibiotic prophylaxis later on are uncontroversial.[1] In severe cases with unsatisfactory results of conservative therapy or in hazardous cases with melting necrotic tissue, surgical approaches have to be considered, including amniotic membrane transplantation, limbal stem cell transplantation or keratoplasty.[7]

Ascorbate is of crucial importance with respect to wound healing, as it regulates modulation of fi-broblast proliferation, cell migration and biosynthesis of collagen fibers and thus prevents corneal ulceration.[6] After severe chemical ocular burn, the level of ascorbate in the anterior chamber may be diminished for up to 30 days and therefore needs to be substituted medicinally. Topical and systemic administration of ascorbate is hence a supportive conservative treatment option, which is often mentioned in literature.[10] Topical administration has shown favorable results in animal stud-ies.[10] Pfister and colleagues reported less perforation in rabbit eyes with chemical burn-related ulceration after topical ascorbate treatment compared to the non-treated group.[11] However, to the very best of our knowledge, no anecdotal reports of cases have been published, in which topical ascorbate has been used in humans - whether successfully or not.[10]

We report a case of severe bilateral chemical eye burn with Euphorbia plant sap with distinct con-junctival liquefaction, total corneal erosion and limbal ischemia (Rooper Hall II-III), in which none of the conventional conservative treatment measures led to considerable easing. Significant recovery could be noted after the beginning of topical ascorbate application. Lacking commercially available eye drops, an off-label ascorbate compound produced for intravenous administration was used.

★ CASE REPORT ★

A 73-year old man presented with severe bilateral chemical ocular burn after Euphorbia plant sap had accidentally splashed into both of his eyes while working in his garden. Visual acuity and intra-ocular tension could not be assessed initially, but were later found to be finger counting and 18mmHg respectively in both eyes. Considerable conjunctival liquefaction could be found on both sides, as well as subtotal and total corneal erosions on the right and the left eye respectively. Fur-ther examination showed corneal haze, distinct Descemet folds and stromal edema with still visible iris structure (figure 1).

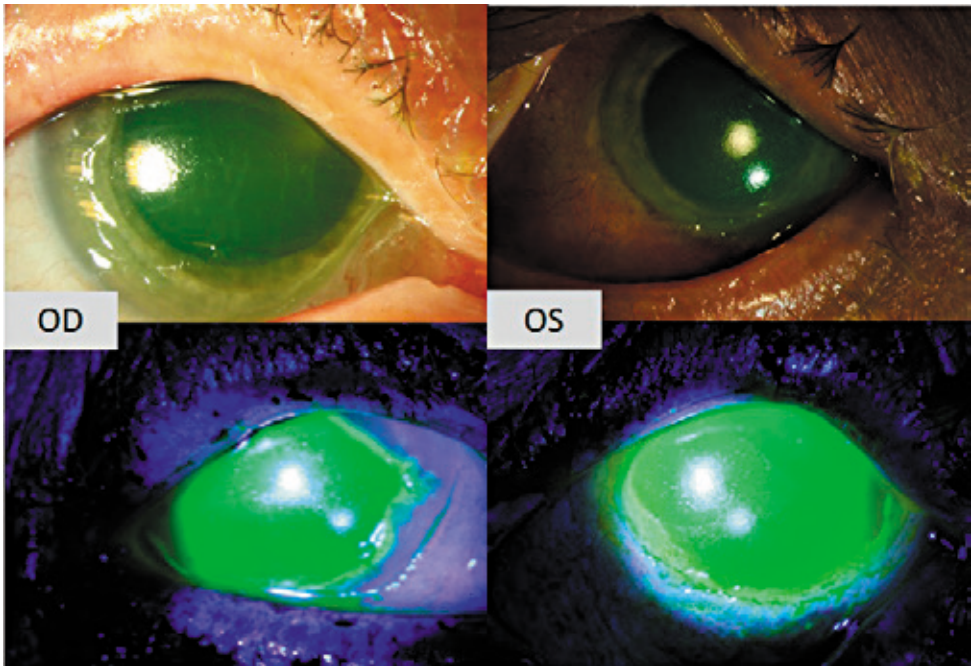


Figure 1: Slit lamp pictures of the right (OD) ant the left eye (OS) without (upper line) and with fluorescein staining (lower line). The right eye (OD) showed subtotal corneal erosion, corneal haze and Descemet folds while the left eye (OS) presented total erosion, corneal haze and Descemet folds.

Limbal vasculature showed ischemia in about 1/3 of the limbus area on the left and less than 1/3 on the right eye. After immediate eye rinsing using diphoterine buffering solution in the emergency of our eye clinic the ph value on the ocular surface was measured to be physiological and the pa-tient was hospitalized as an inpatient. Topical anti-inflammatory treatment with dexamethasone eye drops 6 times daily and antibiotic prophylaxis with ofloxacin eye drops 4 times daily was in-stalled. Ascorbate was first administered orally at a dosage of 1000mg daily.

On the second day of hospitalization no significant recovery could be documented. Corneal surface presented with plenty of filaments on bare hazy stroma. Corneal epithelium was loose with diffuse irregular edges on the right eye. No corneal wound healing could be recognized and stromal ede-ma and Descemet folds persisted on both eyes. The conjunctivas were still distinctively irritated and limbal ischemia was still unimproved. As no substantial improvement had occurred with con-servative measurements, amniotic membrane transplantation was planned and organized for the next day. Also, in anticipation of distinct long-lasting visual impairment and dependency, inpatient rehabilitation was organized for the coming weeks to months. In order to exploit all conservative treatment options, topical ascorbate application was begun as a final recourse late the previous day before amniotic membrane transplantation was scheduled. Since no ascorbate eye drops are commercially available, we chose to use an I/V ascorbate compound off label. The intravenous solution was transferred to a sterile syringe (figure 2) and from there applied onto the cornea by experienced nurses. Ascorbate was topically applied 6 times a day additional to intense steroid and antibiotic treatment.

Figure 2: Ascorbate compound of an intravenous injection which was transferred to a sterile syringe and applicated onto the patient's cornea

In the morning of the third day of hospitalization, approximately 18 hours after onset of topical ascorbate treatment, the patient reported almost complete pain relief. Corneal healing had initiated with noticeable reduction of stromal edema and corneal erosions, the latter to 4 by 6 millimeters on the right side and 5.5 by 6.5 millimeters on the left side. Visual acuity was subjectively and objec-tively increased to 0.1 (20/200) and 0.08 (20/250) respectively. As clinical signs as well as subjec-tive visual acuity showed such a surprising improvement within a short time and to a great extent the scheduled amniotic membrane transplantation was suspended.

By day 6 of hospitalization the cornea was completely re-epithelialized, stromal edema was mark-edly reduced especially on the right eye and limbal vasculature showed an improved perfusion in the areas of former ischemia on both sides. Visual acuity was 0.6 (20/30) with best correction on the right side and 0.1 (20/200) without correction on the left side, whereas advanced cataract impaired vision concurrently (figure 3). The patient could be discharged in an independent and pain-less condition.

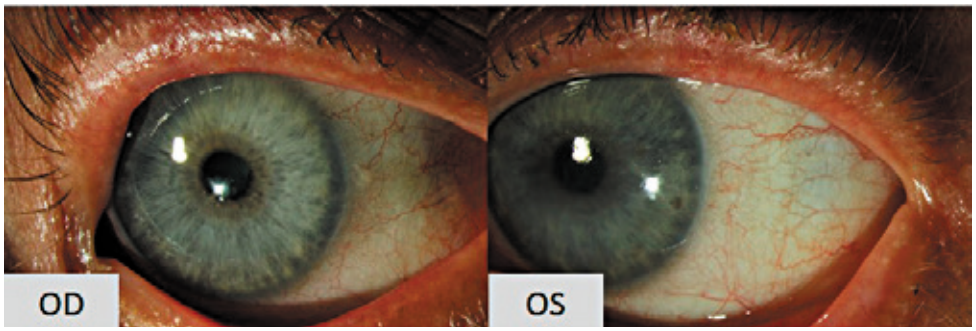


Figure 3: Slit lamp picture of the right (OD) ant the left eye (OS) six days after chemical injury with Euphorbia plant sap. The corneas are cleared up (right>left) with complete reepithelialization. Limbal vasculatur and conjunctiva recovered fully.

Follow up until 1 month after the accident showed a complete restitution for the right eye with visual acuity of 0.7 (20/30). On the left eye, which suffered from more severe ocular burn, an endothelial rarefication and beginning endothelial dysfunction developed thus being responsible for the re-duced visual acuity of 0.3 (20/60) 1 month after the initial event. Endothelial cell counting showed 1452 cells per mm² on the right side while no conclusive measurement was possible on the left side (figure 4). Pachymetry showed corneal thickness of 553 micrometers on the right side and 822 micrometers on the left side. Endothelial keratoplasty was discussed with the patient but deferred due to a still satisfactory vision on the right eye.

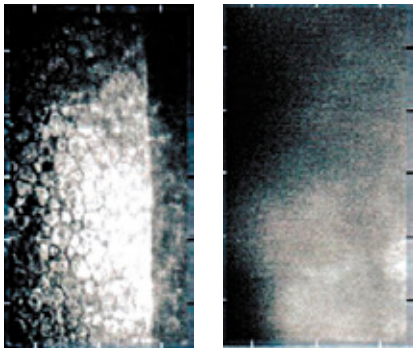


Figure 4: Endothelial cell counting of the right eye (OD) and the left eye (OS). Endothelial cell counting showed 1 452 cells par mm². On the left side no conclusive measurement was possible.

★ DISCUSSION ★

Although it cannot be proven that the topical ascorbate treatment contributed significantly to the patient's quick recovery based on the data given in this case, a causative relationship is very sug-gestive considering the circumstances. The patient in our case suffered severe chemical ocular burn bilaterally. Extensive conservative measures including instantaneous irrigation as well as in-tensive lubrication, topical anti-inflammatory treatment with steroids and antibiotic prophylaxis over several days did not lead to a notable improvement. Off-label topical ascorbate therapy was in-stalled as a final recourse before amniotic membrane transplantation was planned. Only a few hours later remarkable recovery began and within only four days the patient could be discharged with almost complete restitution. It needs to be assumed that without ascorbate treatment the find-ings would have remained stable and surgery would have had to be performed, leaving the patient with an uncertain prognosis.

Topical ascorbate application as a supportive treatment in ocular chemical burns has been men-tioned in the literature for quite some time. Nevertheless, ascorbate eye drops are not commercial-ly available forcing clinicians to use off-label products for sight-threatening emergency cases. Posi-tive effects of topical ascorbate have also been shown in animal studies. However, no studies or case reports concerning its use in humans have been published yet.[7] Based on biochemical ra-tionales that ascorbate is a cofactor in collagen synthesis and

sustained by the findings in our case it appears plausible that topical ascorbate treatment in fact has a significant supportive potential in the healing process and prevention of corneal stromal ulcers and perforations after severe chemical ocular burns. Therefore topical ascorbate may be considered not only as a final recourse in desperate situations but rather as a first line treatment in combination with steroid and antibiotic eye drops. Still further case reports and clinical trials are necessary to confirm these results.

★ CONCLUSION ★

Topical ascorbate is an efficient supportive treatment in chemical eye burns. Controlled human studies examining the potential and safety of topical ascorbate should be planned. Positive results provided, we would suggest that topical ascorbate should be implemented in standard treating al-gorithm for ocular burns and we emphasize that – in particular – its availability needs to be provid-ed for emergency treatment.

★ REFERENCES ★

1. Kuckelkorn R, Schrage N, Keller G, Redbrake C. Emergency treatment of chemical and thermal eye burns. Acta Ophthalmol Scand 2002;80(1):4-10.

2. Cejkova J, Cejka C, Trosan P, Zajicova A, Sykova E, Holan V. Treatment of alkali-injured cornea by cyclosporine A-loaded electrospun nanofibers - An alternative mode of therapy. Exp Eye Res 2016(6):128-137.

3. Kuckelkorn R, Luft I, Kottek AA, Schrage NF, Makropoulos W, Reim M. Chemical and thermal eye burns in the residential area of RWTH Aachen. Analysis of accidents in 1 year using a new automated documentation of findings. Klin Monbl Augenheilkd 1993;203(1):34-42.

4. Basak SK, Bakshi PK, Basu S, Basak S. Keratouveitis caused by Euphorbia plant sap. In-dian J Ophthalmol 2009;57(4):311-313.

5. Eke T, Al-Husainy S, Raynor MK. The spectrum of ocular inflammation caused by euphor-bia plant sap Arch Ophthalmol 2000;118(1):13-16.

6. Sofat BK, Sood GC, Chandel RD, Mehrotra SK. Euphorbia royleana latex keratitis. Am J Ophthalmol 1972;74(4):634-637.

7. Brodovsky SC, McCarty CA, Snibson G, Loughnan M, Sullivan L, Daniell M, Taylor HR. Management of alkali burns: an 11-year retrospective review. Ophthalmology 2000;107(10):1829-1835.

8. Wright P. The chemically injured eye. Trans Ophthalmol Soc U K 1982;102 (Pt 1):85-87.

9. Cho YW, Yoo WS, Kim SJ, Chung IY, Seo SW, Yoo JM. Efficacy of systemic vitamin C supplementation in reducing corneal opacity resulting from infectious keratitis. Medicine (Baltimore) 2014;93(23):e125.

10. Mackway-Jones K, Marsden J. Ascorbate for alkali burns to the eye. Emerg Med J 2003;20(5):465-466.

11. Pfister RR, Paterson CA, Hayes SA. Effects of topical 10% ascorbate solution on established corneal ulcers after severe alkali burns. Invest Ophthalmol Vis Sci 1982;22(3):382-385.

Francesca URBAN, Claudio GORLA, Giuseppe SCARPA
UCO Ophthalmology, Ospedale Ca' Foncello, Treviso
ITALY

NEUTROPHIC ULCER SECONDARY TO HERPETIC KERATITIS

★ INTRODUCTION ★

This report provides details of a case study relative to a persistent corneal ulcer resulting from a herpetic corneal infection. Despite the prescription of an antiviral therapy, a deep stromal defect had persisted; clinical location and aspect were secondary to a neurotrophic deficit that was inhibiting the healing process. Neurotropism is a peculiar characteristic of herpetic viruses. The typical recurring nature of infections is in fact due to the capacity of the virus to localise at a ganglionic level, travelling along the axons of peripheral nerves in a reactionary manner. Moreover, the virus can cause damage to corneal nervous fibres, known as neurotrophic keratitis. Trigeminal nerve endings in corneal tissue are responsible for corneal sensitivity, but also for the modulation of trophic mediators that play a critical role in maintaining the integrity and functionality of the epithelial surface. The combination of these two elements - altered epithelial tropism and reduced corneal sensitivity - causes a vicious cycle that inevitably leads to the development of persistent epithelial defects and stromal ulcers, and eventually corneal perforation. Neurotrophic keratitis can also be caused by non-infective conditions: damage to the trigeminal nerve (whether post-operative, traumatic or neoplastic), the abuse of topical drugs, the use of contact lenses and systemic diseases such as diabetes or a Vitamin A deficiency. Regardless of the underlying cause, the disease is divided into three stages of severity (Mackie classification):

- **stage I:** Epithelial dystrophy and/or superficial punctate keratitis
- **stage II:** Persistent epithelial defect
- **stage III:** Corneal ulcer, which may evolve until perforation.

★ CASE PRESENTATION ★

A 63-year old female patient was sent to our observation for a neurotrophic persistent corneal ulcer consequent to a herpetic corneal infection. The patient, who was generally in a good state of health, reported irritation in her right eye. At a subsequent eye examination, the patient was diagnosed with dendritic epithelial keratitis and was treated with topical ganciclovir, which led to complete re-epithelialization. After 1 month, irritation relapsed with evidence of central corneal ulcer. A topical and systemic antiviral therapy was therefore prescribed, which led to a partial improvement in the patient's clinical condition, however after 2 months of treatment the central stromal defect persisted. In addition to the systemic antiviral therapy, the patient was prescribed a topical steroid and tear substitutes. The patient was also advised to take a systemic amino acid-based supplement. In any case after 1 week, the patient's clinical condition had not changed significantly. It was therefore decided to apply a therapeutic contact lens, however once again, limited improvement was noted.

The slit lamp test revealed a central stromal defect, clean and not very wide, but quite deep. The adjacent corneal sensitivity proved to have subsided (Figures 1 and 2). Although the limits of the defect were already very clear, the fluorescein eye stain test was used to accurately outline the lesion (Figure 3). An epithelial and stromal defect in neurotrophic keratopathy is typically oval-shaped with flat margins, in distinct contrast with the irregular aspect and dendritic margins of the active herpetic ulcer.

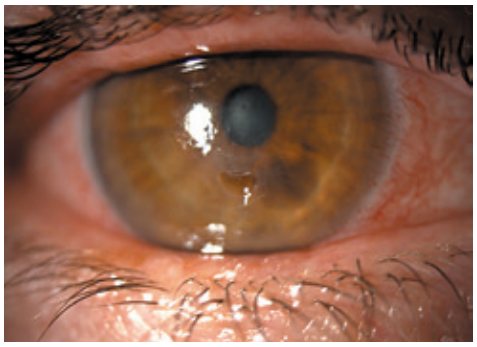


Figure 1: The slit lamp test revealed a central corneal ulcer with a distinct outline.

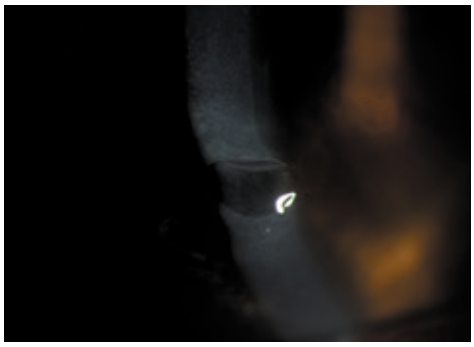


Figure 2: The slit lamp test revealed a stromal defect with minimal width, but significant depth.

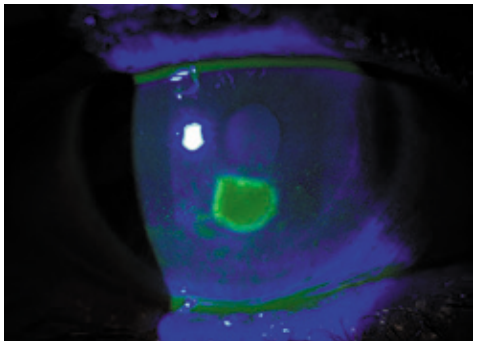


Figure 3: The fluorescein eye stain test revealed a central superficial punctate keratitis and a corneal ulcer.

★ DISCUSSION ★

Considering the persistence of the stromal defect and neurotrophic nature of the residual ulcer, before assessing surgical options, it was decided to begin treatment with matrix regenerating agent (RGTA) in addition to the therapy already underway. 1 drop of this poly(carboxymethyl glucose sulfate) solution was prescribed every other day, for 2 weeks.

The patient was monitored with photographic documentation, to monitor outcome of corneal lesion. The patient did not report any irritation or discomfort linked to the matrix regenerating agent drops throughout the entire treatment. After 1 week of treatment, an initial filling of the stromal defect was noted in the most central area of the ulcer, revealed with both a diffused light and slit lamp (Figures 4 and 5). After 2 weeks of treatment, the ulcer had completely closed and re-epithelialized (Figures 6 and 7). The slit lamp indicates modest stromal thinning and fine sub-epithelial opacity in the ulcer area (Figure 8). Given the persistence of this irregularity in the corneal surface, it was recommended to continue with the tear replacement drops and to maintain the systemic antiviral therapy at a maintenance dose to prevent any relapses. The patient's visual acuity gradually increased until 9/10. The irritation and hyperaemia objectively improved, although the patient continued to suffer from modest photophobia and the perception of spots.

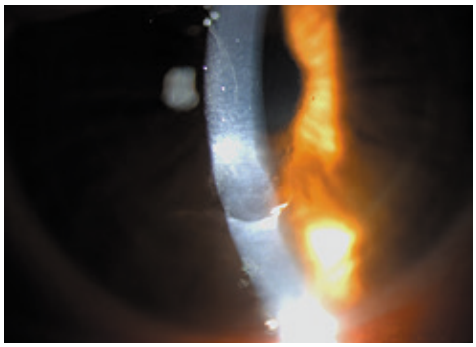


Figure 4: Detail of the partial filling of the ulcer after the first week of treatment with matrix regenerating agent (RGTA), under a slit lamp

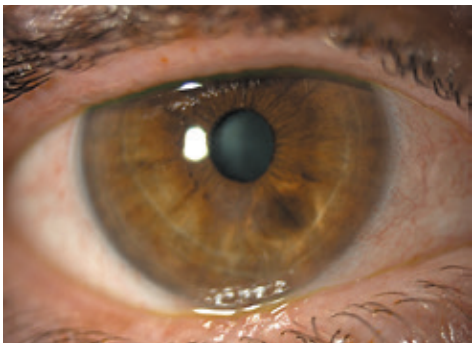


Figure 5: After 2 weeks of matrix regenerating agent, fine stromal opacity and an intact epithelium was observed in the pre-existing neurotrophic ulcer.

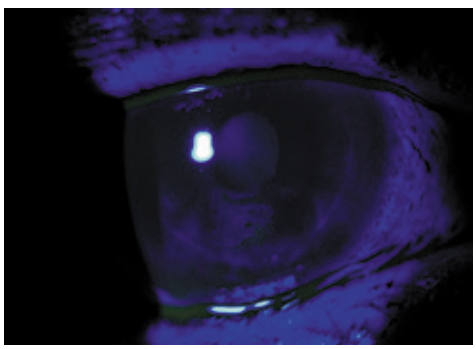


Figure 6: The fluorescein eye stain test revealed the complete recovery of the epithelium.

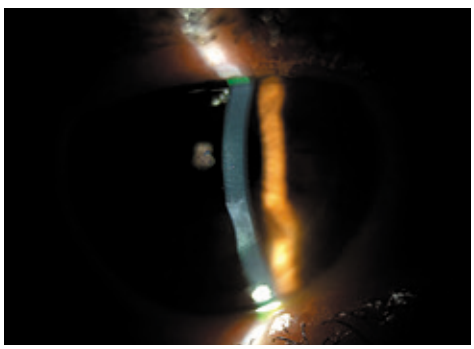


Figure 7: The slit lamp test revealed slight unevenness in the pre-existing corneal ulcer

★ CONCLUSION ★

This case highlights the potential of matrix regenerating agent (RGTA) as an additional medical alternative to conventional treatments, prior to opting for surgical solutions to neurotrophic persistent and refractory corneal ulcers.

★ REFERENCES ★

1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol 2014; 8: 571-579

2. Müller LJ et al. Corneal nerves: structure, contents and function. Exp Eye Res 2003; 76: 521-542

3. Kowtharapu BS et al. Corneal epithelial and neuronal interactions: role in wound healing. Exp Eye Res 2014; 125: 53-61

4. Hamrah P et al. Corneal sensation and subbasal nerve alterations in patients with herpes simplex keratitis: an invivoconfocalmicroscopystudy.Ophthalmology2010;117:19301936

5. YoungRCetal.Theincidence,recurrenceandoutcomesofherpessimplexviruseye disease in Olmsted County, Minnesota, 1976 through 2007: the impact of oral antiviral prophylaxis. Arch Ophthalmol 2010; 128(9): 1178-1183

José Guilherme NERI MIRANDA PIRES
Centro Hospitalar de Lisboa Central
PORTUGAL

BILATERAL LINEAR ENDOTHELIITIS IN THE CONTEXT OF LEPTOSPIROSIS: FROM A CUTANEOUS RASH TO A NEW CLINICAL ENTITY?

★ INTRODUCTION ★

Endotheliitis is a poorly understood clinical entity that manifests as corneal oedema, keratic precipitates and light anterior chamber reaction. Although it was previously described as a pathology confined to the endothelium, new confocal microscopy (CM) studies show that there might be additional stromal involvement.

Etiologically, viral infections such as VHS, VHZ and CMV are believed to play a role in inducing an anterior chamber-associated immune deviation (ACAID) type reaction that will progress to the clinical manifestations of endotheliitis. Furthermore, since it appears to be an immune-mediated disease, autoimmune disorders, such as systemic lupus erythematous (SLE), may also play a role in the ethiology of this disease

Leptospirosis is a zoonotic infectious disease, caused by the spiroquete Leptospira interrogans, which may present with protean manifestations.

In Europe, the disease is more frequent in Mediterranean countries, especially in the wet seasons of spring and fall.

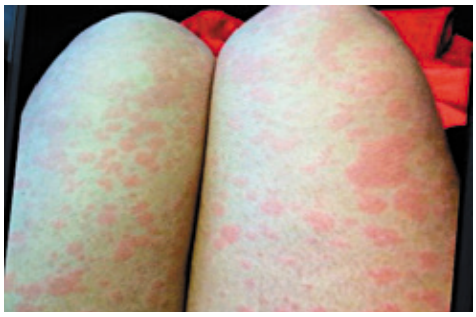
Leptospirosis is described as a biphasic disease, although clinically the two phases may not be clearly separated. The first phase is characterized by nonspecific symptoms such as fever, headaches, myalgia and conjunctival suffusion. It is also in this first phase that sepsis may occur. The second phase, often called autoimmune, is characterized by more complex and potentially severe manifestations.

Ocular manifestations can appear both in the acute septicaemia phase and in the autoimmune phase being conjunctival suffusion the first symptom to appear. Other acute ocular complications may be present including subconjunctival haemorrhage, retinal haemorrhage, vitritis, choroiditis, macular oedema or papillitis. As the disease progresses iritis, iridoscleritis, uveitis or panuveitis, chorioretinitis and similar complications may occur in the immune phase, which can last from 2 weeks to up to 6 months after the first presentation.

The authors report an intriguing case of bilateral lineal endotheliitis in a 32-year-old immunocompetent Portuguese woman with a previous history of Leptospirosis infection.

★ CLINICAL CASE ★

A 32-year-old female, with previous medical history of endometriosis, presented to the emergency room (ER) with a pruriginous maculopapular rash that spared only the scalp (figures 1 and 2), associated with high fever (38.8°C), asthenia and myalgia. She was firstly diagnosed as having chickenpox leading to the initiation of oral acyclovir therapy, 800 mg five times a day, making a cumulative dose of 12000 mg. Since the symptoms were refractory to treatment she returned to the ER within 48 hours presenting also with dizziness and angioedema of the lids and lips.



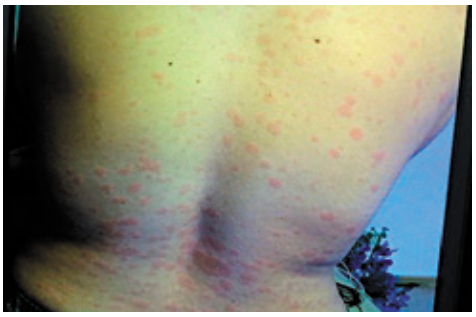


Figure 1 and 2: Maculopapular rash, presenting lesions with an average diameter of 2 cm that did not disappeared to digitalpressure

At this stage, the patient was hospitalized and a full work-up was done. An asymptomatic urinary tract infection (UTI) was found in addiction to an uprising PCR (12,43 mg/dL) and hepatic damage (aspartate aminotransferase four times normal value and alanine aminotransferase three times normal value). No abnormalities were found in imaging scans. Haemocultures and serological test were ordered and a positive *Leptospira interrogans* IgM was found. The diagnosis of Leptospirosis was made and the patient was initiated on doxycycline 100mg twice a day for ten days.

Seven days after the initial symptoms the patient referred blurry vision and a red eye which motivated an Ophthalmology appointment. On ocular examination at presentation, her best-corrected visual acuity (BCVA) was found to be, nevertheless, 20/20 in both eyes (OU). The intraocular pressure was 18 mm Hg (OU). Slit-lamp examination revealed a peri central keratitis (OU) and a normal posterior pole and retinal periphery (OU). The patient began therapy with topical ofloxacin (3 mg/ml, three times a day) in both eyes and came back eight days later, presenting with a BCVA of 0.9 (OU). At examination, a clear lineal endotheliitis was present, which had spread to the central zone of the cornea. (OU) (figure 3).

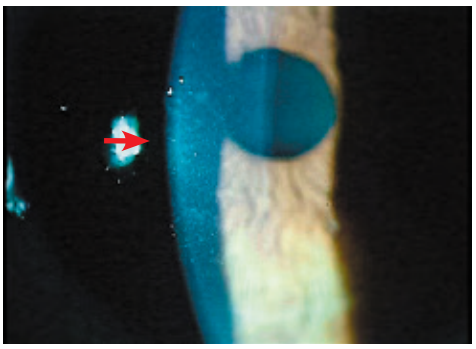


Figure 3: Lineal endotheliitis (arrow)

Topical dexamethasone (1mg/ml, three times a day) and oral valacyclovir (1000 mg twice a day, for ten days) therapy was initiated that led to the resolution of the endotheliitis (figure 4) when the patient was re-evaluated five days later. A CM was performed before therapy initiation and repeated 3 weeks after (figure 5 and 6), that showed the presence of *cornea pseudoguttata* lesions (OU).

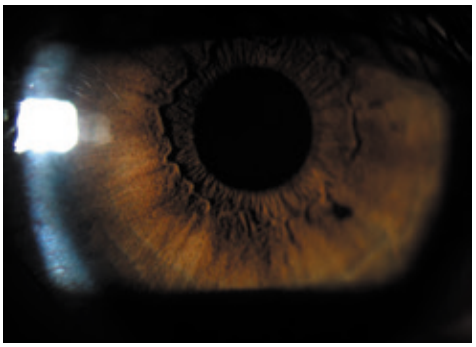
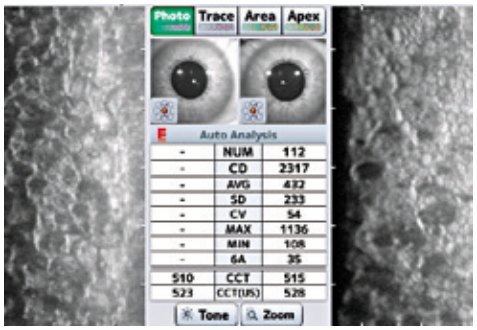


Figure 4: Resolution of endotheliitis, with a normal cornea appearance



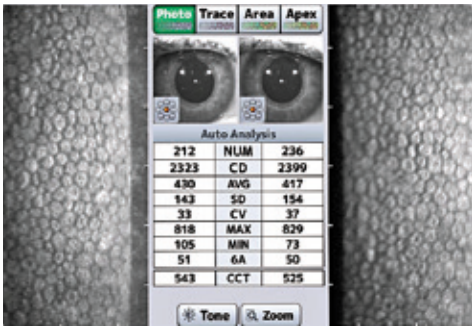


Figure 5 and 6 : CM before therapy initiation (figure 5) and 3 weeks after (figure 6) – images obtained with Tomey Confoscan

Simultaneously, due the presence of an inflammatory monoarticular unilateral sacroiliitis, and with the help of a PET-scan (figure 7), the diagnosis of reactive arthritis was made.

Retrospectively, the work-up done by the patient was once again reviewed and was negative for HSV-1 IgM and IgG, HSV-2 IgM and IgG and CMV IgG, HIV 1 and 2, Ag HBs, HCV RNA and auto-immune antibodies.

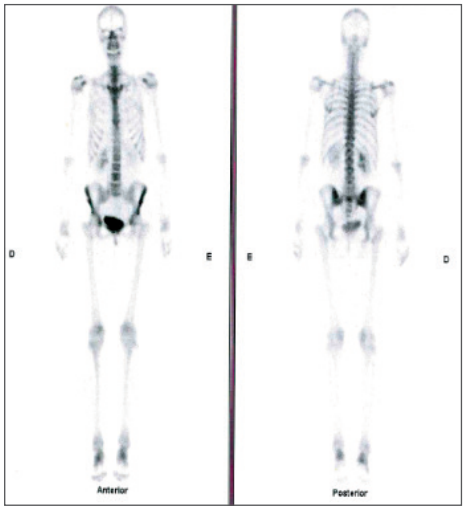


Figure 7: PET-scan showing an hypersignal in the sacrococcigeal area compatible with a reactive arthritis

★ DISCUSSION ★

As far as the authors know, there are no published cases of Leptospirosis induced endotheliitis.

It has been described the occurrence of viral super-infection in the context of Leptospirosis, making HSV a possible causative agent of endotheliitis in our patient. Nonetheless, there are other factor to be held in account: the patient initiated acyclovir therapy when she was misdiagnosed as having chickenpox (having received a superior dose than the one needed for the treatment of viral endotheliitis), making it less likely of her having a re-infection in the following weeks; the serologies for HSV-1, HSV-2 and CMV were negative which led us to believe that she had no prior contact with HSV or CMV; finally, the patient developed a reactive arthritis, a rare immunological known manifestation of Leptospirosis, probably the result of a crossed immunological reactivity.

Early diagnosis and treatment of endotheliitis is needed to avoid irreversible endothelial damage. Valacyclovir treatment was given in association with topical dexamethasone, making it impossible to know how would have been the response if only corticotherapy was administered. Since the patient responded well to treatment we felt that additional invasive diagnostic test, such as aqueous humour PCR, were unnecessary, which would have been a valuable piece to solve this equation.

Ophthalmologic manifestations of Leptospirosis seem to be more frequent than previously described. Therefore, we think that bearing in mind the pathophysiology of Leptospirosis, endotheliitis is a possible manifestation of the autoimmune phase of the disease.

★ CONCLUSION ★

We present a case bilateral lineal endotheliitis associated with systemic Leptospirosis infection, a difficult recognizable disease that demands a high clinical suspicion to be diagnosed.

A clinical diagnosis was made without resourcing to more invasive procedures. Standard endotheliitis treatment was applied with restauration of visual acuity and normal corneal anatomy. We could not assess the efficacy of corticotherapy in isolation but we can postulate that it would have been sufficiency due the auto-immune mechanism of pathology.

We are the first authors to recognize the possibility of induced endotheliitis by the spiroquete *Leptospira interrogans*.

★ REFERENCES ★

1. Olsen TW1 et al, Linear endotheliitis. Am J Ophthalmol. 1994 Apr 15;117(4):468-74;
2. Zheng X1 et al. Experimental corneal endotheliitis in rabbit, Invest Ophthalmol Vis Sci. 2000 Feb;41(2):377-85;
3. Porzukowiak TR1 et al., In Vivo Confocal Microscopy Use in Endotheliitis, Optom Vis Sci. 2015 Dec;92(12):e431-6
4. Rathinam SR1. Ocular manifestations of leptospirosis., J Postgrad Med. 2005 Jul-Sep;51(3):189-94;
5. Holland EJ, Mozayeni RM, Schwartz GS. Herpes simplex keratitis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. , eds. Cornea. Vol. 2. Cornea and external disease: clinical diagnosis and management. St. Louis: Mosby, 1997:1191–223
6. Koizumi N, Suzuki T, Uno T, et al. Cytomegalovirus as an etiologic factor in corneal endotheliitis. Ophthalmology 2008;2013:292–7
7. Fox GM, Crouse CA, Chuang EL, et al. Detection of herpes virus DNA in vitreous and aqueous specimens by the polymerase chain reaction. Arch J Ophthalmol 1991;2013:266–71

Marlena KONKOL
Copernicus Hospital, Gdańsk
POLAND

RGTA MATRIX THERAPY IN THE TREATMENT OF ALKALI-RELATED OCULAR BURN

★ INTRODUCTION ★

Chemical ocular injury is a real ophthalmic emergency and requires urgent intervention as it can lead to severe visual impairment and extensive damage to the ocular surface.

Early recognition and treatment is required to achieve the best possible outcomes for this potentially blinding entity.

It is estimated that chemical injuries to the eye represent about 7,7-18% of all ocular traumas. [1] About two thirds of these injuries occur in young males, as well as two thirds occur at the workplace rather than at home and in two thirds of all cases alkali is a causative agent of chemical injury to the eye.

Alkali injuries are more severe than acid injuries as alkalis due to their lipophilicity tend to penetrate more deeply and more rapidly than acids. Alkali agents cause saponification of the fatty acids of a cell membrane, for that reason they can totally destroy the cell structure.[2] Once the surface epithelium is damaged alkalis can penetrate deeper into a corneal stroma destroying collagen fibres

and proteoglycan ground substance of the extracellular stromal matrix (ECM). Proteoglycans are macromolecules composed of a glycosylated protein core with attached covalently glycosaminoglycan side chains. Extracellular matrix consists mainly of type I collagen and glycosaminoglycans (GAGs) such as keratan sulphate (Gal) and chondroitin/dermatan sulphate (GlcUA).

The limbal stem cells which function is to provide corneal reepithelialization can be damaged either directly or indirectly due to the limbal ischemia. Strong alkalis can penetrate further into the anterior chamber and cause intraocular inflammation, raised IOP (due to alkali-related destruction of the trabecular meshwork) or decreased IOP (due to destruction of a ciliary body epithelium).

The severity of ocular injury depends on the toxicity of the chemical, the duration of contact of the chemical with the eye and the depth and the extension of penetration.

To determine the prognosis and treatment of chemical injuries to the eye several classification systems have been proposed.

The Roper-Hall classification system is based on the degree of corneal haze and the range of perilimbal ischemia.[3,4]

Roper-Hall Classification System			
Grade	Limbal Ischemia	Corneal Involvement	Prognosis
I	No limbal ischemia	Epithelial damage	Good
II	<1/3	Haze, visible iris details	Good
III	1/3 to 1/2	Total epithelial loss, stromal haze, iris details obscured	Guarded
IV	>1/2	Opaque cornea with iris and pupil obscured	Poor

Dua classification scheme is based on extension of limbal ischemia as well as a percentage of bulbar conjunctival involvement.[5]

Grade	Clinical findings (LIMBAL INVOLVEMENT)	Conjunctival involvement	Analogue scale	Prognosis
I	0 clock hours	0%	0/0%	Very good
II	<3 clock hours	<30%	0.1-3/1-29.9%	Good
III	Between 3-6 hours	30-50%	3.1-6/31-50%	Good
IV	Between 6-9 clock hours	50-75%	6.1-9/51-75%	Good to guarded
V	Between 9-12 clock hours	75-100%	9.1-11.9/75.1-99.9%	Guarded to very poor
VI	Total limbus (12 clock hours) involved	Total conjunctiva (100%) involved	12/100%	Very poor

According to McCulley clinical course and treatment of ocular chemical injury can be divided into the following phases: immediate, acute (healing phase), early reparative, and late reparative.[6]

Immediate phase treatment

Immediate emergency treatment is comprised of copious irrigation with normal saline or Ringer solution for 15-20 minutes with double-eversion of the upper eyelid and removal of contaminating remains of the chemical and necrotic parts of a corneal epithelium.

Acute phase treatment

The main treatment aim in the healing phase is not only to regenerate of a healthy corneal epithelium (reepithelialization) but also to balance the processes of collagenolysis with collagen synthesis. Acute phase treatment includes:

1. Topical antibiotics.
2. Cycloplegic agents such as atropine or cyclopentolate.
3. Antiglaucoma agents.
4. Preservative-free artificial tears can reduce the risk of recurrent erosions and accelerate visual rehabilitation.
5. Therapeutic soft contact lens can promote reepithelialization.

6. Supplementation of ascorbate- a cofactor of the collagen synthesis reduces the incidence of corneal thinning and ulceration. Oral ascorbate (2 g/day) and topical 10% solution 1-2 hourly are used.
7. Collagenase inhibitors such as systemic tetracyclines promote corneal healing by inhibiting collagenolytic activity by restriction of the gene expression of neutrophil collagenase and epithelial gelatinase.[7]
8. Preservative free topical steroids reduce inflammation caused by neutrophil infiltration and stabilize cytoplasmatic and lysosomal membranes of neutrophils. They are used initially 4-8 times daily and must be reduced after 7-10 days because of the risk of corneal ulceration.[8,9]
9. To prevent symblepharon formation a massage of fornices and lysis of conjunctival bands shall be performed using sterile glass rod under a topical anesthesia.
10. Severe cases require a surgical treatment such as: advancement of Tenon's capsule, limbal stem cell transplantation, amniotic membrane onlay or even penetrating keratoplasty in case of corneal perforation.

The patient who has not achieved complete epithelialization by the 21st day is at significant risk of permanent vision loss.

The purpose of this study was to present the results of treatment of alkali related ocular burn with topical RGTA matrix therapy (Cacicol).

★ CASE REPORT ★

21-year-old man presented at the Accident and Emergency Department because of sodium hydroxide (NaOH) related burn to the left eye (LE). The clinical manifestations on admission to the Ophthalmology Department were: total loss of corneal epithelium, evident stromal haze and a half limbal ischemia, which corresponds with grade III group in Roper-Hall grading system and IV grade in Dua Classification for Ocular Surface Burns system respectively. The visual prognosis in this group of patients is "guarded" going by the Roper Hall Classification and „good to guarded" going by the Dua Classification for Ocular Surface Burns respectively.

Visual acuity (VA) of the left eye on admission was 20/30 and intraocular pressure (IOP) was 26 mmHg.

After seven days (a borderline time between acute and early reparative phases) of intense treatment there was still a horizontal band of cornea without epithelium.

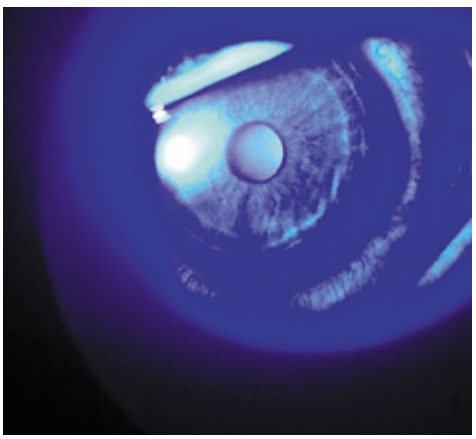


Figure 1: Horizontal epithelial defect with positive fluorescein staining

A decision on the use of RGTA matrix therapy (Cacicol) was made.

During the next three days after Cacicol has been instilled we observed complete epithelialization of the cornea.

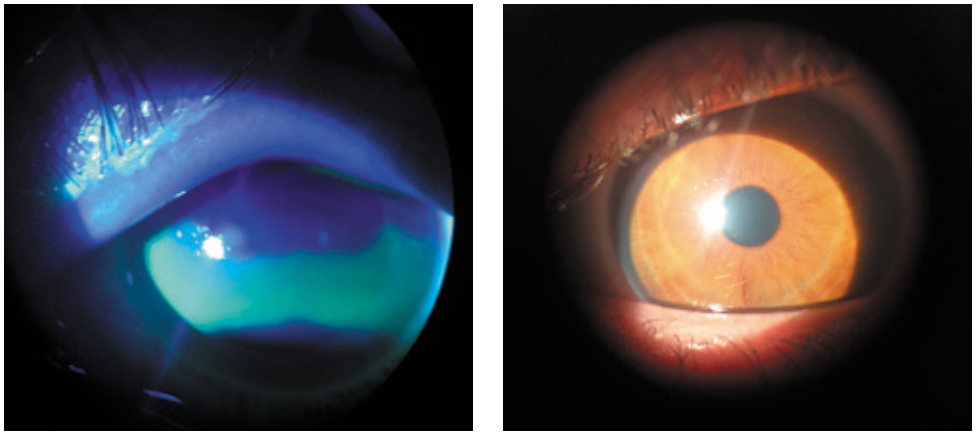


Figure 2-3: Total epithelialization on 10th day of treatment, 3 days after Cacicol has been instilled.

On 11th day the patient was discharged from the hospital. His visual acuity was 20/20 and IOP was 13 mmHg.

Four weeks after the injury cornea was still completely epithelialized.(Fig. 4-5)

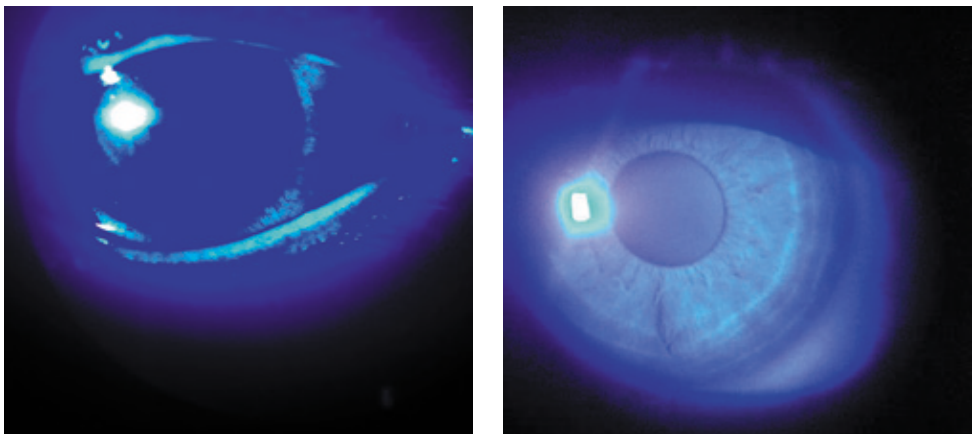


Figure 2-3: Total epithelialization on 10th day of treatment, 3 days after Cacicol has been instilled.

★ DISCUSSION ★

Alkali related injury to the eye is potentially blinding entity. Patient with a chemical ocular injury needs immediate evaluation and intensive treatment. The aim of the treatment is restoration of a normal ocular surface anatomy and corneal clarity.

Therapeutic options for grade III of alkali burn, with a guarded visual prognosis, include not only conservative but often also a surgical treatment.

Cacicol belongs to family of RGTA (ReGeneraTing Agents) that enhances speed and quality of tissue healing by initiating processes of tissue regeneration. By mimicking the heparan sulfate structure it prevents degradation of extracellular matrix proteins and promotes epithelial healing.[10]

There are very few data in the literature on using this non-invasive method of treatment in alkali related injury to the eye.

★ CONCLUSION ★

This study demonstrates that a non-invasive RGTA matrix therapy can bring promising results in the treatment of patients with severe alkali related burns to the eye. Further research is needed to evaluate it's efficacy and safety in this group of patients.

★ REFERENCES ★

1. Pfister RR. Chemical injuries of the eye. Ophthalmology. 1983;90:1246–53.

2. Baruch F, Colby KA. Evaluation and initial management of patients with ocular and adnexal trauma. In: Miller JW., Azar DT, Blodi B eds. Albert and Jakobiec's Principles and Practice of Ophthalmology, 3rd ed. Philadelphia: WB Saunders Elsevier: 2008:5071-92.

3. Hughes W, Alkali burns of the eye. Rewiew of the literature and summary of present knowledge. Archives of Ophthalmology, 1946.

4. Roper-Hall MJ, Thermal and chemical burns. Transactions of the ophthalmological societes of the United Kingdom, 1965,pp. 631-653

5. Dua HS, King AJ, Joseph A, A new classification of ocular surface burns. The British journal of ophthalmology, 2001(11): pp. 1379-1383.

6. Smolin G, Thoft RA The Cornea, McCulley JP: Chemical injuries. 2ed: Scientific Foundation and Clinical Practice. Boston Mass: Little Brown and Co; 1987. pp. 527–42.

7. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea, 2000. 19(3):p.274-7.

8. Dohlman CH, Cade F, Pfister RR Chemical burns to the eye: paradigm shifts in treatment. Cornea, 2011. 30(6):p.613-4

9. Donshik PC et al. Effect of topical corticosteroids on ulceration in alkali-burned corneas. Archives of Ophthalmology, 1978. 96(11):p. 2117-20.

10. Kymionis GD, Liakopoulos DA, Grentzelos MA et al.Combined topical application of a regenerative agent with a bandage contact lens for the treatment of persistent epithelial defects. Cornea 2014, 33(8):868-872.

Kateryna SEREDA
State Institution «Filatov Institute of Eye Diseases and Tissue Therapy NAMS of Ukraine», Odessa - **UKRAINE**

CASE OF SUCCESSFUL TREATMENT OF BILATERAL ACANTHAMOEBA KERATITIS

★ INTRODUCTION ★

Acanthamoeba keratitis (AK) refers to the severe pathology of the eye surface that results from the human body infection by free-living in soil amoebas [7]. This disease is characterized by corneal epithelium loss, stromal thinning, radial keratoneuritis development, annular infiltration and central or paracentral corneal abscess formation [2].

Factors contributing to the development of AK are hygiene rules failure, swimming at various reservoirs, wearing different types of contact lenses (CL) (hard and soft) [6]. CL wearing is a major risk factor for AK. Among patients with AK 75-89% used contact lenses [10].

Initially, AK is diagnosed correctly in 23.3% cases, but more often diagnosed wrongly as herpetic keratitis in 47.6%, as bacterial keratitis – in 25.2%, as fungal keratitis – in 3.9% of the cases. German researchers revealed that it takes an average of 5,1 ± 16,8 months from disease onset to the definitive diagnosis and about 3,1 ± 5,2 month from diagnosis to the first penetrating keratoplasty [5]. It was established that patients with AK need penetrating keratoplasty in 40.5% and retransplantation in 13.3% of cases.

AK treatment presents considerable difficulties due to the late diagnosis of the disease, as well as an extremely high resistance of AK cystic forms to chemical and physical influences [3].

Thats why the search of new methods of AK treatment is of a current interest. One of them is photodynamic therapy (PDT), that is a photodestruction of infectious agents using photosensitizer by irradiation with light of a certain wavelength [1,4,8,9,11].

The PDT technique in keratitis. Methylene blue 0.1% aqueous solution and 10% dimethylsulfoxide aqueous solution were dropped three times at intervals of 15 minutes, followed by irradiation with low-energy laser with a wavelength of 630-670 nm and a spot diameter of 3000 microns. Duration of the procedure was 3 minutes. The number of PDT procedures is determined individually for each patient.

We report a case of successful treatment of the bilateral acanthamoeba keratitis, where standard therapy was first supplemented with PDT using methylene blue and dimethylsulfoxide.

★ CLINICAL CASE ★

16 year-old woman consulted at our Institution describing redness, tearing, photophobia and pain in both eyes for 2 weeks. The best corrected visual acuity (BCVA) of right eye (RE) was 0.1 and of the left eye (LE) was 0,2 cc sph –3,75 Д=0,85. In the slit lamp evaluation in both eyes we objectify blepharospasm, conjunctival hyperemia, tearing and edema of eyelids In the RE we observed dendriform corneal erosion of 1,0mm wide by 2,0 mm high, stromal edema and diffuse infiltration. Preservation of the anterior chamber depth without inflammatory reaction was observed.

Patient history reveals the use of contact lenses "Paragon" during last 3 years for Myopia -3.75 diopters. We also know that the first symptoms of the disease appeared after diving in the swimming pool. The results of the blood, urine, liver analysis and microbiological study revealed no deviations. It was diagnosed bilateral herpetic keratitis and appropriate treatment was administered: antiseptic 0.02% chlorhexidine, antiviral and mydriasis drops, injections of heparini, laferobioni and valaciclovir per os.

In two days due to the lack of positive reaction to antiviral therapy, basing on medical history and increasing infiltration of the corneal stroma AK was suspected. We added to the treatment instillations of fluconazole as well as intravenously ornidazole and fluconazole and itraconazole per os. In the slit lamp evaluation in both eyes we objectify rounded limited infiltrates (figures 1,2).

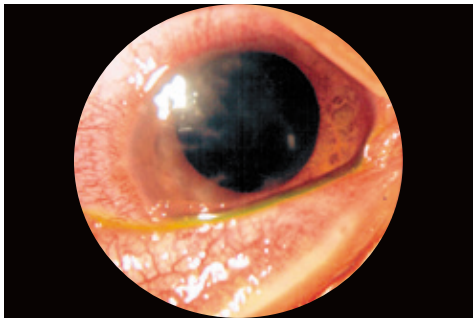


Figure 1: Right eye - Conjunctival hyperemia, corneal rounded limited infiltrates, stromal edema.

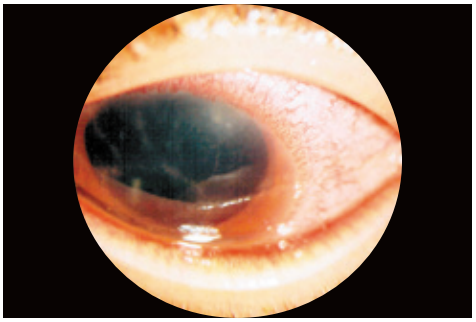


Figure 2: Left eye - Conjunctival hyperemia, corneal rounded limited infiltrates, stromal edema.

In five days the patient complained of severe pain, tearing, blepharospasm right eye. In the slit lamp evaluation in RE we objectify hyperemia and edema of eyelids and conjuctiva, infiltrate of 5.0 mm in the center of the cornea and several satellites at the corneal periphery (figure 3). In LE we observed limited paracentral rounded infiltrates, not stained with fluorescein (figure 4).
BCVA of the RE was 0,06 and of the LE was 0,3 cc sph – 4,0 Д=1,0.

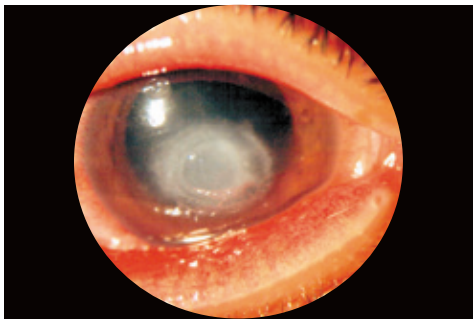


Figure 3: Right eye - Conjunctival hyperemia, infiltrate of 5.0 mm in the center of the cornea.

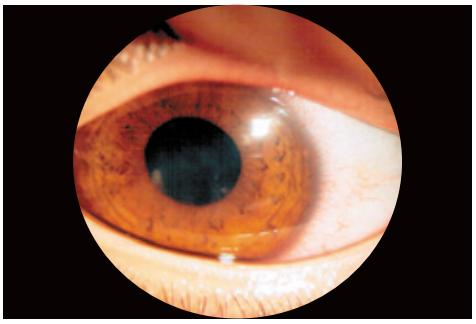


Figure 4: Left eye - Limited paracentral rounded infiltrates, not stained with fluorescein.

In three days the patient complained of severe pain in left eye, the same as in the right eye. In the slit lamp evaluation in RE we objectify central corneal abscess formation with a circular thinning and peripheral satellites (figure 5,6). BCVA was 0,01. In the slit lamp evaluation in LE we objectify hyperemia of conjuctiva, central corneal infiltration of 3,0mm and stromal edema (figure 7). BCVA was 0,1.

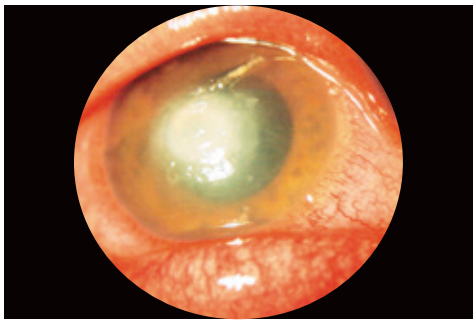


Figure 5: Right eye - Central corneal abscess formation with a circular thinning.

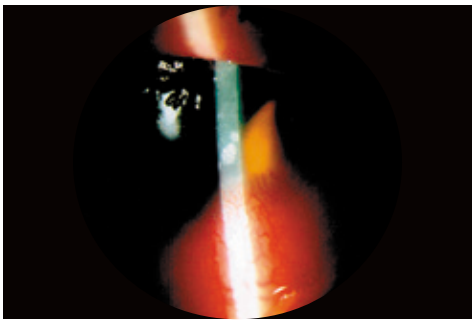


Figure 6: Left eye - Peripheral corneal satellites.

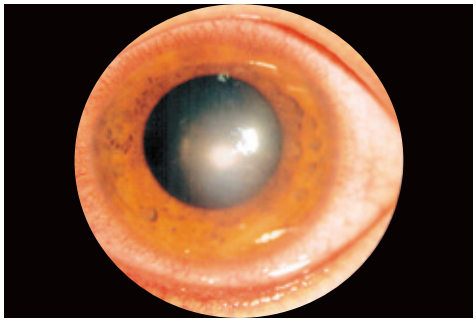


Figure 7: Left eye - Central corneal infiltration of 3,0mm, stromal edema.

We started a course of photodynamic therapy with methylene blue and dimethylsulfoxide in both eyes.

In a week after the start of the PDT it was observed the absence of disease progression.

PDT course included 33 procedures in both eyes untill infiltrate resorbtion was admitted.

During hospital discharge BCVA of the RE was 0,3 cc sph – 3,75 Д=0,85 and BCVA of the LE was 0,3 cc sph – 3,75 Д=1,0.

In the slit lamp evaluation in both eyes we objectify central nebular corneal opacity of 3,0mm in diameter and small opacities at the corneal periphery in the places of satellites (figure 8,9).

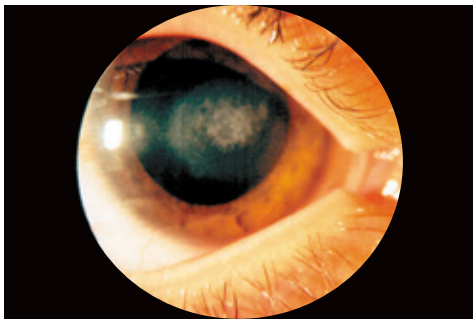


Figure 8: Right eye - Central nebular corneal opacity.

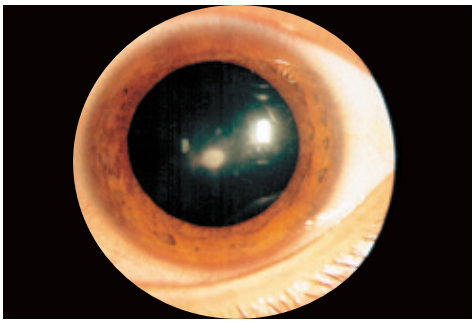


Figure 9: Left eye - Central nebular corneal opacity.

The patient was followed up for 12 months, and disease recurrence was not observed.

★ DISCUSSION ★

Acanthamoeba keratitis is a severe corneal pathology which is characterized be progressive course, difficult diagnosis and resistance to therapy.

In the diagnosis of acanthamoeba keratitis important role belongs to the anamnesis (contact lenses, swimming in natural reservoirs), biomicroscopy of the cornea with the identification psevdodendritical figures or recurrent epithelial damage, which are the earliest clinical signs of the disease.

It revealed that the photodestruction of infectious agents can be very helpfull in the treatment of AK.

Complex treatment of a bilateral acanthamoeba keratitis, which includes biguanide derivative antiseptics, amebicidal, antifungial drugs, the use of pathogenetic and symptomatic therapy, and the use of PDT with methylene blue and dimexid allowed to stop inflammation and restore visual acuty.

★ CONCLUSION ★

First used in ophthalmic practice combined treatment of Acanthamoeba keratitis which included photodynamic therapy with 0.1% methylene blue and 10% dimethylsulfoxide showed significant therapeutic effect and restored vision acuty.

★ REFERENCES ★

1. □□□□□□□□□.□.□□□/□□□□□□□□□.□,□□□□□□□□□.□,□□□□□□□□. □. – □., 2006. – 129 □.

2. □□□□□ □□□□□□□□□. □□□□□□□□□□141□□□□□. «□□□□□□□□-□□□□□□», 2004, □□□.99.

3. Aksozek A et al. Resistance of Acanthamoeba castellanii cysts to physical, chemical, and radiological conditions. J Parasitol2002;88(3):621-623.

4. Buettner G. The apparent production of superoxide and hydroxyl radicals by hematoporphyrin and light as seen by spin-trapping / G. Buettner, L. Oberly // Fed. Biol. Sci. Letts. – 1980. – Vol. 121. – P. 161–164.

5. DOG 2013. «First Results of the German Acanthamoeba Keratitis Registry». Szentmary N, Daas L., Epping T., et al.

6. Geerling G., Maier P., Seitz B. Infectious keratitis: Herpes under Control, Acanthamoeba and Fusarium on the Rise. Klin Monatsbl Augenheilkd 2015;232: 735-737

7. Lorenzo-Morales J, Khan NA., Walochnik J. An update on Acanthamoeba keratitis: diagnosis, pathogenesis and treatment. Parasite 2015; 22:10

8. Patrice T. Photodynamic Therapy / Patrice T. – Cambridge : UK, 2003. – 287 p.

9. Szentmary N., Goebels S., Bischoff M. et al. Photodynamische Therapie bei infektioser Keratitis. Ophtalmologe 2012; 109:165-170

10. Szentmary N., Daas L., Matoula P et al. Akanthamobenkeratitis. Ophthalmologe 2013;110:1203-121.

11. Wainwright M. Photodynamic antimicrobial chemotherapy (PACT) / M. Wainwright // J. Antimicrob. Chemother. – 1998. – Vol. 42. – P. 13–28.

Alexandra-Maria JURCA
Municipal Clinical Hospital Timisoara
ROMANIA

EFFICACY OF THEALOZ-DUO FOR THE TREATMENT OF DRY EYE DISEASE IN COMPUTER USERS

★ INTRODUCTION ★

Dry eye disease it's one of the most common ocular comorbidities, and may overlap with other causes of ocular surface disease, such as ocular allergy and meibomian gland dysfunction

Dry eye syndrome is a multifactorial disease whose outcome is malfunctioning of the tear film due to insufficient tear production qualitative or quantitative or increased tear film evaporation, with potential damage to the ocular surface[1]. Prevalence of dry eye syndrome increases with age, studies show a prevalence between 5-30% of the adult population. American Woman's Healt Study and Physician' Health Study shows that 3,23 milions of woman and 1,68 milions of mens over 50 years old have a moderate to severe grade of dry eye[2].

Dry eye is one of the most frequent ophthalmic disease, causing complaints of burning, itching, or even dryness. Risk factors are : endogenous(age, ethny, systematic risk factors, etc.) and exogenous (Video terminal, contact lens wearing, corneal refractive surgery , etc.)[3].

The aim of this study was the assessment of the influence of computer workers in dry eye symptomatology, and also to evaluate the therapy on cornea tissue using different topical medications (artificial tears).

★ CASE REPORT ★

Were admitted to the study 45 subjects video terminal operators (VDT), 18 M and 27 F, mean age of 28,3 (TABLE 1) with signs and symptoms of dry eyes and no acute ocular pathology, no previous eye surgery and no topical medication during one-two month prior to the start of study. In all patients was considered the subjective symptoms and the objective signs, at the time of enrollment visit, and after 30 days of treatment.

Age category	M	F	Total / Category
20-30	8	14	22
30-40	3	7	10
40-50	7	6	13
Total	18	27	45

Table 1. Distribution of patients by age / gender

Treatment : All subjects were treated with a tear substitute (Thealoz Duo – Trehalose and hyaluronate) - ° 1 drop 3 times/in both eyes/day for 30 days. ° Thea Pharmaceuticals.

★ RESULTS ★

In all subjects, video terminal operators (VDT), included in our study, after 30 days of treatment with Thealoz Duo, was observed the disappearance of symptoms present for inclusion in the study.

All the patients responded to Ocular Surface Disease Index (OSDI) questionnaires and the results are:

- The average OSDI score before and after treatment: OSDI A 4.37 - 3.55, OSDI B 4.62 – 4.00, OSDI C 2.64 – 2.22, OSDI D 11.64 – 9.77 . OSDI score was 24.26 before treatment and 20.34 after treatment. (Fig. 1)

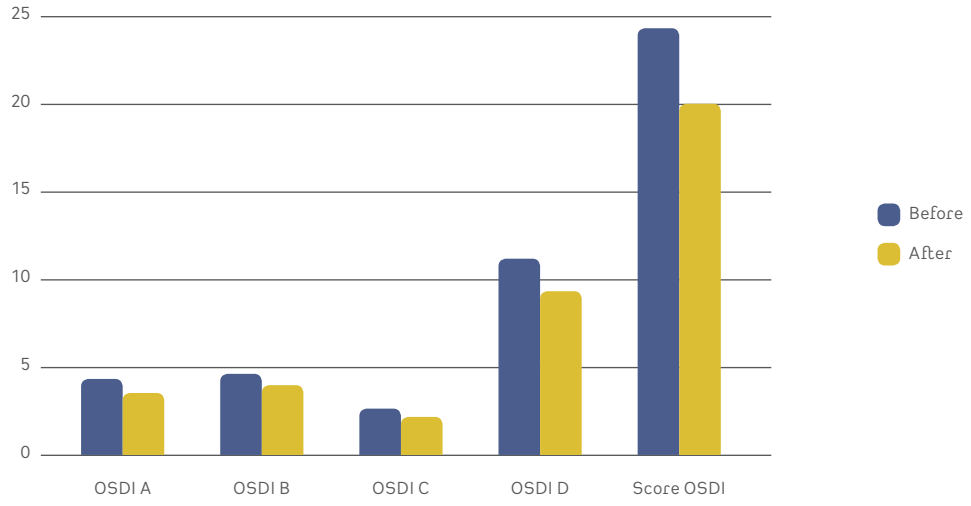


Figure 1: OSDI questionnaire answers before and after treatmens

- The data shows a change with improved tear test, with the following results before and after: Schirmer I (Fig.2) <5 mm/5 min 2.12% - 3.16%, <10 mm/5 min 6.10% - 8.04% . After 30 days of treatment, 9 of the patients had Schirmer I test results > 10mm/5 min.

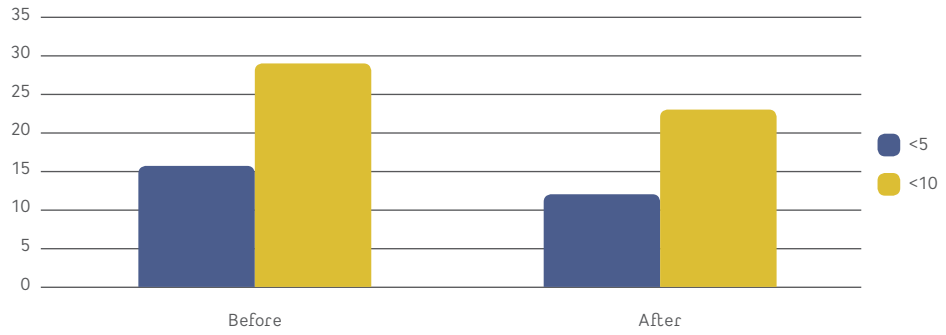


Figure 2: Schirmer I test before and after 30 days of treatment

- T-BUT (Fig.3) before and after treatment: <5sec 3% - 3.33%, <10 sec 7.11% - 7.8 %. Tear ph shows also a change with improved results after treatment: Ph >7.2-8< had 77.77% of patients before treatment and 86.66% of patients after treatment, ph > 8 had 22.22% before and 13.33% after treatment.

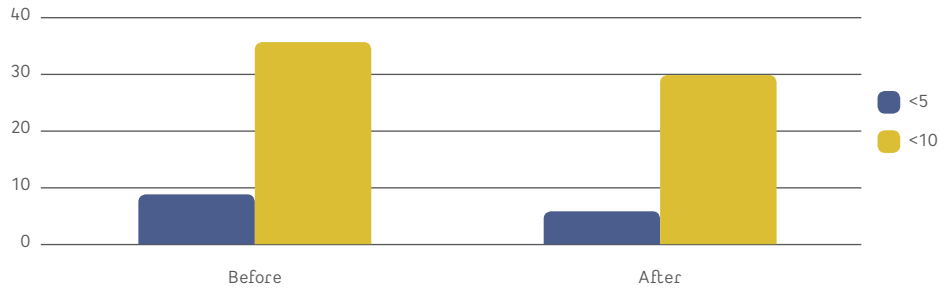


Figure 3: T-BUT test before and after 30 days of treatment

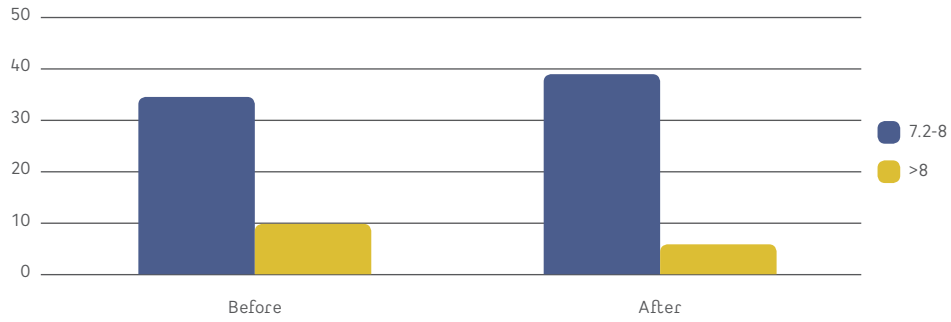


Figure 4: Tear PH before and after 30 days of treatment

★ DISCUSION ★

Dry eye is a common problem among computer users. The OSDI questionnaire, Schirmer I test, TBUT and tear ph measurement is very easy to perform and may offer benefits in supporting the diagnosis of dry eye[4].

These results indicate that the use of video display terminals is associated with an increase tear evaporation due to decreased frequency of blinking, which can lead to dry eyes. Artificial tears provide relief from dry eye symptoms[5].

Sodium Hyaluronate and trehalose contained by Thealoz Duo protects the epithelial cells on the ocular surface, improving their resistance to the daily stresses of dry environments and tear film changes in a dry eye[6]. Thanks to hypotonic formulation, it addresses the chemistry imbalance of the tear film in chronic dry eye. Previous study shown that Thealoz Duo is an effective combination of two active ingredients for the treatment of dry eye[7].

★ CONCLUSION ★

The statistically significant change of OSDI questionnaire score and of the tear test(Schirmer I, T-BUT, Tear PH) obtained after treatment with Thealoz Duo and the disappearance of symptoms, showed a clinical efficacy of the treatment for video terminal operator patients. These results are are similar to the previous studies[8].

★ REFERENCES ★

1. Lin PY, Tsai SY, Cheng CY, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shihpai eye study. Ophthalmology. 2003;110:1096–1101. [PubMed]

2. Schaumb erg DA, Sulliv an DA, Buring JE, Dana MR. Prev alence of dry eye syndrome among US women. Am J Op hthalmo l 2003:136;318-26

3. Pisella P-J., Boudouin C., Hoang-Xuan T., Rapport SFO 2015, La surface oculaire.

4. Unlü C, Güney E, Akçay Bİ, Akçalı G, Erdoğan G, Bayramlar H - Comparison of ocular-surface disease index questionnaire, tearfilm break-up time, and Schirmer tests for the evaluation of the tearfilm in computer users with and without dry-eye symptomatology, Clin Ophthalmol. 2012;6:1303-6. doi: 10.2147/OPTH.S33588. Epub 2012 Aug 10.

5. Tsubota K. The effect of wearing spectacles on the humidity of the eye. Am J Ophthalmol1989;108:92-93

6. http://www.thea-pharmaceuticals.co.uk/assets/products/Thealoz-Duo-Patient-Information.pdf

7. Pinto-Bonilla JC, Del Olmo-Jimeno A, Llovet-Osuna F, Hernández-Galilea E- A randomized crossover study comparing trehalose/hyaluronate eyedrops and standard treatment: patient satisfaction in the treatment of dry eye syndrome, Ther Clin Risk Manag. 2015 Apr 13;11:595-603. doi: 10.2147/TCRM.S77091. eCollection 2015.

8. Calvão-Santos G, Borges C, Nunes S, Salgado-Borges J, Duarte L - Efficacy of 3 different artificial tears for the treatment of dry eye in frequent computer users and/or contact lens users, Eur J Ophthalmol. 2011 Sep-Oct;21(5):538-44. doi: 10.5301/EJO.2011.6324

Karine DAVTYAN
Privat clinic "Sfera"
RUSSIA

SUCCESSFUL TREATMENT OF A CORNEAL HERPETIC ULCER USING CACICOL

★ INTRODUCTION ★

DA 60 year old, high myopic woman came to the clinic August 11-th 2016 complaining on a painful, red left eye, which started 2 months ago. She also complained of photophobia, tearing and blurred vision in her left eye. The patient already was unsuccessfully treated in other centers and got a diagnose: OS: Pharmacologically resistant herpetic ulceration of the cornea.

★ CASE HISTORY ★

Beginning of June she got an acute pain in her left eye. The patient was diagnosed with a **herpetic corneal ulceration** in her left eye. She already had in her anamnesis several herpetic keratitis during last years.

She was treated in previous clinic by instillation of:

1. ***Antiviral therapy: Acyclovirum, Ganciclovir sodium***
2. ***Immunomodulating therapy:*** sol. Acidumpolyadenilicum+Acidumpolyuridilicum
3. ***Antibacterial therapy:*** sol. Levofloxacini, chloramphenicol+colistimethate sodium+ tetracycline
4. ***Mydriatics:*** sol. Tropcamidi+ sol. Phenylephrine hydrochloridi
5. **Reperative therapy:** Deproteinized calf blood extract
6. Different types of subconjunctival injections.

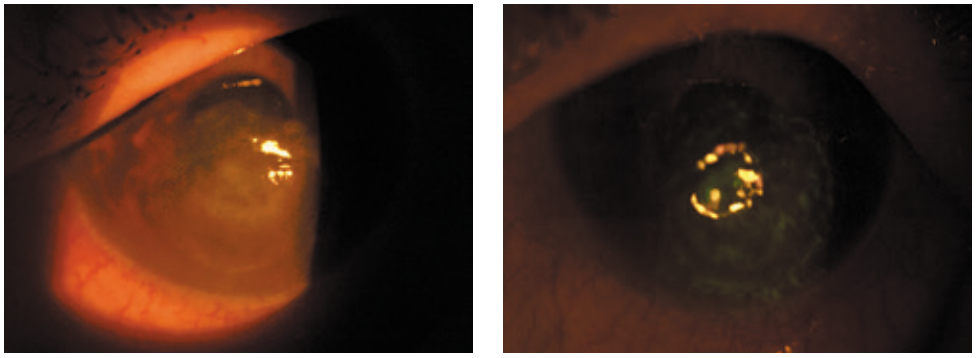
Also 2 times she passed **diatermocoagulation of the cornea** and 3 times of **autocytokinotherapy** (this is type of therapy, which is use blood of patient mixed with antiviral drugs or antibiotics for installations and subconjunctival injections). She noted a slight positive dynamics after treatment.

First examination (11/08/2016)

VA OS = Pr. L. certae

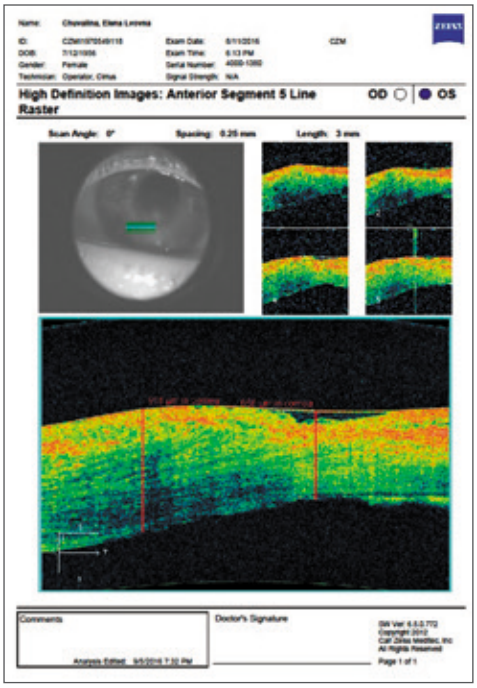
Slit lamp Examination OS

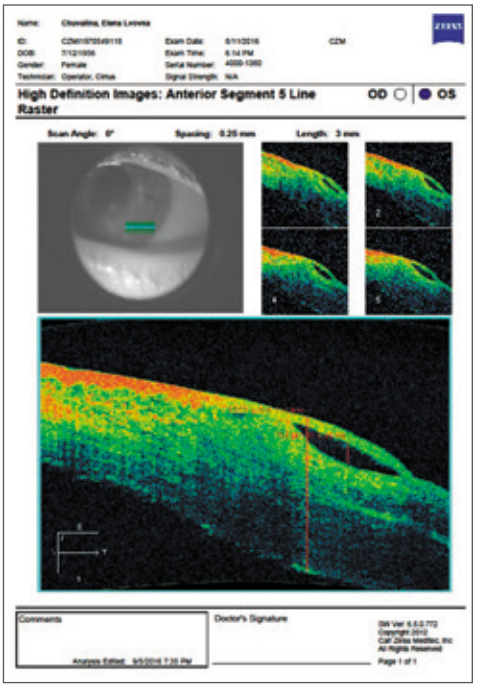
- Eyelid edema, blepharospasm, photophobia
- Significant conjunctival hyperemia (+3), subconjunctival hemorrhages
- Central epithelial oval shaped defect of 5.2 mm x 6.0 mm below to the center of the cornea with irregular edges
- Stromal defect - 2/3 of the cornea depth
- A dense, white stromal infiltration on the edges of ulceration with bullous epithelium on the surface .
- Significant folds of Descemet's membrane.
- Other structures were not clearly visible



Fluorescein test (11/08/2016)

11/08/2016 - OCT: bullous transformation of epithelium, irregular endothelium, the thickness of focus 656 mkm, ulceration with irregular edges.





Treatment which patient was receiving before her visit:

1. Sol.Acidumpolyadenilicum+Acidumpolyuridilicum 5-6 times per day
2. Sol. Levofloxacini 5-6 times per day
3. Sol. Tropcamidi+ sol. Phenylephrine hydrochloridi 5-6 times per day
4. Deproteinized calf blood extract 5-6 times per day
5. Chloramphenicol+colistimethatesodium+tetracycline 1 times at night

She refused correction of previous therapy, we could not cancel the current therapy and we could only add: instillation of Cacicol (Polycarboxymethylglucose sulfate) once in 3 days during 6 weeks.

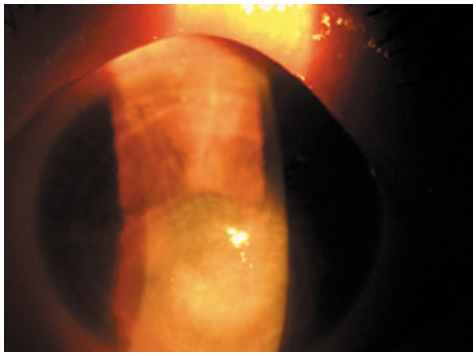
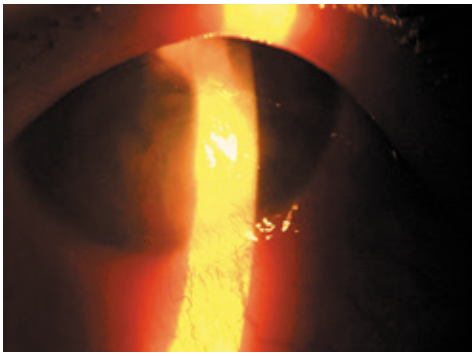
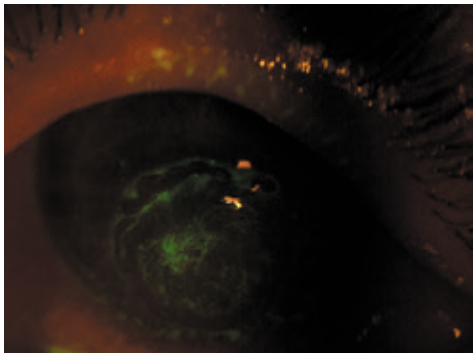
Second examination (22/08/2016)
11 days of using Cacicol – 4 instillations

The patient noted significant improvement in VA and other symptoms

VA OS = 0,02 u/c

OS Slit lamp Examination

- Blepharospasm and photophobia were less
- Conjunctival hyperemia remained (+2)
- Central oval shaped focus of 5.1 mm x 5.9 mm below to the center of the cornea with regular edges was covered by epithelium on its surface
- Visible vascularization in the deep layers of cornea appeared.

Fluorescein test (22/08/2016)

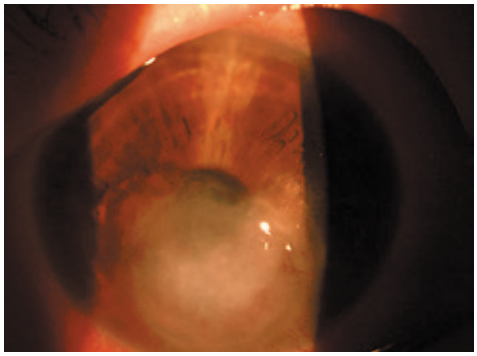
Treatment:

1. Sol. Levofloxacini 3 times per day
2. Sol. Tropcamidi+ sol. Phenylephrine hydrochloridi 4 times per day
3. Deproteinized calf blood extract 5-6 times per day
4. **Polycarboxymethylglucose sulfate** once in 3 day

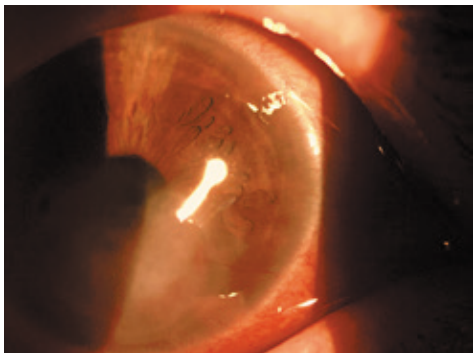
Third Examination 31/08/2016 (20 days of using Cacicol – 7 instillations)

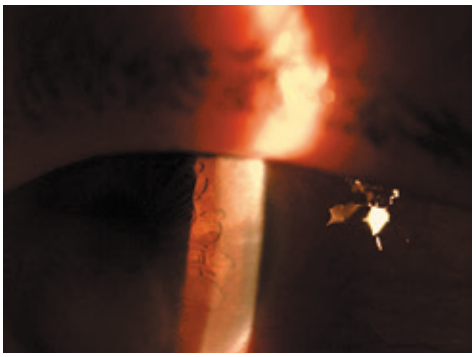
VA OS 0,02 with sph – 6,0 D = 0.03

- Blepharospasm and light sensitivity were less
- Hyperemia of conjunctiva was reduced up to +1
- The size of central oval shaped focus of decreased: 5.0 mm x 5.5 mm and it has got more regular margins with structured borderline.
- The number of new vessels increased
- A dense, white stromal infiltration reduced
- Bullous epithelium on the surface reduced and remained only on upper margin of the focus.
- Folds of Descemet's membrane almost disappeared.

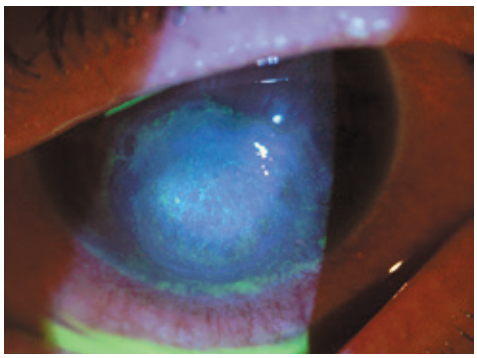


The vascularization in the deep layers of cornea intensified and located in the inferior part of cornea.

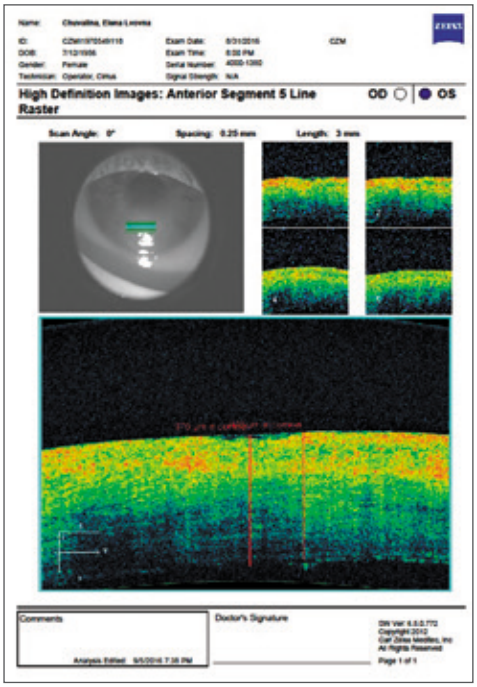


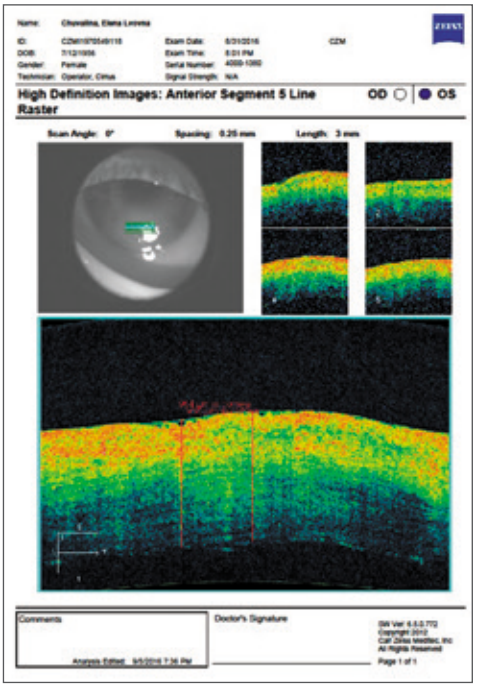


Fluorescein test



31/08/2016 - OCT: : bullous transformation of epithelium disappeared, the thickness of focus increased up to 974 mkm, the ulceration was closed.





Treatment:

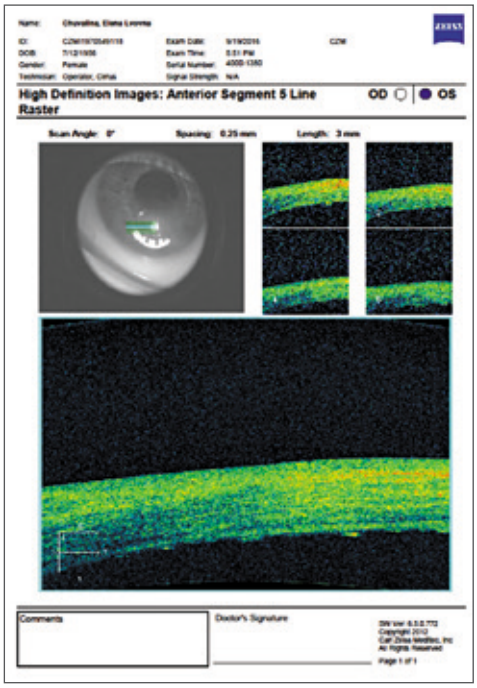
1. Sol. Tropcamidi 0,5 % 3 times per day
2. Deproteinized calf blood extract 1 times at night
3. Sol. Dexamethasoni 0,1% 4 times per day
4. **Polycarboxymethylglucose sulfate once in 3 day**

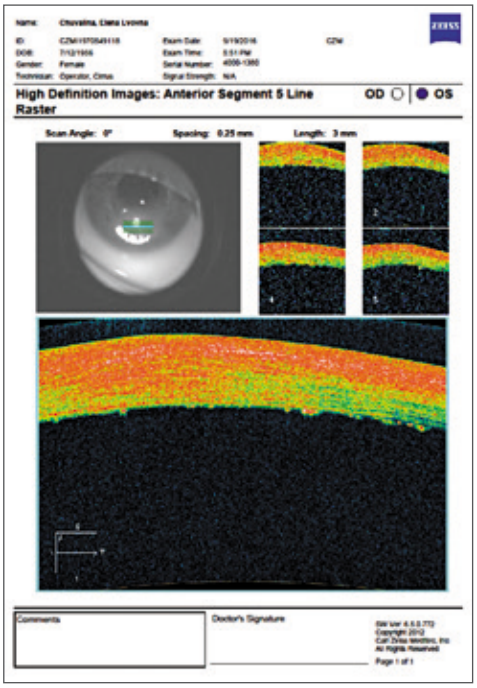
Forth Examination 19/09/2016 (38 days of using Cacicol – 11 instillations)

VA OS 0,02 -0,03 with sph – 6,0 D = 0.1

- Blepharospasm and light sensitivity disappeared
- Hyperemia of conjunctiva was almost disappeared
- The size of central oval shaped focus decreased and became more transparent: 4.0 mm x 4.5 mm and it has got regular margins with structured borderline.
- The number of new vessels significantly increased
- A dense, white stromal infiltration reduced
- Bullous epithelium and folds of Descemet' s membrane disappeared.
- The vascularization in the deep layers of cornea intensified and located in the inferior, temporal and nasal part of cornea.

31/08/2016 - OCT: bullous transformation of epithelium disappeared, the thickness of focus decreased up to 608mkm, the ulceration was closed.





Treatment:

1. Sol. Dexamethasoni 0,1% 2 times per day
4. **Polycarboxymethylglucose sulfate was cancelled**

★ DISCUSSION ★

The decision to use Cacicol was made by internal ethics Committee of the clinic because of known effect of Cacicol and insufficient traditional treatment during last two month and high risk of cornea perforation.

Due to absence of local registration patient was asked to sign the off label treatment agreement.

No side effect was noted during treatment.

★ CONCLUSION ★

- Improvement of subjective symptoms was noted after 1,5 week using Cacicol
- Size of focus decreased significantly from 5,2x 6,0 before treatment to 4,0x 4,5 after at 1,5 month of treatment (11 installation of Cacicol)
- Complete corneal regeneration of epithelium we achieved within 1,5 weeks of treatment.
- Cacicol was well tolerated and no side effects or complaints were noted

This study confirmed improvement of cornea healing and patient comfort. Cacicol is effective and safety approach for difficult cases.

WWW.THEA-TROPHY.COM

EDITION 2016 - 2017

NON-SURGICAL TREATMENT OF CORNEAL DISORDERS

CLINICAL CASES

TROPHY CONTEST

THEA INTERNATIONAL CONTEST OF CLINICAL CASES IN PATHOLOGIES OF THE EYE

Théa
Driving innovation

12, rue Louis Blériot Z.I. du Brézet 63017 Clermont-Ferrand CEDEX 2 FRANCE
Tél. +33 4 73 98 14 36 • Fax. +33 4 73 98 14 38
www.laboratoires-thea.com

WTROBR00118