Amniotic Membrane Transplantation in Children With Symblepharon and Massive Pannus

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Objective: To report our pediatric experience with amniotic membrane transplantation for ocular surface and fornical reconstruction.

Methods: Retrospective case review of children who underwent superficial keratectomy, symblepharon lysis, and fornical reconstruction using amniotic membrane transplantation. The underlying diagnosis, visual acuity, level of discomfort at first and last visits, and surgical details were noted.

Results: Four patients (5 eyes) were included. Two patients had epidermolysis bullosa (1 recessive dystrophic and 1 junctional), 1 had laryngo-onychocutaneous syndrome, and 1 had measles-related keratitis and was positive for human immunodeficiency virus. Their mean age when initially seen was 8.7 years (age range, 4-16 years), and mean follow-up was 18.25 months (range, 12-29 months). The mean visual acuity preoperatively was 1.1 logMAR (logarithm of the minimum angle of resolution) (range, 1-1.3), and postoperatively was 0.7 (range, 0.2-1.2). All patients experienced increased ocular comfort with anatomical restoration of corneal and conjunctival surfaces. Visual acuity improved in 3 eyes. Only the patient with laryngo-onychocutaneous syndrome had recurrence of granuloma, at 9 months after surgery.

Conclusion: Amniotic membrane transplantation with symblepharon lysis is effective for ocular surface reconstruction in the management of epidermolysis bullosa and other conditions that cause corneal scarring and symblepharon in children. In this small series, children with epidermolysis bullosa fared better and the effects of surgery lasted longer compared with patients with other causes of symblepharon and massive pannus.

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ALTHOUGH HUMAN AMNIO-otic membrane has been used previously,\(^1,2\) its recent use in the treatment of ocular disorders has been popularized by Kim and Tseng.\(^3\) Amniotic membrane forms the innermost layer of placenta and consists of a thick basement membrane that promotes epithelial cell migration and adhesion and an avascular stromal matrix that reduces inflammation, fibrosis, and neovascularization. It has been used in the treatment of conjunctival disorders,\(^4,5\) persistent corneal epithelial defects,\(^3\) and painful bullous keratopathy.\(^6\) Although there are case reports of the use of amniotic membrane transplantation (AMT) in children,\(^7,8\) there is little in the literature about its use in pediatric ocular surface and fornical reconstruction in patients with severe pannus and symblepharon.

REPORT OF CASES

CASE 1

A 4-year-old girl with dystrophic epidermolysis bullosa (EB) was seen in August 2003. At examination, visual acuity was 1.2 logMAR (logarithm of the minimum angle of resolution) OD and 0.5 logMAR OS using the Kays Picture test. There was bilateral symblepharon formation, inferiorly in the right eye (Figure 1A) and temporally in the left eye, with severe corneal pannus. Treatment with topical fluorometholone 0.1% suspension and lubricants was begun, and right-sided symblepharon lysis and AMT were performed in October 2003. Postoperative treatment included frequent application of topical, preservative-free dexamethasone and chloramphenicol eyedrops, with tapering over a few weeks. Visual
acuity improved to 0.5 logMAR OD. Vision in the left eye deteriorated, and left-sided symblepharon lysis and AMT were performed in June 2004. At last follow-up 29 months postoperatively, visual acuity was 0.2 OD and 0.4 OS using Kays Picture test. The patient was able to open her eyes comfortably, with well-formed fornices. The corneal surface was healthy, with some peripheral superficial corneal scarring at the site of the original symblepharon.

An 8-year-old boy with junctional EB was seen in June 2002, although, according to his mother, he had ocular involvement since the age of 2 years. Ophthalmic examination revealed rotatory nystagmus, perception of light acuity bilaterally, and dense bilateral symblepharon (Figure 2A). Ultrasonographic and electrodiagnostic examinations yielded normal findings. Despite a guarded prognosis, at his mother’s insistence, in June 2004, symblepharon lysis and fornix reconstruction with AMT were performed in the left eye. Postoperative treatment included a combination of topical steroid and antibiotic eyedrops. At 6-week follow up, visual acuity improved to counting fingers close to his face and the nystagmus had disappeared. The fornices were well formed and there was some subconjunctival scarring (Figure 2). Treatment with cyclosporin eye ointment at night and steroid eyedrops was initiated. Three months later (Figure 2B), visual acuity was hand movements OS, but there was a small inferotemporal recurrence of symblepharon. The cyclosporin ointment therapy was increased to 3 times daily, together with prednisolone eyedrops and chloramphenicol ointment. The prednisolone was tapered over the next 12 months. At last follow-up 19 months postoperatively, visual acuity had improved to 0.5 OS crowded logMAR at 50 cm. The inferotemporal symblepharon persisted; therefore, prednisolone therapy was reinstituted 4 times a day and the cyclosporin ointment was discontinued.
CASE 3

A 16-year-old girl with laryngo-onychocutaneous (LOGIC) syndrome was seen in October 2002. She had consanguineous Asian parents and a history of surgical resection of recurrent conjunctival granulomas, with adhesions to the cornea, from the age of 2 years. When first seen, visual acuity was hand movements OD and 0.9 logMAR OS. There was marked right corneal vascularization with ghost vessels and a localized inferotemporal symblepharon, together with an area of deeply staining conjunctival ulceration associated with tarsal conjunctival granulomas. The left cornea showed areas of vascularization related to symblepharon at the 2-o’clock and 6-o’clock positions. A right divergent squint was present, without obvious motility restriction. Treatment with topical fluorometholone, lubricants, and fucithalmic ointment was begun, which improved overall eye comfort. Despite topical treatment, 1 year later, the vascularization in the right cornea was still marked and a well-developed symblepharon was present in the superotemporal quadrant. In February 2004, right-sided symblepharon lysis and AMT were performed. Postoperative treatment included frequent administration of steroid-antibiotic ointment (Maxitrol Ophthalmic Suspension [0.1% dexamethasone, 3500 IU/g neomycin sulfate, and 6000 IU/g polymyxin B sulfate]; Alcon Laboratories Inc, Fort Worth, Tex), with tapering over a few weeks, plus oral amoxicillin for 1 week. Two and a half months postoperatively, despite receiving a regimen of topical steroid-antibiotic ointment, fluorometholone eyedrops, lubricant ointment (Lacri-Lube; Allergen Inc, Irvine, Calif), and prednisolone eyedrops, granulation tissue was noted in the superotemporal fornix. Treatment with cyclosporin ointment was begun. At last follow-up 13 months after surgery, visual acuity was hand movements OD and counting fingers OS. There was corneal subepithelial fibrosis with no fluorescein staining. Granulation tissue was present in the temporal sector with symblepharon. Oral thalidomide was prescribed by her pediatrician, which resulted in stabilization of the ocular condition.

CASE 4

A 7-year-old African girl was seen in June 2004. She had measles 1 year earlier, and, since then, her eyes had been red and painful. Ophthalmic examination revealed bilateral severe corneal vascularization, with central granulomas in the right eye (Figure 3). The fornices were shallow owing to symblepharon, and visual acuity was logMAR 1 in both eyes. These clinical findings raised suspicion of an immune system abnormality. After appropriate counseling, the patient underwent testing for human immunodeficiency virus (HIV), which yielded a positive result, and systemic antiretroviral therapy was begun. In November 2004, right-sided superficial keratectomy was performed to remove scar tissue, with AMT. A combination of topical steroid and antibiotic was administered 4 times a day postoperatively. Three weeks later, the amniotic membrane was still in place and looked organized (Figure 4A). Despite an increase in topical steroid dosage, the membrane remained organized. In January 2005, the amniotic membrane was surgically removed and found to be fibrotic and vascularized (Figure 4B-D), and histologic analysis showed chronic lymphocytic infiltration. To reduce the inflammation, steroid-antibiotic eyedrops (Maxitrol Ophthalmic Suspension; Alcon Laboratories Inc) were administered hourly, with tapering over a few weeks. At last follow-up visit 12 months after surgery, the corneal surface had epithelialized. However, visual acuity was hand movements OD and logMAR 1 OS (eye not operated on). Centrally, the cornea had developed marked scarring and vascularization.

METHODS

All patients underwent superficial keratectomy to remove abnormal corneal tissue. The abnormal tissue adherent to the eyelids (tarsal conjunctiva) was also dissected and removed. The fornices were freed. The preserved amniotic membrane with the stromal surface down was sutured to the eyelid margins with interrupted 10-0 polyglactin 910 (Vicryl). Where needed, silicone sheets, 0.25 mm thick, were used to maintain the fornix with 4-0 polypropylene (Prolene) sutures, which were passed, double armed and 4 to 6 mm apart, through the silicone sheet and eyelid and tied to a bolster on the skin. A central temporary tarsorrhaphy was performed using 6-0 polypropylene sutures to protect the graft. Bolsters were used on the skin to prevent any sutures from cheese-wiring (Figure 5). Postoperatively, all patients received topical steroid and antibiotic 3 to 4 times daily. At 3 weeks after surgery, the central tarsorrhaphy was opened and the silicone sheet was removed in all patients.
RESULTS

Amniotic membrane transplantation was performed in 5 eyes in 4 patients. All patients reported increased ocular comfort. Visual acuity improved in 3 eyes. The amniotic membrane had been absorbed at 3 weeks on opening the tarsorrhaphy in 3 eyes, with good ocular surface integrity. In 2 eyes, the amniotic membrane persisted. In the left eye in 1 patient (case 1), it resolved after 4 days of increased topical steroid therapy. In another patient (case 4), the amniotic membrane had become organized and required excision with the patient under general anesthetic (Figure 4).

COMMENT

Amniotic membrane can be used as a patch when epithelialization is expected to occur beneath the membrane or as a graft when epithelialization is expected to occur on the membrane with its incorporation into the host tissue. The membrane usually falls off when being used as a patch, whereas as a graft it may be completely absorbed, leaving clinically little or no visible trace, or, occasionally, a few remnants of the disintegrated membrane may be visible as wavy white lines or superficial scar tissue.14 This is what was seen in the patient in case 1 and resolved with increased topical steroid therapy. In the patient in case 4, however, the membrane became thickened and organized, requiring surgical removal. This child tested positive for HIV. The immunologic response to AMT is negligible, with no evidence of rejection or HLA antibodies in human volunteers.15 Despite initial reports,16,17 radiobiological studies of in vitro cultured amniotic cells suggest that small quantities of class 1 major histocompatibility complex (HLA A, B, and C) and class 2 major histocompatibility complex (HLA-DR) antigen are expressed.16 Extracellular antigens are complexed with major histocompatibility complex class 2 molecules for presentation to helper CD4+ T cells. The principal effect of HIV infection on the immune system is destruction of CD4+ T lymphocytes.18 We presume that the abnormal CD4+ T lymphocytes in our patient were unable to recognize the amniotic membrane as foreign and destroy it, resulting in an abnormal immune reac-

Figure 4. Same patient as in case 4. A, Three weeks after surgery, there is an organized amniotic membrane (white arrow), which was excised (B). C and D, Underlying cornea after excision of amniotic membrane.
tion that caused the membrane to become thick and organized, with lymphocytic infiltration.

We describe 4 patients with symblepharon and massive corneal pannus. Two patients had EB, 1 had related LOGIC syndrome, and 1 had infectious keratitis and was positive for HIV. All of these causes of symblepharon and corneal pannus are rare.

Epidermolysis bullosa includes a group of conditions associated with abnormalities of the basement membrane zone of skin and mucous membranes. In dystrophic EB, mutations occur within the collagen VII gene that encodes the anchoring fibril protein, resulting in lack of adherence and disruption of the corneal or conjunctival epithelium when any friction or trauma occurs to that area. In junctional EB, mutations in the genes encoding α6, β4 integrin, collagen XVII, or 1 of the 3 chains of laminin 5 contribute to defects in the formation of hemidesmosomes or anchoring filaments. Repeated corneal and conjunctival blistering can lead to corneal abrasion, punctate keratitis, symblepharon, ectropion, entropion, corneal scarring with decreased vision, and even blindness. Most severe ophthalmic complications have been reported in dystrophic and junctional EB and can be managed with ocular lubricants. However, massive symblepharon with corneal scarring that prevents opening of the eyes requires surgical intervention. Our case reports, to our knowledge, are the first to describe the use of human AMT with good success in patients with EB. The use of AMT helped reconstruct the damaged corneal and conjunctival surface and prevented the recurrence of symblepharon by decreasing the inflammation and vascularization. Both of our patients with EB were able to open their eyes comfortably after surgery and had improved vision.

Laryngo-onychocutaneous syndrome (LOGIC or Shabbi syndrome) is an autosomal recessive disorder characterized by the proliferation of dermal and submucosal granulation tissue and was first described in families originating from the Punjab region in Pakistan. The condition is characterized by erosive or ulcerative skin lesions associated with excess granulation tissue at sites of trauma such as digits, elbows, and knees. Ocular complications result from invasive fibrovascular granulation tissue growth causing symblepharon and corneal scarring. The granulation tissue begins in the lateral fornices. No effective treatment is available. It has been reported that simple excision of the granulation tissue results in rapid recurrence, as in our patient. Excision of the tissue followed by application of fluorouracil on the conjunctival surface has shown no benefit. We used AMT in our patient, although there was recurrence of granulomas, as has been previously been reported.

The LOGIC syndrome and junctional EB (case 2) share a similar genetic basis: mutations in laminin 3 cause a lethal form of junctional EB, while an unusual N-terminal deletion of the laminin 3a isoform leads to LOGIC syndrome. Intraoperative mitomycin C has been used in conjunction with AMT, in ocular surface diseases and recurrent pterygium. Mitomycin C is thought to reduce chronic conjunctival inflammation and to help the amniotic membrane restore a deep fornix after symblepharon lysis. Whether it is feasible to consider its use in pediatric cases similar to ours remains of interest. However, because of the possibility of serious long-term adverse effects of mitomycin C, for example, scleral ischemia or necrosis, caution is advised.

In our series, patients with EB fared better and the effect of surgery lasted longer than in patients with symblepharon and massive pannus from other causes. Although vision did not improve in all patients, it did in both patients with EB. We suggest that this technique is useful for ocular surface reconstruction in children with symblepharon and massive pannus. However, it seems especially helpful in patients with EB. Its vision potential in patients with altered immune systems should be guarded, given our experience in 1 patient with HIV.

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REFERENCES