Amniotic Membrane Grafts for Nontraumatic Corneal Perforations, Descemetoceles, and Deep Ulcers

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Purpose: To describe the clinical outcome of amniotic membrane transplantation (AMT) for nontraumatic corneal perforations, descemetoceles, and deep ulcers.

Design: Retrospective, noncomparative, interventional case series.

Participants: Thirty-four eyes of 33 consecutive patients operated on for nontraumatic corneal perforations or descemetoceles at four academic departments of ophthalmology. Associated autoimmune disorders included rheumatoid arthritis (n = 6), Stevens-Johnson syndrome (n = 3), ocular cicatricial pemphigoid (n = 2), systemic lupus erythematosus (n = 1), and one eye with Mooren's ulcer, as well as neurotrophic, or exposure keratopathy (n = 10), postinfectious nonhealing ulcers (n = 6), and postsurgery (n = 5).

Intervention: Three or four layers of amniotic membrane (AM) were applied over the ulcer bed and anchored with 10-0 nylon interrupted or running sutures. A large AM piece was used as a patch to cover the entire corneal surface.

Main Outcome Measures: Formation of anterior chamber depth, epithelialization of the AM grafts, and stability of the corneal stromal thickness.

Results: The mean follow-up period was 8.1 ± 5.7 (ranging from 2–23) months. A successful result was observed in 28 of 34 eyes (82.3%). Of the successful cases, 23 eyes needed one AMT procedure, whereas 5 eyes needed two procedures to achieve a successful result. In five eyes, a subsequent definitive surgical procedure such as penetrating keratoplasty or lid surgery was needed. Failure was observed in six eyes with rheumatoid arthritis, neurotrophic keratopathy, or graft melting.

Conclusions: AMT is an effective method for managing nontraumatic corneal perforations and descemetoceles. It can serve as either a permanent therapy or as a temporizing measure until the inflammation has subsided and a definitive reconstructive procedure can be performed. This treatment option is also beneficial in those countries where corneal tissue availability is limited. *Ophthalmology 2002;109:694–703 © 2002 by the American Academy of Ophthalmology.*

Corneal perforations and descemetoceles may result from a variety of inflammatory or infectious causes. The short-term therapeutic goals include immediate sealing of aqueous leak, providing a tectonic support of the perforated or descemetocele site, and eliminating the causes of perforation while avoiding further damage to the anterior segment. Available therapies include tissue adhesives,[1–3] bandage contact lenses,[4] penetrating or lamellar keratoplasty,[1,5–7] patch grafts, or conjunctival flaps.[8] Unfortunately, these therapies are associated with a considerable number of complications. Penetrating keratoplasty (PK) performed to seal a corneal perforation may be complicated with synechiae, glaucoma, uveitis, and graft failure in the setting of an inflamed or infected eye.[5] Lamellar keratoplasty (LK) may provide an inadequate sealing, whereas in some cases it may even result in a double chamber between the donor and recipient cornea. Tissue adhesives may dislodge and are used as a temporary measure, obviating the need for a PK within a few days.[6,7] In addition, these procedures address only the tectonic problem, without solving the ongoing inflammation or severe aqueous tear deficiency encountered in small perforations or descemetoceles associated with

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rheumatoid arthritis or neurotrophic keratopathy.[6] Continued tissue degradation in these conditions may result in graft melting or dislodgment of the tissue adhesive.

One alternative for the management of small or impending corneal perforations is to reconstruct the surface with amniotic membrane (AM) grafts. AM is the innermost layer of the placenta and consists of a thick basement membrane and an avascular stroma. It can be used as a substrate to replace damaged mucosal surfaces and has recently been used successfully for reconstructing corneal[9–13] and conjunctival[14–16] surfaces damaged by various insults in various ocular surface disorders. These studies have shown that AM transplantation (AMT) facilitates epithelialization and reduces inflammation, vascularization, and scarring. Several studies have recently described the use of the AM for the management of deep corneal ulcers,[17] descemetoceles, and corneal perforations.[18–20] Herein we report the outcome of AMT for the initial surgical management of corneal perforations and descemetoceles.

Patients and Methods

Patients

This study included 34 eyes (33 patients) with small nontraumatic corneal perforations or descemetoceles, that were managed at four different facilities (Bascom Palmer Eye Institute, n = 8; Loyola University, n = 4; University of Essen, n = 10; Mahidol University, n = 12) from February 1995 through August 2000. Surgeries were approved by the respective institutional review boards of each of the participating centers and consecutively performed at each center. Indications for surgery included a corneal perforation of nontraumatic origin that is < 0.5 mm in diameter as assessed by slit-lamp examination with a positive Seidel sign or a descemetocele of any size. Patients in whom a large perforation was noticed with a flat chamber and iris prolapse were not eligible for this surgical procedure. Clinical data, including patient demography, etiology, surgical procedure, subsequent surgical procedures, visual acuity, and the final outcome and complications, were retrieved in a retrospective manner. All clinical data were entered into a standardized data form that was formulated by one of the authors (SCGT) and used by all participating surgeons. Patients were evaluated by their respective surgeons. Surgical success was defined as the cessation of aqueous leak, formation of a deep chamber, complete epithelialization of the AM outermost layer, and formation of a visible stromal thickness at the operated site by the first month of follow-up. Failure was defined as persistence or recurrence of aqueous leak, lack of epithelialization, or recurrent corneal ulceration. The need to perform a subsequent surgical procedure was considered a failure if the indication was tectonic support or sealing of a persistent leakage. If, however, AMT was beneficial in managing a perforation or a descemetocele, but a subsequent procedure, such as penetrating keratoplasty, was performed for improvement of vision (e.g., removal of a central scar), the initial AMT was considered a success.

Human Amniotic Membrane Preparation

The method of AM preparation has been previously described.[10,12,14] In this study, AM for two of the facilities (of AS, TJ, and SCGT) was obtained from Bio-Tissue (Miami, FL), where AM was similarly prepared. All donors whose placentas were processed at Bio-Tissue were screened against human immunodeficiency virus types 1 and 2, hepatitis B and C viruses, and syphilis at delivery and at 6 months after delivery. The other authors (PP, DM, and KPS) procured and preserved AM and screened the donors at their respective facilities following the same protocol.

Amniotic Membrane Transplantation

Patients were anesthetized with either a peribulbar block supplemented with intravenous sedation or general anesthesia. The base of the perforation or descemetocele site and surrounding thinned cornea were cleaned of the necrotic tissue (Fig 1A). After thawing, AM was removed from the filter paper and spread over the cornea with the basement membrane side facing up (Fig 1B). The side of the basement membrane could be distinguished from the stromal side by touching it with a sponge (i.e., Weckcel [Edward Weck & Co, Inc., Research Triangle Park, NC]); the latter is sticky, but the former is not. Three to four pieces of the AM were trimmed to fit the shape and size of the corneal ulcer, and applied one over the other to fill the ulcer bed (Fig 1C, D; Fig 2A). All AM layers were applied with the basement membrane side facing up. A running 10-0 nylon suture or a few interrupted sutures were placed to anchor the AM grafts to the cornea (Fig 1E, F; Fig 2B) with an attempt to include a few layers in the suture. Finally, a large piece of the AM was applied over the entire cornea as a temporary patch (Fig 1G, H; Fig 2C), and anchored with a running 10-0 nylon suture to the perilimbal episclera.

Postoperative medications included topical 1% prednisolone acetate and 0.3% ofloxacin four times daily. In cases that were culture positive, the preoperative topical fortified antibiotics (1.4% tobramycin with 5% cephazolin or 5% vancomycin) were continued postoperatively. In cases in which the anterior chamber was not reformed within the following 1 to 2 weeks, the patient underwent a second procedure of AMT. Patients were followed-up daily after the AMT procedure for the first week and thereafter weekly for the first 2 postoperative months.

Results

The demographic data, clinical presentation, and surgical outcome are summarized in Table 1. There were 34 eyes in 33 patients (13 men, 20 women). The average age was 56.3 ± 20.2 (ranging from 7–87) years. The mean follow-up period was 8.1 ± 5.7 (ranging from 2–23) months. The patients were further subdivided into four groups according to the underlying causes. The first group included 13 eyes in 12 patients with autoimmune disorders: rheumatoid arthritis (6 eyes), Stevens-Johnson syndrome (3 eyes), ocular-cicatricial pemphigoid (2 eyes), systemic lupus erythematosus (1 eye), and Mooren's ulcer (1 eye). The second group included 10 eyes with perforations or descemetoceles secondary to neurotrophic or exposure keratopathy. The third group (6 eyes) included postinfectious keratitis. The fourth group (5 eyes) included perforations or descemetoceles after various anterior segment surgical procedures.

AMT was successful in the reconstruction of the perforation or descemetocele in 28 of 34 eyes (82.3%) after one or two procedures. In these eyes, the visual acuity at the last follow-up improved by 4 lines or more in 8 eyes, by 1 to 3 lines in 12 eyes, and did not change in 14 eyes. One procedure of AMT was needed in 22 of the 28 successful eyes. In these eyes, no aqueous leakage was evident at any time after surgery, with reformation of the chamber depth at the first postoperative day. The outermost large patch of the AM dissolved in 2 weeks after surgery, and complete epithelialization over the AM graft that was implanted to fill the defect

Table 1. Patients Data and

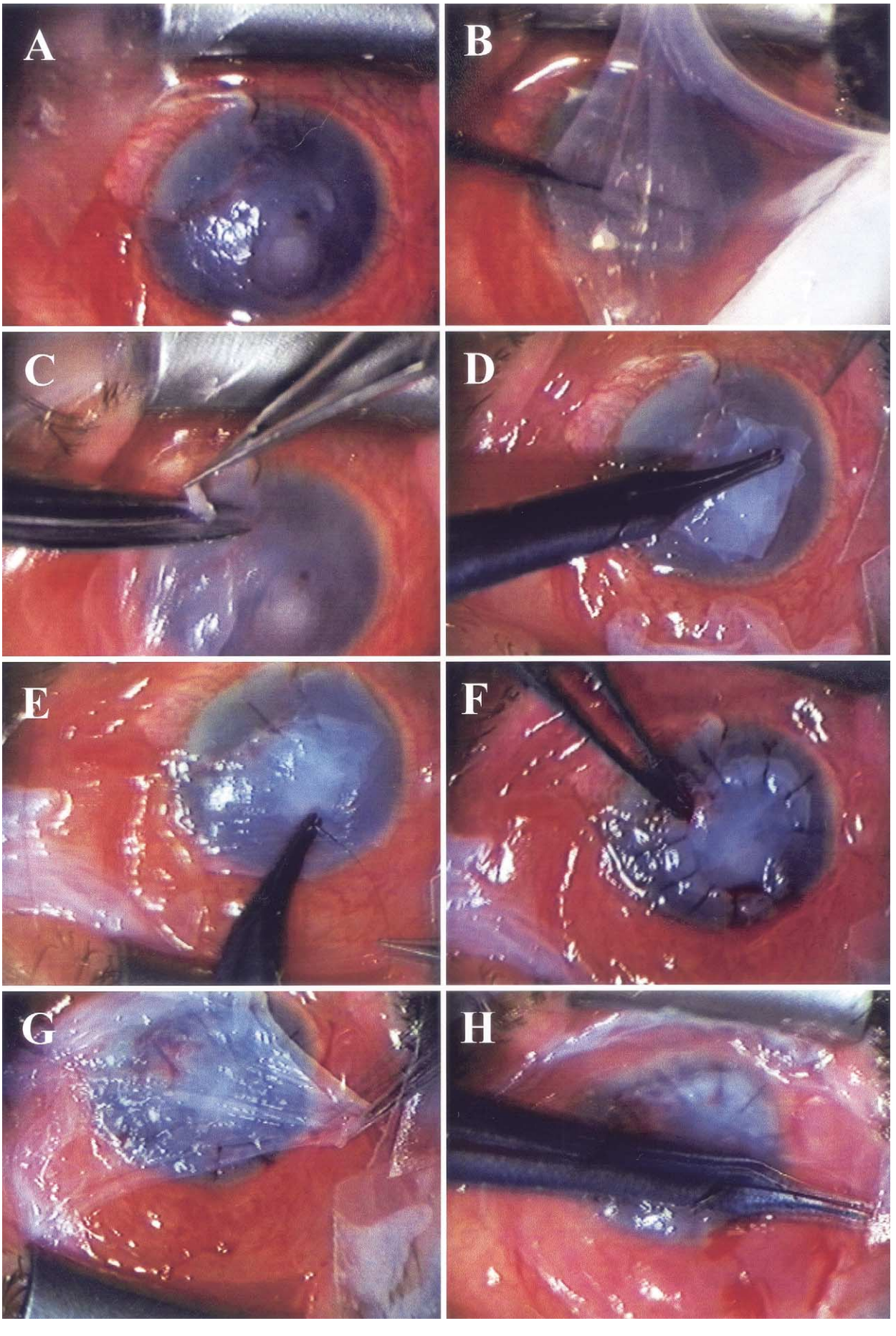
Patient No./ Gender/ Age	Eye	Diagnosis	Etiology	Surgical Management: *No. of Amniotic Membrane Transplant Procedures*	Surgical Management: *Subsequent Procedures*
Autoimmune disorders (RA and SJS)					
1/F/49	OD	Perforation	RA, KCS	1	Conjunctival flap
2/F/70	OS	Perforation	RA, severe KCS, recurrent corneal perforations	1	PKP
3/F/74	OS	Descemetocele	RA	1	
3/F/74	OD	Descemetocele	RA	1	
4/F/77	OS	Descemetocele	RA	1	Repeated PKP (3x) caused by corneal melting, punctal occlusion
5/F/64	OD	Deep ulcer/descemetocele	RA	1	Bandage CL, punctal occlusion, lid eversion to correct entropion
6/M/56	OD	Descematocele	SJS, severe limbal deficiency	1	
7/M/38	OD	Perforation	SJS, LD	1	PKP 1 month later
8/M/34	OS	Perforation	SJS	1	
9/F/77	OD	Descemetocele	OCP	2	Bandage CL
10/M/73	OS	Descemetocele	OCP	1	Punctal occlusion
11/F/62	OD	Deep ulcer/descemetocele	SLE	2	Dislocation of first AM, refixation and bandage CL, punctal occlusion
12/F/15	OS	Large deep ulcer/peripheral limbocorneal melting	Mooren's ulcer (unknown etiology)	1	Bandage CL
Neurotrophic keratitis/exposure					
13/M/62	OD	Neurotrophic ulcer, descemetocele	Acoustic neuroma with damage to C, N, V, VII, and VIII	2	Tarsorrhaphy
14/M/42	OS	Perforation	HSV, neurotrophic ulcer	1	
15/M/48	OD	Perforation	Neurotrophic ulcer	1	
16/F/77	OS	Descemetocele	Neurotrophic ulcer	1	PKP 3 months later
17/F/64	OD	Descemetocele	Neurotrophic, postradiation	5	Enucleation
18/M/34	OS	Perforation	HSV, neurotrophic ulcer	1	
19/F/73	OD	Descemetocele	Neurotrophic ulcer	2	
20/M/41	OD	Descemetocele	Neurotrophic ulcer & exposure, lid malposition secondary to radiation	2	
21/F/47	OS	Descemetocele	Exposure, lid malposition secondary to BCC	1	
22/M/53	OS	Perforation	Exposure, thyroid ophthalmopathy	2	
Infectious keratitis					
23/M/81	OS	Leakage from MRSA ulcer at graft–host junction	PKP for HSV	1	
24/F/7	OD	Perforation	HSV, neurotrophic ulcer, secondary bacterial infection	2	PKP 5 months later
25/F/68	OD	Perforation	Infectious ulcer	1	
26/M/43	OD	Descemetocele	Infectious ulcer	1	
27/M/66	OD	Deep ulcer with centrally located descemetocele	Infectious ulcer	1	Bandage CL
28/F/17	OS	Descemetocele	Infectious ulcer with hypopyon, necrotizing keratits, contact lens wearer	1	Bandage CL
Post surgery/trauma					
29/F/87	OS	Graft melt, thinning, and leakage at graft–host junction	PKP for PBK	1	PKP with Gunderson's conjunctival flap
30/F/52	OS	Descemetocele	PBK	1	
31/F/85	OD	Dellen, perforation	Dellen after cataract surgery	1	
32/F/61	OD	Descemetocele	Post phacoemulsification burn	1	
33/F/62	OD	Dellen/ descemetocele	Dellen after multiple cyclocryocoagulation	1	

AM = amniotic membrane; BCC = basal cell carcinoma; CF = counting fingers; CL = contact lens; CSA = cyclosporine A; HM = hand motion; HSK = methicillin resistant *Staphylococcus aureus*; OCP = ocular cicatricial pemphigoid; OD = right eye; OS = left eye; PBK = pseudophakic bullous keratopathy;

Surgical Outcome

Follow-up (mos)	Visual Acuity: *Preoperative*	Visual Acuity: *At Last Follow-up*	Outcome	Remarks
6	20/300	CF 4 ft	Failure	Perforated after 3.5 mos
2	LP	LP	Failure	Leakage at 2 wks
10	20/200	20/200	Success	Focal scar, no thinning
8	CF	20/40	Success	Focal scar, no thinning
12	HM	HM	Failure	Methotrexate, 7.5 mg, Im/wk for immunosuppression
2	20/200	20/50	Success	OD autologous serum as drops; azathioprine 2 × 50 mg/day; healed within 2 wks
4	HM	CF 1 ft	Success	
17	HM	HM	Success	
23	20/60	20/40	Success	Secondary ulcer after exposed suture
2	HM	CF	Success	First AM — dissolved 1 wk, second AM — healed at 3 wks; autologous serum as drops
10	20/200	20/40	Success	
2	CF	20/300	Success	Rod/cone dystrophy; systemic CSA; 2 × 50 mg/day and azathioprine, 75 mg/day
8½	20/300	20/30	Success	Stromal thinning but vascularized
18	20/200	20/100	Success	First AM — dissolved 1 wk, second AM — 3 wks healed
2	20/200	20/60	Success	
2	HM	CF	Success	
5	HM	LP	Success	
6	20/200	LP	Failure	Radiation keratopathy and retinopathy, blind painful eye, enucleated
7	20/200	20/200	Success	Later — HSK recurred, managed with antivirals
6	20/200	20/200	Failure	Lesion recurred 2 wks after each procedure, healed with pressure patch
10	LP	LP	Success	Lesion recurred 1 wk after primary procedure
15	20/80	20/40	Success	Exenteration for spreading BCC
7	20/80	20/40	Success	Leakage 1 wk after primary procedure
20	4/200	20/80	Success	Healed in 2 wks
12	HM	CF 1 ft	Success	Recurred 6 wks after first procedure
2	HM	CF	Success	Healed at 3 wks
2	20/30	20/25	Success	Map dot fingerprint epithelial dystrophy
2	20/80	20/30	Success	Healed within 9 days; systemic acyclovir
10	CF	20/100	Success	Healed within 3 wks; vascularized corneal scar
6	HM	HM	Failure	Healed 2 wks, MRSA ulcer recurred at 5 mos, with progressive thinning and descemetocele
9	CF	CF	Success	
12	CF	20/100	Success	Healed — 3 wks
13	20/40	20/40	Success	
2	20/80	20/40	Success	Cicatricial conjunctivitis, allergy

herpes simplex keratitis; HSV = herpes simplex virus; KCS = keratoconjunctivitis sicca; LD = limbal deficiency; LP = light perception; MRSA = PKP = penetrating keratoplasty; RA = rheumatoid arthritis; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus.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was evident in the ensuing 1 to 2 weeks (i.e., 3 to 4 weeks after the procedure). A stable stromal thickness with variable scar tissue developed within the first 3 months postoperatively. In most of the eyes it was possible to visualize the AM grafts as opaque or as semitransparent tissue that became incorporated in a scar tissue forming at that site. In all of these eyes there was an increase in the stromal thickness at the operated site.

In 6 of the 28 successful eyes (cases 9, 11, 13, 20, 22, and 24), a second AMT was needed to seal the perforation. In four of these six eyes (cases 9, 13, 20, and 22), the repeat AMT was performed when the first AM graft dissolved during the first postoperative week. In one eye (case 11), the AM graft was dislocated, and it was therefore resutured and secured with a bandage contact lens, resulting in a successful outcome. In another eye (case 24) of a 7-year-old girl, with herpes simplex keratitis and secondary bacterial infection and perforation, there was an initial sealing of the perforation. However, the graft failed to epithelialize, and the leakage was evident 6 weeks postoperatively. This patient had a repeat AMT, which resulted in a permanent seal and restored the stromal thickness, and subsequently received penetrating keratoplasty 5 months later to improve her vision.

A subsequent procedure was performed in 5 of the 28 successful cases. Penetrating keratoplasty for visual rehabilitation was performed in cases 7, 16, and 24 after 1, 3, and 5 months, respectively. This was performed after the initial wound had a stable and noninflamed scar tissue. One patient had surgery to correct entropion (case 5), and another needed tarsorrhaphy to control exposure keratopathy secondary to seventh cranial nerve damage (case 13).

In six eyes, AMT was not successful in sealing the leakage (three eyes) or in resolving the descemetocele (three eyes). Three of the six failed eyes had severe keratoconjunctivitis sicca secondary to rheumatoid arthritis (cases 1, 2, and 4), two eyes had neurotrophic keratopathy (cases 17 and 19), and one eye had an ulcer and melting at a corneal graft wound (case 29). Case 1 had an initial good result but developed marked thinning at the operated site, which eventually perforated 3.5 months after the procedure. A conjunctival flap was applied over the thinned cornea. Case 2 had severe keratitis sicca and had been previously operated on twice with a corneoscleral lamellar graft for recurrent peripheral corneal ulceration. AMT was performed for a central corneal perforation and rendered her eye quiet and the anterior chamber reformed. However, the leakage from the perforation site became evident 2 weeks later, leading to a flat anterior chamber. Therefore, a PK was performed. Case 4 failed after progressive corneal melting, and subsequently required three PK procedures. Case 17 had a severe postradiation neurotrophic keratopathy and retinopathy. Because PK was likely to fail because of his severe aqueous tear deficiency, five repeated AMT procedures were performed to seal the perforation. He eventually had intractable pain develop, and because his vision was light perception, it was decided to enucleate the eye. Case 19 had a descemetocele develop in a neurotrophic ulcer. The AM grafts detached within a few days after the procedure, and a repeat AMT was performed, which dissolved after 2 weeks with descemetocele. The patient finally healed after a prolonged period of pressure patching. The sixth failed case (case 29) had melting and an aqueous leak in a corneal graft wound performed for pseudophakic bullous keratopathy. The wound initially healed 2 weeks after AMT, and she had a deep chamber with a quiet ocular surface 3 months postoperatively. Five months after surgery, she had a methicillin-resistant *Staphylococcus aureus* ulcer develop, with progressive thinning and descemetocele, which was managed with PK and a conjunctival flap.

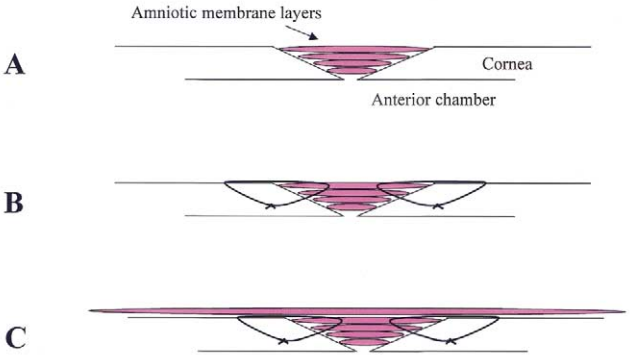

Figure 2. Schematic drawing showing the orientation of the amniotic membrane (AM) grafts in the ulcer bed. **A,** Application of a few layers of AM. **B,** Anchoring sutures of the AM to the cornea. **C,** AM patch covering the entire cornea.

Representative Cases

Perforated Herpes Simplex Neurotrophic Ulcer. *Case 14.* A 42-year-old male presented with a persistent nonhealing corneal ulcer in his left eye from an unknown cause after foreign body sensation that started a month before his referral. His visual acuity was 20/200. He had a deep corneal ulcer in the lower part of the left cornea, measuring 3.5 mm × 3.5 mm, with a loss of 90% of the stromal thickness in the center of the ulcer. He was managed topically with nonpreserved 1% methylprednisolone and 0.3% ofloxacin and with doxycycline tablets (100 mg a day). Two weeks later he was seen with a perforation at the center of his ulcer (Fig 3A). With the patient under general anesthesia, AMT was performed using three layers to fill the ulcer bed. The anterior chamber was formed but shallow the first postoperative day. Two weeks later, the chamber was deep, and the AM graft was completely epithelialized (Fig 3B, C). A new epithelial defect appeared supranasal to the AM graft with surrounding stromal edema. A diagnosis of herpes simplex keratitis was made, and the patient was started on systemic acyclovir, 200 mg, five times a day. The sutures were removed 5 weeks postoperatively. During the following weeks, new blood vessels and scar tissue developed in the operated area, with complete healing of the epithelial defect (Fig 3D). The stromal thickness at the perforation site seemed normal and stable with a deep anterior chamber.

Perforated Microbial Ulcer. *Case 25.* A 68-year-old woman had a blunt trauma to her right eye 25 years previously and had a traumatic cataract and angle recession. Three years earlier, she had trabeculectomy with mitomycin, anterior vitrectomy, and placement of anterior chamber lens. Her vision was limited to 20/70 because of chronic cystoid macular edema. She had a large corneal ulcer at the superior part of the cornea, which was cultured positive

Figure 1. Surgical steps for repair of a corneal perforation with multilayer amniotic membrane grafts. **A,** The base of the perforation site is cleaned off. **B,** The amniotic membrane (AM) is removed from the filter paper and spread over the cornea with the basement membrane side facing up. **C,** The first AM layer is trimmed to fit the ulcer size. **D,** Several layers are placed on top of each other to fill in the ulcer, all with the basement membrane side facing up. **E,** Interrupted sutures are placed to anchor the AM grafts to the cornea. **F,** The knots are buried. **G,** AM patch is applied over the entire cornea. **H,** A running 10-0 nylon suture anchors the AM patch to the perilimbal episclera.

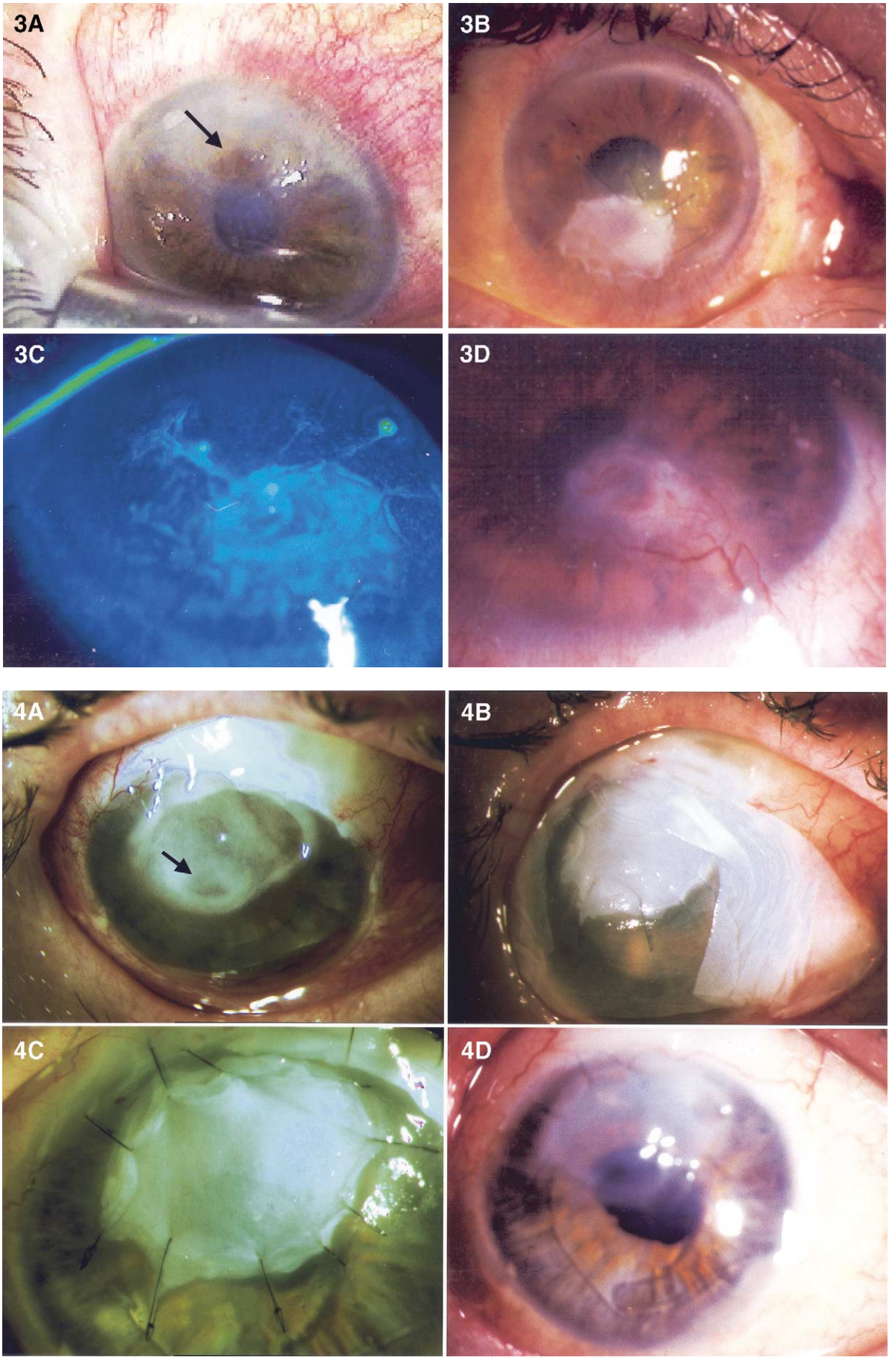
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Figure 3. A, Surgical microscopic view of a 42-year-old male who had a progressive corneal ulceration develop that eventually perforated (arrow). Three-layer amniotic membrane transplantation was performed with the patient under general anesthesia. **B** and **C,** Two weeks postoperatively, the anterior chamber was deep, and the amniotic membrane graft was fully epithelialized. **D,** Scar tissue with neovascularization 3 months postoperatively. **Figure 4. A,** A 68-year-old female presented with a nonhealing deep corneal ulcer (arrow) after infection with *Pseudomonas*. **B,** One week later, the anterior chamber was deep, and the amniotic membrane (AM) patch began to dissolve. **C,** Two weeks postoperatively, the AM graft is epithelialized, and the anterior chamber depth is stable. **D,** A stable corneal scar with normal thickness and regular epithelial surface is evident 7 months postoperatively.

for *Pseudomonas aeruginosa*, and her visual acuity worsened to hand motions. The ulcer was managed with topical 5% cephazolin and 1.4% tobramycin for 2 weeks. The infiltrate resolved after 2 weeks, and the topical antibiotics were tapered. However, the ulcer failed to epithelialize and progressively thinned at the upper portion (Fig 4A). A week later, as the ulcer became extremely thin and persistent, it was decided to perform multilayer AMT. The AM patch remained attached to the surface for 3 weeks (Fig 4B, C). A month after surgery, the AM graft was completely epithelialized (Fig 4D). The cornea was thin at the ulcer site, but stable at the last visit (i.e., 7 months after surgery).

Discussion

Corneal perforations and descemetoceles are the final outcome of a process of tissue degradation resulting from inflammatory or infectious insults.[21] Tissue degradation may continue even after surgical repair of corneal perforation and deep ulcers is performed and may limit the success of PK or LK and tissue adhesives. An ongoing inflammatory insult to the ocular surface, as in ulcers associated with rheumatoid arthritis or herpes simplex keratitis, may cause early rejection of corneal grafts. Previous studies have shown that emergent PKs in perforated eyes have higher rates of graft failure than those that are performed several weeks to months after the perforation had occurred.[1,5,22] The use of tissue adhesives is also limited for a large perforation and may need to be reapplied as a result of dislodgment from the ulcer bed because of mechanical disruption or continuous inflammation and tissue destruction in the surrounding stroma.[3]

Therefore, the strategy of managing corneal perforations caused by inflammation or infection cannot simply address the tectonic aspect but must also solve the continuous destruction of the corneal stroma leading to perforation. Surface reconstruction must include filling in new collagen to the ulcer bed, as well as a new basement membrane to promote rapid epithelialization while suppressing inflammation and avoiding LKs or PKs. By postponing such definitive surgical procedures as PK or LK until the inflammation has subsided, the success rate may be promoted. In this regard, human AM, which consists of a thick basement membrane and an avascular stroma, may be an effective alternative. We and others have found that AMT is beneficial for corneal and conjunctival surface reconstruction in a variety of indications. AMT can promote healing of persistent corneal epithelial defects[10,17,23] and create a stable healthy epithelium in bullous keratopathy.[13] AM has also been found to be useful in conjunctival surface reconstruction after removal of large conjunctival lesions such as pterygium, conjunctivochalasis (a redundant conjunctiva), tumors, symblepharon, and scars.[14,15,24–27]

Our study demonstrated successful results in managing corneal perforations and descemetoceles in 28 of 34 eyes (82.3%), of which 22 needed one procedure, and 6 others needed two procedures to achieve good sealing. Our report is the largest case series to date presenting AMT as a feasible surgical treatment for a variety of ocular surface disorders in which progressive tissue, degradation has resulted in loss of corneal tissue leading to a perforation or an impending perforation. We found that the ocular surface inflammation was markedly reduced with complete epithelialization in 3 weeks, and stable corneal thickness was demonstrated within the first 2 months postoperatively. Our experience is comparable to that of two recent studies using the same method for managing deep ulcers and corneal perforations, which reported similar success rates in 8 of 11 eyes[18] and in 9 of 11 eyes,[17] respectively. These latter studies have noted complete epithelialization in the first 4 weeks with suppression of inflammation and a stable corneal thickness during the ensuing months.

Five of our six failed eyes were in patients with rheumatoid arthritis or neurotrophic keratopathy, and were associated with severe keratitis sicca and exposure. Similarly, neurotrophic keratopathy[17] and rheumatoid arthritis[18] were noted to be the main causes associated with failure in previous studies. In eyes that have neurotrophic keratopathy, additional measures such as permanent punctal occlusion and tarsorrhaphy may increase the likelihood of success. The management of perforation resulting from rheumatoid arthritis is difficult, and conventional therapies are associated with a high risk of graft failure, recurrent graft melts, and failure of tissue adhesives.[6] To prevent the ongoing inflammation from inflicting more damage to the surface, systemic immunosuppression may help in preparing such eyes for reconstruction.[6,28,29] Nevertheless, AMT as a temporizing measure is useful in controlling inflammation and gaining time before PK or LK, as seen in case 1, in which the AM graft lasted for 3.5 months (Table 1). This temporizing role of multilayered AMT was further demonstrated in three successful cases that then underwent a PK a few months after AMT.

The therapeutic effect of AM in managing perforations and deep ulcers may involve two basic actions that work synergistically in suppressing inflammation and promoting epithelialization. The AM stromal matrix was found to suppress the expression of certain inflammatory cytokines that originate from the ocular surface epithelia, including interleukin-1α and interleukin-1β,[30] interleukin-2, interleukin-8, interferon-γ, and tumor necrosis factor-α (Bültmann S, et al. Invest Ophthalmol Vis Sci 1999;40[Suppl]:S578, Heiligenhaus, et al. Invest Ophthalmol Vis Sci 2000; 41[Suppl]:S56, Tsai, et al. Invest Ophthalmol Vis Sci 2000; 41[Suppl]:S454). In addition, AM contains various forms of

protease inhibitors[31] and is capable of excluding inflammatory cells by facilitating rapid apoptosis.[32,33] The suppression of inflammation is a key element in preventing further tissue degradation of the corneal stroma. The temporary patch that covered the entire cornea (Fig 1C; Fig 2H) further augmented the effect of suppressing inflammation. We have recently demonstrated the profound antiinflammatory effect of a large AM patch sutured over the entire ocular surface after acute chemical or thermal burns.[34]

The second key action of AM in restoring the healthy surface is to promote rapid epithelialization over its basement membrane. It has been reported that AM supports the normal phenotype of a nongoblet conjunctival epithelium in culture[35,36] and AMT maintained a normal conjunctival epithelium with goblet cell differentiation in vivo.[16] Lately, experimental data from our laboratory further support that AM had a high content of nerve growth factor and permit corneal epithelial cells to express TrkA, a high-affinity receptor for nerve growth factor (Touhami et al, Invest Ophthalmol Vis Sci 2001;41[Suppl]:S303). Nerve growth factor has been reported to promote healing of neurotrophic corneal ulcers.[37] Collectively, these actions may explain why deep ulceration and perforation can be effectively repaired by AM.

In conclusion, we have demonstrated the efficacy of AMT in repairing deep corneal ulcers leading to perforation or descemetoceles that result from inflammation or infection in severe ocular surface diseases. AM can serve as either a definitive or a temporizing treatment during this acute situation, so that the definitive PK or LK can be avoided or postponed to increase the graft's success. This usefulness is of paramount importance in those countries in which there is a shortage of corneal tissues. Its antiinflammatory properties and contents of a basement membrane and collagen without allogeneic cells render the AM an ideal substrate replacement for repairing deep ulcers and perforations associated with inflammation-mediated tissue destruction.

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