TROPHY
CONTEST

THEA INTERNATIONAL CONTEST OF CLINICAL CASES IN PATHOLOGIES OF THE EYE

EDITION 2015 - 2016

MANAGEMENT OF CORNEAL DISORDERS

THE BEST 10 CLINICAL CASES

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Thea
Driving innovation

PREFACE

Mr. JEAN-FRÉDÉRIC CHIBRET

M. Jean-Frédéric CHIBRET
President of Laboratoires Théa

Education and the sharing of knowledge have always been an important tradition for the Chibret family. Théa supports many projects and pedagogical 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 to 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 their experience. Due to its success, the contest has been opened to countries outside Europe and has now become "inteR-national".
Each year there is a specific theme. Three winners are designated by experts who deliberate confidentially and objectively, and are invited by Théa to present their clinical case at the Théa symposium which is organised alongside the ARVO congress.
Each year, more and more participants are vying to submit their latest research and present their cases during an international symposium. In the first year, only 26 cases were submitted, however in the most recent competition we received close to 100, which is an incredible growth over just 4 years.

After "Glaucoma", "Glaucoma and Ocular Surface", "Persistent or recurrent corneal ulcers", the last topic was chosen for 2016: "Management of corneal surface diseases".
The cornea is the gateway to the eye, in such that 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 and involving various process such as inflammation, infection, degeneration, injuries, and inherited dystrophies.
This means 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. Especially the international jury, which this year consisted of: Prof. Christophe BAUDOUIN (France), Prof. Marie-Josée TASSIGNON (Belgium); Prof. Uwe PLEYER (Germany); Prof. Jacek SZAFLIK (Poland); Prof. Ulf STENEVI (Sweden); Prof. Pascale ARAGONA (Italy); Dr. Óscar Gris (Spain) and Dr. Alex Shortt (United Kingdom).
Finally, we would like to also thank all participants in past TROPHY competitions and warmly invite any young residents and fellows in ophthalmology to take part in the future competitions.

PREFACE

Prof. BEATRICE COCHENER

Béatrice Cochener
MD, PhD
Brest University Medical School,
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Laboratoires Théa's first edition of the TROPHY contest for clinical cases in ophthalmology took place in 2012 and was undoubtedly a success.
Each year, more and more participants are vying to submit their latest research and present their cases during an international symposium. In the first year, only 26 cases were submitted, however in the most recent competition we received close to 100, which is an incredible growth over just 4 years.

This year, the fourth edition covered a very specific topic: "Management of corneal disorders".

This particular subject was chosen because care of corneal problems has evolved so rapidly during the last few years (transplants, laser, etc.). Corneal research is on the rise at the moment, mainly due to the fact that solving and treating problems with the cornea and the ocular surface is key in modern ophthalmology.

No less than fourteen countries participated in the 2015 contest and 92 cases were submitted.

After a panel of acknowledged ophthalmologists in each of these countries selected the best their country had to offer, an international jury of experts selected the three best cases overall.

The first place was awarded to " Treatment of spontaneous corneal microperforation linked to autoimmune hepatitis: the corneal regeneration with cacicol", by Dr Amparo Gargallo Benedicto of Spain. She presents a case of micro corneal perforation associated with autoimmune hepatitis basis, it is a rare disease in which there have been no previous reported cases of corneal perforations. She opted for the non-invasive topical treatment, Cacicol, combined with contact lens and topical lubricants, receiving a good treatment outcome, with resolution of the corneal perforation and progressive reduction of corneal thinning without having to resort to surgery.

The second place went to "Successful surgical management of bilateral corneal melting in severe ocular graft-versus-host disease" by Dr Régine Vogt of Germany. She observed that ocular graft-versus-host disease (oGvHD) is frequently seen after allogeneic stem cell transplantation. oGvHD may cause severe complications like corneal ulcers and perforations. If conservative treatment is not successful for corneal perforation in patients with oGvHD, amniotic membrane transplantation using a sandwich technique is advised.

The third place was given to "Corneal hemangioma treated with photodynamic therapy" by Dr Josefina Cynthia Villalobos Ojeda of Mexico. At the time of writing, this type of treatment has not yet been reported in any other case study of corneal hemangioma, so this case report seems very important, and even we do not have the pathology report. However the clinic picture and the response to treatment supports the diagnosis.

The three winners had the opportunity to present their cases to an international audience at the THEA symposium during the 2016 ARVO congress in Seattle.

As well as these three winners, all of the other top ten cases are reported in this brochure, and all the finalists' cases are available online.

It is easy to apply, submissions are open and can be accessed online at www.thea-trophy.com.

Just like in previous years, the professional judging panels of ophthalmological experts will assess the submitted cases with respect to 4 specific criteria: the originality of the case; clarity; quality of illustrations; and how the case contributes to overall ophthalmic knowledge in the field of study. The type of documents that can be submitted for judging are isolated case reports, reports covering a series of cases or any type of innovative clinical research.

Congratulations to all previous and recent winners. I now warmly invite all residents and fellows to participate in this contest in the future.

Let's continue the TROPHY success story!

TROPHY WINNERS AT THEA 2016 ARVO SYMPOSIUM

Théa gave 3 applicants the opportunity to present an unpublished clinical case to an international audience during the Théa symposium at the 2016 ARVO meeting.

From left to right : Jean-Frédéric Chibret, President of Laboratoires Théa, Dr Amparo Gargallo Benedicto, Théa Trophy winner, Henri Chibret, Foundateur of Laboratoires Théa and Pr. Béatrice Cochener

TROPHY WINNERS AT THÉA ARVO SYMPOSIUM IN SEATTLE ON MAY 3RD, 2016.

From left to right : Jean-Frédéric Chibret, Dr. Régine Vogt, Dr. Josefina Cynthia Villalobos Ojeda, Henri Chibret, Dr. Amparo Garagallo Benedicto

Théa Trophy 2015-2016 winners

TOP 10
EDITION 2015 - 2016

"TREATMENT OF SPONTANEOUS CORNEAL MICROPERFORATION LINKED TO AUTOIMMUNE HEPATITIS: THE CORNEAL REGENERATION WITH CACICOL" P.14

Dr. Amparo GARGALLO BENEDICTO
Department of Ophthalmology, Valencia University Clinic Hospital, Valencia – **SPAIN**

"SUCCESSFUL SURGICAL MANAGEMENT OF BILATERAL CORNEAL MELTING IN SEVERE OCULAR GRAFT-VERSUS-HOST DISEASE" P.22

Dr. Régine VOGT
Department of Ophthalmology, University Medical Center Regensburg, Regensburg – **GERMANY**

"CORNEAL HEMANGIOMA TREATED WITH PHOTODYNAMIC THERAPY" P.32

Dr. Josefina Cynthia VILLALOBOS OJEDA
MEXICO D.F. – **MEXICO**

Dr Amparo GARGALLO BENEDICTO

Department of Ophthalmology, Valencia University Clinic Hospital, Valencia – **SPAIN**

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★ RESUME ★

Amparo Gargallo Benedicto, was born November 28th, 1988 in Teruel, Spain. She was licensed in medicine from the University of Valencia.

She is currently working in Clinical University Hospital of Valencia in the field of Ophthalmology.

Author and co-author of seven scientific works.

TREATMENT OF SPONTANEOUS CORNEAL MICROPERFORATION LINKED TO AUTOIMMUNE HEPATITIS : THE CORNEAL REGENERATION WITH CACICOL

★ INTRODUCTION ★

Corneal perforations can be derived from a variety of disorders and may lead to devastating ocular sequelae. After infectious and traumatic, inflammatory eye perforations are the most frequent etiology and they presented in the context of systemic autoimmune diseases as rheumatoid arthritis, systemic lupus erythematosus or with granulomatosis polyangiitis among others. Less commonly they may occur as secondary complications of severe dry eye disease, idiopathic or associated with Sjögren's syndrome, neurotrophic keratopathy or corneal ectasia.

We report a case of spontaneous eye micro-perforation in a patient without previous ocular diseases, with diagnosis of autoimmune hepatitis as only pathological history.

Autoimmune hepatitis is a rare disorder, with an incidence of 0.1-0.9 per 100,000 persons per year, which usually affects middle-aged women. According to immunologic pattern differs in types 1 and 2. The most common form in adults and globally is the type I, characterized by hypergammaglobulinemia and positive antinuclear antibodies (ANA) and/or positive anti smooth muscle (AMS), and the type 2 is most common in children have positive liver-kidney microsomal type 1 antibodies (LKM) [1,2]. Autoimmune hepatitis may present with keratoconjunctivitis sicca in the context of associated Sjogren syndrome [3,4], in which if described aggressive cases of sterile corneal melting leading to spontaneous perforation, especially when the diagnosis is delayed [4]. However there have been no published cases of ocular perforation with corneal thinning associated with underlying immune disorder in patients with autoimmune hepatitis. Described in the literature there are two anterior

uveitis cases associated with autoimmune hepatitis, one before the era of diagnostic tests for hepatitis C [5] and another later , which is associated the presence of uveitis with corneal stromal injury secondary to autoimmune hepatitis without details of corneal involvement [6].

Corneal perforation are emergencies that require immediate attention. It is essential to identify and treat the underlying cause may with orally broad-spectrum antibiotic coverage and referrral to a specialist unit. There are different options for the treatment of corneal perforations less than 2 mm: therapeutic contact lenses, tissue adhesives, the free conjunctival autograft or amniotic membrane.

In our case we present the evolution and results of treatment with topical RGTA-cacicol combined with therapeutic contact lens and autologous serum.

★ CASE PRESENTATION ★

71 year-old woman evaluated at the emergency room of our hospital describing itching and secretion in the left eye (LE) of 2 weeks. The best corrected visual acuity (BCVA) was 0.15. In the slit lamp evaluation we objectify a moderate ciliary hyperemia with a central infiltrated corneal ulcer of 0.5 mm wide by 3 mm high, central descematocele and corneal perforation of 1 mm in diameter with spontaneous positive Seidel. Preservation of the anterior chamber depth without inflammatory reaction was observed. (Figures 1-3).

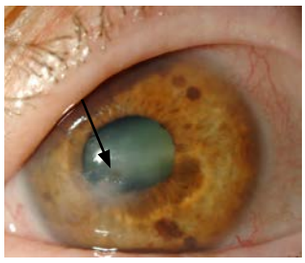


Figure 1 – Central corneal ulcer with thinning, descemetocele and central microperforation (arrow). No signs of infection are observed.

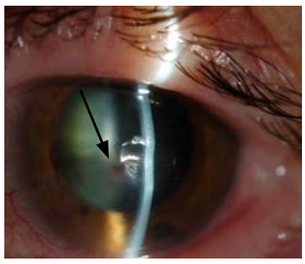


Figure 2 – Corneal ulcer with thinning. Corneal micropreforation indicated by the arrow.

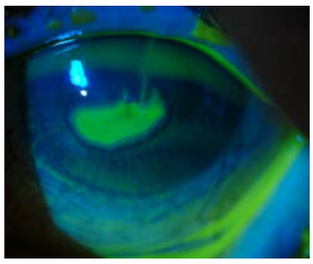


Figure 3 – Epithelial defect with positive fluorescein staining and positive Seidel´s test.

Exploration of the contralateral eye was normal. In the emergency room we put a therapeutic contact lens (TCL), with this anterior chamber remained. The eye was occluded with mydriatics and topical antibiotic coverage plus systemic quinolone

No history of trauma, ophthalmic diseases or previous eye surgeries. Among the pathological systemical history included a diagnosis of autoimmune hepatitis with cirrhosis and secondary portal hypertension. The profile autoimmune antibodies was positive for ANA and SMA and negative for LKM. In biochemistry stands elevated ESR, transaminases, alkaline phosphatase and hypergammaglobulinemia. Liver virus serology was negative. At present, the patient has no systemic treatment of their disease.

Evolution control is performed by anterior segment photographs and OCT (Triton Swept Source OCT). At 24 hours anterior chamber depth is manteined without Seidel.

The possibility of treating microperforating with cyanoacrylate or amniotic membrane arises, but given the anterior chamber depth maintenance without progression of corneal thinning, we decided conservative treatment including artificial tears and Cacicol 1 drop every 48 hours, associated with TCL and topical antibiotic coverage (ofloxacin every 6 hours).

Progressively decreases both epithelial defect and the size of the perforation. On the third day of treatment, in the absence of TCL, not Seidel was observed. In the anterior segment OCT, we observed an epithelial closure, anterior and posterior, by a fibrous bridge leaving an anterior intraestromal defect in the area of maximum thinning. (Figure 4).

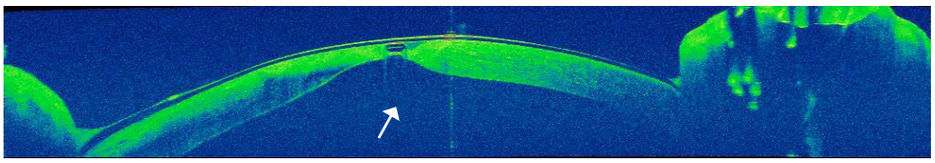


Figure 4 – Anterior segment OCT (Triton DRI OCT) on the third day of treatment. Under the TCL, we observe anterior epithelial closure and posterior closure by a fibrous bridge (arrow) leaving an intrastromal defect of (arrowhead).

During the first week begins progressive epithelialization of the ulcer (Figure 5) with a pattern of diffuse superficial keratitis associated, and progressive corneal stroma regeneration with decrease of thinning (Figure 6)

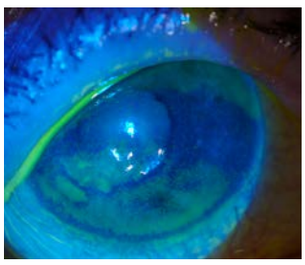


Figure 5 – Epithelialization of the corneal ulcer with negative Seidel test. Irregular distribution of fluorescein is appreciated and diffuse keratitis associated.

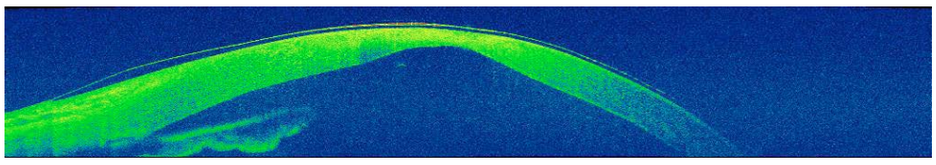


Figure 6 – Anterior segment OCT at day 10 of treatment. Regeneration of the anterior corneal stroma is observed with complete resolution of intracorneal visible defect in Figure 3.

By possible association with Sjogren's syndrome we ask an autoimmune hepatitis analysis and internal medicine evaluation. The results showed a positive antiRo antibodies and the diagnosis of secondary Sjögren's syndrome is confirmed.

At present the MAC is 0.05, with nuclear cataract N4, complete epithelization of the lesion with secondary corneal scarring (Figure 7). In the OCT control after 3 months corneal thickness increase is observed in the thinning area, without risk of perforation (Figure 8). Continued monitoring for basic autoimmune hepatitis and treatment is maintained with artificial tears and autologous serum awaiting penetrating keratoplasty and cataract surgery.

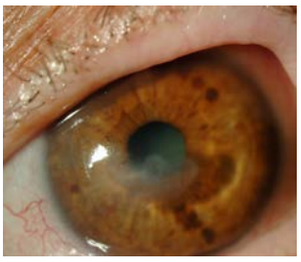
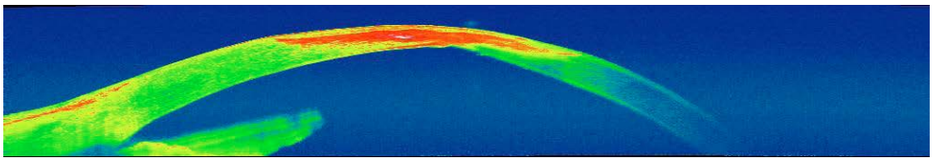


Figure 7 – Complete epithelization of the ulcer. Corneal leukoma that compromises the visual axis is observed.



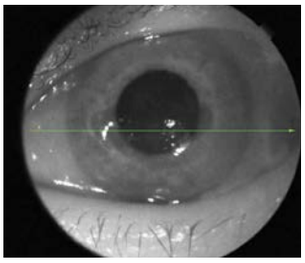


Figure 8 – 3-month follow-up anterior segment OCT. We observe restoration of corneal thickness with high reflectivity in the area of corneal leukoma by stromal fibrosis.

★ DISCUSSION ★

The unique history of our patient is the autoimmune liver cirrhosis without surgical antecedent, trauma, or previous eye diseases, nor contralateral eye disorders to suspect a clear etiology. Is not rare the corneal involvement for systemic autoimmune diseases, generally as peripheral ulcerative keratitis and occasionally in the center, however to date not been reported corneal ulceration and ocular perforation in the case of autoimmune hepatitis. The known association of this disease with Sjögren's syndrome should make us think of this possibility and should perform appropriate tests.

Therapeutic options for corneal perforation less than 2 mm are TCL, tissue adhesives such as cyanoacrylate, free conjunctival autograft or amniotic membrane. If infected tissue adhesives, this may induce increased neovascularization and generate stromal scarring. The amniotic membrane requires debride the edges of the lesion and as conjunctival autograft requires stitches to the cornea.

Moreover, the GTA therapy restores the balance between the protein matrix and cytokines linked to heparan sulfate and ensures balance in the corneal microenvironment. This in turn prevents degradation of extracellular matrix proteins and promote epithelial and stromal healing. It is administered topically and is usually used in cases of persistent epithelial defects [7.8] and chronic corneal ulcers [9]. It has also been used after penetrating keratoplasty [10] and has recently been used successfully in the treatment of corneal ulcers postquirúgicas [11]. It is a non-invasive treatment that not induces stroma scarring apparently due to the healing itself.

★ CONCLUSION ★

We present a case of micro corneal perforation associated with autoimmune hepatitis basis as only pathological history, a rare disease in which there have been no reported previous cases of corneal perforations. We opted for the non-invasive topical treatment, Cacicol, combined with contact lens and topical lubricants, getting good treatment outcome, with resolution of the corneal perforation and progressive reduction of thinning without resorting to surgery. We could not assess the effect of Cacicol in isolation but it could be an alternative therapy for selected cases of corneal micro-perforations combined with the use of temporary TCL.

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★ RESUME ★

Regine Vogt, MD, was born November 8th, 1986 in Berlin, Germany. She was licensed in medicine from the Regensburg University.
She is currently a resident in Ophthalmology program in the University Hospital Regensburg.
Participated in five courses and nine national and international scientific conferences.
Author and co-author of five scientific works.

SUCCESSFUL SURGICAL MANAGEMENT OF BILATERAL CORNEAL MELTING IN SEVERE OCULAR GRAFT-VERSUS-HOST DISEASE

★ INTRODUCTION ★

Graft-versus-host disease (GvHD) is a major complication after allogeneic stem cell transplantation (aSCT) with an incidence of about 50% [1]. The traditional differentiation of acute and chronic GvHD, when occuring before or after day 100 of aSCT has been redefined, since overlap forms are seen frequently. The current consensus is that GvHD is considered as acute or chronic based on clinical manifestations [2]. Pathomechanisms for cGvHD include impaired tolerance mechanisms leading to immunodysregulation and immunodeficiency. Allo- and autoreactive T and B lymphocytes as well as indirect presentation of alloantigens by antigen-presenting donor cells play a major role and maintain chronic inflammation and subsequent fibrosis [1].
Ocular manifestations are frequent long-term complications and affect 50 to 80% of patients with cGvHD [3]. In general, different ocular tissues can be affected by cGvHD. Keratokonjunctivitis sicca caused by chronic inflammation and subsequent atrophy of the lacrimal gland and chronic conjunctivitis is the most common manifestation [4]. Additionally, involvement of the lids, the meibomian glands, and the cornea is frequently seen [5]. Corneal involvement of cGVHD includes superficial punctate keratopathy, filamentary keratitis, corneal calcifications, and persistent corneal erosion with a risk for development of corneal ulcers and subsequent perforation [6].

★ CASE PRESENTATION ★

We present a case of a 56 year old male patient who developed bilateral corneal perforation due to severe chronic graft-versus-host disease.
In April 2009 the patient was diagnosed with acute myeloic leukemia and underwent allogeneic stem cell transplantation in March 2010. After transplantation he developed acute graft-versus-host disease of the GI tract and the skin, which was treated with high-dose systemic corticosteroids and tacrolimus. He first presented in the Department of Ophthalmology in January 2011 where he complained about bilateral foreign body sensation. Severely reduced Schirmer's scores of OD 0 mm and OS 1 mm and marked inflammation of the ocular surface including bilateral telangiectasias of the eyelids, chronic posterior blepharitis and subtarsal hyperemia were seen. Additionally, subtarsal fibrosis of the upper eyelid of the left eye was present. According to the NIH consensus criteria 2 he was diagnosed grade 2 ocular graft-versus-host disease. Corneal epithelium was clinically not affected at this time. Topical treatment with cyclosporine 0,05% twice daily and preservative-free artificial tears was initiated.
Two months later the patient presented again with moderate reduction of vision of OD 20/30 and OS 20/40. He had discontinued topical cyclosporine treatment. Pronounced bilateral superficial punctual keratitis as well as mild keratinization of the eyelids were seen (Fig. 1). Long-term topical cyclosporine application was reinitiated and punctum plugs were implanted bilaterally.

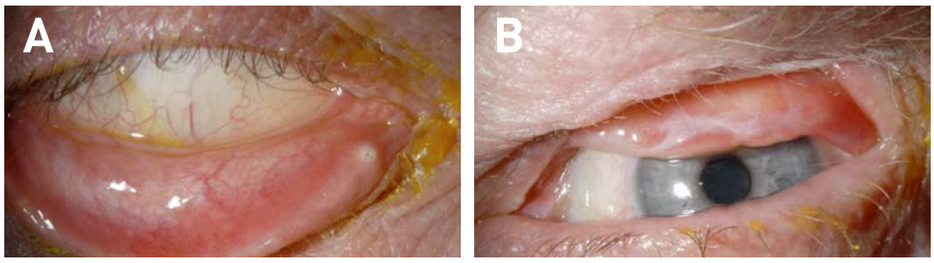

Figure 1 – A) Right and B) left eye two months after first diagnosis of ocular GvHD. Marked subtarsal fibrosis of the left eye.

The patient was seen regularly in the Department of Ophthalmology as well as in the Department of Hematology/Oncology. During the following controls gradual reduction of superficial punctual keratitis but ongoing conjunctival inflammation was seen under topical cyclosporine treatment.
Six months later, the patient presented with a perforated sterile corneal ulcer and partial incarceration of the iris (Fig. 2). He reported having suffered a minimal trauma during morning toilette. Since then vision of his left eye had deteriorated rapidly. No signs of corneal infection were seen.

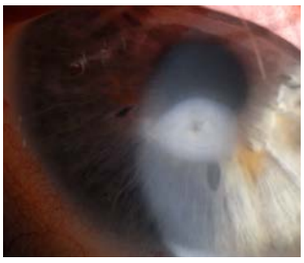

Figure 2 – Left eye with perforated central ulcer.

BCVA was measured OD 20/30 and OS 20/80. Amniotic membrane transplantation was performed using the sandwich technique (graft and patch) and combined synechiolysis and lavage of the anterior chamber. Intravenous ceftriaxon was given in order to prevent secondary bacterial infection. Postoperatively, BCVA was measured OD 20/30 and OS hand movements. Two days after surgery the patient was discharged with preservative-free topical treatment (cyclosporine 0,05% 2/d, ofloxacin 5/d, cyclopentolate 3/d, dexpanthenol 3/d, natriumhyaluronate 5/d, dexamethasone 3/d). The day after discharge, he presented in our outpatient clinic for follow-up. Beside reduced vision OS he reported being symptom-free, but anterior chamber of the left eye was markedly flattened. Amniotic membrane graft and patch, however, remained in place. It was discussed whether to perform penetrating keratoplasty with presumed limited long-term prognosis due to ongoing inflammation and severe dry eye or better to avoid keratoplasty and stabilize the ocular surface by means of a conjunctival flap. The patient refused penetrating keratoplasty at this time. Finally, healing of the corneal defect was achieved by a modified conjunctival flap according to the Gunderson technique 7 and additional temporary tarsorrhaphy. The technique can be described as follows: Removal of the corneal epithelium and peritomy with relaxing incisions is followed by dissection of a thin conjunctival flap without buttonholes and containing only minimal Tenon's capsule. This bipedicle flap (1.5 times width of the ulcer) is positioned on the cornea and fixed by multiple 10.0 nylon sutures without traction. Conjunctival incisions are closed with 8.0 sutures. Two weeks after surgery, sutures of the medial part of the tarsorrhaphy were removed and a well-covered corneal surface with a deep anterior chamber of the left eye was seen. Three weeks after surgery, complete opening of the tarsorrhaphy was performed (Fig. 3).

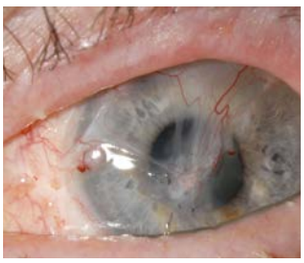

Figure 3 – Left eye three weeks after conjunctival flap surgery using a modified Gunderson technique with temporary tarsorrhaphy.

Following controls in our outpatient clinic revealed a stable ocular surface with moderate inflammation in both eyes. Topical cyclosporine 0,05% 2/d and topical lubrication 5/d was continued. Sutures of the conjunctival flap were removed step by step. However, superficial punctuate keratitis remained unchanged bilaterally (Fig. 4).

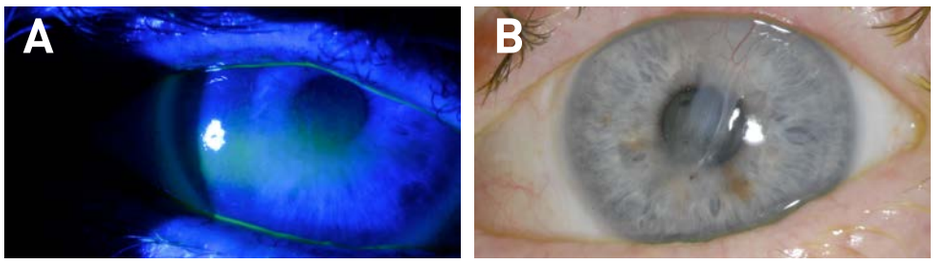

Figure 4 – A) Superficial punctuate keratitis of the right eye. B) Left eye five months after conjunctival flap surgery and temporary tarsorrhaphy.

Four months after surgery of the left eye, the patient presented with deterioration of right eye's visual acuity (OD 20/50, OS 1/35) caused by a central sterile trophic corneal ulcer (Fig. 5). Inpatient treatment for intensive topical application including preservative-free ofloxacin, natriumhyaluronate and dexpanthenol as well as autologous serum eye drops was started. Additionally, a therapeutic contact lens was applied.

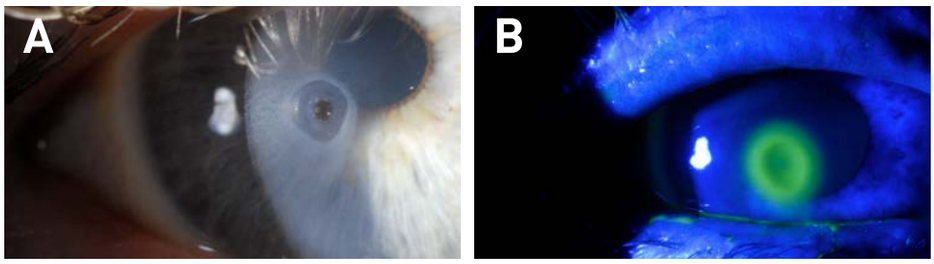

Figure 5 – A) Perforated central ulcer of the right eye, B) with fluorescein staining.

Five days later, slit-lamp examination revealed development of a descemetocele. However, the anterior chamber remained deep. Over the next days, a slowly developing fibrosis of the corneal ulcer margins could be seen and the allover size of the ulcer was regressive (Fig. 6). Nevertheless, two weeks after the corneal ulcer was seen first, a Seidel-I-positive corneal perforation of the right eye occurred. Amniotic membrane transplantation in a sandwich technique (graft and patch) was performed but again was not successful. The day after surgery anterior chamber flattened.

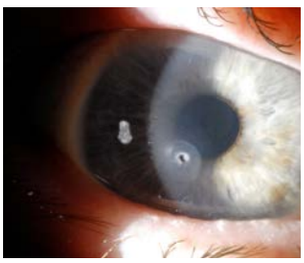

Figure 6 – Right eye with perforated central ulcer: fibrosis of the corneal ulcer margins.

As on the other eye, we used a modified conjunctival flap technique according to Gunderson7 (see description above) and temporary tarsorrhaphy to stabilize the ocular surface. The patient could be discharged two days after surgery. Again, sutures of the tarsorrhaphy were removed gradually over the next weeks, starting ten days after surgery (Fig. 7).

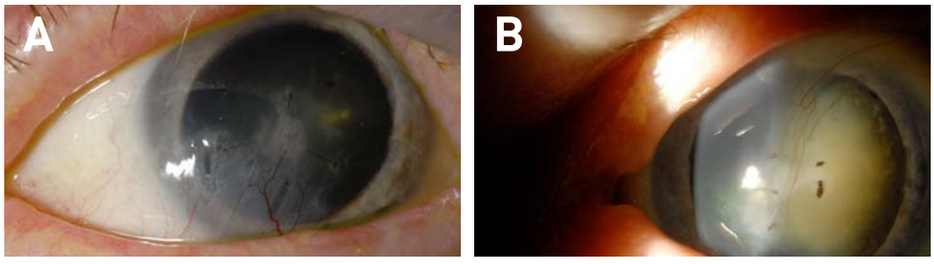

Figure 7 – A) Right eye two months after conjunctival flap surgery and temporary tarsorrhaphy. B) Left eye one year after conjunctival flap surgery and temporary tarsorrhaphy.

Ocular surface and inflammatory conditions remained stable bilaterally, but the patient's visual acuity worsened due to marked cataract (20/200 OD, 1/50 OS). Performance of cataract surgery was discussed reviewing gain of life quality versus potential severe complications like corneal melting. One year after coverage with conjunctival tissue, cataract surgery of the left eye was performed in general anesthesia. It was decided to leave the residues of the conjunctival flap unchanged during surgery. Post-surgical care included a bandage contact lens and topical treatment with phosphate-free and preservative-free dexamethasone 2/d, ofloxacin 5/d, natriumhyaluronate 5/d and dexpanthenol 2/d. One week later, BCVA improved to 20/60 OS. Marked superficial punctuate keratitis and a minimal epithelial defect were seen, but disappeared within the next 4 weeks under intensive topical lubrication (Fig. 8).

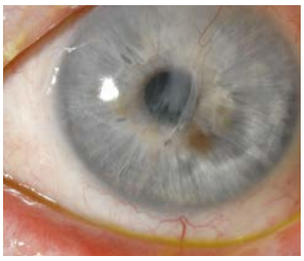

Figure 8 – Left eye four weeks after cataract surgery.

Since satisfying results could be obtained on the left eye, cataract surgery of the right eye was also considered. Unfortunately, the patient's general condition deteriorated significantly due to progressive systemic GvHD. He died of acute respiratory distress syndrome caused by Influenza.

★ DISCUSSION ★

Corneal perforation in patients with ocular GvHD is a rare, but severe sight-threatening complication. In a retrospective analysis over ten years 3 out of 61 patients (4,9%) with ocular GvHD suffered corneal perforation 8. Another retrospective study reported that only 2 out of 620 patients, who underwent allogeneic stem cell transplantation, developed corneal perforation 9. Patients with GvHD who develop corneal perforation seem to be at risk for bilateral disease. Moreover, a marked tendency to recurrence despite intensive treatment is seen [10-12].

Pathophysiology of corneal perforation in patients suffering from GVHD is not completely understood. Perforated corneal specimens from patients with chronic GVHD contain macrophages and matrix metalloproteinase 9 [13]. In addition, apoptotic cells and lymphocytes (mainly CD8+) infiltrating the perforation sites were detected [11, 12, 14].

In general, evidence level for treatment of patients with ocular GvHD is low [3]. Intensive lubrication and topical anti-inflammatory treatment form the basis for additional therapy. Surgical treatment with penetrating keratoplasty is reported in most cases [8, 9, 12]. Nevertheless, results are inconsistent. After several weeks of postsurgical intensive lubrication, a stabilized ocular surface was reached, but in a number of patients recurrent melting and/or rejection of the transplant was seen, which required complete tarsorraphy or even evisceration [11, 15]. Small-sized perforated ulcers were reported

to be effectively treated with therapeutic contact lenses in a limited number of patients [10]. Amniotic membrane transplantation is another therapeutic option in patients with perforated ulcers [16, 17]. However, cases of repeated unsuccessfully transplanted amniotic membranes in patients with corneal perforation due to ocular GvHD are reported [15].

In our case, application of therapeutic contact lens and intensive topical treatment including lubricants, autologous serum eye drops and anti-inflammatory treatment were insufficient to prevent ongoing corneal melting. Amniotic membrane transplantation, which was performed in both eyes initially, did not stabilize the ocular surface. We therefore used a modified conjunctival flap technique and additional temporary tarsorrhaphy in both eyes. Our main goal was to first stabilize the ocular integrity, enabling further surgical procedures to restore visual acuity in the future when eventually GVHD is less active. Using this surgical technique, we could avoid penetrating keratoplasty at a time point, which is associated with a markedly reduced prognosis due to dry eye disease and inflammation in patients with ocular GVHD.

Although studies concerning cataract surgery in patients with GvHD do not report severe complications after surgery, corneal perforation in these patients remains a feared complication [18, 19]. Therefore, intensive topical treatment and frequent pre- and postoperative monitoring of patients with ocular GvHD is necessary. Cataract surgery should not be performed in patients with unstable ocular surface conditions [20]. In our case, due to previous corneal melting, recurrent corneal complications triggered by cataract surgery were feared. However, since visual acuity caused by pronounced bilateral cataract lead to significant reduction of life quality, surgery was performed. Due to intensive perioperative lubrication and close monitoring of our patient, an acceptable gain of visual acuity without major complications could finally be achieved. Especially in patients with severe ocular GvHD preoperative stabilization of the ocular surface and intensive postoperative care is essential for adequate surgical results.

★ CONCLUSION ★

- Ocular graft-versus-host disease (oGvHD) is frequently seen after allogeneic stem cell transplantation.
- Close monitoring of affected patients is needed since oGvHD might cause severe complications like corneal ulcers and perforations.
- In early stages of corneal melting, treatment with intensive lubricating and anti-inflammatory treatment as well as therapeutic contact lenses can be tried.
- If conservative treatment is not successful for corneal perforation in patients with oGvHD, amniotic membrane transplantation using a sandwich technique is indicated.
- In cases of unsuccessful amniotic membrane transplantation, conjunctival flap surgery accompanied by temporary tarsorrhaphy is a therapeutic option to stabilize the ocular surface in severe ocular GVHD in order to avoid penetrating keratoplasty.
- Cataract surgery in patients with oGvHD can lead to deterioration of the ocular surface and corneal melting, but can be performed successfully if ocular surface and inflammatory conditions are well-controlled pre- and postoperatively.

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★ RESUME ★

Josefina Cynthia Villalobos Ojeda, was born September 2nd, 1985 in Mexico City. She was licensed in medicine from mexican faculty of medicine Universidad La Salle.
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Author and co-author of five scientific works.

CORNEAL HEMANGIOMA TREATED WITH PHOTODYNAMIC THERAPY

★ INTRODUCTION ★

The hemangioma is a benign vascular hamartomatous lesion [1] that has been reported in different intraocular locations; choroid being the most common; there are two types: circumscribed and diffuse, although there aren´t any reports of hemangioma of the ocular surface, if it has been reported in the conjunctiva or episclera. [2,3]

Various modalities of treatment have been reported for circumscribed choroidal hemangioma with decrease of visual acuity; including argon laser photocoagulation, cryotherapy, external beam radiotherapy, proton beam radiotherapy, episcleral plaque radiotherapy, and transpupillary thermotherapy (TTT).[4,5] All these techniques have been reported with varying degrees of success in stabilizing or improving visual acuity, but the major limitation with all these treatment modalities has been the risk of damage to the overlying retina.

Especifically about Photodynamic Therapy (PDT) it is a non-thermal, photobiochemical procedure that offers site-specific vascular occlusion and tumour destruction with minimal damage to adjacent neural structures. It uses a photosensitizer molecule called ¨Verteporfin¨ (Visudyne; Novartis; Basil, Switzerland); the selective tissue damage is achieved by sequestration of the photosensitizer in the target tissue and focal activation of the photosensitizer by low energy directed light. [6]

PDT has been used extensively in the field of dermatology for a variety of inflammatory conditions and premalignant and malignant tumours including basal cell carcinoma (BCC).[7]The preliminary results suggest that PDT may be an alternative treatment for ocular surface squamous neoplasia, particularly with diffuse presentation.[8]

It has been used in different retinal tumors as we mentioned previously, it offers site-specific tumour destruction while sparing surrounding structures. The vascular effects of PDT may include remodelling of the vascular wall with reduced permeability rather than vascular occlusion.[9]

★ CASE PRESENTATION ★

A healthy 42 year-old women presented to our ophthalmology institution complaining of 8 months of evolution of red eye and discomfort in left eye, without treatment. She had no previously ocular history or trauma.
Visual acuity in the right eye was 20/20 and in the left eye was 20/50; No anterior or posterior segment alterations on right eye. On left eye we find vascular tortuosity on temporal limbal conjunctiva and a vascularized tumor of 6.5 x 4 mm that involves all the corneal stroma, with the gonioscopic lens we can see how the descemet and endothelium has been displaced back to the anterior chamber because the tumor (fig.1 and fig. 2) ; the anterior chamber angle shows hematic stasis in the trabeculum; intraocular pressure was normal in both eyes .
We find also on the left superior eyelid a superficial hemangioma (fig.3)

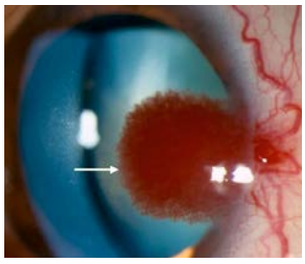

Figure 1 – Vascularized tumor on temporal side of Left eye (white arrow)

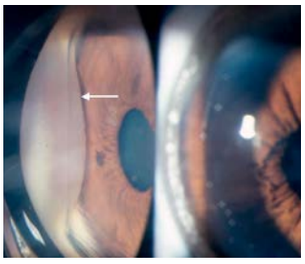

Figure 2 – Gonioscopic lens examination of the tumor (white arrow)

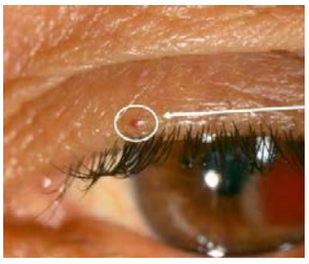

Figure 3 – Superficial hemangioma on eyelid (white arrow)

Imaging studies

We realized an ultrabiomicroscopy (UBM) of the left eye. This is an echography of high resolution with a high frequency of 50 MHz that allows us to study the anterior segment of the eye showing us at stromal level in the III o´clock meridian the homogeneous lesion with high density, between Bowman and Descemet layer that extends up to 5 mm in the sclera with corneal thickness of 3.95 mm (fig.4), and with the standardized A scan we can see the high internal reflectivity and no signs of vascularity (fig.5)
Also we can see at the same meridian the irregularity in the limbal surface because the presence of nutritional conjunctival vessels (fig.6).

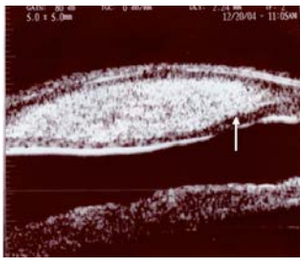

Figure 4 – UBM of III o´clock meridian

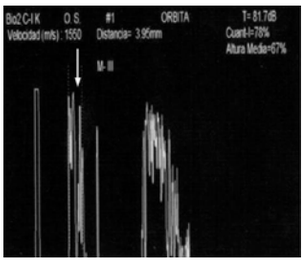

Figure 2 – Standardized A Scan

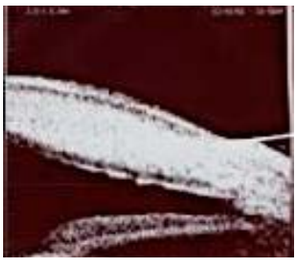

Figure 3 – UBM of III o´clock meridian

In the angiography with fluorescein of the anterior segment we can see the presence of blood vessels that stain in late stages at corneal level and escleral nutritional vessels (fig.7, 8).

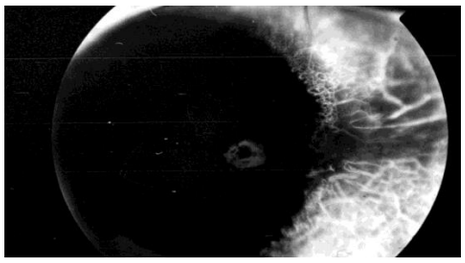

Figure 7 – Angiography with fluorescein (early stage)

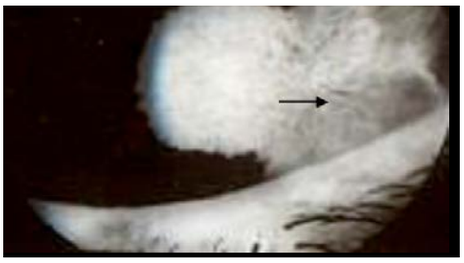

Figure 8 – Angiography with fluorescein (late stage)

With the imaging studies it was diagnosed as a corneal hemangioma and we decided to treat with photodynamic therapy .

Treatment

The patient is treated with photodynamic therapy with Verteporfirin. We apply 5.4 miligrams and give 4 spots of 86 seconds with no effect adverse (Fig.9). The dosis was calculated with the weight of 77 kilograms and the height of 1.54 metres and a body surface area of 1.82 square meters .

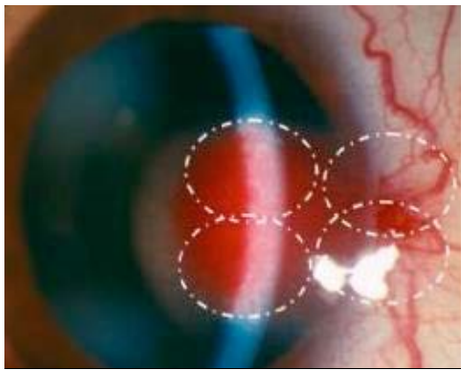

Figure 9 – Localization of the spots of the photodynamic therapy.

Evolution

At day 1. Visual acuity decrease to hand motion because an important corneal edema and absence of corneal epithelium in the region of the treatment, we can see how big was the edema with an ultrabiomicroscope of the region (fig.10), we give prednisolone acetate every hour, ofloxacine every four hours and sodium hyaluronate every 2 hours .
At 1 week the visual acuity improve to 20/400, the corneal edema was better, and we can only see hematic impregnation of the area and the absence of nutritional conjunctival vessels (fig. 11).

Figure 10 – UBM of III o´clock meridian

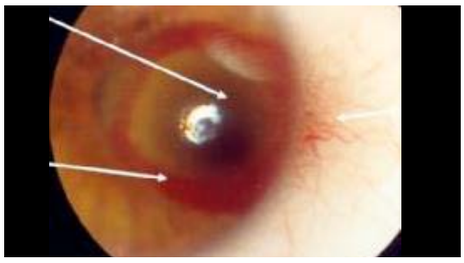

Figure 11 – One week post photodynamic therapy

At one month visual acuity improve to 20/25 and we can only see some thin vessels on the surface of the cornea (fig.12); At UBM we can see the normal architecture of the cornea (fig.13).

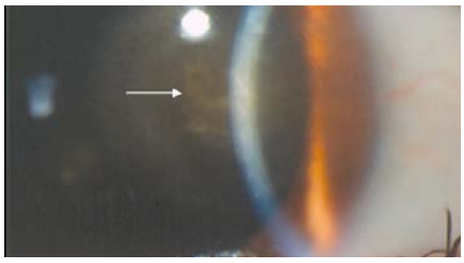

Figure 12 – UBM of III o´clock meridian

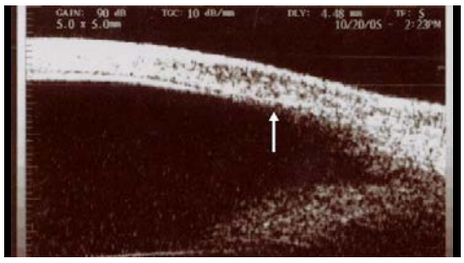

Figure 13 – One week post photodynamic therapy

★ DISCUSSION ★

The hemangioma type lesions are considered benign lesions, as mentioned in the introduction, can be found in different parts of the eye and orbit, in choroid they are treated only if they progress and cause exudation compromising the visual acuity. In our case it is a very atypical location that was causing low visual acuity due to growth being the cornea such important optical structure; for this reason it was necessary to treat it.

For choroidal hemangiomas the different treatments as argon photocoagulation and cryotherapy has been reported to have adverse effects to adjacent structures.

Its remarkable the inflammation caused by the application of photodynamic therapy, which was expected due to the application of a molecule as verteporfirin and laser activation through a photochemical effect that would alter normal function of endothelial cells.

It is important to observe that treatment response was very favorable and that so far there has been no recurrence of the lesion, as already mentioned previously the use of photodynamic therapy has been most studied for choroidal hemangiomas, in which has had good results acting on the vascular endothelium respecting adjacent structures.

In the choroidal hemangiomas the goal of therapy is to stop the exudation that can spread to the macular area causing low visual acuity; and not to the disappearance of the tumor; although in this case the treatment causes the complete disappearance of all the hemangioma.

We know that these lesions are well treated with radiotherapy, but the hospital we work in is only ophthalmological, and is easier to have the antiangiogenic agent at the retina department rather than radiotherapy.

★ CONCLUSION ★

At the moment it has not been reported any other case of corneal hemangioma in the literature, so this case report seems very important, and even we do not have the pathology report, the clinic picture and the response to treatment supports the diagnosis.

It is important to know the different types of treatment that we could have for different pathologies, because we can apply even if they are not in the area where they were initially described.

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OCULAR SURFACE TOXICITY ASSOCIATED WITH TOPICAL INTERFERON α2B IN THE TREATMENT OF CORNEAL INTRAEPITHELIAL NEOPLASIA

★ INTRODUCTION ★

We should remember that the most common ocular surface tumors arising from the conjunctiva are squamous neoplasia, melanocytic tumors and lymphoid tumors. Ocular surface squamous neoplasia (OSSN) is a solar-related condition in immunosuppressed patients. OSSN is a term that is used to describe all the epithelial lesions of the cornea and conjunctiva, from dysplasia to invasive squamous cell carcinoma [1].

Ocular surface squamous neoplasia (OSSN) has an estimated incidence in the United States of 0.03 per 100000 persons. Higher incidences have been reported in other parts of the world with more sun exposure [1]. Usually the patient presents with foreign body sensation, irritation, redness or a growth on the ocular surface. More than 95% of these lesions occur in the limbal region, a mitotically active region.

The classic treatment consists in surgical excision alone or in combination with cryotherapy or medical therapy. With surgical excision alone, the rate of recurrence is high (5% to 33% with negative margins and up to 56% with positive surgical margins) [2]. The "no touch" technique is the preferred technique leaving wide margins of 4-6 mm. Rose Bengal staining or UHR-OCT can be used to delineate the margins. Cryotherapy works initially by its thermal effect and by obliteration of microcirculation with a recurrence at about 12%; side effects include iritis, abnormal intraocular pressure, sector iris atrophy, hyphema, ablation of peripheral retina, corneal neovascularization, and limbal stem cell deficiency [3].

The current option is to use topical chemotherapy due to high recurrence rate of OSSN. Mitomycin-C, 5-fluorouracil and interferon α2b are useful in the treatment of OSSN. A potential advantage of medical therapy is the ability to treat the entire ocular surface and this way the microscopy and subclinical disease is also treated.

Interferon α2b is part of a family of proteins, which are secreted by leukocytes, and they have antiviral and antineoplasic properties. It has been used in the treatment of OSSN with success rates of above 80%. It can be used as topical eye drops or a subconjunctival injection. Interferon drops are very gentle and well tolerated; common reported side effects include mild conjunctival hyperemia and follicular conjunctivitis. Topical INF α2b (1 million IU/mL) is dosed four times daily and given continuously until the tumor resolvers (an average of 3 months).

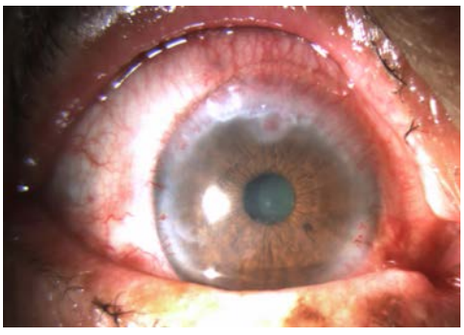
Usually mild side effects are reported with topical INF α2b such as pain, irritation, itching, redness and flu-like symptoms. But we have to be careful and have a close follow up of our patients because large desepithelizations can occur.

★ CASE PRESENTATION ★

A 81-year old female presented to our hospital with red eye and secretion on her right eye of 2 months of evolution.

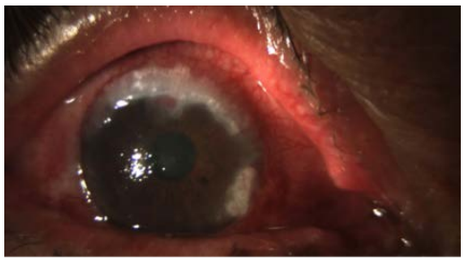
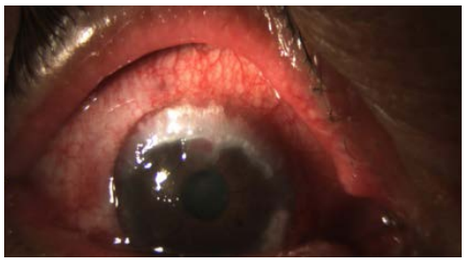
Medical history revealed age related macular degeneration and secondary geographic macular atrophy OU that was treated with oral antioxidants. Her systemic evaluation was not notable, and her family history was not significant.

On ocular examination her visual acuities were hand motion at 30 cm OU. Intraocular pressure was 14 mmHg OD and 13 mmHg OS. Slit lamp examination showed an elevated, gelatinous, irregular-surface mass with well defined borders on the superior limbus from M10 to M3, with hyperemia and diffuse superficial punctate keratitis in her right eye, she also had neovascularization 360° in the limbus. Her left eye showed normal examination in the anterior segment. She had a disciform macular scar with multiple drusen in macula and peripheral retina OU.

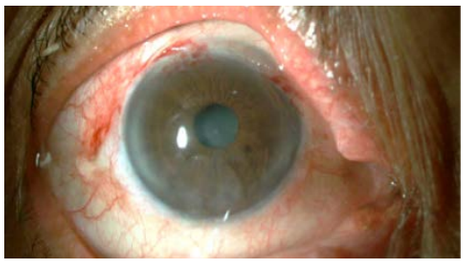
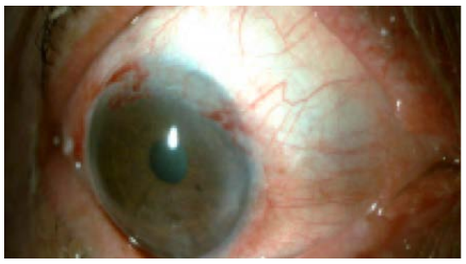


So with the clinical data shown above the diagnosis of corneal intraepithelial neoplasia was done. And we decided to begin topical chemotherapy with interferon α2b (1 million IU/ml) four times a day for a month and we scheduled next follow up a month later to evaluate the size and the response of the lesion.

A month later, the patient refers conjunctival hyperemia and irritation as side effect of the interferon α2b. Clinical examination revealed cilliary injection 360°, in the inferior limbus there is evidence of clinical healing of the lesion, no neovascularization was seen in the inferior area. Nevertheless worsening of the superior and nasal area is evident with desepithelization and corneal thinning/ melting, it seemed that the lesion was bigger; at this moment corneal interferon α2b toxicity was suspected.

With this important toxicity we decided to stop interferon α2b, and surgical excision with cryotherapy was done, with a lower risk of stem cell deficiency because the inferior and temporal area did not show disease anymore.

One month postoperative follow up there was no clinical evidence of conjunctival-corneal epithelium neoplasia, and the pathology report confirmed the clinical diagnosis and reported negative margins.

★ DISCUSSION ★

As noted previously ocular surface neoplasia encompasses a range of different epithelial squamous malignancies, from dysplasia to invasive carcinoma. And in countries with a lot of ultraviolet light exposure is very common. Traditional treatment for OSSN is excision with "no touch technique". But with clear margins as in our patient the recurrences are up to 33%. [3] However, tumor excision has risks as limbal stem cell deficiency and symblepharon formation, therefore medical treatment alone has become really popular. In particular, topical INF α2b has gained appeal for OSSN treatment because of its minimal toxicity, but it does have side effects as noted in our case. [4]

When comparing both treatments (surgical excision and topical INF α2b) there is no statically significant difference between both treatments in number of recurrences. And usually the side effects where similar with discomfort, pain, irritation, itching, redness and flu-like symptoms. Corneal epithelial defects rarely develop during treatment. It also is described a paradoxical response with the use of interferon α2b in an HIV positive patient. [5]

It is known that from the topical chemotherapies the safest one is interferon α2b, nevertheless we should have a close follow up for our patients that are treated with topical therapies to be aware of the possible side effects, so it is recommended to see the patient a week or two after starting the topical interferon α2b, knowing that we will not find a clinical response yet, but we should look for possible side effects, and then it is recommended to check the patient a month later, and depending on the response to the therapy continue or change the management. Following these recommendations we were able to detect rare side effects in our patient and we offered him a better option for her in that moment. When we started with topical interferon we had a big lesion that reduced it size with the topical treatment, and that make us possible to do a surgical resection without have a big risk of stem cell deficiency.

★ CONCLUSION ★

OSSN is a common pathology in some endemic countries with a great solar exposure, when diagnosed it is important to decide which treatment is better for the patient on an individual basis, depending on the age of the patient, the immunologic status, the size of the lesion. And both surgical and medical treatment offers different benefits and risks. When the topical interferon α2b is chosen even knowing its safety, patients should have a close follow up to detect and treat aggressive side effects as corneal thinning and desepithelization.

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TREATMENT OF OCULAR MANIFESTATIONS IN CHRONIC ALLERGIC CONJUNCTIVITIS: IS TOPICAL APPLICATION OF TACROLIMUS AN OPTION?

★ INTRODUCTION ★

Allergic conjunctivitis affects 20% of the general population and are classified as acute allergic conjunctivitis (seasonal and perennial) and chronic allergic conjunctivitis (vernal keratoconjunctivitis and atopic keratoconjunctivitis) [1].

There are insufficient data to objectively evaluate the incidence of chronic allergic conjunctivitis. It is commonly accepted that atopy affects 5% to 20% of general population. The prevalence of atopic dermatitis (AD) in children is as high as 20%, where as atopic keratoconjunctivitis (AKC) occurs in 20% to 40% of individuals with AD [2,3]. On the other hand, vernal keratoconjunctivitis (VKC) is a relative rare ocular allergic disease affecting children and young adults living in warm climates associated in approximately half of cases with other allergic manifestation, the disease is usually seasonal, lasting from the beginning of spring until autumn. However, perennial cases that are persistent throughout the year are not rare, especially in patients living in subtropical or desert climates. The prevalence of VKC in Europe ranges from 1,2 to 10,6 cases per 10.000 population [4].

The symptoms of chronic allergic conjunctivitis (CAC) are much more severe than in seasonal or perennial allergic conjunctivitis. AKC commonly involves the lower eyelid tarsal conjunctiva and when it involves the cornea

it can evolve from punctate epithelial erosions, corneal scars, shield ulcers, Horner – Tantras spots, subepithelial vascularization to keratoconus causing decreased of visual acuity in 6% of patients and even blindness [1,5]. In addition to the cutaneous manifestations of AD, the periorbital skin and cheeks are commonly involved in AKC with eczematoid changes including erythema and thick and dry scales, Dennie-Morgan lines involving the skin of the eyelid result in a single or double infraorbital crease secondary to edema or thickening [6].

The most characteristic sign of VKC is giant papillae on the upper tarsal conjuntiva. These "cobblestone-like" swelling may be several millimeters in diameter. Usually 10 - 20 are found on the tarsal conjunctiva and they can be seen easily by "flipping" the upper lead [3]. On both diseases these symptoms are accompanied by intense itching, pathognomonic sign of allergic conjunctivitis, tearing, photophobia, and thick mucus secretion.

Most cases of allergic conjunctivitis can be controlled with artificial tears, avoiding potential triggers of disease and mast cell stabilizers membrane drugs [7], but in the case of CAC it is difficult to keep patients only with this treatment, thereby it requires adding topical corticosteroids. Prolonged use of topical corticosteroids increases iatrogenic risk of cataracts, glaucoma, infections and delayed corneal repair, hence the importance of finding alternative treatments with greater anti-inflammatory effect which can significantly reduce the use of steroids and improve clinical status. [8-11]. In this context, tacrolimus is emerging as a new alternative in addition to the above described therapeutic regimens. Its effect on the calcineurin - T cell pathway interferes with the pathologic chronification of the CAC [12-15]. Tacrolimus is a macrolide derived from Streptomyces tsukubaensis [16,17] initially used to prevent solid organ transplantation rejection. In the ophthalmologic field it has been used as an alternative drug in refractive diseases to conventional treatment such as chronic conjunctivitis scar, necrotizing scleritis, nodular scleritis and Mooren's ulcer and in preventing rejection of corneal and limbal transplantation due to their high immunosuppressive power [12-18].

★ CASE PRESENTATION ★

Case 1

March, 2015

Chief complaint: Bilateral intense itching and purulent discharge for months

History of present Illness: The patient is a nine year old male patient was admitted to the hospital after several months of bilateral ocular intense itching, redness, tearing, photophobia, and purulent discharge. It was the first time that he went under an ophthalmologic evaluation. The previous episodes were treated with antihistamines drops and short term topical corticosteroid by his pediatrician.

Medical history: Asthma and severe atopic dermatitis

Medication: His atopic dermatitis was treated with omalizumab

Ocular examination: Intense photofobia noted during the exam.

- Neurological status: alert and oriented x 3, non-focal.

- Best Corrected Visual Acuity both eyes (OU): 20/40.

- Extraocular motility: Full OU.

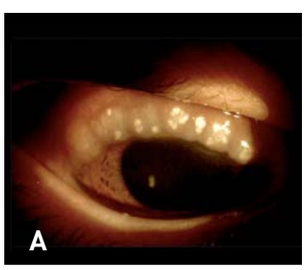
- Pupils: Normal with no afferent pupillary defect.

- Confrontation visual field: Full OU.

- IOP OU: 12.00 mmHg

- Slit lamp examination OU: pseudoptosis, Dennie-Morgan lines, blepharoconjunctivitis, madarosis, purulent discharge on the conjunctival sulcus, hyperemia of palpebral and bulbar conjunctiva, follicular reaction, papillary lesions on the tarsal conjunctiva, gelatinous infiltrates of the upper limbus, Horner Trantas spots at the upper limb and superficial punctate keratopathy.

The severity of the disease and the effectiveness of the treatment were evaluated using the 5-5-5 exacerbation grading scale presented by Shoji J, et al [19].



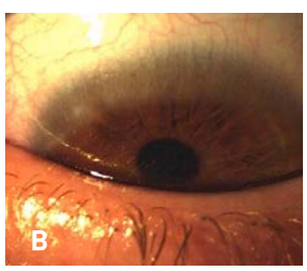


Figure 1 – OD: (a) Broad, gelatinous, thickened, opacified, mucoid nodular infiltrates. Horner - Trantas spots (punctiform calcified concretions) are at the apices of the nodules. (b) Cornea after treatment.

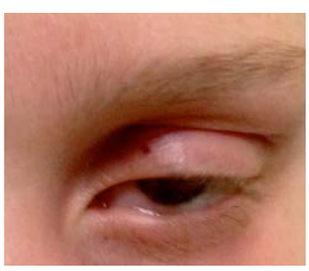


Figure 2 – OS: Pseudoptosis, Dennie-Morgan lines

Course: The patient´s course and presentation is classic for atopic keratoconjunctivitis. The day of presentation, the patient was started with topical azitromicin twice a day during three days for the associated bacterial conjunctivitis. After the initial antibiotic treatment we decide to start with topical tacrolimus ointment 0,02% twice a day during three months as a compassionate drug use. An informed consent was signed by his parents.
Three days after antibiotic treatment, no purulent discharge was observed. Twenty days after the initial treatment with tacrolimus ointment we observed reduction of the pseudoptosis, mild redness and no photophobia. One month after the initial treatment neither blepharoconjunctivitis, follicular reaction, papillary lesions on the tarsal conjunctiva, Horner-Trantas nodules or punctate epithelial erosions where observed. The BCVA was 1 on both eyes. Every three months we reduce at half the previous dose. No elevation of IOP was noted. The patient referred a burning sensation which last 2 weeks.
The initial score at the 5-5-5 exacerbation grading scale was 114 points on the right eye and 123 points on the left eye. Six months after treatment there is no ocular manifestation of atopic keratoconjunctivitis.

Case 2

August, 2014

Chief complaint: Recurrent corneal erosion in the left eye.

History of present Illness: An eighth year old male patient referred by his pediatrician. The patient complained of 2 year history of persistent "soreness" on his left eye and excessive tearing, itching, blepharospasm and photophobia. He had these complaints intermittently, along with mucous discharge during many years. He has been prescribed by his pediatrician with eye drops, ointments and oral medications with no success. These particular episode was severe and unremitting.

Medical history: The patient´s past medical history was significant for exercise induce asthma.

Medication: At presentation it included topical combination of tobramycin/dexamethasone four times a day and erythromycin ointment three times a day for his left eye. No systemic medication was reported.

Ocular examination: Moderate pain and photofobia noted during the exam on his left eye.

- Neurological status: alert and oriented x 3, non-focal.
- Best Corrected Visual Acuity both eyes (OU): 20/20.
- Extraocular motility: Full OU.
- Pupils: Normal with no afferent pupillary defect.
- Confrontation visual field: Full OU.
- IOP 11.00 mmHg.
- Slit lamp examination
- OD: Normal

- OS: Normal eyelid skin, mucous discharge on the conjunctival sulcus, hyperemia of palpebral and bulbar conjunctiva, follicular reaction, giant papillae in the superior tarsal conjunctiva, superior shield ulcer and superficial punctate keratopathy on central cornea. There was a corneal opacification at 2 o´clock.

The severity of the disease and the effectiveness of the treatment were evaluated using the 5-5-5 exacerbation grading scale.

Course: The symptoms of itching, photophobia and tearing and findings of giant papillae on eversion of the superior lids and a shield ulcer were consistent with the diagnosis of vernal keratoconjunctivitis. At the patient´s initial visit we decided to start with topical tacrolimus ointment 0,02% twice a day during three months as a compassionate drug use. An informed consent was signed by his parents.

Two months after the initial treatment with tacrolimus ointment 0,02%, the shield ulcer disappeared along with the allergic symptoms. Under fourth months of treatment, the giant papillae dramatically resolved completely along with all of the corneal and superior tarsal conjunctiva lesions. The initial score at the 5-5-5 exacerbation grading scale was 123 points on the left eye. The patient had since tapered and maintained twice a week the tacrolimus ointment. There is no evidence of recurrence. The actual score at the 5-5-5 exacerbation grading scale is 0. No elevation of te IOP was noted. Te patient referred a burning sensation which last 2 weeks.

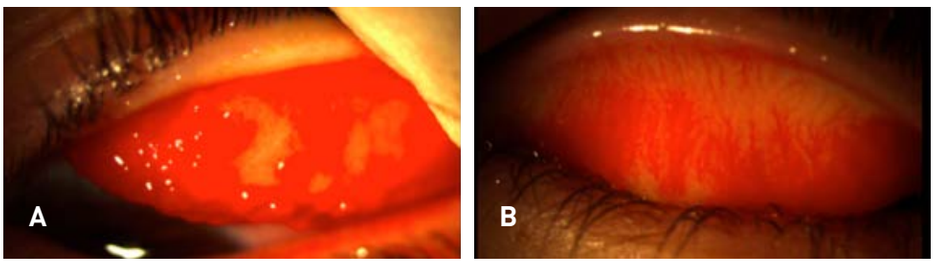


Figure 3 – OS: (a) Giant papillae before topical treatment with tacrolimus ointment 0,02%. (b) Superior tarsal conjunctiva four months after treatment.

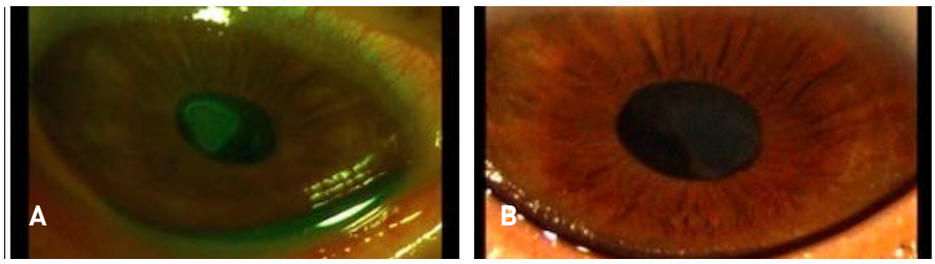


Figure 4 – OS: (a) Shield ulcer before topical treatment with tacrolimus ointment 0,02%.(b) Cornea after treatment.

★ DISCUSSION ★

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are classified as chronic allergic conjunctivitis (CAC) [2]. In spite of common clinical and immunological features shared with acute allergic conjunctivitis, CAC differs from them for age of onset, clinical findings, low percentage of patients with positive response to standard allergic diagnostic tests and scarce response to traditional treatments [20].

Historically, AKC is rarely recognized as a diagnostic entity before puberty and is thought to occur predominantly in adults. If a young patient were to present with AKC-like symptoms and atopic dermatitis, they might be diagnosed as VKC [21]. Brémond D, et al published a recent report where AKC in children is defined as the presence of severe allergic conjunctivitis with atopic dermatitis that is diagnosed before 16 years of age. This may be accompanied by the presence or absence of the following clinical features: conjuntival hyperemia with eczema, madarosis and blepharitis, with absence of Horner - Trantas spots and giant papillae [22].

The multifactorial assessment of key clinical signs presented with a history of eczema and conjunctivitis/keratitis, may promote accurate diagnosis of AKC in children. In a epidemiological study of 134 patients with allergic conjunctivitis, 55% of patients with AKC reported an onset of symptoms before 10 year of age [23]. In Japanese population, VKC cases with any history of atopic dermatitis is diagnosed as AKC, regardless of patient age [21]. In Europe, this cases would only be diagnosed as AKC if the symptoms continued past puberty and occurred concurrently with keratoconjunctivitis, this shows that there is a lack of standardized diagnostic criteria a lack of common language between physicians. Probably because AKC and VKC are different manifestations of the same disease sharing the same physiopathological pathway.

On case 1, it would be incorrect to diagnose the patient as a VKC just because of the presence of Horner - Trantas spots in the context of clear manifest signs and symptoms of atopic dermatitis based on Brémond D recommendation. On case 2 it is accurate to establish the VKC diagnose because giant papillae and a shield ulcer are present just in one eye. The only manifestation of atopy was exercise induce asthma.

The exact pathogenic mechanisms of CAC are not fully elucidated. The immunopathogenesis are based on type I and IV hypersensitivity reactions and both entities share the same cellular lines based on histological findings in conjunctiva of patients with AKC and VKC. The cells implicated in the process are monocytes, fibroblast, mast cells, eosinophils, basophils and T cells [7,23]. Probably the difference between them is the "trigger" necessary to activate the different pathways.

We conducted a systematic review to find a clinical grading scale to evaluate the manifestations and severity of CAC and the effect of medical treatment. Shoji Jm et al, presented a useful scoring system based on its simplicity of the grading method judging the presence or absence of the clinical signs and the low inter-observer variability, The observations found were classified following 3 graded groups of clinical observations: the 100-point-grade group (100 points for each observation) includes active giant papillae, gelatinous infiltrates of the limbus, exfoliative epithelial keratopathy, shield ulcer and papillary proliferation at lower palpebral conjunctiva; the 10-point-grade group (10 points for each observation) includes blepharitis, papillary proliferation with velvety appearance, Horner-Trantas spots, edema of bulbar conjunctiva, and superficial punctate keratopathy; and the 1-point-grade group (1 point for each observation) includes papillae at upper palpebral conjunctiva, follicular lesion at lower palpebral conjunctiva, hyperemia of palpebral conjunctiva, hyperemia of bulbal conjunctiva, and lacrimal effusion. The total points in each grade group were determined as the severity score of the 5-5–5 exacerbation grading scale. Therefore, using this exacerbation grading scale, the accumulation of severity scores could be found in severe cases. It is obvious that as the condition of the patient improves the severity score decreases [19].

Treatment of CAC is aimed at controlling symptoms, decreasing recurrence and exacerbations, and reducing vision loss. Although it is important to control the manifestations, its is equally important to minimize treatment side effects. It is generally accepted that CAC requieres high doses of steroids or systemic immune suppressants, but they can cause drug renal dysfunction, hyperglycemia, osteoporosis and cataracts. In addition, intense topical steroid treatment frequently causes an elevation of intraocular pressure in 2% of CAC [24]. In this context tacrolimus, a potent immunosuppressive macrolide, merge as a therapeutic option. The mechanism of action is mainly as a competitive blocker of calcineurin which is required for the activation of T cells for induction of inflammatory cytokine arrays, this is similar to its predecessor cyclosporine, however the potency of tacrolimus is 30 times greater than cyclosporine in terms of its inhibitory effects on calcineurin phosphatase activity with a lower burning sensation in the eye which was the main complain of the cyclosporine users [25]. The immune suppressive effects of tacrolimus are not limited to T-lymphocytes, it also acts on B-cells and mast cells.

In our case, tacrolimus was prescribed as a compassionate use and the formulation was developed on our hospital with a concentration of 0,02% [26] because the permeability through the non - keratinized corneal tissue exceeded the transdermal absorption rate [27, 28]. On previous publications the usual concentration is 0,03%, based of the dermatological drug presentation, PROTOPIC®, however it includes propylene carbonate, as an excipient, which can cause intense itching and irritation of the conjuntiva. [29].

The beneficial effects of topical tacrolimus appear relatively well sustained, it is specially efficacious for the treatment of ocular surface inflammatory diseases where calcineurin pathways are involved, when signs and symptoms were completely resolved, we switched to intermittent use which appeared to be effective in blocking relapses. These observations are similar to those reportes by patients for control of dermatitis lesions of atopy [30]. Side effects of topical tacrolimus been reported in the dermatological literature to be transient burning sensation and recurrent herpetic lesions [31]. Our cases also reported a burning sensation in the treated eyes which disappeared after 2 to 4 weeks of continued use. No skin thinning or atrophy was associated, neither herpetic keratitis.

★ CONCLUSIONS ★

We describe 2 patients with chronic allergic conjunctivitis that were treated with topical tacrolimus ointment 0,02% and it was especially efficacious on controlling the chronic manifestations of the diseases. In our cases on their follow-up visits, they remained asymptomatic, with no corneal or conjunctival manifestations. The treatment was well tolerated for long periods without serious adverse effects or elevation of IOP.

Tacrolimus has a rapid onset of action and sustained therapeutic effect. Is a safe and effective alternative therapy for pediatric patients affected with pathologies that involves the T cells pathway when is necessary to establish a chronic non steroidal treatment.

However additional studies are necessary to determinate the optimal dose and therapeutic regimen of tacrolimus in CAC cases.

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CONGENITAL CYSTIC EYE : A CASE REPORT

★ INTRODUCTION ★

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Congenital cystic eye is a rare ocular malformation with fewer tan 40 cases reported. The condition derived by a partial or complete failure in the invagination of the primary optic vesicle in which neuroectodermal elements are not able to develop into the future eye structures. The primary optic vesicle is formed but instead of the anterior part of the vesicle invaginating to lie in apposition with the posterior part, a cyst persists at birth and replaces the eye [1]. The size of the cyst is variable. The failure in invagination of the primary optic vesicle occurs between the 2mm and 7 mm stage of fetal development. The exact etiology of congenital cystic eye remains unknown [31].

Early accounts of the condition were described by Taylor and Collins [2], and Mann [3]. Most reports have been based on experience with one case, attesting to the rarity of this condition [4]. Association of congenital cystic eye with intracranial anomalies is not well recognized and thorough analysis looking for a globe is needed to differentiate from anophthalmos with cyst and microphthalmos with cyst. [1] In this study in addition to the review of congenital cystic eye, we report the clinical, imaging and histopathologic findings, as well as treatment of one case of congenital cystic eye in which structures of the eye are formed, including the cornea , making of this a cyst.

★ CASE PRESENTATION ★

An 11 daγs old male is seen, product of a 4th gestation, normoevolutive pregnancγ, obtained bγ cesarean section due to breech presentation, in stable condition at birth. No relevat familγ historγ to current condition. He is brought bγ his parents because theγ have noticed a mass in his right eγe and ansence pf a palbebral aperture.

Ophthalmic phγsical exam, right eγe visual acuitγ non assessable due presence of a corneal mass wich appears to adhere to the superior eγelid an does not allow for a palbebral aperture, left eγe rejevts light . Apparent proptosis in right eγe, ipsilateral superior eγelid with purplish coloration (Fig.1.0) transillumination positive. (Fig.1.1)

Figure 1.0

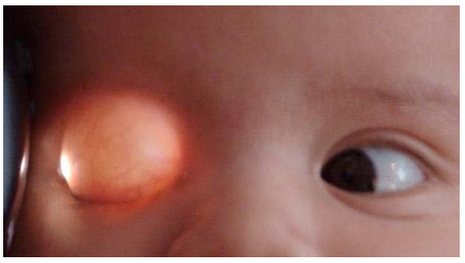

Figure 1.1

Exploration of the anterior segment of the right eγe with evidence of opalescent cornea, vascularization inferior with small calibre vessels wich don't allow for further assessment of the anterior segment due to the aforementiomed opacitγ. (Fig. 1.3)

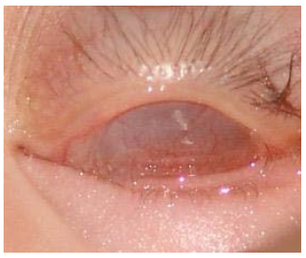

Figure 1.3

An AB mode ultrasound (Fig. 2.0) was performed in both eγes as a diagnostic approach,wich showed a corneal cγst in the right eγe and microphthalmos and aphakia, the left eγe has no apparent structural alterations.

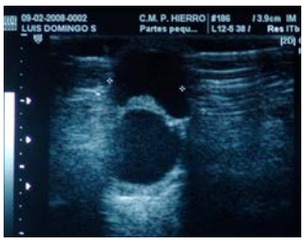

Figure 2.0

Simple tomography of the orbit corroborated a cyst mass, microphthalmos, and absence of the lens. (Fig.2.1)

One month later, marsupialization of the corneal cyst is performed and histological specimen is sent to pathology, wich confirms a congenital cyst as the result .

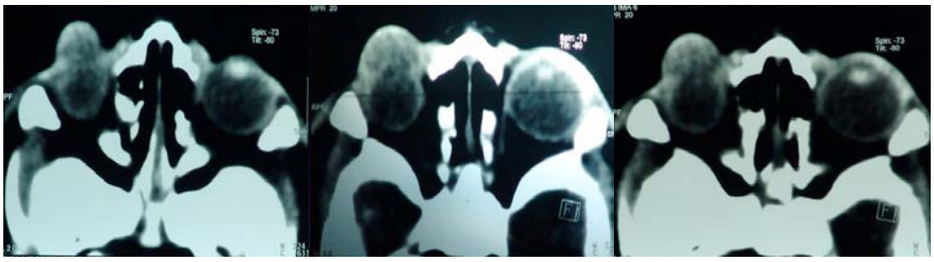

Figure 2.1

★ DISCUSSION ★

The term congenital cystic eye was first used by Mann [3] to describe a rare ocular malformation caused by an arrest in the invagination of the primary optic vesicle between the 2-mm and 7-mm stages of fetal development. It is believed that around the third week, when the embryo is 3.2 mm long, the anterior brain sends out two symmetrical diverticula, which are the primitive optic vesicles [5]. At four weeks, when the embryo has reached a length of 4.5 mm, the primary optic vesicle begins to invaginate in order to transform itself into a secondary optic vesicle or optic cup [6]. Congenital cystic eye results due to an arrest in the invagination of the primary optic vesicle during this time period.

Cystic orbital lesions account for approximately 10 -30% of all nonthyroid orbital lesions. Congenital cystic eye is the rarest cystic orbital lesión [24]. There is no gender preponderance.

Shields and Shields [28] recently classified congenital cystic eye under neural cysts, the other associated with ocular mal-development being microphthalmos with colobomatous cyst and those associated with brain and meningeal tissue, cephalocele and optic nerve meningocele, respectively.

The exact etiology in the formation of cystic eye at the molecular level remains unknown, the frequent presence of inflammatory cells in the cyst suggests an inflammatory cause [7]. It is a unilateral, non-hereditary disorder of unknown etiology. However two cases of bilateral congenital cystic eyes have been reported [10,22]. Although the fellow eye in cases of unilateral cystic is usually normal, a case of micropthalmia wyth cyst and persistent hyperplastic primary vitreous each have been reported in the literature [13,21]. In some cases were reported multiple cysts.[19].

Most cases seem to be unassociated with an obvious prenatal insult [5, 18, 28]. A coincidence of maternal varicella infection and congenital cystic eye is described and the possibility of a causal relationship speculated (13). Chromosomal studies performed in several cases have not yielded any abnormalities (13, 17, 21, 22, 24). Genetic investigations in one patient revealed a gross defect of a chromosome 13 (13q) deletion syndrome, so-called Orbeli syndrome (18).

Congenital cystic eye is evident at birth in most cases, however the cystic character of the lesion may not be evident at birth. The size of the cyst may vary from 18 · 10 · 5 mm (22), to 50 · 45 · 45 mm (21). The progressive enlargement of the cyst may be due to fluid produced by glial tissue as in the cystic part of microphthalmos with cyst. The fluid can be proteinaceous, serosanguineous, or dark and viscous (4, 24). In one study the biochemical analysis of the fluid taken from the cyst was similar to that of serum (17).

Congenital cystic eye may occur in isolation or with other ocular and non-ocular malformations (24). Nonocular abnormalities are more frequent when there is bilateral involvement (24), and this association has recently been reported in cases of bilateral microphthalmos with orbital cysts (30). Associated eyelid abnormalities include accessory limb (8), skin tags (9), notch and periocular dermal appendages (12, 21) on the same side as the congenital cystic eye and a colobomatous eyelid defect on the opposite side (21). Reported non-ocular abnormalities include facial clefting, cleft lip and palate and saddle nose (8, 10, 13, 21, 22), malformation of the nostril (9), choanal atresia (22), multiple punched-out lesions of the scalp and face (21), electroencephalographic abnormal signs in the region of the Rolandic area (9), microphallus with hydrocele, hypoconvex fingernails on short stubby fingers (13), and bifid thumb (5). Only a handful of reports describe intracranial abnormalities associated with congenital cystic eye (10, 13, 17, 21, 22). This may be related to the fact that most reports of congenital cystic eye predate the era of sophisticated neuro-imaging, and the paucity of well-documented cases. Associated intracranial anomalies include malformation of the sphenoid bone (21), agenesis of the corpus callosum (13, 19, 21), basal encephalocele (22), microcephaly and midbrain deformities (13, 17, 19, 21, 22, 24). Sacks and Linderberg (10) studied the central visual pathways of a patient who had bilateral congenital cystic eyeballs. In their patient the intracranial portion of one optic nerve was tubular, representing a remnant of the optic stalk; no chiasm was found. Since the ocular anomalies precluded the formation of the retina in their patient, all fibers found in the anterior pathways were efferent, accounting for 5–10% of the normal complement of nerve fibers derived from the anterior hypothalamus. They found that lateral geniculate bodies consisted of disorganized groups of normal neurons forming normal radiations while the calcarine cortex was normal. Patients with bilateral anophthalmos represent a distinct group from those with unilateral anophthalmos.

It is thought that, if the arrest of the invagination of the primary optic vesicle occurs at an early stage of development, the lesion may be a simple cyst with no recognized ocular structures (8, 13). However, if the insult occurs later in development, partial invagination of the optic vesicle may result in surface ectodermal elements, such as lens and cornea. The presence of retinal differentiation, such as rosette formation, multiple cellular layers, and limiting membrane has been noted previously as well (9, 11, 12, 19, 21, 22). In addition,

the presence of retinal pigment epithelium [12, 20], rudimentary iris [11],ciliary processes [10], and primitive choroids [9] have also been reported. Absence of optic nerve has been observed in most of the previously reported cases of congenital cystic eyes [10, 13, 24] however, Baghdassarian et al. [11], observed an optic-nerve-like structure that was continuous with neuroglial tissue in the posterior aspect of a cyst.

Differential diagnosis for cystic anomalies in the orbit include microphthalmos with cyst, heterotropic brain tissue and meningoencephalocele [27, 28]. In meningoencephalocele, the orbit may be involved secondarily, presenting with a cystic structure in the superomedial canthal area and proptosis soon after birth. This lesion is caused by a defect of the cranio-orbital bones and may occur in neurofibromatosis due to a sphenoid bone hypoplasia. Cystic eye should be differentiated from microphthalmos with cyst. In microphthalmos with cyst, a small eye is present with a visible or palpable mass behind the lower eyelid. Microphthalmos with cyst is one of the colobomatous anomalies of ocular development that arise from failed closure of the fetal fissure, corresponding to the 7-mm to 14-mm stage of embryonic development, and is more commonly reported than congenital cystic eye [30]. Congenital microphthalmos with cyst develops from incomplete closure of the fetal cleft, which results in a cyst attached to the sclera. Congenital cystic eye is histopathologically similar to the cystic portion of microphthalmos with cyst[31]. There are a few differentiating features between congenital cystic eye and the microphthalmos globe with orbital cyst. In most congenital cystic eyes, the cyst is centrally placed in the orbit or may bulge more toward the upper eyelid. In microphthalmos with cyst, the cyst bulges the lower eyelid because the cyst is attached to the inferior portion of the globe. There are exceptions in which bulging of the lower eyelid occurs with congenital cystic eye [22, 24]. In microphthalmos with cyst, there is evidence of ocular development with a small globe with cornea, iris, ciliary body, lens, vitreous cavity, retina and choroids [24]. The lack of surface ectodermal elements in congenital cystic eye is a common feature except in a few cases [11, 12, 22].

Imaging studies such as U/S, CT scan and MRI may help in establishing the diagnosis. Imaging features are scantily described. The few reports on imaging features of congenital cystic eye describe the appearances on CT. The usual finding is an intraorbital cystic mass which may be unilocular or multilocular. The mass may have an enhancing soft tissue component depending on the amount of glial proliferation. A thin optic nerve stalk may be found. Extraocular muscles are usually absent or hypoplastic. A globe is not identified. MRI findings of congenital cystic eye have not been described [33]. A cavity lined by neuroglial tissue is the characteristic histopathologic finding [32].

Surgical excision of the cystic eye is indicated in most cases. It is recommended that every effort should be made to excise the entire congenital cystic eye when surgical removal is undertaken.

★ CONCLUSION ★

Congenital cystic eye is usually evident at birth and has a varied presentation. Our case is one of the few cases reported where there ocular estructures including cornea. A high degree of suspicion and knowledge about the varies presentations of this condition, and coordinated efforts by Ophthalmologist and pediatricians are needed for its early recognition and appropriate treatment. It should be suspected in patients with an unrecognizable eye globe. Although no protocol exists regarding the proper management of this rare congenital condition, in most instances surgical intervention is indicated to achieve optimal cosmesis.

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A NOVEL SURGICAL TECHNIQUE FOR THE MANAGEMENT OF SEVERE HERPETIC CORNEAL SCARRING WITH CONCURRENT CATARACT

★ INTRODUCTION ★

Herpes simplex virus is one of the most common viruses acquired by humans[1]. Infection in early childhood with herpes simplex virus 1 (HSV1) is common with most people remaining latently infected throughout life. At least 90% of the world's population is latent for HSV1 infection[2].

Reactivation of latent virus occurs in about 13.2/100000 people per year[3]. Mean age of onset is in the late 30s and is a predominantly unilateral disorder[4]. The virus initially presents as a blepharitis or epithelial keratitis. Recurrent episodes are predominantly stromal keratitis. Recurrences cause visual morbidity from irreversible corneal scarring, thinning, neovascularisation and eventually blindness[2]. This is the leading cause of infectious corneal blindness in industrialised nations[1].

At this stage corneal grafting surgery is usually indicated. The mean age for penetrating keratoplasty was shown to be 55.5 years in a study and patients required an average of 23 outpatient visits in the 2 years following surgery[5]. As this predominantly involves people of working age, there is a significant financial cost to economies with lost working days.

We present a case of a patient with long term bilateral HSV1 keratitis. Her unique social circumstances were such that a novel approach was necessary in order to reduce surgical visual rehabilitation time compared with conventional corneal grafting options.

★ CASE PRESENTATION ★

A 54 year old caucasian female with bilateral herpes simplex keratitis (HSK), commencing in her adolescent years, presented to the corneal service. She had seen her optometrist for an update of her glasses after noticing that her vision had become blurred. Her optometrist advised her that she was no longer legal to drive after an updated refraction.

Best corrected visual acuity (BCVA) in clinic was noted to be Snellen 6/18 in both eyes. Both corneas showed marked corneal stromal scarring and thinning with mild corneal neovascularisation. The ocular surface did not show signs of dry eye. Bilateral mild nuclear sclerotic and posterior subcapsular cataracts were noted. Fundal examination did not reveal any abnormalities, although the view was slightly limited due to the lens opacities. The patient reported that she had not had an episode of HSK in either eye for the last few years.

Surgical management options

The risks and benefits of either penetrating keratoplasty (PKP) combined with cataract surgery or deep anterior lamellar keratoplasty (DALK) combined with cataract surgery were discussed, in particular the timeframe for visual rehabilitation. This was not suitable for the patient as she was the sole carer for her husband who had medical problems and usually drove him to hospital for his medical appointments.

A second option of solely removing the cataract was discussed with the risks of HSK recurrence, refractive surprise due to an irregular cornea and biometry inaccuracy, the requirement for potential intraocular lens (IOL) exchange and alteration of the irregular astigmatism with the phacoemulsification corneal incision. There would also still remain the corneal scarring that would potentially have to be addressed at some point in the future. This again did not appeal to the patient.

Taking into account the social circumstances, a further option was considered in the form of automated anterior lamellar keratoplasty (AALK). This would satisfy the requirement for shortened rehabilitation and would also address some of the subsequent issues with biometry calculation for IOL implantation alongside cataract surgery.

The thickness of the trephine for both donor and host was evaluated and a value of 250um was ultimately decided. In view of the thinnest point on the host cornea being 223um (figure 1), a further step was formulated, otherwise the cornea would be penetrated during host trephination. This was in the form of hydration of the area of localised thinning.

Surgical technique

A donor cornea was set up on a Gebauer artificial anterior chamber. The epithelium was debrided and ultrasound pachymetry revealed a thickness of 625um. The cornea was marked on the anterior surface to help identify orientation and a 250um trephination was applied. The donor corneal trephine was maintained in physiological saline.

The patient was operated under local anaesthesia. Routine preoperative sterilisation of the ocular surface was carried out. The right eye cornea was measured and marked. Stromal hydration of the 223um and surrounding region was carried out utilising physiological saline in a 1ml syringe with a 27G needle (figure 2). Five minutes were allowed for the saline to disperse within the stroma. The host cornea was trephined (Gebauer) using a 250um blade. After removal of the trephined lenticule, it was noted that the cornea had not been penetrated and that the remaining tissue bed appeared relatively regular. The lenticule was sent for histopathological processing.

The donor cornea was placed on the remaining host bed to assess fit. Trephination of the donor cornea diameter to 8mm was required for a precise fit. Two onlay sutures with 10/0 nylon were applied to stabilise the donor cornea (figure 3). Interface debris were gently flushed using preservative free chloramphenicol in saline loaded into a 1ml syringe with a Rycroft cannula. A subconjunctival injection of cefuroxime (20mg)/betnesol (4mg) was administered into the lower fornix. A 16mm bandage contact lens was placed on the eye. (A video of the procedure is available)

Postoperative medication was as follows; guttae chloramphenicol 0.5% preservative free qid, guttae dexamethasone 0.1% preservative free qid and PO acyclovir 400mg 5 times daily.

Postoperative course

Postoperative review at 1 week showed satisfactory positioning of the graft and the onlay sutures were removed. At 6 weeks postoperatively, the graft was clear, BCVA was 6/12 and the patient had already noticed an improvement in the overall quality of her vision.

The topical drops were subsequently tailed off over 8 weeks, however, the oral acyclovir was maintained at a dose of 400mg bd. Histopathological processing of the host trephined lenticule revealed a regular cut with no involvement of Descemets membrane (figure 4). A refraction carried out at 6 months postoperatively was +4.25/-4.75 x 30, 6/9.

Cataract surgery

Corneal topography subsequently showed regular astigmatism of 3.3D (figure 5) with a thinnest point in the cornea of 252 microns. Biometric calculations (IOL master 500) were carried out with a view to cataract surgery. The patient underwent routine right phacoemulsification with a toric intraocular lens implant (Superior 2.7mm incision at 100 degrees, Rayner monofocal toric IOL, 23.5D with 4D astigmatic power) at 8 months post AALK graft. The postoperative topical drug regime was guttae chloramphenicol 0.5% preservative free qds, guttae dexamethasone 0.1% preservative free 6 times daily and PO acyclovir 400mg bd daily.

One day post cataract surgery, there was marked corneal oedema and vision was 6/60. At 2 weeks post cataract surgery, the oedema settled and vision improved to 6/18 unaided, 6/9 with pinhole. The topical drops are currently being tailed off over 4 weeks and the oral acyclovir is being maintained at 400mg bd.

★ FIGURES ★

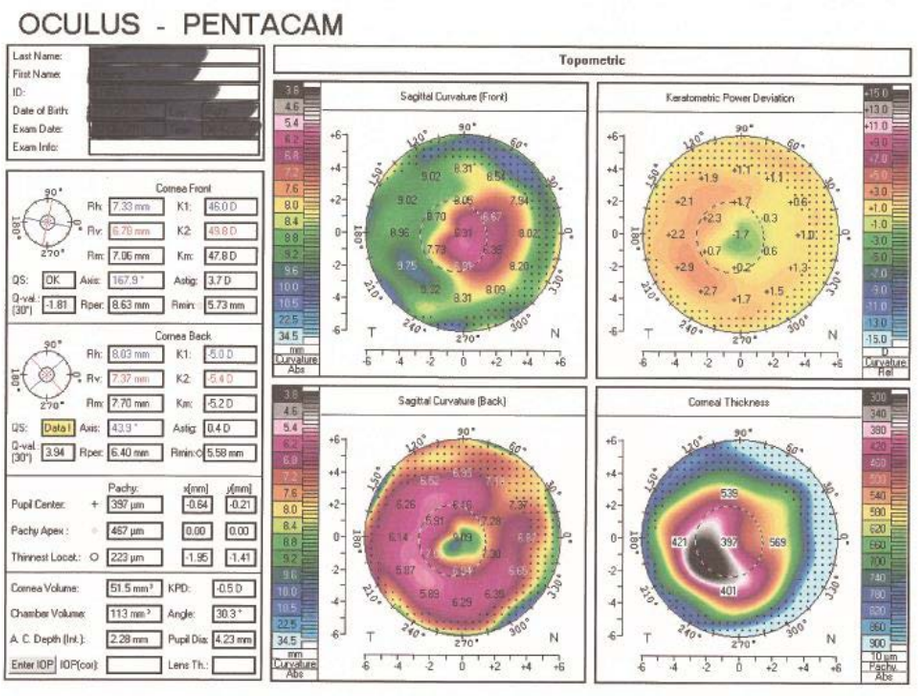

Figure 1 - Corneal topography right eye preoperative

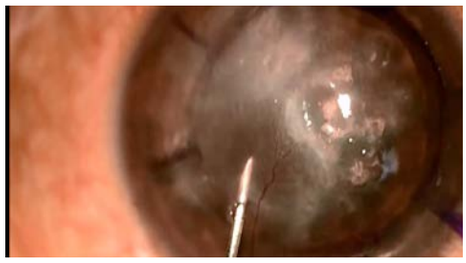

Figure 2 - Stromal hydration of thinned area of cornea

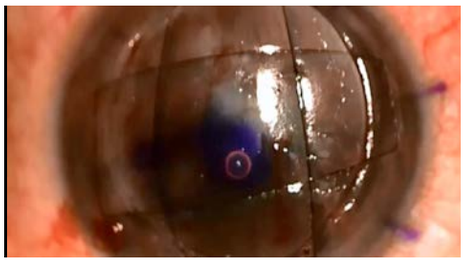

Figure 3 - Donor cornea on host bed with 2 onlay sutures

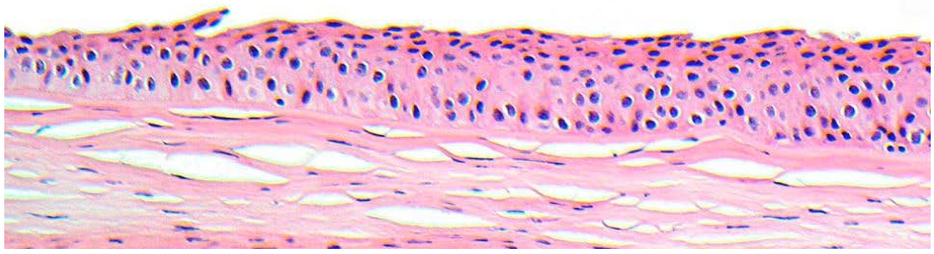

Figure 4 - Histopathological specimen of host trephined corneal lenticule. The specimen shows corneal epithelium and a regularly trephined stroma but no Descemets membrane or endothelium. There is some processing artefact in the stroma.

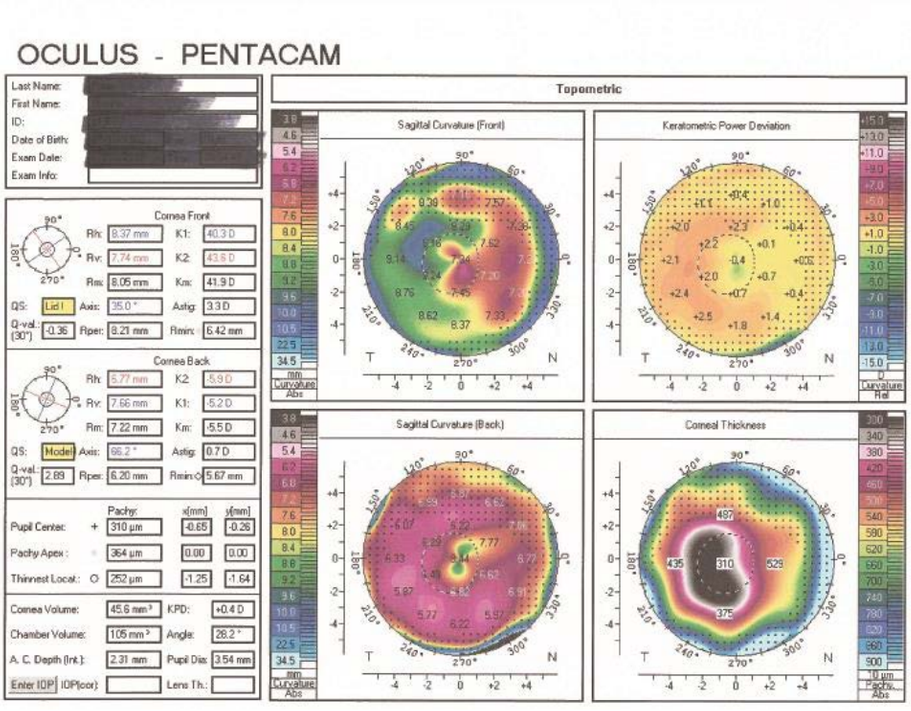

Figure 5: Corneal topography right eye 6 months postoperative

★ DISCUSSION ★

The conventional treatment of HSK scarring has been with PKP and has shown good outcomes[6, 7]. In situations where there is also a cataract, then a triple procedure is indicated. This has been carried out concurrently or sequentially with the cataract surgery following the PKP[8-10].

In the concurrent situation, a particular difficulty is the biometric calculation of the intraocular lens power, due to the corneal pathology. Assessing suboptimal IOL biometric outcome can be very difficult in light of the varying refractive outcome of the corneal graft. Eventually, when it is feasible to start manipulating corneal sutures, the corneal cylindrical power can be minimised and at this point the spherical abnormality can become evident[9].

Consequently, sequential PKP and later cataract surgery has been advocated with the distinct advantage of addressing the spherical component and potentially high levels of astigmatism, when the corneal graft has settled and possibly had all the sutures removed. This can delay the patient's potential vision for well over 12 months and there is also the insult to the endothelium with the cataract procedure[8, 10].

In our case, concurrent cataract surgery could have been carried out with the risk of suboptimal biometric IOL calculation. However, due to the rapid stabilisation of the corneal surface, cataract surgery was only slightly delayed, in order to obtain more accurate biometric calculations.

There has been a general trend away from PKP towards anterior or posterior lamellar grafting in order to directly address the level of the pathology[11-13]. The key benefits of deep anterior lamellar keratoplasty (DALK) are that it is an extraocular procedure and eliminates the risk of endothelial rejection[14]. In addition, the biomechanical properties of the cornea are less affected as less tissue is replaced[15]. Overall, outcomes have shown improved endothelial cell density[14, 16], improved graft survival[16] and less graft rejection[17].

Deep anterior lamellar keratoplasty is only possible when there is no endothelial compromise, therefore there will always remain a role for PKP in addressing anterior and posterior corneal pathologies in one procedure[14]. The visual rehabilitation timeframe of DALK is still similar to PKP, inspite of the improved safety profile. Hence, DALK was excluded as an option for our patient.

Removal of cataract combined with DALK has also been published as a safe and effective procedure[18, 19].

Superficial anterior lamellar keratoplasty, utilising either femtosecond laser or a microkeratome, has been shown to be an effective treatment modality for pathology confined to the anterior layers of the cornea. Examples include Reis-Bucklers and anterior stromal dystrophies and superficial corneal scars[20-22]. The procedure has been reported with the use of fibrin glue in place of sutures and concurrent cataract has also been successfully removed[23]. There are, however, no reports of this procedure in cases of HSK scarring with significant localised thinning.

The remaining residual corneal thickness of 252um is a point of concern, inspite of stability at 8 months post-operative. In the LASIK procedure, a minimum residual stromal bed of 300um has been shown to be a key criterion in minimising post-LASIK ectasia (PLE)[24, 25]. More recent studies have shown that the percentage tissue ablated with LASIK is a more defining risk factor for PLE than the residual stromal bed[26, 27]. Both these criteria, however, are not entirely applicable in this case, as this was not a 'normal' cornea.

Theoretically, if we were to take these criteria on board, a potential option for future development of this procedure would be to crosslink the donor cornea ex-vivo prior to trephining. A similar method has been published of crosslinking a donor cornea in order to successfully carry a Boston keratoprosthesis[28, 29]. A previous corneal graft carrying the keratoprosthesis had problems with keratolysis and the additional crosslinking ex-vivo ensured that a similar outcome did not ensue. Corneal crosslinking has clearly been demonstrated to improve biomechanical strength and halt the progression of keratoconus and PLE[30, 31].

In future, if there is post-corneal graft ectasia in this patient, the stromal thickness is not at the prerequisite value of 400um for collagen crosslinking. Hypoosmolar riboflavin has been used to swell the cornea in situations where the corneal thickness has been below 400um but above 350um[32]. Clearly, in our situation the corneal thickness is nowhere near the lower end of these values.

Recently, there have been publications showing the use of a contact lens imbibed with riboflavin, for crosslinking corneas below the 400um cut off[33, 34]. The rationale behind this approach is that a contact lens can supplement the deficient corneal thickness towards a safer value. Perhaps a combination of a contact lens and hypotonic riboflavin would be required to safely crosslink a 252um cornea with ectasia. The difficulty of crosslinking for post-graft ectasia adds further weight to the aforementioned idea of crosslinking the donor cornea ex-vivo prior to trephining and grafting onto the host.

A donor lenticule of 300-350um could have been used for the procedure. However, there was concern about potential graft instability and the subsequent requirement of graft/host suturing. This would have eliminated any potential advantage of the procedure over carrying out a standard DALK procedure that has a visual rehabilitation time of 12-18 months.

★ CONCLUSION ★

Herein we present a novel 2 step surgical method aiding in the visual rehabilitation of herpetic corneal scarring and concurrent cataract. Visual rehabilitation was significantly speeded up compared to PKP or DALK. Also, the patient maintained globe structural integrity and the host endothelium compared with PKP.

Subsequent successful phacoemulsification and toric IOL implant was achieved with a final BCVA of 6/9 and a satisfied patient.
This technique has the potential to significantly alter the timeframe for visual rehabilitation in cases of severe herpetic or similar corneal scarring. This is particularly pertinent in corneal pathologies that affect the working age population.

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CORNEAL NEUROTISATION: A NOVEL THERAPEUTIC APPROACH TO NEUROTROPHIC KERATOPATHY

★ INTRODUCTION ★

Corneal sensory innervation – supplied by the ophthalmic branch of trigeminal nerve (V_1) – is essential in maintaining the health and integrity of the cornea, especially the epithelial layer. Reports have shown that corneal nerves play a pivotal role in blink reflex, corneal wound healing, tear production and secretion, and limbal stem cell function[1-4]. Diseases affecting the corneal sensory nerves can result in partial loss (corneal hypoesthesia) or complete loss (anaesthesia) of the corneal sensitivity.

Neurotrophic keratopathy (NK) is an uncommon degenerative corneal disease characterised by impairment of corneal sensation. Depending on the severity of NK, which can be graded by Mackie's classification (Table 1), the clinical features can range from punctate epitheliopathy, persistent epithelial defect, to corneal perforation. Various aetiologies have been implicated in the manifestation of NK and the common causes include herpetic keratitis, chemical eye injury, nerve transection due to anterior segment surgery and injury to the trigeminal nerve (Table 2).

The management of NK is clinically challenging, especially when it is complicated by concurrent ocular co-morbidities such as exposure keratopathy, dry eyes and infective keratitis. Various medical and surgical therapeutic strategies are available for NK; however the majority of the treatment to date aims at protecting the corneal surface and promoting corneal epithelial healing instead of addressing the underlying corneal anaesthesia. In other words, NK is a chronic and incurable corneal disease that requires long term monitoring and treatment unless the corneal sensation can be restored.

Table 1 - Mackie's classification of neurotrophic keratopathy	
1. STAGE I	a. Rose Bengal staigning
	b. Decreased tear break-up time
	c. Epithelial hyperplasia and irregularity
	d. Punctate keratopathy
	e. Superficial vascularisation
	f. Stromal scarring
2. STAGE II	a. Epithelial defect, usually superior half of the cornea
	b. Edge of the defect become smooth and rolled
	c. Stromal oedema
3. STAGE III	a. Corneal ulcer
	b. Stromal melting
	c. Perforation

Table 2 - Causes of neurotrophic keratopathy	
1. GENETIC	a. Familial dysautonomia (Rileу-Daу syndrome)
	b. Mobius syndrome
	c. Goldenhar-Gorlin syndrome
2. OCULAR	a. Infection (herpes simplex, herpes zoster)
	b. Corneal dystrophy I
	c. Contact lens wear
	d. Topical anaesthesia abuse
	e. Chemical eye injury
	f. Latrogenic (post-laser in situ keratomileusis, post-keratoplasty)
3. NEUROLOGICAL	a. Latrogenic injury to trigeminal nerve (e.g. post acoustic neuroma removal, post trigeminal neuralgia surgery)
	b. Tumour
	c. Stroke
	d. Aneurysm
4. SYSTEMIC	a. Diabetes
	b. Multiple sclerosis
	c. Vitamin A deficiency

In 2009 Terzis et al.[5] reported a small series using an innovative and effective surgical technique in restoring the ipsilateral anaesthetic cornea with the use of contralateral supraorbital and supratrochlear nerves (corneal neurotisation). Herein the author describes a case of NK, complicated by simultaneous exposure keratopathy, following the removal of cerebellopontine angle meningioma in a young patient, who eventually underwent the corneal neurotisation surgery. The objectives of this case report are threefold: first, to highlight the clinical challenges and the step-wise therapeutic approach in the management of combined NK and exposure keratopathy; second, to report the efficacy and the potential role of corneal neurotisation in NK; and third, to discuss about the recent development in the treatment of NK.

★ CASE PRESENTATION ★

A 25-year old male was referred to the ophthalmology department for management of exposure keratopathy following the removal of left cerebellopontine angle meningioma in May 2008. Examination revealed multiple cranial nerve palsies (V – VIII nerve), evidenced by left sided total corneal anaesthesia, abduction deficit, facial nerve palsy, and hearing loss. Patient was started on intensive topical lubricants and a lateral temporary tarsorraphy was performed. In July 2008 the temporary tarsorraphy started to loosen up. There was evidence of mild corneal epitheliopathy without any frank epithelial defect or ulcer (stage I NK). A repeat lateral temporary tarsorraphy was subsequently performed by the oculoplastic team.

In September 2008 the repeat temporary tarsorraphy came apart. Further examination revealed a small inferior paracentral corneal epithelial +/- stromal defect with inferior punctate epithelial erosions (PEEs), moderate inferior corneal haze (stage III NK) and significant corneal exposure with active and passive lagophthalmos of 6mm and 8mm, respectively. His best-correct visual acuity (BCVA) at the time was 6/9 OU. Botulinum toxin (30 units of Dysport) was used to induce total left upper lid ptosis and a frost suture was also inserted temporarily to offer an immediate protection while waiting for the Botox-induced ptosis to take place. Patient was also started on prophylactic topical antibiotic drops and intensive topical lubricants. A week later patient underwent left upper lid gold weight implantation combined with lower lid tightening and permanent lateral tarsorraphy.

In September 2009 patient developed worsening neurotrophic keratopathy evidenced by a central corneal epithelial and stromal defect (stage III NK) with increased inferior corneal neovascularisation despite the absence of passive lagophthalmos. His BCVA was 6/18 OS and remained 6/6 OD. Patient was restarted on intensive topical lubricants, including G. Celluvisc 1% 1 hourly, Oc. Lacrilube QDS and G. Prednisolone 0.5% minims BD. The corneal epithelium subsequently healed after 3 weeks of intensive topical treatment. Two months later, patient developed a recurrent moderate-sized central corneal epithelial and stromal defect (stage III NK) with progressing inferior corneal neovascularisation and scarring secondary to neurotrophic keratopathy despite good lid closure (Figure 1). At that stage his BCVA deteriorated further to counting fingers (CF) OS. Lower lid punctal plug and bandage contact lens were inserted. Patient was re-started on prophylactic topical antibiotic and lubricating eye drops, and topical steroid drop was discontinued. The corneal defect improved after 3 weeks and fully resolved after 2-3 months following the treatment.

Figure 1 – Slit-lamp photography demonstrated central corneal and stromal defect with scarring and inferior corneal neovascularisation secondary to progressive neurotrophic keratopathy.

In May 2010 patient's left affected eye remained stable and comfortable with no further corneal defect (Figure 2). Patient was keen to further explore the long-term treatment option in view of the partial obscuration of the visual axis and the cosmetic appearance caused by the partial ptosis induced by the gold weight implant (Figure 3). It was explained that removal of the upper lid gold weight could potentially increase the risk of corneal exposure, breakdown, secondary infection and further scarring, unless the corneal sensation was restored. Following intensive discussions with a multidisciplinary team, which consisted of a plastic surgeon, a corneal surgeon and an oculoplastic surgeon, patient had opted for the corneal neurotisation surgery – a potential therapeutic approach to permanently restore the corneal sensation.

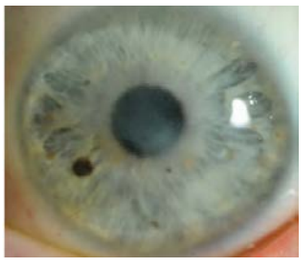

Figure 2 - Slit-lamp photography showed quiescent left eye with central corneal scarring and inferior corneal neovascularisation.

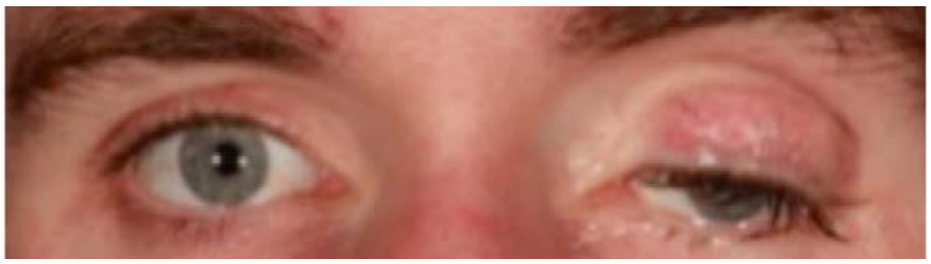

Figure 3 - Facila photography demonstrated left partial ptosis induced by Botulinum toxin injection. The visual axis was partially obscured by the ptosis.

Corneal neurotisation surgery, using the technique described by Terzis et al., was performed in January 2012. Preoperatively patient's corneal sensitivity of the left eye on Cochet-Bonnet aesthesiometer (CBA) was 0mm centrally and all 4 corneal quadrants (0mm refers to complete absence of corneal sensation and 60mm refers to normal corneal sensation). Right corneal sensation was entirely normal (60mm on CBA). At 2-month postoperative, patient's right forehead motor and sensory functions returned to normal and patient was subjectively more aware of the sensation of the left eye. BCVA was 6/60 OS and 6/6 OD.

In February 2013 (13-month postoperative), patient's corneal sensation had improved to a completely normal level in 3 quadrants (60mm with CBA) except the superior-nasal quadrant (0mm with CBA). In April 2013 (15-month postoperative), corneal nerves were successfully identified via in-vivo confocal microscopy (IVCM) (Figure 4). Patient regained an entirely normal sensation (60mm with CBA) throughout the entire cornea by February 2014 (2-year postoperative). BCVA had improved to 6/24 OS and remained 6/6 OD. In April 2014, removal of the left upper lid gold weight was performed. Patient felt that the vision had improved since the removal of gold weight and he was much happier with his cosmetic appearance. Most importantly, there was no

further recurrence of corneal epithelial defect/ulceration. During the last visit in November 2015 (approximately 4-year postoperative), patient's corneal sensation remained completely normal (60mm with CBA throughout the cornea) with no evidence of corneal epithelial defect and peri-limbal nerve graft fascicles remained visible (Figure 5). His BCVA was 6/6 OD and 6/18 OS. However no corneal nerve was identifiable on IVCM (Figure 6).

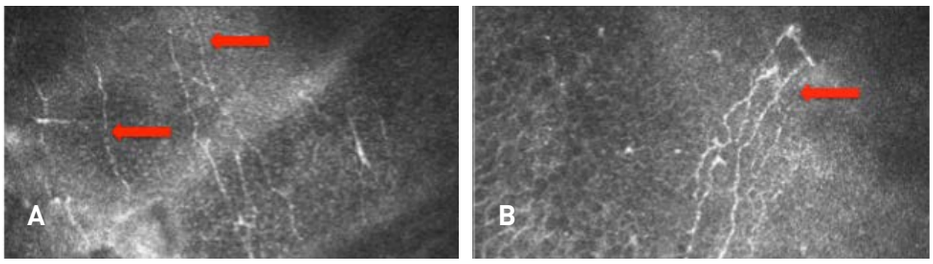

Figure 4 - At 13-month postoperative following corneal neurotisation surgery, corneal nerves (red arrows) were visualised on in-vivo confocal microscopy at the depth of 40-microns (A) and 45-microns (B).

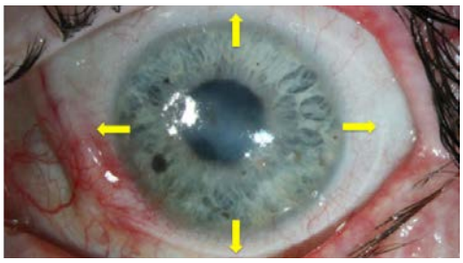

Figure 5 - Slit-lamp photography of the left eye demonstrated stable central corneal scarring without any epithelial defect at 4-year postoperative following corneal neurotisation surgery. Supraorbital and supratrochlear nerve grafts from contralateral side were visible around the limbus (yellows arrows).

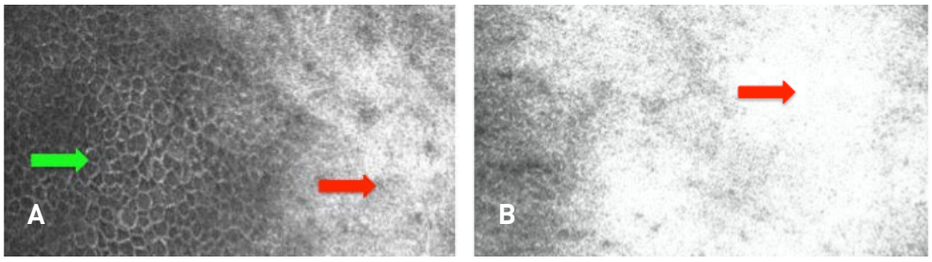

Figure 6 - At 4-year postoperative following corneal neurotisation surgery, in-vivo confocal microscopy of the central cornea showed the demarcation between normal corneal epithelium (green arrow) and scarred area (red arrow) at the depth of 36-microns (A) and more diffuse scarring (red arrow) in the deeper corneal layer at 42-microns (B). No corneal nerves were visualised throughout the cornea.

★ DISCUSSION ★

NK is classified as an orphan disease (ORPHA137596) with an estimated prevalence of less than 5/100,000 people[6]. (Management of NK is often clinically challenging especially when it is complicated by other concurrent ocular surface diseases, including exposure keratopathy (as demonstrated in this case). Fundamentally the treatment of NK can be divided into medical vs. surgical treatment, or adjunctive vs. permanent; the choices and intensity of the treatment are largely dependent on the severity of NK[6,7].

In this case report the author highlighted the challenges in managing dual concurrent corneal pathologies, namely NK and exposure keratopathy, and the step-wise therapeutic approach taken in dealing with this particularly difficult case. Patient received 4 years of various medical and surgical treatments, including intensive lubricating eye drops, topical steroid and antibiotic drops, insertion of punctal plug, insertion of bandage contact lens, a temporary frost suture, 2 temporary lateral tarsorraphy, a permanent lateral tarsorraphy, Botox-induced upper lid ptosis, lower lid tightening and implantation of gold weight in upper lid before he went for corneal neurotisation surgery in an attempt to permanently restore corneal sensation in the affected eye. This case demonstrated that despite all possible treatment measures and good lid closure, neurotrophic keratopathy could still potentially progress with recurrent breakdown of the corneal epithelium with underlying stromal involvement and subsequent corneal scarring and neovascularisation, leading to severe visual impairment. Further complications, including secondary corneal infection and perforation, may occur if the disease continues to progress.

The concept of neurotisation, which involves the transfer of a healthy nerve segment into the affected area to restore either the sensory or motor functions, has been applied across different specialties but not in ophthalmology until recently[8-12]. In 2009 Terzis et al.[5] first reported the use of a revolutionary technique to restore ipsilateral corneal sensation with the use of contralateral supratrochlear and supraorbital nerves in 6 patients who suffered from unilateral facial nerve palsy and neurotrophic keratopathy. The surgery involves identification of both nerves of the contralateral / unaffected side via a bicoronal incision, dissection proximal to supraorbital margin, tunnelling the nerve branches over the nasal bridge to the ipsilateral upper lid crease, passing the nerves through superior conjunctival fornix and inserting the nerves in the potential space between the sclera and Tenon's capsule circumferentially around the limbus of the affected cornea. Their patients achieved significant improvement in corneal sensation around 6-12 months subjectively and 30-36 months objectively[5]. In 2014 Elbaz et al.[13] reported another novel and effective corneal neurotisation technique by harvesting the medial cutaneous branch of the sural nerve followed by coaptation with the supratrochlear nerve (donor nerve) either unilaterally or bilaterally. In comparison to the technique described by Terzis et al., this approach allows restoration of bilateral corneal sensitivity and obviates the need for a large bicoronal incision, which can potentially leave a large scar over the scalp.

The regenerative ability of the corneal nerves has been reported in various observational and experimental studies. It was shown that the dissected corneal nerves (e.g. following laser in situ keratomileusis, photorefractive keratectomy, and penetrating keratoplasty) could regenerate and re-innervate the cornea[14-16], emanating from the peripheral cornea and branching towards the central and superficial corneal layer. Despite the success in restoring the corneal sensation observed clinically in the previous studies, Terzis et al.[5] and Elbaz et al.[13] did not confirm the corneal re-innervation on anatomical or morphological ground (i.e. direct visualisation of the corneal nerves postoperatively). Elbaz et al.[13] postulated the improvement in corneal sensation is attributed to the axonal regeneration of the nerve graft fascicles inserted around the corneal limbus with subsequent growth into the corneal stromal or subepithelial level.

The patient in this case described improvement in corneal sensation subjectively by 3-month postoperative and significant objective improvement by 13-month postoperative with full restoration of the corneal sensation achieved by 24-month postoperative (60mm in all 4 quadrants). Corneal re-innervation following corneal neurotisation was successfully demonstrated and confirmed on morphological ground in this patient with the use of IVCM at 15-month postoperative; however, the corneal nerves were not visualised at 4-year postoperative, suggesting that alternative indirect mechanism may be accountable for the restoration of corneal sensation following corneal neurotisation. The author hypothesises that the restoration of corneal sensation could be due to the stimulation of nerve growth factor (NGF) from the perilimbal nerve graft fascicles following the neurotisation surgery. Future studies will be required to further elucidate this concept.

In recent years there is growing evidence in the literature demonstrating the efficacy of newer biological treatments, including the use of NGF, neurotransmitters, and matrix therapy agent. Nerve growth factor is a polypeptide that is crucial for survival, growth and differentiation of neurons in the nervous system[17]. It simulates neurite sprouting by neural cells and restores the function of damaged neurons[17,18]. Studies have shown that the ocular surface healing and immune-modulating properties of NGF renders it a potential therapeutic agent for NK[19,20]. Bonini et al.[20] reported that topical NGF achieved complete resolution of persistent corneal epithelial defect secondary to NK by approximately 1 month with significant improvement in corneal sensitivity and visual acuity in 43 patients. The exact mode of action of NGF on ocular surface is not well defined. It is hypothesised that NGF improves corneal sensation and corneal healing by replenishing the deficit of release of endogenous NGF21 or by simulating corneal sensory innervation, proliferation and differentiation of epithelial cells[22]. Yanai et al.[23] also demonstrated that neurotransmitters like substance P and insulin-like growth factor-1 promote corneal epithelial healing in patients with NK. Furthermore the clinical efficacy and safety of a new matrix therapy agent (RGTA, CALCICOL20), resembling heparin sulfates, has been reported in a non-controlled, prospective clinical study in 11 patients with severe NK[24]. All these innovative avenues can potentially revolutionise the management of NK and provide permanent solution to this previously deemed incurable and severe debilitating disease.

★ CONCLUSIONS ★

Neurotrophic keratopathy is a chronic, serious, potentially blinding and refractory clinical condition that often poses clinical challenges to the clinicians, especially when it is complicated with other concurrent ocular comorbidities, including exposure keratopathy. Corneal neurotisation surgery, aiming to address and repair the underlying corneal anaesthesia, provides a safe and efficacious expansion to the current therapeutic armamentarium of NK. However newer therapeutic agents (e.g. nerve growth factor, neurotransmitters and matrix therapy agent) may serve as alternative and non-invasive therapeutic solutions to this disease in the future; however randomised controlled trials are required to confirm the long-term safety and efficacy of these treatments, including corneal neurotisation surgery.

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AN ATYPICAL KERATOCONJUNCTIVITIS: A PRIMARY OCULAR MANIFESTATION OF BEHÇET DISEASE?

★ INTRODUCTION ★

Behçet's disease is an autoimmune, rare and severe multisystemic inflammatory disease characterized by recurrent oral aphthous ulcers, genital ulcers, skin lesions, and both anterior and posterior uveitis.

We report a rare case of bilateral keratoconjunctivitis associated with Behçet's disease. We described it as a combination of atypical subconjunctival infiltrates, marginal corneal infiltrates and peripheral ulcerative keratitis.

Conjunctival and corneal manifestation has rarely been reported in Behçet's disease. Few cases of conjunctival ulceration were reported. A peripheral ulcerative keratitis (PUK) associated with Behçet's disease [1] and a bilateral small circular ulcerative keratitis in Behçet's disease [2] were reported. But it appears that this uncommon keratoconjunctivitis as a possible primary ocular manifestation in Behçet's disease never has been described before in the literature review. This raises our interest in this case.

★ CASE PRESENTATION ★

A 34-years-old Caucasian woman presented to our ophthalmology department with ocular pain in both eyes and redness persisting for 08 days.
During the 4 months before presentation, she experienced increased episodes of both oral and genital ulceration. The patient had oral ulcerations and a folliculitis-like rash at the time of presentation.

Slit lamp on the initial examination showed blepharitis, severe chemosis with diffuse yellowish-white subconjunctival infiltrates only in the bulbar conjunctiva [figure 1,yellow arrow] and marginal corneal infiltrates in both eyes [figure 2, red arrows]. A very deep ulcerative lesion in the peripheral cornea was also found in the left eye [figure 1.c, red arrow]. There was no inflammation in the aqueous or fundus. The patient had neither previous ophthalmologic history, nor contact lens use.

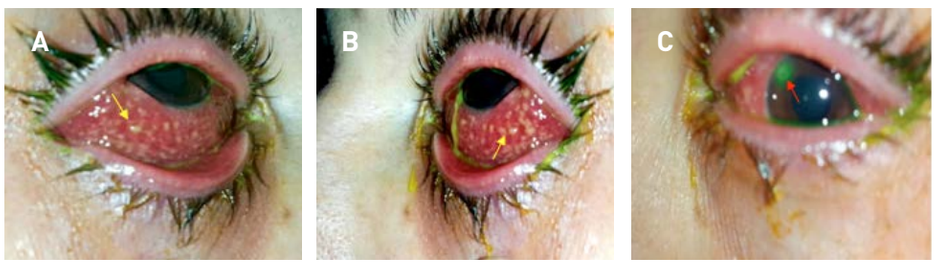

Figure 1 – Anterior eye segments of the right and left eye at first presentation:
The detail pictures show on the right and left eye (a, b): yellowish-white subconjunctival infiltrates only in the bulbar conjunctiva (yellow arrow) and on the left eye (c) a peripheral ulcerative keratitis with fluorescein eye drop (red arrow).

Autoimmune screenings for rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody and anti-dsDNA antibody were negative. Additionally positive HLA-B51 was noted.
Corneal scraping for bacteria and fungi, and polymerase chain reaction for herpes simplex virus were negative, also the results of conjunctival culture were negative which discounted an infectious microbial cause.

Given the severe local inflammatory signs, the patient was treated with an intravenous bolus injection of Methylprednisolone 500g daily doses for 03days with an oral relay of prednisone 1mg/kg/day and topically with Dexamethasone a six times daily.

Oral Colchicine 0.5 mg daily was given to control oral and genital ulceration. After 2 days of treatment the chemosis with subconjunctival infiltrates disappeared [figure 2] but the corneal lesions stayed the same [figure 2].

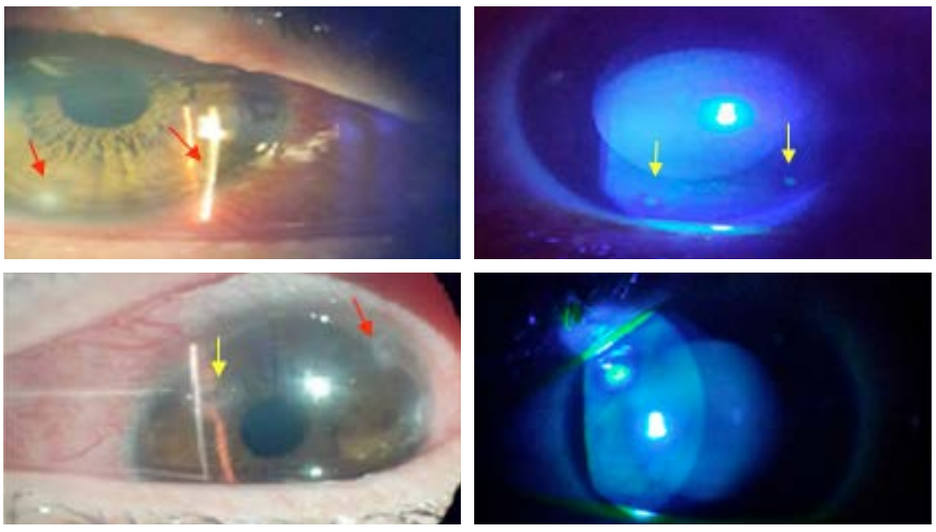

Figure 2 - Anterior segment photography at day 3 of treatment with and without fluorescein eye drop: The detail pictures show on the right eye (top right and left) and left eye (bottom left and right) the marginal corneal infiltrates (red arrow) .Also the peripheral ulcerative keratitis on the left eye (yellow arrow) which remains the same.

After day 7 of treatment, we noticed a low process of cicatrisation of the deep peripheral corneal ulcer [figure 3.c, yellow arrow] on the left eye. Additionally we observed the occurrence of an epithelial defect on the marginal corneal infiltrate on the left eye [figure 3.c, red arrow].Therefore we added 0.1% Ciclosporin topically once daily to help corneal cicatrisation.

At day 30 of treatment, symptoms were absent. Slit lamp examination showed that the corneal infiltrates were healed with low grade corneal opacity[figure 3.b, double green arrow] and the deep ulcer was also practically healed on the left eye with moderate corneal scarring [figure 3.d, blue arrow]. So we decided to stop topical Ciclosporin treatment.
There was no impact on visual acuity in both eyes which was 20/20 at day 30.
After a follow-up period of 3 months, no recurrence was registered. Oral prednisone was maintained at 10 mg daily dose.

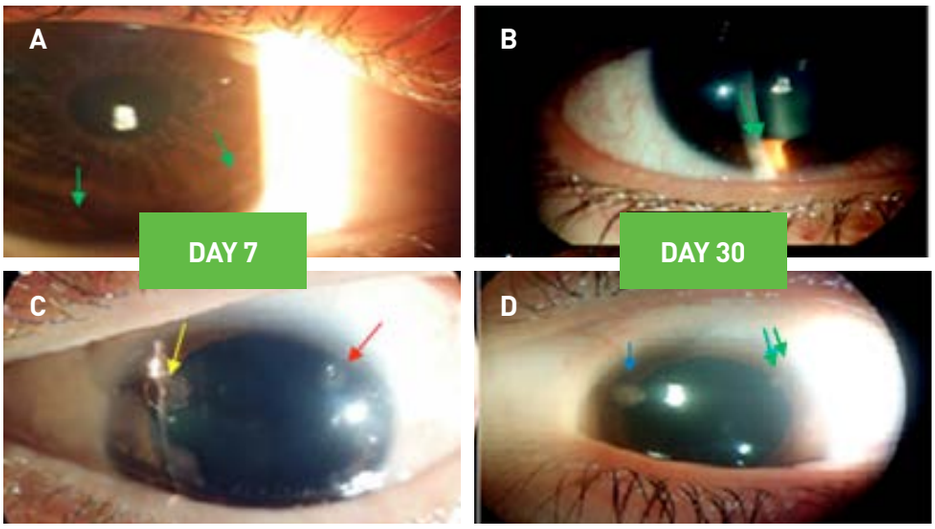

Figure 3 - Anterior segment photography at day 7 before Ciclosporin treatment (right images) and at day 30 (left images):
The detail pictures show the healing process of the corneal infiltrates in the right eye at day 7(figure 3.a, green arrow). And at day 30 low grade corneal opacity are observed. (Figure 3.b, double green arrow).
On the left eye: the deep aspect of the corneal ulcer (yellow arrow) and the occurrence of an epithelial defect on the marginal corneal infiltrate (red arrow) are noticed. At day 30, complete corneal healing was achieved and corneal opacities occurred (figure 3.d, blue and double green arrow).

★ DISCUSSION ★

The conjunctiva may be involved in many immunological diseases because of its rich in vessels and inflammatory cells. Auto-immune conjunctivitis in systemic vasculitis or other general inflammatory diseases were reported [3].

The conjunctiva is a mucous membrane, as are the oral and genital mucosa. So it should not be surprising that it can be involved in Behçet's disease. The conjunctival pathology in Behçet's disease is rare but few cases of conjunctival ulceration were reported [4].

We suggest that the subconjunctival infiltrates showed in our case could be another manifestation of the conjunctival pathology in Behçet's disease.

It would have been useful to perform a conjunctival biopsy of the subconjunctival infiltrates but their rapid resolution did not allow us to perform it.

In addition to this, noninfectious ulceration of the peripheral cornea remains a major diagnostic and therapeutic challenge. The pathogenesis in most of these disorders is unclear, however, on the basis of systemic connective tissue diseases, autoimmune mechanisms are most likely involved. The peripheral cornea has distinct morphological and immunological characteristics that predispose for inflammatory reactions. Major differences exist regarding humoral and cellular components of the immune system. In the peripheral cornea there is more high-molecular IgM and initial complement component C1 than in the central cornea and may predispose for immune complex formation.

The close contact to the conjunctival vasculature provides the basis necessary to generate an immune response. Langerhans cells and macrophages as important antigen presenting and processing cells are present in higher number in the peripheral cornea.

Peripheral ulcerative keratitis is associated with many systemic diseases and is the initial manifestation of collagen vascular diseases in 50 % of cases [5].

Corneal manifestation has also been reported in Behçet's disease. A peripheral ulcerative keratitis (PUK) associated with Behçet's disease [1] and a bilateral small circular ulcerative keratitis in Behçet's disease [2] were reported.

The current case suggests that despite its rare occurrence, both involvement of conjunctiva and cornea can develop in patients with Behçet's disease. It leads in our case to an atypical form of keratoconjunctivitis. A combination of subconjunctival infiltrates marginal corneal infiltrates and peripheral ulcerative keratitis.

Yong-Sok Ji et al reported that Behçet's disease-associated PUK can be treated effectively using topical and systemic cyclosporine A [5].

In our case Behçet's disease associated bilateral keratoconjunctivitis showed good response to topical and systemic corticosteroids. The addition of topical 0.1% Ciclosporin seems very useful for corneal cicatrisation.

★ CONCLUSIONS ★

The keratoconjunctivitis should be noted as an uncommon but possible primary manifestation of Behçet's disease. Therefore, routine examination of both conjunctiva and cornea is recommended in patients with Behçet's disease.

Behçet's disease-associated keratoconjunctivitis can be treated effectively using topical 0, 1% ciclosporin, local and systemic corticosteroids.

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TREATMENT OF CHRONIC ALKALI CHEMICAL BURN SEQUELAE IN A PEDIATRIC PATIENT: A CASE REPORT.

★ INTRODUCTION ★

Chemical eye injuries can be cause by acidic or alcaline compounds. Alcali frequently cause more severe damage to the eye than acids. By causing colliquative necrosis, penetration into the eye occurs as long as contact is maintained, therefore, in the most severe cases, perforations have been described. The ocular surface and cornea are especially susceptible to chemical eye injuries, since they are the first structures to be encountered. Chemical burns are absolute ophthalmic emergencies, where copious irrigation is mandatory after a brief interrogation about the substance nature. Other incident details should be asked during and after initial irrigation. In the acute phase, postirrigation treatment consists of tissue debridment, topical and systemic antibiotics, topical cycloplegics, corticosteroids and artificial tears. Bandage contact lenses, amniotic membranes and tarsorrafy may be applied as needed. In the chronic phase autologous or allogenic limbal stem cell transplants, cul-de-sac restorations, amniotic membrane grafts, keratoplasty and keratoprosthesis may be warranted[1]. Amniotic membranes constitute the inner layer of three placental membranes. They are grafted at the time of a cesarian section, after contagious infections have been ruled out. Amniotic membranes harbor regenerative substances, such as antiadhesive, bacteriostatic, antiinflamatory, antiapoptotic, antiangiogenic and antialgic compounds[2]. The application in Ophthalmology was first described by de Rotth in 1942[3]. Currently they are applied in ocular surface rehabilitations and in the treatment of symblephara, pterygia, persistent epithelial defects, ocular

surface burns and pemphigoid, as well as in glaucoma and strabismus surgery[2]. Limbal stem cell transplants may be warranted, which can be autologous or allogenic. In pediatric age, ocular surface rehabilitations are challenging due to the risk of amblyopia. To the best of our knowledge, there is no large-scale study to be found in scientific literature particular regarding ocular surface rehabilitations in this treatment group. The authors present the case of a 6 year old boy who was rescued from Cape Verde five months after a chemical burn with calcium hydroxide.

★ CASE PRESENTATION ★

A seven year old boy was rescued from Cape Verde and referred to the Cornea Department, five months after a calcium hydroxide chemical burn to the left eye. The acute treatment had consisted of irrigation and chloramphenicol ointment. The personal and familial histories were irrelevant and there was no systemic involvement. Ocular movements of the left eye were significantly compromised due to a symblepharon of the inferior fornix. The direct pupillary reflex of the left eye could not be evaluated due to opacification of ocular media, but the consensual reflex of the right eye was present. The best corrected visual acuity (BCVA) was of 20/20 on the right eye and light perception on the left eye. On slit lamp biomicroscopy an extensive symblepharon of the inferior fornix was noted. Lacrimal function was preserved. The ocular surface was covered by conjunctivalization that only spared the superior ¼ of the cornea. The anterior chamber, lens and posterior structures could not be observed. The examination of the right eye showed no significant changes. Left eye ecography revealed an apparently normal posterior segment. The patient was proposed for ocular surface rehabilitation surgery, with conjunctivoplasty, autologous limbal stem cell transplant (CLAU), inferior cul-de-sac restitution with an amniotic membrane graft covering the inferior fornix and ocular surface. The neovascular tissue covering the cornea and conjunctiva was carefully removed, followed by symblepharon lysis. Luckily for the patient, the corneal neovascular pannus was superficial, without significant stromal involvement. For CLAU, a limbal cell graft was obtained from a corneal area between the 10 and 2 o'clock positions of the fellow healthy eye. The graft was divided into two equal parts which were reinserted at the 6 and 12 o'clock positions of the diseased eye. The amniotic membranes were thawed and rinsed with BSS, 10 minutes prior to the procedure. The graft was positioned over the cornea, conjunctiva and CLAU, and held in place with 9/10 Nylon suture to the episclera and 10/10 Nylon suture to the corneal limbus. Another graft was used to rebuild the inferior cul-de-sac, in order to prevent further adhesions. A conformer was introduced at the end of the surgery to hold the amniotic membrane grafts in place during the first post-operative (PO) month. The patient was medicated with artificial tears and tobramycin/dexamethasone drops in the first two PO months, with a progressive

taper. No complications were registered. Visual acuity improved progressively, reaching 20/25 in the 15th PO month, with a negligible refraction of -0.5 sphere. Despite the good visual acuity, conjunctivalization relapse started on the third PO month. Due to the absence of visual compromise a further intervention was postponed. In the 40th PO month, conjunctivalization started to aggravate, together with symblepharon relapse on the temporal aspect of the inferior tarsus. Visual acuity decreased to 20/200. A second intervention was performed on the 44th PO month, with symblepharon lysis, fibrovascular tissue debridment and amniotic membrane grafting to the inferior fornix and ocular surface. Visual acuity started improving, finally reaching 20/30 on the 58th PO month, which the patient maintained until the end of the follow-up period. No further recurrences of symblepharа occured. The total follow-up time comprehended 83 months, with a final outcome of significantly improved visual acuity, ocular movements and final aesthetic result, notwithstanding some remnant neovascularization and conjunctivalization of the cornea.

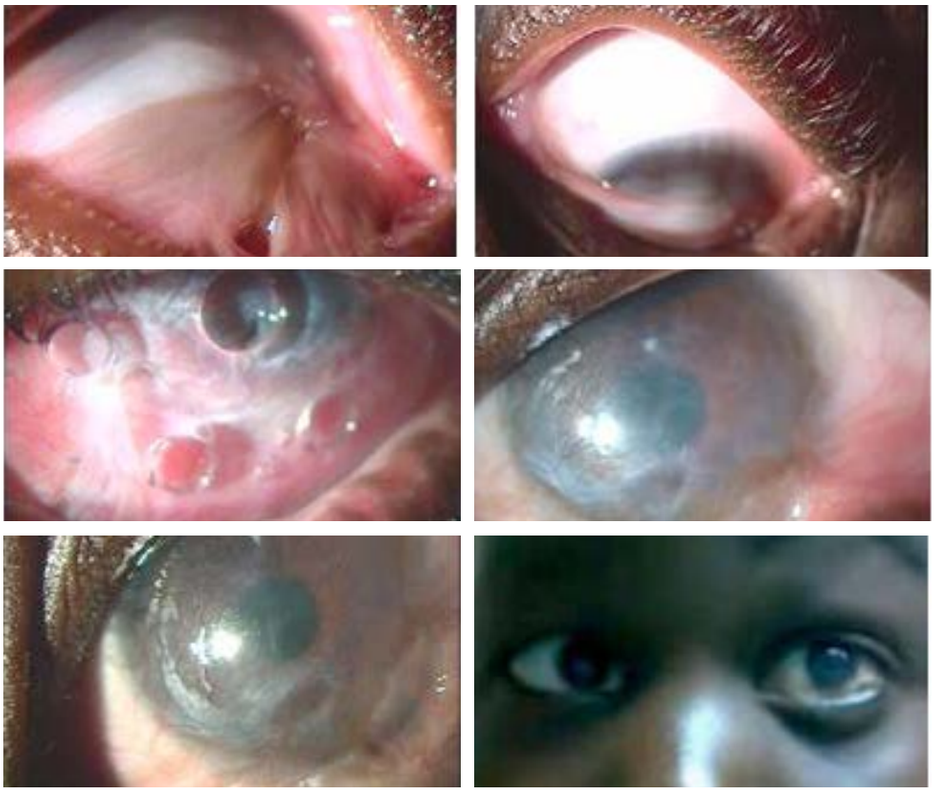

Figure 1 - Patient before surgery, with BCVA of light perception and strong opacification of media (A,B), one week after the first surgery, with the conformer en place (C), at three months PO, with first signs of neovascular pannus relapse (D) at 58 weeks, already after the second intervention, with BCVA of 20/30(E,F).

★ DISCUSSION ★

Ocular surface chemical burns can give rise to various complications. Limbal stem cell destruction leading to corneal overgrowth with neovascular tissue and aberrant cicatrization with consequent tissue adherence are some of its complications. According to Roper-Hall [4] they can be categorized into four different stages, depending on corneal opacification and extension of limbal stem cell ischemia. More recently, Dua [5] proposed another classification with two additional stages and an additional variable, the conjunctival involvement. Amniotic membranes are frequently referred in scientific literature due to regenerative and proepithelialization properties. The highly rich basal membrane and stromal matrix harbor various essential substances, such as cytocines, prostaglandines, integrins, fibronectins, protease inhibitors and molecules involved in TGF-beta and VEGF pathways, contributing to its antiinflamatory, antifibrinogenic, antialgic and antiapoptotic response. In order to create an adequate microbiologic environment for the migration and adhesion of epithelial cells the membrane should be placed with the basement membrane side up, thus allowing epithelialization over the graft [1,6,7,8]. Since thawed membranes have no viable cells, they represent a non-immunogenic tissue with rejections being very rare [9]. Together with the already enumerated aspects, its high availability and low complication rate make it very appealing for the surgery of ocular surface rehabilitation [10]. When limbal stem cell involvement is extensive, sole amniotic membrane grafting is frequently not enough. In this situation, an additional source of limbal stem cells is needed. Limbal stem cells can be grafted from the fellow eye, in case of unilateral disease and absence of epithelialization compromise. In the case of bilateral disease, living related donor conjunctival limbal allograft (lr-CLAL) can be performed. If there is no available donor, remaining possibilities are ex-vivo cell expansions and cadaver keratolimbal allografts[11]. Some studies have been published regarding ocular surface rehabilitations in the adult population, where the majority of authors concluded that in partial limbal stem cell deficiency amniotic membrane grafts suffice, whereas a more advanced compromise requires additional stem cell delivery [6,7,12,13]. In the case of partial limbal stem cell insufficiency which affects more than 50% of the limbus (grade IV, according to Roper-Hall), authors disagree when it comes to treatment strategies. Some suggest sole amniotic membrane grafting as long as the limbal stem cell insufficiency does not exceed 300° of corneal circumference[14]. In the present case, although there was a small area of potentially healthy limbal cells (between the 10 and 2 o'clock positions), the cornea team favored a limbal stem cell transplant in addition to amniotic membrane grafting in order to increase the possibility of a satisfactory final result. Since the involvement was unilateral a CLAU procedure could be performed. At the end of follow-up, a partial success was observed, with frank improvement of visual acuity, ocular motility and final aesthetic result, despite some persisting corneal disease. Note that the time for BCVA achievement was long,

corresponding to 15 months after the first and 14 months after the second surgery. Best potential visual acuity of the affected eye could not be obtained at the end of the follow-up period (20/25 in the 15th month versus 20/30 in the 83th month), although a significant increase from the pre-operative value was achieved (light perception versus 20/30).

★ CONCLUSION ★

Ocular surface rehabilitation in pediatric age is a challenging task. Rapid tissue restitution with a graft similar in characteristics to the original tissue is necessary in order to avoid amblyogenic mechanisms. Some studies have been published regarding the application of amniotic membranes for the rehabilitation of the ocular surface in the adult population, whereas none was found regarding the pediatric population. The present case report describes the case of a six year old boy with severe ocular surface sequelae from an alkali burn. The results obtained with CLAU in conjunction with amniotic membrane grafting for the rehabilitation of the ocular surface and cul-de-sac restitution where not ideal, with persistence of some neovascular tissue and BCVA compromise. Nevertheless, ocular movements, BCVA in comparision to the inicial observation and final aesthetic result showed significant improvements.

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