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Acute corneal melt and perforation – A possible complication after riboflavin/UV-A crosslinking (CXL) in keratoconus

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ABSTRACT

Purpose: To report two cases of acute corneal melting and perforation requiring emergency penetrating keratoplasty after corneal crosslinking (CXL) in advanced keratoconus.

Observations: Case 1 was a 34 and case 2 was a 16-year old male, both with progressive keratoconus, who underwent CXL (Dresden protocol). After riboflavin imbibition, patients had a minimal pachymetry of 337 μm and 347 μm, and therefore required stromal swelling by hypoosmolar riboflavin resulting in pachymetries of 470 μm and 422 μm, prior to the 30 minute UV-irradiation with 3mW/cm^2. In case 1, on the 7th postoperative day a 4mm linear perforation occurred. Extensive post-hoc examinations revealed no infectious cause. In case 2, a corneal melting developed within 24 hours, from which *Staphylococcus aureus* was cultured.

Conclusions and importance: Acute corneal melting and perforation may occur after CXL. Dysfunctional collagen metabolism, atopia, thin preoperative pachymetry and the use of hypoosmolar substances may have initiated this complication in our cases.

1. Introduction

Photochemical corneal crosslinking using riboflavin and ultraviolet A (UV-A) irradiation (CXL)[1] is a technique to strengthen the cornea in keratoconus and post-LASIK keratectasia.[2,3] The standard Dresden protocol consists of epithelial debridement to assure a sufficient penetration of the riboflavin (vitamin B2) solution into corneal stroma. Thereafter, riboflavin is photo-activated by 365 nm UV-A irradiation, inducing the release of reactive oxygen species which provoke the formation of new covalent bonds with the extracellular matrix.[4]

CXL is a safe procedure with a low rate of complications.[5] The incidence of infectious keratitis after CXL is a rare complication (0.0017%).[6] However, a fulminant course may occur and require emergency keratoplasty.[7–12]

This is somewhat surprising, since CXL has initially been introduced to halt corneal melting with or without infectious keratitis, as published in 2000[13] by the Dresden group. Previously, a meta-analysis indicated that adjuvant CXL expedites the healing of infectious keratitis when compared to standard antimicrobial treatment alone.[14] Here, we report two such cases of initially uneventful CXL which were complicated by corneal perforation and required emergency penetrating keratoplasty.

2. Case reports

2.1. CXL-treatment

For CXL treatment, in both cases corneal epithelium was completely abraded within an 8–9mm diameter under topical anesthesia with oxybuprocain 0.4% (Bausch&Lomb). Split lamp examination revealed no marked stromal thinning after de-epithelialization in both cases. Intraoperative thinnest ultrasound-pachymetry after epithelial removal and 30 minutes imbibition with 0.1% riboflavin in 20% dextran (MedioCROSS D, Avedro, Waltham, MA) was 337 μm in case 1 and 347 μm in case 2. Subsequently, riboflavin 0.1% hypotonic solution (MedioCROSS H, Avedro, Waltham, MA) was administered topically every 5 min for 30 min. Corneal thickness increased to 470 μm and 422

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μm, respectively. Standard UV-A irradiation with a radiant exposure of 5.4 J/cm^2 and an irradiance of 3mW/cm^2 was performed while riboflavin administration was continued every 5 minutes. Postoperatively a sterile bandage contact lens (Bausch&Lomb) was applied and unpreserved ofloxacin eye drops 0.3% (Bausch&Lomb) (4 times a day) as well as unpreserved lubricants (every hour) were prescribed. For pain relief patients received oral paracetamol (case 1) or metamizole intravenously (case 2). Non-steroidal anti-inflammatory drops were prescribed in neither case.

2.2. Case 1

A 34-year-old caucasian male with striking red hair presented with progressive keratoconus. Clinical history revealed unilateral right hearing loss in childhood and a primary spontaneous pneumothorax at the age of 24. A blue sclera was not apparent. Best spectacle corrected visual acuity (BSCVA) was 20/100 on OD, 20/40 on OS. In the right eye to be treated by CXL, maximum corneal curvature was 60.4 D. Thinnest corneal pachymetry measured by Scheimpflug imaging (Pentacam HR, Oculus, Germany) was 274 μm (Fig. 5).

Postoperatively, a sterile bandage contact lens (Bausch&Lomb) was applied and the patient was started on unpreserved ofloxacin eye drops 0.3% (Bausch&Lomb ((4 times a day) as well as unpreserved lubricants (every hour). Follow-up on day 1 was normal, with signs of a healing corneal epithelium and no signs of corneal stromal melting or infection. The patient continued to wear a bandage contact lens and apply unpreserved topical ofloxacin and lubricants. When he was reviewed on day 7 and the contact lens was removed, a 4 mm long corneal perforation with extremely soft, melted perilesional corneal stroma was found to extend from the corneal center almost to the nasal limbus, without any clinical signs of inflammation or infection (Fig. 2a).

An emergency penetrating corneal transplantation (8.25 mm/8.0 mm) was performed (Fig. 2b). After the treatment topical the patient was started on systemic prednisolone (100 mg daily, tapered over three weeks), prednisolone 1% eye drops (Théa Pharma), hydrocortisone 2.5% ointment, ofloxacin 0.3% (Bausch&Lomb) eye drops and lubricants on day 1. Further healing was uneventful. Contact lens corrected VA was 20/15 at 6 months postop.

An ex-post general clinical examination did not reveal any systemic disease, especially no signs of autoimmune or connective tissue disorders. Laboratory tests on markers of systemic diseases as complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, autoantibodies (rheumatoid factor, anti-nuclear, anti-neutrophil cytoplasmic antibodies) were normal. However a history of mild seasonal allergic rhinitis was recalled upon repeated questioning, but without any signs of activity at presentation.

2.3. Case 2

Case 2 was a 16-year-old male who was referred with a recently diagnosed bilateral progressive keratoconus. General clinical history was unremarkable. BSCVA was 20/30 on both eyes. Four weeks before the current surgery of the right eye, he had an uneventful CXL treatment on the left fellow eye (maximum corneal curvature 61.5 D, thinnest pachymetry 407 μm). For the right eye, Scheimpflug imaging revealed maximum corneal curvature of 58.4 D and a thinnest pachymetry of 412 μm (Fig. 6).

After CXL, a sterile bandage contact lens (Bausch&Lomb) was inserted and the patient was started on unpreserved ofloxacin eye drops 0.3% (Bausch&Lomb ((4 times a day) as well as unpreserved lubricants (every hour). In the morning of day 1 postop (approximately 16 hours after treatment) the patient presented with a dense fibrin anterior chamber reaction. Therapy was immediately changed to: topical preservative-free ofloxacin 0.3% (Bausch&Lomb) QDS, atropine 1% (Ursapharm) BD and hyaluronate 0,2% QDS. Six hours later the patient was reviewed and showed a complete corneal decompensation with severe stromal melt in the inferior thirds close to the limbus. The anterior chamber was completely flat and the eye soft. Although Seidel-testing was negative, corneal perforation was suspected (Fig. 4a). Moxifloxacin 0.5% (Novartis) and gentamicin 0.3% (Ursapharm) eye drops were then commenced at half hourly intervals and a few hours later emergency penetrating keratoplasty (11.5 mm/11.0 mm) performed (Fig. 4b). Postoperatively, the patient was started on systemic prednisolone (100mg daily, tapered over three weeks), prednisolone 1%

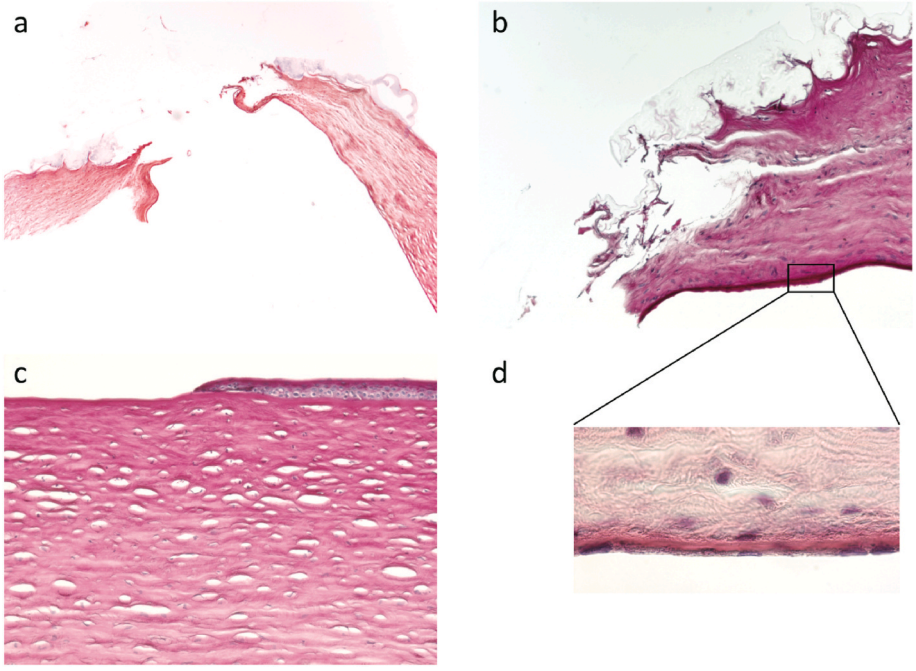

Fig. 1. Case 1, Corneal explant from emergency penetrating keratoplasty performed 7 days after corneal crosslinking: (a) Overview (Gram stain, original magnification 25×). (b) Site of perforation (PAS stain, 100x): stromal thinning, disruption of stromal architecture, no epithelium in place. (c) Normal anterior stroma of the CXL-treated cornea distant to the site of corneal melting, with intact epithelium (PAS, 100x). (d) Endothelial layer with normal cell morphology and density (400x).

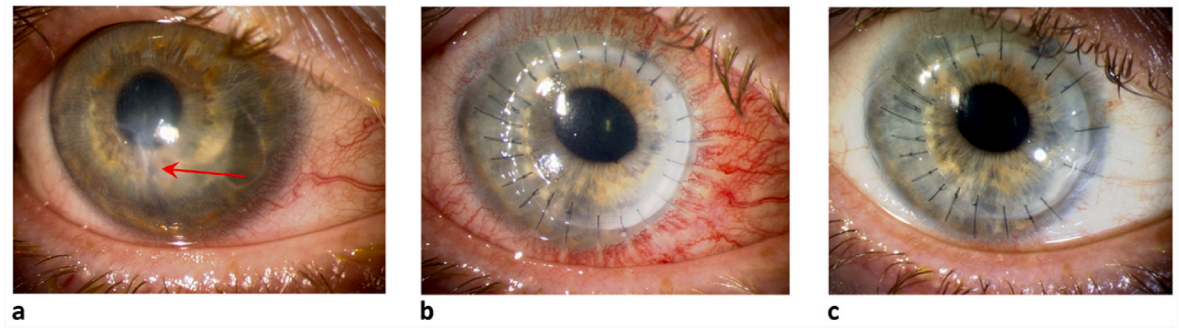

Fig. 2. (a) Case 1: A rupture-like ulceration with fistulation at the keratoconus apex (arrow) occurred at day 7 after CXL, leading to a shallow anterior chamber. (b) 3 days after penetrating keratoplasty: Some sutures had to be anchored in the limbus since the surrounding stromal tissue was found to be extremely soft. (c) 3 months after keratoplasty BSCVA recovered to 20/32, but several sutures loosened within the first 2 weeks and had to be removed.

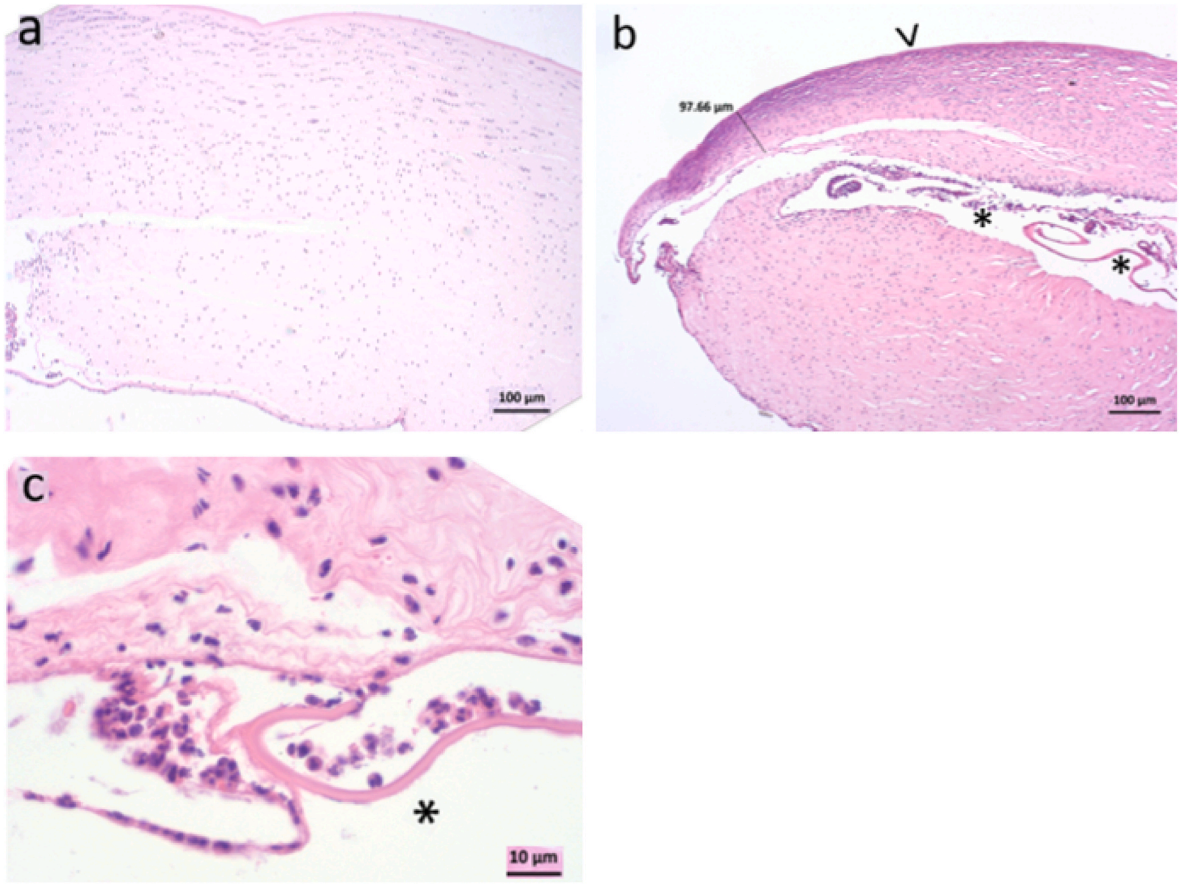

Fig. 3. Case 2, Corneal explant from emergency penetrating keratoplasty performed 1 day after corneal abrasion and crosslinking. (a) Neutrophil corneal infiltration over the whole thickness of the edematous cornea. (b) Stromal thinning (measurement line indicated) and fistulating corneal perforation. Asterisks highlight the endothelial side, arrowheads the epithelial side. (c) Neutrophils with detached Descemet's membrane and loss of endothelial cells. H&E stains for all subfigures, magnifications indicated by bar on the lower right (a, b: 50×; c: 400x original magnification).

(Théa Pharma) eye drops, preservative-free ofloxacin 0.3% (Bausch&Lomb) and lubricants on day 1. Due to the large corneal graft diameter and increased risk of rejection, immunosuppressive therapy with mycophenolate mofetil (2g per day) was initiated. Corrected VA after 3 weeks was 20/40.4 weeks after treatment, the patient presented with signs of graft rejection (Fig. 4c). Systemic immunosuppressive therapy was continued and topical steroid application intensified, but graft failure could not be prevented and the patient was listed for later DMEK surgery.

Upon repeated questioning the patient admitted to having self-applied a non-sterile black fabric eye patch postoperatively, for comfort, which he had brought into hospital from home. Of all eye drops, contact lenses and solution used postoperatively, fresh samples from the same batches were sent for microbiological investigation, but were culture negative.

2.4. Histology and microbiology

In case 1 histology of the corneal specimen revealed stromal thinning and disruption of stromal collagen architecture at the site of perforation (Fig. 1). The CXL-treated cornea *not* directly adjacent to the site of perforation displayed normal stroma with a slight reduction in

Fig. 4. (a) Case 2: About 24 hours post CXL-treatment the patient presented with a decompensated cornea with severe stromal melt in the inferior thirds (b) 5 days after penetrating keratoplasty, which was performed with interrupted 10.0 nylon sutures (c) 4 weeks after penetrating keratoplasty, the transplant shows signs of reception, BSCVA was reduced to counting fingers.

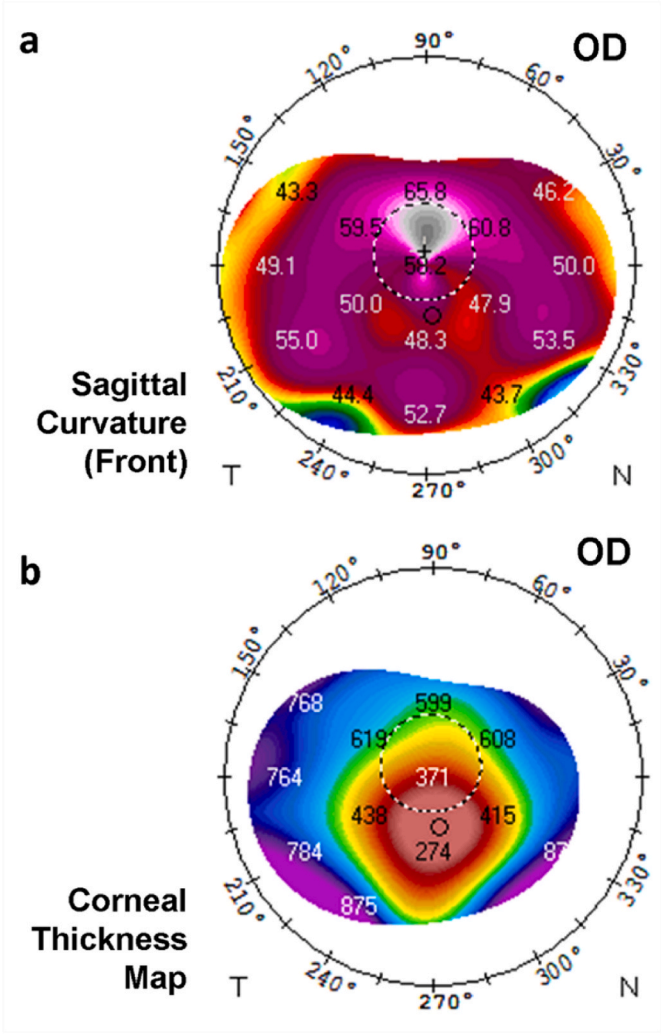

Fig. 5. Case 1: Preoperative Scheimpflug imaging of OD
a) Sagital Curvature Font b) Corneal Thickness Map.

keratocyte density in the anterior stroma, sporadically with pyknotic nuclei. No signs of inflammation, especially no neutrophil infiltration, bacteria, fungi or protozoae were found in Gram, H&E, or PAS stains. Bacterial cultures as well as PCR for Herpes simplex of scraping samples and conjunctival swabs were negative.

Histology of case 2 showed complete loss of corneal epithelium (Fig. 3) and an edematous corneal stroma with dense infiltration of polymorphonuclear neutrophils. Further, severe thinning of the stroma could be observed, next to a narrow perforation accompanied by detachment of the Descemet's membrane and loss of endothelium. No bacteria, fungi or protozoa could be demonstrated in H&E, EVG or PAS stains. Cultures taken from corneal tissue sample were positive for Staphlyococcus aureus, but were negative for contact lenses and solution as well as all eye drops used postoperatively.

3. Discussion

Standard CXL requires epithelial debridement and therefore, has an inherent risk of postoperative infection and corneal melting. It has been used to prevent progressive corneal melting in infectious and non-infectious keratitis, since the procedure increases resistance to collagenases. CXL has been described to successfully prevent imminent emergency keratoplasty in patients with microbial keratitis and rosacea associated stromal melting.[13,14]

In the two cases presented here acute corneal melting occurred after CXL. So far 7 cases with severe postoperative ulceration and perforation have been reported after CXL (Table 1).[7–12] Of these, 2 were culture--negative,[7,8] while microbiology identified Alternaria spp.,[9] Acanthamoeba,[10] *Staphylococcus aureus* and Methicillin Resistant *Staphylococcus aureus* (MRSA)[11] and unidentified gram-negative rods.[12]

While in our case 1 histology, microbiology and clinical findings make an infection unlikely, in case 2 *Staphylococcus aureus* was isolated suggesting microbial keratitis as the cause of melting. Patient 2 also admitted of self-applying a non-sterile black fabric eye patch for comfort which could have been a source of infection. However, the fulminant course of the melting process as well as the negative histological work-up raises doubts about *Staphylococcus aureus* being the solitary pathological cause. In the 7 reported cases the interval between CXL and corneal perforation ranged from 2 days to 2 months, while our case 2 perforated within 24 hours.[7–12] Staphylococcus-associated corneal ulcers in naïve cornea typically show a usually well-demarcated, discrete round or oval infiltrate, with a more protracted clinical course.[15] However, staphylococcus-associated ulcer may present different in post-CXL cornea.

In our cases, histology distant to the site of melting showed normal stromal architecture consistent with the findings in CXL-treated eye bank corneas.[16] The reduced density of keratocytes, sporadically with pyknotic nuclei, correlates with the keratocyte apoptosis observed in animal studies[17] and has been confirmed *in vivo* by confocal microscopy.[18] Since the endothelium was unaffected even adjacent to the site of perforation and keratocyte still present in the corneal stroma a cytotoxic UV-A overdose seems unlikely, as overdosing results in a complete loss of keratocytes *and* endothelial cells, as observed by Wollensak.[19]

In both of our cases, the intraoperative corneas were very thin after epithelial removal. Some keratoconus can show marked stromal thinning with partially filled epithelial hyperplasia. In such chases an

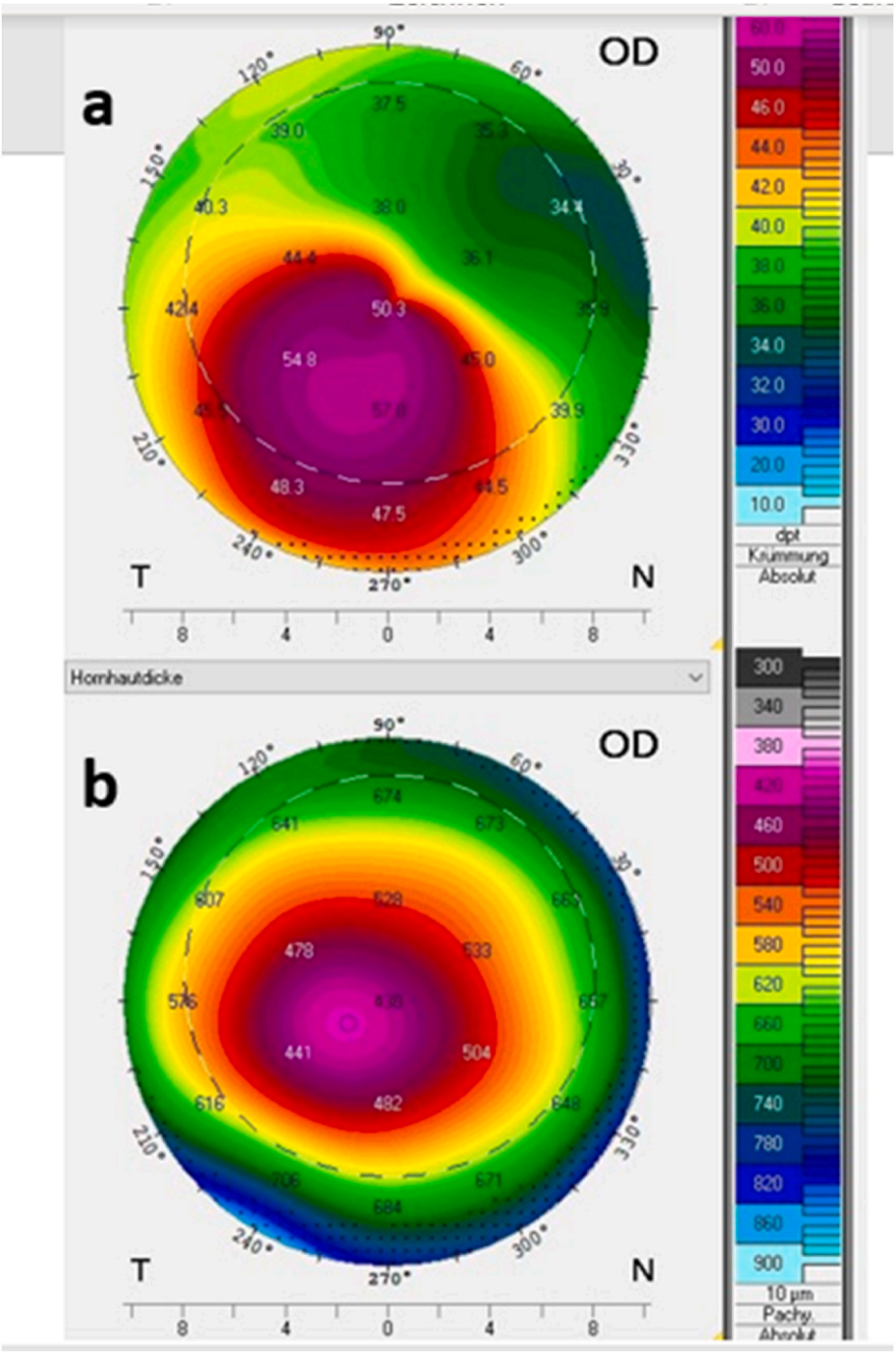

Fig. 6. Case 2: Preoperative Scheimpflug imaging of OD
a) Sagital Curvature Font b) Corneal Thickness Map.

anterior segment OCT can be helpful to reveal stromal thinning.

Preoperative pachymetry lower than 400 µm was suspected as a potential risk factor by Sharma et al.[20] Thus both of our cases were imbibed with hypoosmolar riboflavin to induce swelling prior to UV-A-irradiation, as described to be safe in a series of 20 patients by Hafezi et al. Thinnest pachymetries in their cases were between 362 and 448 µm.[21] Even though CCT in case 1 was 428 µm, the *minimum* thickness was 274 µm, which may be beyond the safe limit of hypoosmolar swelling. Hypothetically, the use of hypoosmolar riboflavin solution could have triggered an acute hydrops in our case. Corneal swelling exerts mechanical stress on Descemet's membrane, especially at the thinnest region of the cornea. This could have led to its rupture, with subsequent influx of aqueous humor, further weakening the stroma by disruption of collagen fibers and ultimately leading to corneal perforation. However, this was neither obvious on split lamp examination nor histology. Recently, Hafezi et al. introduced the individualized "sub400 protocol" using an immediate hypoosmolar riboflavin imbibition for 20 minutes with an individualized UV-energy exposure.[22] This reduces the risk of excessive corneal swelling and stress for Descemet's membrane.

Less frequently, systemic conditions are associated with corneal melting. In both cases no clinical signs could be found for syndromes of abnormal collagen synthesis like Ehlers-Danlos syndrome or osteogenesis imperfecta, all associated with keratoconus. Rheumatoid arthritis as a cause of corneal melting was also excluded. However,

Table 1
Published cases with severe postoperative keratolysis causing melt and perforation after CXL in patients with keratoconus.

Author	N (cases)	Age (years), Sex	Other diseases	CXL Epithelium On/Off	Time to perforation (after treatment)	Microbiological test results
Rama et al. (2009)[10]	1	32, M	None	Off	5 days	Acanthamoeba
Labiris et al. (2011)[7]	1	23, M	None	Off	2 months	Negative
Rana et al. (2014)[11]	2	19, F	History of atopy with allergic eye disease	On	7 days	*Staphylococcus aureus*
		18, M	History of atopy with allergic eye disease	Off	2 days	MRSA
Maharana et al. (2018)[9]	1	11, F	Not known	Off	11 days	Alternaria spp.
Zhang et al. (2019)[8]	1	60, F	Potentially pathogenic variants in the ZNF469 gene	Off	8 days	Negative
Schear et al. (2020)[12]	1	17, M	Childhood asthma, Scheuermann's disease	Off	5 days	Unclear: "gram-positive spore-forming bacillus – unable to identify further, *Streptococcus parasanguinis*, *Streptococcus cristatus*, or *Neisseria* species."
Tillmann et al.	2	34, M	History of mild seasonal allergic rhinitis	Off	7 days	Negative
		16, M	None	Off	1 day	*Staphylococcus aureus*

history of unilateral hearing loss and spontaneous pneumothorax on the same side as the corneal melt, as well as striking red hair in case 1 were remarkable. Red hair and hearing loss have been described in brittle cornea syndrome (BCS), an autosomal recessive disease characterized by a thin and fragile cornea that tends to perforate spontaneously.[23] The BCS gene *ZNF469* on chromosome 16q24 has been suggested to play a regulatory and structural role in the assembly of collagen fibrils. Zhang et al. point out a possible association of corneal perforations after CXL and patients with pathogenic *ZNF469* variants.[8] *ZNF469* is mapped in close proximity not only to the location of the red hair-color gene, *MC1R*, but also to a suggested keratoconus locus on chromosome 16q22.3–q23.1 .[24,25] It is conceivable that patient 1 could harbor a sub-clinical mutation in *ZNF469* that led to corneal melting triggered by CXL. However, routine tests for these mutations are not available. The absence of genetic testing in this case is a limitation. As Zhang et al. proposed, identifying clinical and genetic risk factors, including screening of *ZNF469*, may be useful in the prevention of significant complications following CXL.

Case 1 had a history of mild seasonal allergic rhinitis. There is evidence that a history of atopia may increase the risk of post CXL-infection.[26] These patients may be candidates for dual antibiotic therapy.

4. Conclusion

CXL is considered a safe and effective method to mechanically strengthen the cornea in keratectasia or to prevent corneal melt and treat intractable microbial keratitis. However, our cases demonstrate that contrary to the intention, this treatment may also lead to acute corneal melting and perforation. The pathomechanism leading to this rare complication in our cases remains obscure but an individual risk including pathogenic ZNF469 variants or subclinical atopy as well as the intraoperative use of hypoosmolar swelling in a thin cornea are the most likely possibilities. Hence, safety parameters established by the CXL-inventors should be meticulously respected and patients appropriately counseled when indicating CXL for corneal ecstatic disease.

5. Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Declaration of competing interest

Dr. Seiler receives research fund by Avedro/Glaukos. Otherwise the authors declare that they have no financial interests to disclose relating to this manuscript.

All authors attest that they meet the current ICMJE criteria for Authorship.

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