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A troublesome triad: atopic dermatitis, conjunctival CIN, and recurrent corneal ulcers

INTRODUCTION

Atopic dermatitis (AD) is a dermatological disease leading to dry and scaly skin. Even though the causes for AD are not fully understood, there is strong evidence that mutations within the filaggring gene (FLG) strongly increase the risk for developing AD [1, 2]. Many AD patients suffer from severe chronic ocular surface disorders, indicating that AD leads to a complex immunological disturbance of the ocular surface. AD manifestations can involve the lid margin, the conjunctiva, the limbus, and the cornea resulting in any combination of blepharitis, conjunctivitis, limbal insufficiency and/or keratitis [3, 4]. Common clinical ocular problems are punctate epithelial keratopathy, persistent epithelial defects, shield ulcers, and corneal vascularization [5 - 7]. Additionally, bacterial and viral superinfections [8] as well as malignant tumors of the conjunctiva (e.g. conjunctival intraepithelial neoplasias [9]) can worsen the clinical course. Interestingly, apart from the ocular surface complications, AD is also associated with keratoconus [10].

We here present a patient suffering from a combination of severe surface alterations due to AD and additional pre-terminal glaucoma. The ocular surface alterations resulted in limbal insufficiency leading to recurrent therapy-refractory corneal ulcers in the right eye and complete corneal conjunctivalisation of the left eye. Additionally, a conjunctival intraepithelial neoplasia (CIN) in the right eye complicated the clinical course.

Management of AD associated ocular surface alterations is challenging. The increased incidence of ocular surface malignancies [11, 12], the worse outcome of glaucoma (i.e. due to the increased usage of topical and systemic steroids as well as due to scaring of the inflamed conjunctiva after filtrating surgery [13]), and severe corneal defects that are restricted in their curability, require complex immunosuppressive and surgical treatments as presented here in our clinical case.

CASE PRESENTATION WITH ILLUSTRATIONS

A 53-year old male patient was referred to our hospital for a second opinion in March 2010. Medical history revealed a severe atopic dermatitis and discitis.

Visual acuity in the right eye was 6/60 and defect light perception in the left eye. The patient had cataract surgery in both eyes in 1998 due to a bilateral steroid induced lens opacification. Both eyes had a long-term history of steroid-induced glaucoma with intraocular pressure in the OD up to 55 mmHg and several episodes of IOP exceeding 60 mmHg in the OS; the right eye underwent a trabeculectomy with mitomycin C (MMC) in 2005. Because of a progresssive endothelial decompensation in the right eye a Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) was performed in January 2009. Additionally, a trophic corneal ulcer occurred in the right eye in September 2009 once. The external ophthalmologists decided not to do any further operations in the left eye besides a removal of a small conjunctival cyst in December 2009 because of the absolute glaucoma.

The referral to our clinic was initiated by the patient's local ophthalmologist after histology of surface scrapes of the OD revealed atypical conjunctival alterations.

CLINICAL EXAMINATION

Clinical examination revealed anterior and posterior blepharitis in OU. The right eye showed limbal stem cell insufficiency, corneal and conjunctival scaring and a calcified corneal ulcer (fig. 1 and black arrow fig. 2). The bleb of the previous trabeculectomy (blue

arrow, fig. 2) was flat and densely vascularized. Limbal insufficiency involved the whole limbus resulting in conjunctival and corneal scaring and increased vascularization (green arrows, fig.2). Additionally, the inferior conjunctiva and the inferior cornea were covered with a flat whitish gelatinous tissue (fig. 1 – black asterisk, fig. 2, middle and inferior picture). The cornea of the left eye was completely covered with vascularized conjunctival tissue (fig. 1).

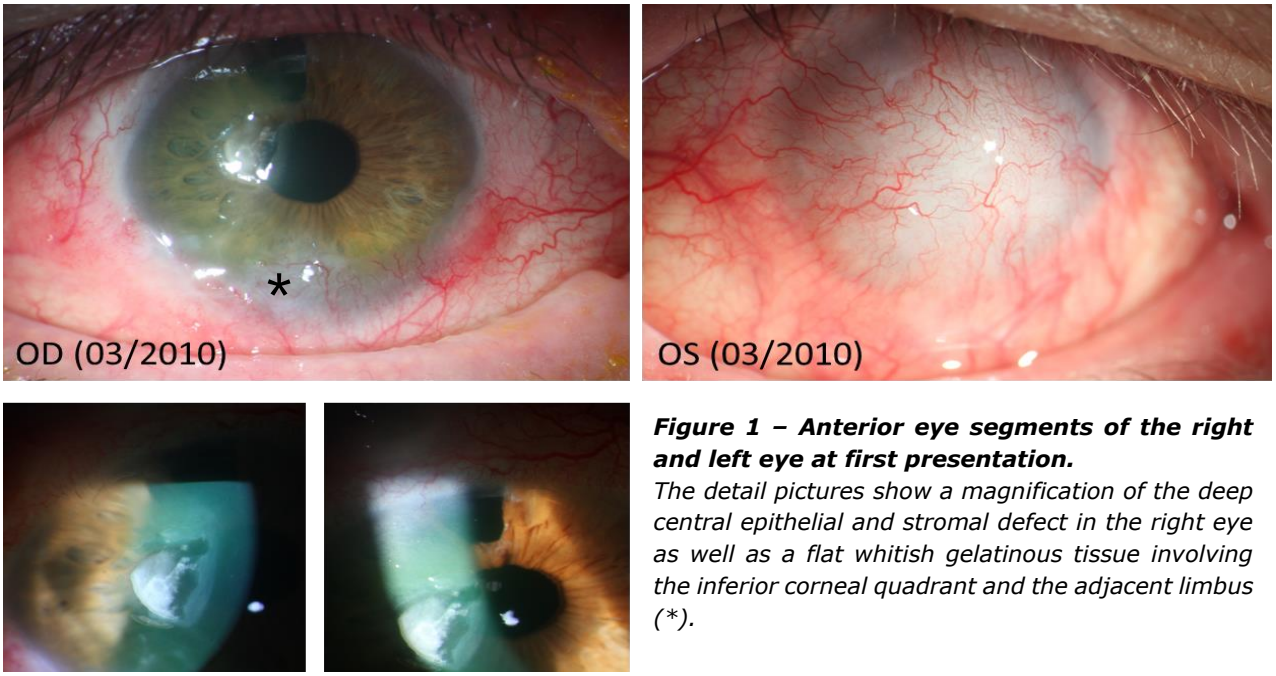

Figure 1 – Anterior eye segments of the right and left eye at first presentation.
The detail pictures show a magnification of the deep central epithelial and stromal defect in the right eye as well as a flat whitish gelatinous tissue involving the inferior corneal quadrant and the adjacent limbus (*).

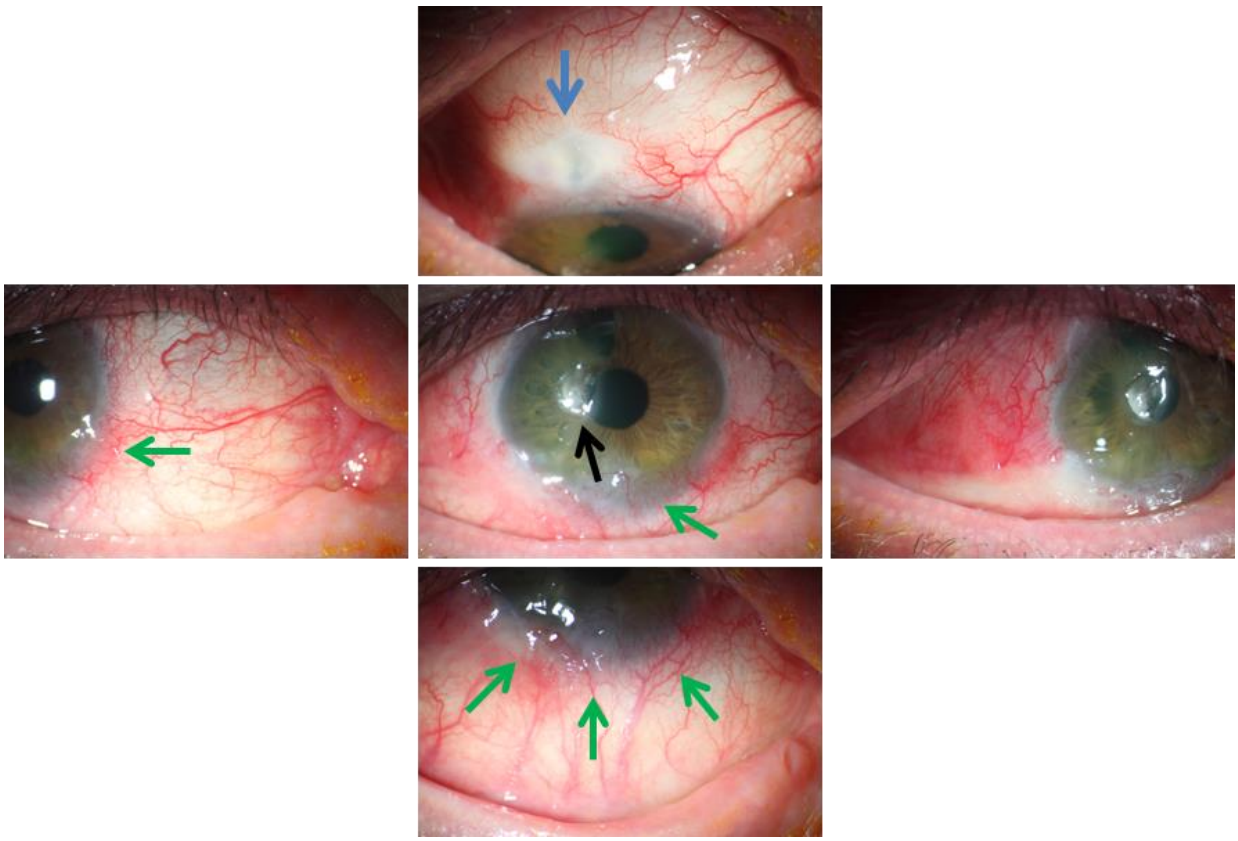

Figure 2 – Further details of the right anterior eye segment. *The bleb of the previous trabeculectomy (blue arrow) was flat and densely vascularized; limbal insufficiency involved almost the whole limbus (green arrows). Additionally, the inferior conjunctiva and the inferior cornea were covered with a flat whitish gelatinous tissue (middle and inferior picture and fig. 1).*

SUPERFICIAL KERATECTOMY AND HISTOLOGY

We removed the whitish conjunctival und corneal alterations by excising parts of the conjunctiva and performed a superficial keratectomy in the inferior corneal quadrant. Additionally, we used a 2 minute intraoperative MMC treatment and closed the defect with an amniotic membrane.

Histology of the excised specimen showed multiple epithelial islets (fig. 3 A and C) above connective tissue (fig. 3 D). The epithelium (fig. 3 B) contained cells with defect maturation in the upper epithelial layers and varying nuclei sizes, indicating the presence of a conjunctival intraepithelial neoplasia (CIN – grade I and II; Fig. 3 B, C, and E). The borders of the excised specimen were free of dysplastic epithelium.

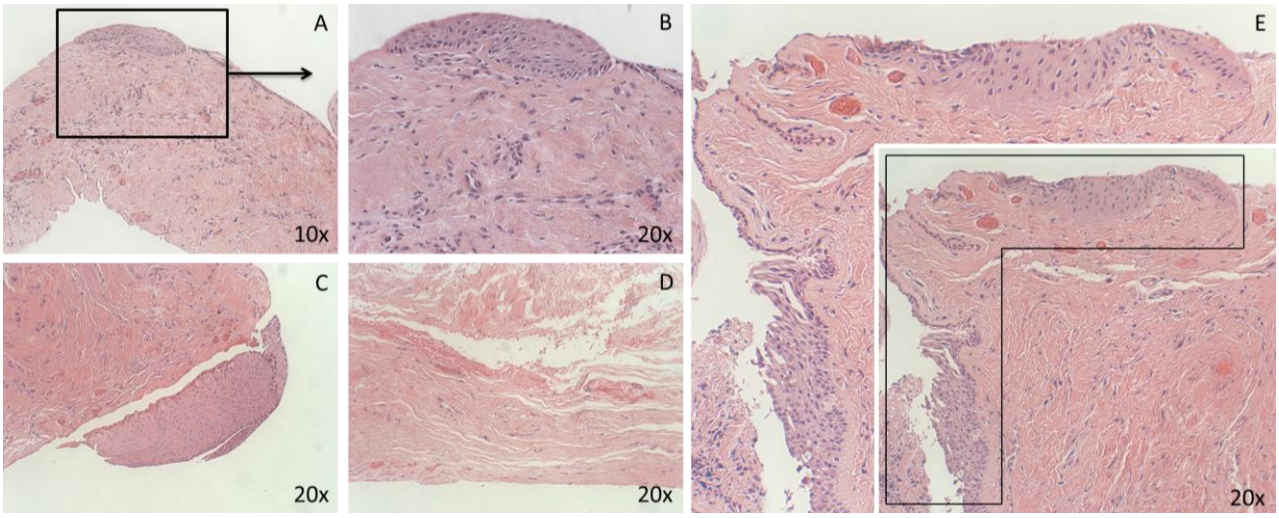

Figure 3 – Histological details of the CIN. *Histology of the excised specimen showed multiple epithelial islets (3A and 3C) above connective tissue (3D). The epithelium (3B) contained cells with defect maturation in the upper epithelial layers and varying nuclei sizes.*

We added a topical post-operative MMC treatment (0,02%; three cycles à two weeks with a one week break in-between each cycle) to prevent recurrence of the CIN [9].

Due to a bacterial-associated discitis in medical history the neurosurgeons and immunologists recommended not to prescribe systemic mycophenolate mofetil or systemic steroids; instead they recommended a trial with systemic cyclosporine A (CsA) treatment, keeping in mind the need of regular infectious-/immunological controls.

LIMBAL KERATOPLASTY

The regime was well tolerated. There were no signs of recurrence of the CIN after 24 months. To minimize epithelial toxicity we stopped the topical MMC treatment after three cycles and prescribed topical Elidel ointment for the peri-ocular skin (OU) as well as lubricating drops every hour in OU, topical anti-glaucomatous drops (dorzolamide combined with timolol twice daily w/o preservatives; OD), and ciclosporine A eye drops (0,1% twice daily, OD).

Unfortunately, the patient presented in A&E in November 2011 with a deep corneal ulcer in the right eye, a surrounding corneal epithelial defect, and sings of a bacterial keratitis. We prescribed topical antibiotics and immediately performed a steam cautery abrasion [14] [first description by Karl Wessely 1912] of the superinfected bacterial plug and injected subconjunctival steroids. We covered the deep corneal defect with amniotic membrane (sandwich graft). Within the following twelve weeks there were four more episodes of recurrent epithelial erosions which were handled with a bandage lens (fig. 4) under topical ofloxacin eye drops (5 times daily in the OD).

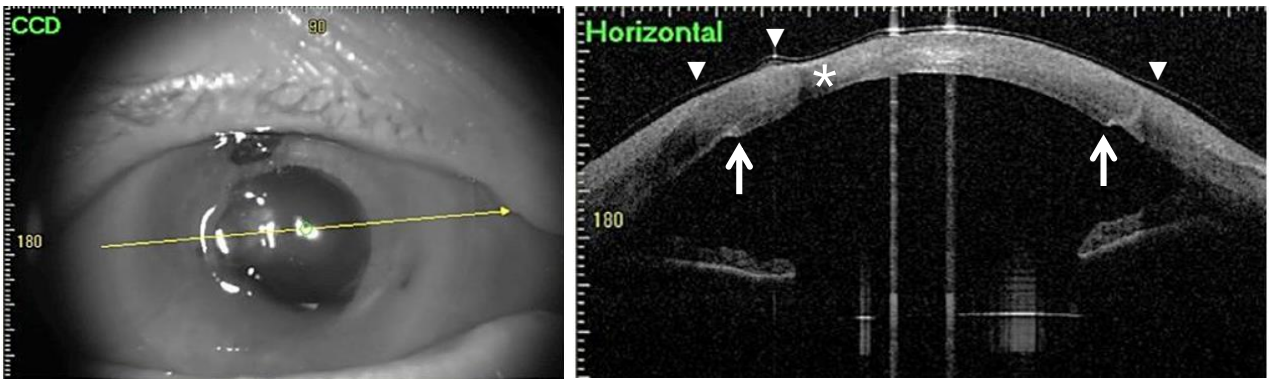

Figure 4 – The clinical course two years after first presentation. *The recurrent epithelial erosions required coverage with contact lenses (▼). Furthermore the corneal ulcer led to a progressive thinning of the corneal stroma (*); the borders of the previous DSAEK performed in 01/2009 can be detected (white arrows).*

Over the next three months the epithelial defect healed but there was a progressive conjunctivalisation of the cornea as seen initially only in the left eye (fig. 1; OS) which lead to a progressive decrease in vision in the right eye.

The conjunctival tissue covering the cornea could not easily be removed without causing further epithelial erosions due to the fragile epithelium in the right eye. The conjunctivalisation progressed until the complete cornea was covered, resulting in hand motion visual acuity in both eyes.

To regain vision in the right eye we discussed further surgical alternatives. Due to the fact that a DSAEK had already been performed in the right eye a Deep Anterior Lamellar Keratoplasty (DALK) was not possible. Penetrating keratoplasty is known to be a high-risk operation in AD patients; the rejection risk is significantly increased due to the ongoing surface inflammation [15, 16]. Additionally, the limbal insufficiency will promote continuous conjunctival overgrowth. We therefore decided to transplant an HLA-matched limbo-corneal allograft to minimize long-term postoperative surface problems [17].

The operation was performed in October 2013. Intraoperatively, the conjunctival tissue could be completely removed from the underlying corneal tissue. The surgery was uneventful.

POSTOPERATIVE FOLLOW-UP

So far the follow-up shows a clear graft. The corneal transplant has sufficient endothelial cell count (fig. 5C); visual acuity in the right eye improved to 6/12. Opposite of the grafted limbus the host limbus between 4.00 to 7.00 o'clock is not able to oppress conjunctival overgrowth – nevertheless the grafted limbus is able to maintain the corneal clarity of the graft center (fig. 5 A and B).

Furthermore, there is a beginning symblepharon formation in the inferior quadrant (fig. 5 B). Even though the patient is happy with the surgical outcome we plan to remove the symblepharon to improve the long-term outcome of the graft.

For the last eleven month after operation no corneal erosions or ulcers occurred. The transplanted limbus requires a sufficient vascularization, as it is the case (fig. 5 A).

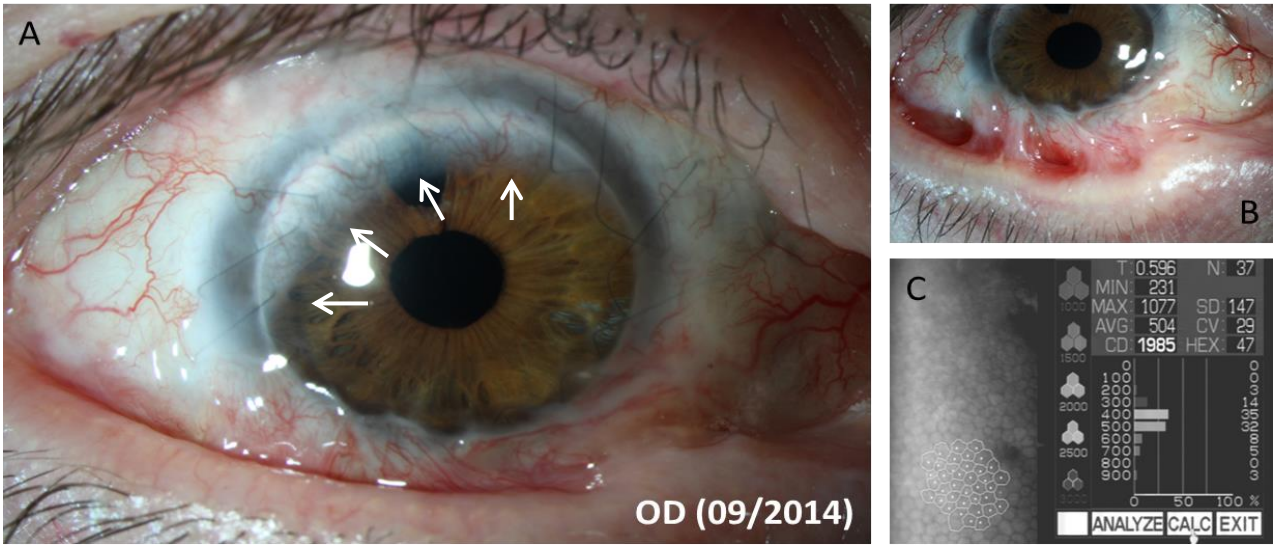

Figure 5 –Limbal corneal transplantation. *The limbus (fig. 5 A, arrows) is showing a sufficient vascularization; the corneal graft has a sufficient and stable endothelial cell count (fig. 5 C). Besides a symblepharon formation in the inferior quadrant (fig. 5 B), the grafted limbus is able to maintain the corneal clarity of the graft center.*

DISCUSSION

In our case the left eye only had hand motion vision due to steroid induced terminal glaucomatous optic nerve damage. The right eye showed limbal insufficiency and consecutive corneal ulcers as well as a conjunctival intraepithelial neoplasia.

Management of ocular complications resulting from AD is challenging. The right eye showed signs of a severe limbal insufficiency resulting in corneal conjunctivalisation additionally to recurrent epithelial defects and consecutive corneal ulcers. A conjunctival intraepithelial neoplasia – most likely related to the AD associated ocular surface alterations – complicated the clinical course. In the left eye the AD lead to a complete conjunctivalisation of the cornea.

AD leads to a breakdown of the ocular surface immune homeostasis resulting in limbal insufficiency, conjunctival dysplasia (e.g. CIN), epithelial defects, and consecutive conjunctivalisation. Dysplastic conjunctival tissue requires complete excision and intensified immunomodulating topical treatment – unfortunately these current therapeutic strategies are often toxic to the already (AD associated) pre-damaged limbal stem cells and the corneal epithelium.

To optimize the long term outcome in AD affected eyes limbal keratoplasty combined with systemic immunosuppression serves as an alternative to regular perforating keratoplasties. Transplanted donor limbal stem cells provide the basis preventing recurrent corneal ulcers; the intact limbal barrier prohibits corneal conjunctivalisation.

CONCLUSIONS

- Atopic dermatitis (AD) is often associated with various changes of the ocular surface
- AD leads to limbal insufficiency resulting in corneal neovascularisation and conjunctivalisation as well as in recurrent corneal erosions and ulcers
- Additionally, conjunctival neoplasia can complicate the clinical course
- Limbal keratoplasty is a surgical alternative to regular penetrating keratoplasties in eyes with severe AD associated ocular surface alterations

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