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 REPORT

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.

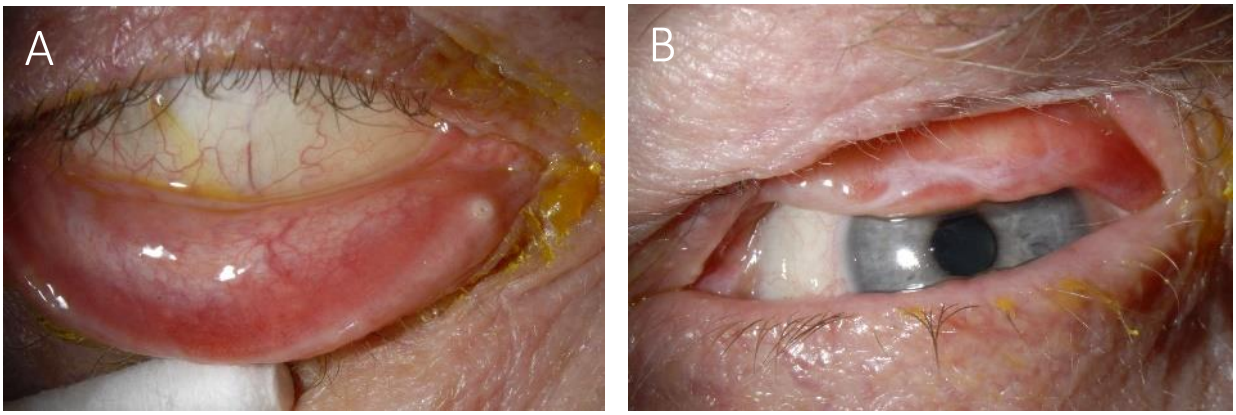

Figure 1: A) Right and B) left eye two months after first diagnosis of ocular GvHD. Marked subtarsal fibrosis of the left eye.

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.

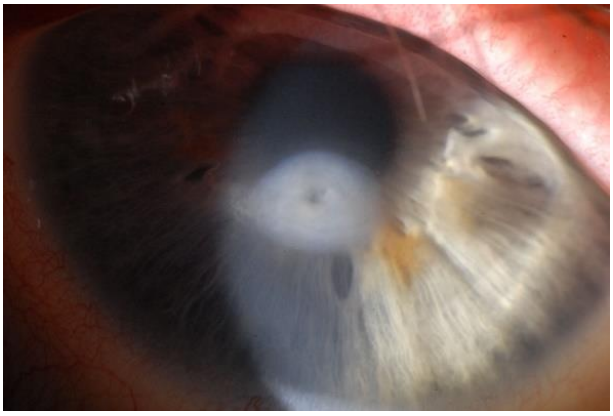

Figure 2: Left eye with perforated central ulcer.

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).

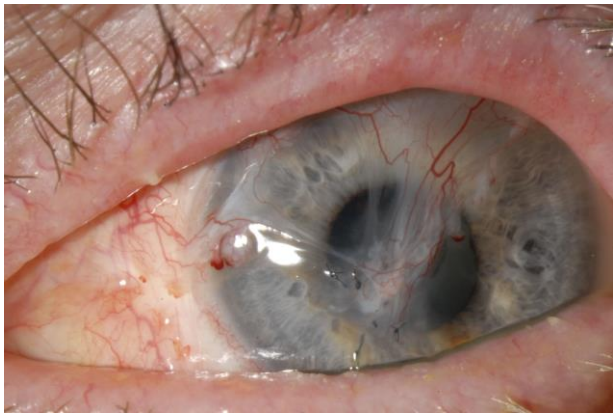

Figure 3: Left eye three weeks after conjunctival flap surgery using a modified Gunderson technique with temporary tarsorrhaphy.

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).

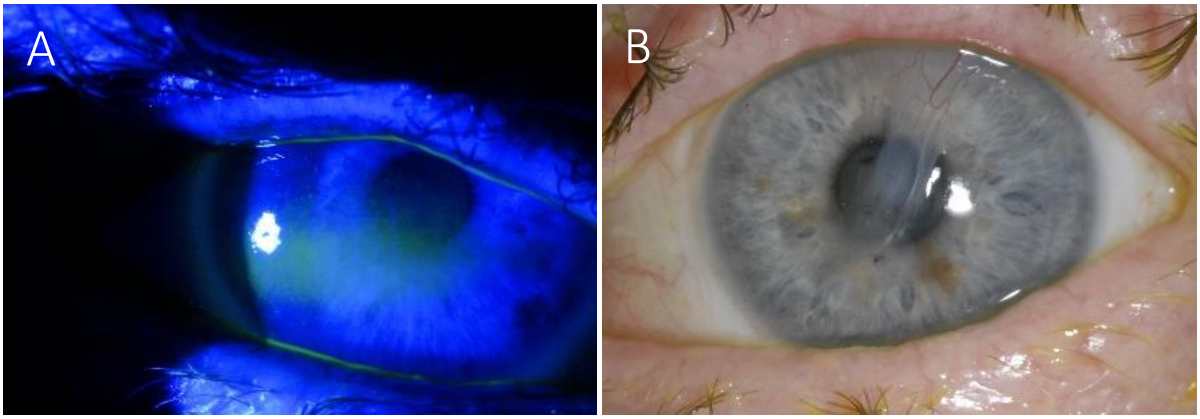

Figure 4: A) Superficial punctuate keratitis of the right eye. B) Left eye five months after conjunctival flap surgery and temporary tarsorrhaphy.

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.

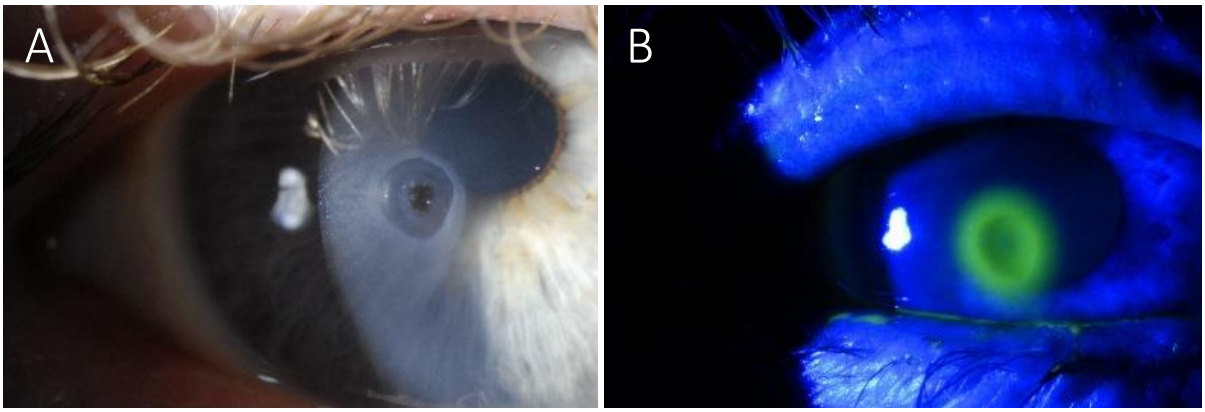

Figure 5: A) Perforated central ulcer of the right eye, B) with fluorescein staining.

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.

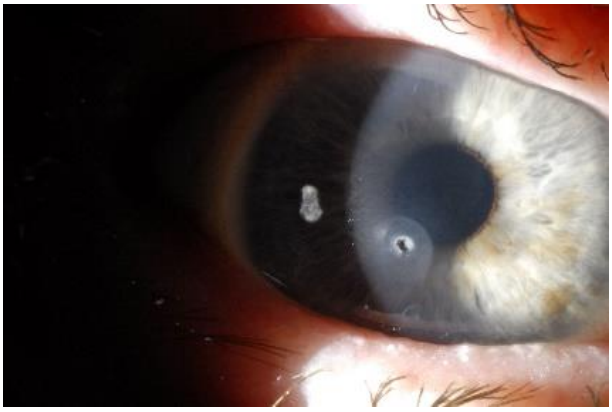

Figure 6: Right eye with perforated central ulcer: fibrosis of the corneal ulcer margins.

As on the other eye, we used a modified conjunctival flap technique according to Gunderson[7] (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).

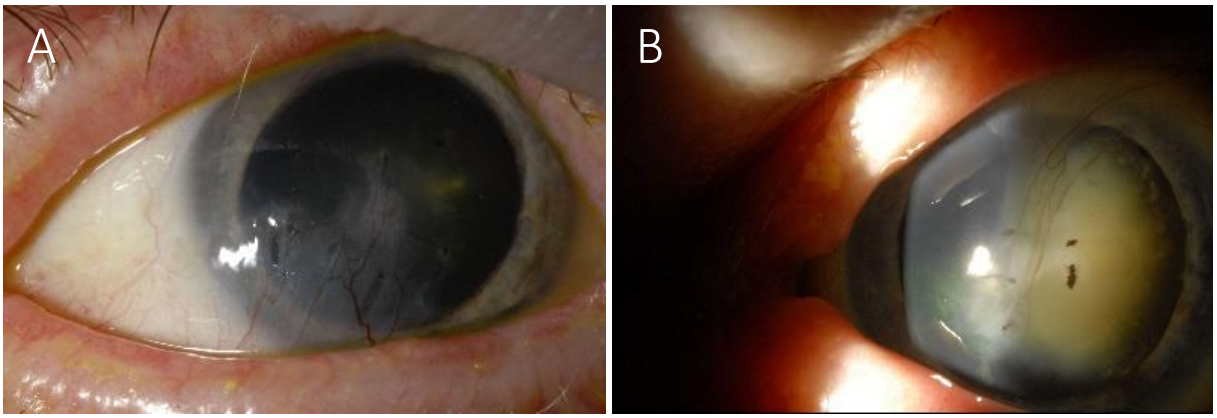

Figure 7: A) Right eye two months after conjunctival flap surgery and temporary tarsorrhaphy. B) Left eye one year after conjunctival flap surgery and temporary tarsorrhaphy.

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).

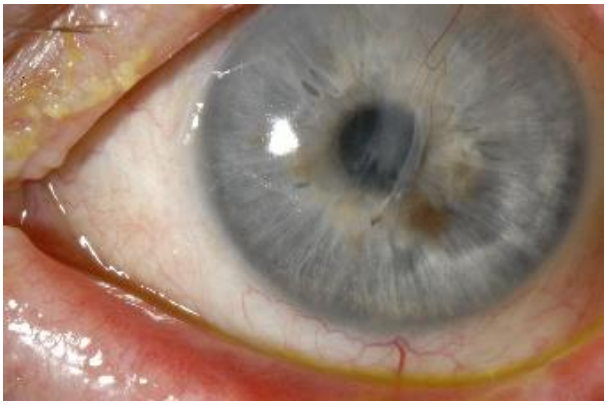

Figure 8: Left eye four weeks after cataract surgery.

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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