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Amniotic membrane transplantation in severe ocular surface disorders

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PURPOSE. *Amniotic membrane transplantation is currently being used as an alternative approach to treat severe corneal surface disorders refractory to medical therapy. The authors report complications of corneal surface disorders after successful amniotic membrane transplantation.*
METHODS. *Case series.*
RESULTS. *Twenty-eight patients with corneal surface disorders due to severe chemical burns, corneal ulceration, or persistent epithelium defects were treated with amniotic membrane transplantation. Four of these patients showed a spontaneous perforation and three patients developed a descemetocele within 6 weeks after the amniotic membrane transplantation.*
CONCLUSIONS. *In this case series, descemetocele and corneal perforation occurred in 25% of the patients after amniotic membrane transplantation. This might be due to the severity of the underlying disease or to the impact of amniotic membrane on corneal fibroblasts and collagenases. The risk of corneal thinning and perforation should be considered in the decision of treatment with amnion and follow-up regimen. (Eur J Ophthalmol 2008; 18: 691-4)*

KEY WORDS. *Amniotic membrane transplantation, Corneal surface disorder, Chemical eye burns, Corneal ulceration, Persistent epithelium defects*

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NTRODUCTION

Kim and Tseng (1) were the first to report the benefits of using amniotic membrane for corneal surface reconstruction. Human amniotic membrane transplantation is currently being used as an alternative approach to treat severe corneal surface disorders like corneal ulcerations, persistent epithelial defects, and chemical burns refractory to medical treatment (2-5). Non-healing states of corneal surface have a high risk of corneal perforation and infection if no treatment is given.
The basement membrane of the amniotic membrane supports the growth of the epithelial progenitor cells by prolonging their life span and maintaining their clonigenicity (6). This capacity might explain why amniotic membrane transplantation facilitates epithelization for persistent epithelial defects with corneal ulceration (2). The amniotic membrane stromal matrix suppresses the expression of certain inflammatory cytokines (7). The suppression of inflammation reduces conjunctival scarring, neovascularization, and fibrosis (8).
The suppressive influence of amniotic membrane on inflammatory cytokines might not only have a beneficial effect for corneal wound healing processes. In the present case series we present the outcome of amniotic membrane transplantation in patients with severe corneal surface disorders.

METHODS

Amniotic membrane transplantations were performed in 28 eyes of 28 patients with corneal surface disorders due

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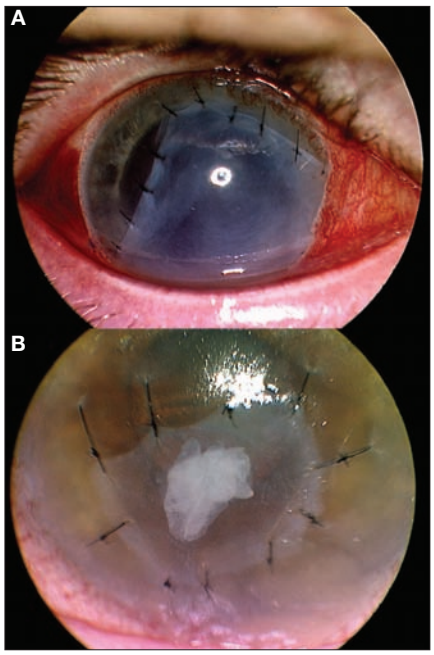

Fig. 1 - *Amniotic membrane transplantation.* **(A)** *Monolayered membrane in a patient after chemical burn.* **(B)** *Multilayered transplantation in a patient with a corneal ulceration.*

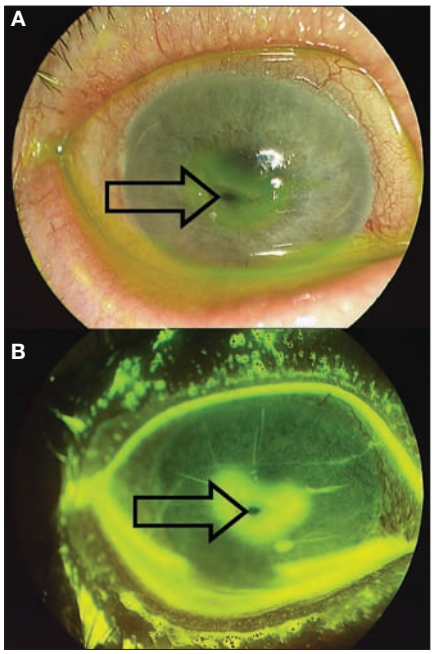

Fig. 2 - *Case 1: Patient with corneal ulceration and spontaneous perforation (arrow) in the center of ulcer 34 days after amniotic membrane transplantation. Ocular surface is colored with fluorescein.* **(A)** *Photograph.* **(B)** *Photograph with blue filter.*

to severe chemical burns (16 eyes), trophic corneal ulceration (9 eyes), and persistent neuroparalytic epithelial defects (3 eyes). The eyes of all subjects had no infectious infiltration of the cornea and the microbiological smears showed no bacterial or fungal infection. Human amniotic membrane grafts were prepared and preserved as previously described (2). The amniotic membrane transplantation was performed as described by Lee and Tseng (2) in a monolayered form (Fig. 1A) in 22 patients with a flat epithelial defect and in a multilayered form (3) in six patients with a deep stromal defect (Fig. 1B).

RESULTS

Twenty-one of 28 patients (75%) showed a stable surface without epithelial defects after amniotic membrane transplantation. Complications occurred in 4 of 16 patients with chemical burns (25%), in 3 of 9 patients with corneal ulceration (33%), and in none of the patients with persistent epithelial defect (0%). Four patients (two with chemical burns and two with corneal ulceration) showed a spontaneous perforation and three patients (two with chemical burns and one with corneal ulceration) developed a descemetocele within 6 weeks after amniotic membrane transplantation. In these seven eyes a penetrating keratoplasty à chaud had to be performed 27 ± 9 days after the amniotic membrane transplantation. We report two cases of the patients with perforation.

CASE REPORTS

Case 1

A 78 year-old woman had a deep trophic corneal ulcer in her right eye without signs of corneal healing after 32 days of topical medication. The microbiological smear showed no bacterial or fungal infection. Multilayered amniotic membrane transplantation was performed and a bandaged contact lens was placed on the surface to preserve the membrane. The 10.0 Vicryl sutures were removed 11 days later. Thirty-four days after amniotic membrane transplantation the patient showed a perforation in the center of the ulceration (Fig. 2, A, and B) and penetrating keratoplasty à chaud was performed.

Case 2

A 40 year-old man was treated for a persistent epithelial defect of the left eye after chemical injury with lime (Fig. 3A). Treatment with a bandage contact lens and excimer laser phototherapeutic keratectomy failed. Nine months after the accident there were no signs of epithelial healing. An overlay amniotic membrane transplantation as described by Letko et al (4) was successfully performed and

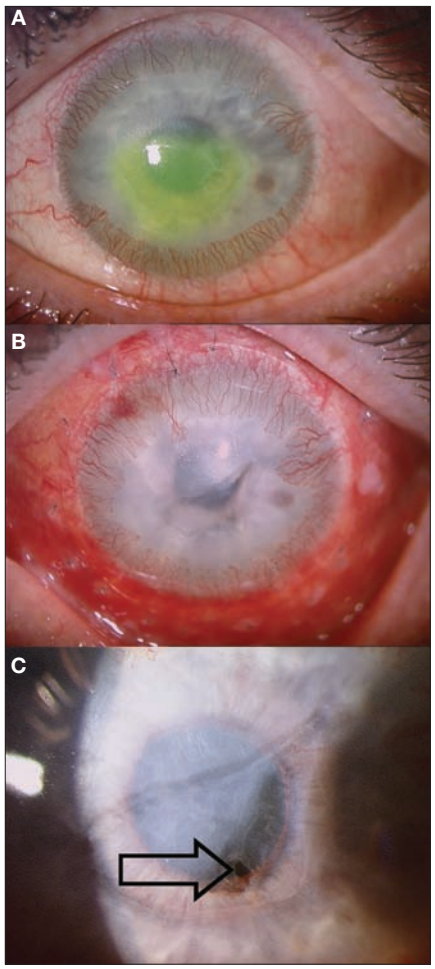

Fig. 3 - *Case 2: Patient with a chemical burned eye.* **(A)** *Persistent epithelial defect.* **(B)** *Ten days after amniotic membrane transplantation (the amniotic membrane may be barely detected).* **(C)** *Perforation (arrow) 13 days after amniotic membrane transplantation.*

bandage contact lens was inserted (Fig. 3B). Thirteen days after transplantation, a spontaneous perforation occurred in the center of the cornea (Fig. 3C) and a penetrating keratoplasty was performed on the same day.

DISCUSSION

The presented clinical case series confirms the results of previous reports on the benefit of amniotic membrane transplantation in corneal surface disorders refractory to non-surgical treatment. The success rate of 75% in our case series agrees with previously reported healing rates up to 70% after the first amniotic membrane treatment (4) and 73% after multilayered amniotic membrane transplantation (5). In our case series, 25% of the patients showed a severe progression of the corneal surface disorder after amniotic membrane transplantation.

Corneal perforation is one major complication of non-healing states of corneal surface if no treatment is given. The rate of perforation depends on the severity of the underlying disease. In our case series this complication could be prevented in most eyes after amniotic membrane transplantation. However, 11% of the eyes developed a descemetocele and 14% a corneal perforation. These complications potentially appeared due to progression of the corneal disorder despite treatment. On the other hand, the effects of amniotic membrane transplantation on corneal wound healing might be causative for progressive corneal ulceration.

This risk of corneal perforation might be supported by the inhibiting influence of amniotic membrane on corneal fibroblasts. Tseng et al revealed that human corneal fibroblasts cultured on human amniotic membrane showed a reduced DNA synthesis and reduced levels of TGF-beta1, 2, 3, and TGF-beta type II receptor transcripts (9). Amniotic membranes can suppress the TGF-beta signaling system although amniotic epithelium has been shown to produce TGF-beta (10). The inhibiting effect of amniotic membrane on the TGF-beta pathway leads to a suppression of the myofibroblast differentiation (9). These results account for the anti-scarring effects of amniotic membrane transplantation in surface reconstruction (11). In contrast, the suppression of the myofibroblast differentiation by amniotic membrane might explain the risk of corneal thinning and perforation after amniotic membrane transplantation in patients with corneal surface disorders.

Furthermore, it is known that matrix metalloproteinases produced by keratocytes can cause progressive stromal ulceration with risk of corneal perforation (12). Amniotic membrane reduces apoptosis in keratocytes after transplantation onto corneal surface (13) and expresses matrix metalloproteinase-9 (14). Increased levels of matrix metalloproteinase-9 may be a second reason for corneal perforation after amniotic membrane transplantation.

Another aspect of corneal perforation after amniotic membrane transplantation is the period of the corneal ulceration before transplantation. The longer the ulceration persists the higher is the activity of leukocytes and proteinases. A clinical sign for high activity of proteinases is the dissolution of amniotic membrane early after transplantation as shown in Figures 2A and 3C. The effect of amniotic membrane might be insufficient to suppress the persisting activity of leukocytes and to trigger epithelization.

An optimized time schedule for amniotic membrane transplantation might therefore be crucial in patients with corneal ulcerations. In our case series the seven patients

with corneal ulceration and a stable surface after amniotic membrane transplantation suffered from ulceration prior to the treatment for 1 up to 87 days (median 15 days). In the case series of Lee and Tseng (2) the period of corneal surface disorders was up to 52 weeks before transplantation was performed. Prospective studies are necessary to determine a potential benefit of early amniotic membrane transplantation.

In summary, our case series confirms the previously reported healing rates of corneal surface disorders after amniotic membrane transplantation. However, 25% of the patients showed severe complications with corneal thinning and perforation. This incidence might be due to the severity of the underlying disease or to the impact of amniotic membrane on corneal fibroblasts and collagenases. The potential risk of perforation after amniotic membrane transplantation should be considered in the decision of treatment with amniotic membrane. Further studies are required to investigate the effects of amniotic membrane transplantation on corneal wound healing processes.

The authors report no proprietary interest.

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