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Amniotic Membrane Transplantation as a New Therapy for the Acute Ocular Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

Stevens-Johnson syndrome and its more severe variant, toxic epidermal necrolysis, have relatively low overall incidence; however, this disease presents with high morbidity and mortality. The majority of patients develop ocular inflammation and ulceration at the acute stage. Due to the hidden nature of these ocular lesions and the concentration of effort toward life-threatening issues, current acute management has not devised a strategy to preclude blinding cicatricial complications. This review summarizes recent literature data, showing how sight-threatening corneal complications can progressively develop from cicatricial pathologies of lid margin, tarsus, and fornix at the chronic stage. It illustrates how such pathologies can be prevented with the early intervention of cryopreserved amniotic membrane transplantation to suppress inflammation and promote epithelial healing at the acute stage. Significant dry eye problems and photophobia can also be avoided with this intervention. This new therapeutic strategy can avert the catastrophic ophthalmic sequelae of this rare but devastating disease.

Keywords

amniotic membrane transplantation; blindness; cicatricial pathology; corneal complication; scarring; Stevens-Johnson syndrome; toxic epidermal necrolysis

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In 1922, Stevens and Johnson69 reported the cases of two boys with eruptive fever, stomatitis, and opthalmalia, later named Stevens-Johnson syndrome (SJS). Lyell[40] described toxic epidermal necrolysis (TEN), a condition characterized by extensive epidermal scalding. Although initially described separately, both diseases are now considered a continuum of epidermal bullous diseases in which epidermal cell death results in subepidermal separation that can be elicited by stroking the skin (i.e., positive Nikolsky sign). A prodrome of fever, malaise, and upper respiratory infection symptoms is usually followed by a vesicular eruption of the mucous membranes. Although there is no universally accepted definition, both diseases are characterized by eruptive lesion involving at least two mucosal surfaces, and can be separated by the percentage of detachment of the body surface area (BSA).57 SJS involves

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less than 10% total BSA, overlapping SJS/TEN involves 10–30% BSA, and TEN involves more than 30% BSA.

Although SJS and TEN are rare, they are important because of high morbidity and mortality; the mortality rate is 3% for SJS and 25–40% for TEN.[42,49,82] Acute ocular complications develop in more than half (i.e., 43–81%) of hospitalized patients for both SJS and TEN, and among them, 25% exhibit severe involvement.[53] Chronic ocular sequelae occur in up to 35% of patients.5 Corneal damage leading to blindness is the most severe long-term complication for survivors of SJS/TEN.[5,53,83] Although ocular morbidity and visual loss can be caused by acute corneal complications, progressive conjunctival scarring is significantly associated with subsequent loss of vision.[16] This review describes the ocular manifestations of SJS/TEN, summarizes literature evidence illustrating how ocular cicatricial complications may emerge even if the vision is not immediately threatened, and how these sight-threatening complications can be prevented by a novel therapy based on amniotic membrane transplantation (AMT) delivered during the acute stage of SJS/TEN. For more information on other aspects of SJS/TEN, see recent reviews[10,37] and references cited therein.

Acute Ocular Manifestation

The estimated annual incidence of SJS/TEN ranges from 0.6 to 10 cases per million person-year.[8,12,45,62] TEN may occur more commonly in older people and people with AIDS.7 The most common cause of the disease is an idiopathic reaction to medications such as antibiotics (penicillin and sulfa), anticonvulsants (phenytoin, carbamazepine, and barbiturate), and nonsteroidal anti-inflammatory drugs.[37,56] Other causes included infection (herpes simplex, mycoplasma pneumoniae, measles, mycobacterium, group A streptococci, Epstein-Barr, yersinia, enterovirus, smallpox vaccination)[17,47,72] and some remained undetermined.86 Although it is known that SJS/TEN causes epidermal cell apoptosis, the pathogenesis of the disease is unclear. Some studies have suggested the involvement of Fas-Fas ligand interaction,[80,81] cytotoxic T-cells,[46,52] tumor necrosis factor-alpha,[48,51] and nitric oxide synthase36 (for a review of pathogenesis of SJS/TEN, see Khalili and Bahna27).

In the acute stage of SJS/TEN, defined as the first two weeks after onset of symptoms, the aforementioned immune dysregulation can attack mucous membranes of the whole body. As stated previously, an overwhelming majority of hospitalized patients develop ocular lesions during the acute stage,[53] with 15–75% of them manifesting bilateral conjunctivitis.[6,25,50] In the eye, although lid skin vesicles may erupt into ulcers like the rest of the body (Fig. 1A), external examination at the bedside frequently only reveals conjunctivitis with redness and mucous discharge (Fig. 1B). However, it should be stressed that epithelial defects or ulcers involve tarsi and fornices in nearly all cases with ocular involvement. These hidden lesions are impossible to ascertain without everting the eyelids (Fig. 1C), a maneuver sometimes hard to practice as acute care often includes respiratory support. As reported, approximately 25% of hospitalized patients develop more severe ocular involvement,[53] manifesting corneal epithelial defects and inflammation (Fig. 1D).

If ocular surface inflammation and ulceration is not quickly managed, the ensuing wound healing usually results in scarring. It remains a mystery why the inflammatory process tends to be relentless and prolonged in patients with SJS/TEN even after they are released from acute care or discharged from the hospital. In a proportion of patients, persistent inflammation and ulceration of the conjunctiva or cornea may extend to destroy corneal epithelial stem cells at the limbus, leading to a pathological state termed limbal stem cell deficiency (Fig. 1E) (for reviews see the literature[20,33,74]). Without limbal epithelial stem cells, the cornea will be covered by the surrounding conjunctival epithelium as well as an extensive fibrovascular scar, causing an immediate loss of vision. Limbal stem cell deficiency cannot be treated by

conventional corneal transplantation, and because limbal stem cell deficiency is usually bilateral in this disease, visual rehabilitation efforts are limited to transplantation of allogeneic limbal stem cells (for reviews see the literature18,21,75) or keratoprosthesis.38,[59,84] Due to continuous ocular surface inflammation and other cicatricial complications detailed subsequently, eyes with total limbal stem cell deficiency caused by SJS/ TEN have the worst prognosis even if subjected to transplantation of allogeneic limbal stem cells.[65] Furthermore, there are also risks derived from taking prolonged, if not indefinite, systemic immunosuppressive agents, while potential complications of keratoprosthesis use include glaucoma, retroprosthetic membrane, tissue necrosis, retinal detatchment, and endopthalmitis.[84] For all these reasons, it is highly desirable to adopt a new strategy to suppress ocular surface inflammation, promote epithelial healing, retain remaining limbal epithelial stem cells, and encourage their expansion at the acute stage.

Chronic Ocular Complications

Chronic ocular sequelae occur in up to 35% of patients.[5] It has been recognized that sight-threatening corneal scarring is the most severe long term complication for survivors of SJS/ TEN.[43,53] Even if the cornea is not affected during the acute stage or after discharge from the hospital, patients with SJS/ TEN may suffer from severe loss of vision due to chronic corneal complications. A potential causative relationship between cicatricial complications of the lid margin and the tarsus and sight-threatening corneal scarring was revealed by a recent study of 38 SJS/TEN patients (Fig. 2).[16] These cicatricial complications are derived in part from the persistent and prolonged conjunctival inflammation and ulceration (Fig.3A). Thus conjunctival scarring commonly occurs as a chronic sequel.[86] This scarring frequently leads to symblepharon and foreshortening of the fornix (Fig. 3B).[28,76] Depending on the location and severity of symblepharon, a number of pathogenic elements ensue. For example, scarring at the lid margin or the tarsus can deform the eyelid, causing entropion or ectropion and allowing lashes and scar tissue to elicit friction-related microtrauma to the cornea during blinking (Fig. 3C). If symblepharon obliterates the tear meniscus, it will interfere with aqueous tear flow and spread to the ocular surface (Fig. 3D). If the superior or inferior fornix is involved, untoward exposure arises to render more dryness both day and night because of inadequate blinking, closure, or limitation of Bell's phenomenon. In the superotemporal fornix, scarring will obstruct secretory lacrimal ductules (Fig. 3B). If scarring involves the extraocular muscle or the upper lid, diplopia and ptosis occur. When scarring affects the lid margin, it frequently causes keratinization and seals meibomian gland orifices resulting in lipid layer anomaly of the tear film (see Fig. 2). SJS/TEN can also cause squamous metaplasia with extensive loss of conjunctival goblet cells (Fig. 3E).[5,55] Collectively, these cicatricial complications exacerbate blink-related microtrauma and produce severe dry eye. Cumulative insults of the aforementioned pathogenic elements will not only lead to severe loss of vision but also cause multiple deficiencies in the ocular surface defense, rendering subsequent reconstructive efforts difficult, if not impossible. Because of these complicating factors, it is no wonder that SJS/ TEN patients find it difficult to escape photophobia, constant irritation, and the devastating outcome of ocular surface failure. For additional reviews and studies about the chronic complications of ocular SJS/TEN see the literature.[5,17,83] Although AMT and other surgical strategies have been used for treating cicatricial complications and limbal stem cell deficiency at the chronic stage,[32,66,76] they are outside the scope of this review and have been discussed by others.[11,58]

Amniotic Membrane Transplantation as a New Strategy for Minimizing Ocular Sequels in Acute SJS/TEN

Because SJS/TEN, especially TEN, is potentially life-threatening, physicians must deploy life-saving measures at the acute stage. Because patients are frequently put on a respirator, their

eyes are often closed and they cannot voice any discomfort caused by inflammation or ulceration, giving the false impression that the eyes are not involved. Even if an ophthalmologist is consulted because skin ulceration involves the lid margin or the conjunctiva showed redness and discharge, the eye examination at the bedside cannot uncover deep-seated ulcers unless the eyelids are fully everted (see Fig. 1). Conventional ocular management may consist of bedside examination, application of lubricating ointment, antibiotics to prevent infection, steroids to control inflammation, cyclosporine, and periodic lysis of symblepharons with a glass rod or insertion of a symblepharon ring.

Systemic corticosteroids, cyclosporine, and intravenous immunoglobulin (IVIG) have shown some potential as treatments for SJS/TEN, although their use remains controversial. Early intervention with high doses of steroids during the acute stage may inhibit inflammation, but may increase the risk of infection and mortality.[14] In addition, a large retrospective review of patients treated with systemic corticosteroids (n = 366) showed no significant reduction in ocular sequelae.53 On the other hand, a few recent case reports and small uncontrolled series proposed beneficial effects achieved by systemic cyclosporine,[2,3,14] and IVIG administered early after lesion onset is thought to hold promise for improvement in survival and a reduction in long-term morbidity.[22,27,37] However, a retrospective review of data from patients in France and Germany who were enrolled in Euro-SCAR, a case-control study of mortality risk factors in SJS/TEN patients, found that neither IVIG nor corticosteroids showed any significant effect on mortality as compared to supportive care alone.[61] Topical corticosteroids and cyclosporine have been suggested as a possible means of decreasing the intensity of ocular surface inflammation in SJS/ TEN.[60] At the present time, no prospective, randomized controlled studies for any of these systemic or topical treatments currently exist, and it remains unclear whether any of these treatments is effective enough to abort inflammation and ulceration. For recent reviews of these treatments for the acute management of SJS/TEN, see the literature.[13,24,61]

Emerging literature data indicate that transplantation of cryopreserved amniotic membrane (AM) in a procedure termed AMT is a new strategy to suppress inflammation, prevent ulcer formation, and promote healing during the acute stage of SJS/ TEN, thus preventing sight-threatening cicatricial complications. Anatomically, AM is the innermost layer of the placental membrane, and consists of a thick basement membrane and an avascular stroma. In ophthalmology, AMT using cryopreserved AM as a permanent graft has been shown to be effective in suppressing inflammation and scarring and promoting healing in patients suffering from a variety of ocular surface diseases (for reviews see the literature[9,19,64,73]). The potential action mechanisms for AMT to exert anti-inflammatory and anti-scarring actions[77] as well as to promote limbal epithelial stem cell expansion[23] have recently been reviewed.

AM's anti-inflammatory actions may be mediated in part by its secretion of anti-inflammatory cytokines interleukin-10, inhibin, activin, and interleukin-1 receptor antagonist as well as anti-inflammatory protease inhibitors such as a1 anti-trypsin inhibitor and inter-a-trypsin inhibitor (for a review see Tseng et al77). AM has been shown to suppress innate immunity by trapping both mono-nuclear and polymorphonuclear granulocytes within its stromal matrix and inducing them to undergo rapid apoptosis.63 AM may also modulate acquired immunity by suppressing alloreactive responses and down regulating production of Th1 and Th2 cytokines. 79 AM's secretion of anti-inflammatory cytokines also contributes to its anti-scarring action. In addition, AM stromal matrix exerts a powerful direct anti-scarring action on ocular surface fibroblasts by suppressing TGF-β signaling at the transcriptional level, leading to downregulation of several downstream genes that are responsible for scar formation.[34,78]

Intriguingly, these therapeutic actions can also be delivered by cryopreserved AM used as a temporary biological bandage. For example, this mode of AMT also helps reduce inflammation

and facilitate wound healing in persistent corneal epithelial defects caused by a number of ocular surface diseases.[35,67] Extending from this earlier observation, AM has also successfully been used for treating chemical and thermal burns at the acute stage.[29,30,41,54,68,71]

Various methods have been used to preserve AM, including fresh (hypothermic storage), dry (freezedried), and preserved (cryopreservation). Fresh amniotic membrane, like cryopreserved AM, has been successful in treating several ocular surface diseases: recurrent pterygium,[39,87] stenosis of the conjunctival sac,[85] acute chemical burn,[4] recurrent Mooren ulcer,[15,39,88] viral keratitis,[39] and symblepharon.[15,39] There are currently no studies on the use of fresh or dry AM for the treatment of acute SJS/TEN. However, there have been two published case series comparing the use of fresh versus preserved AMT for conjunctival reconstruction after symblepharon lysis in chronic SJS/TEN patients. Both reports found that AMT resulted in successful conjunctival reconstruction, with no significant statistical difference in surgical outcome between fresh and preserved AMT.[89,90] Adds et al advocated the use of frozen rather than fresh AM because of safety, logistical, and cost concerns.[1] In the United States, the FDA has ruled that dry AM requires pre-market clinical trials before it can be approved as a surgical graft, and that fresh AM cannot be used as a tissue as it contains live allogeneic cells (for more information, see: www.fda.gov/BiologicBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm).

PROCEDURE

For acute SJS/TEN, cryopreserved AM is sutured to cover the entire ocular surface from lid margin to lid margin as a temporary biological bandage (shown schematically in Fig. 4A and 4B).If the lid margin skin is involved, the lashes are trimmed so that the membrane can be extended to cover the ulcer. If not, the membrane is attached to the gray line by interrupted or continuously running 10-0 or 8-0 nylon/vicryl sutures. From the upper lid margin, AM is then spread to cover the tarsal conjunctiva and fornix before being reflected to cover the bulbar conjunctiva by a muscle hook and anchored to the skin through a double-armed 4-0 black silk or 6-0 prolene suture in a mattress fashion. The same procedure is then performed on the lower lid. Both AMs are fixed to the episclera with a continuous 10-0 nylon suture in a purse-string fashion near the limbus. Alternatively, they can be secured by a symblepharon ring. For surgical videos, visit http://www.osref.org/acute-treat ment-of-severe-ocular-inflammation.aspx from the Ocular Surface Research and Education Foundation, or see a video report by Muqit et al[44] at http://bjo.bmj.com/content/vol91/issue11/images/data/1536/DC1/muqitfinalfast.mov.

SURGICAL OUTCOME

AM as a temporary biological bandage has been successfully used to treat six patients with acute SJS/TEN during the period from 2002 to 2007.[16,26,31,44,70] Table 1 summarizes clinical characteristics and outcomes of 12 eyes of these six pediatric patients (ranging from 4–12 years old), three boys and three girls, who developed SJS (n = 2) or TEN (n = 4) precipitated by medication (n = 4) or infection (n = 2). At the acute stage, five patients presented with external eruptive lesions extending to the lid margin. In the eye, all showed conjunctival inflammation and four patients showed tarsal ulceration, leading to lid adhesion to the globe in five patients. Three patients presented with corneal epithelial defects that were total in three eyes and geographical in three eyes. One eye showed a limbal epithelial defect. AMTwas performed within the first 2 weeks from the onset of the symptoms, based on the sutured method described herein in six patients, using cryopreserved AM obtained from Bio-Tissue (Miami, FL) in four patients. In one eye, AM was stretched by a conformer before suturing.[26] In three eyes, one with a corneal epithelial defect, AM did not cover the cornea.[26,70] In a median follow-up of 9 months (ranging from 4–36 months) after AMT, none of these 12 eyes showed any persistent conjunctival inflammation. As a result, the entire ocular surface remained stable without limbal

stem cell deficiency, and their uncorrected visual acuities ranged from 20/16 to 20/40. It is noteworthy that tarsal ulcerations were covered by AM while the rest dissolved during the acute stage (Fig. 4C and 4D). This explained why scarring was absent in five eyes, but was mild and focal in the tarsal conjunctiva of the remaining seven eyes. In these seven eyes, additional scarring involved the lid margin in four eyes and the corneal periphery in three eyes. Of these three eyes, two had undergone AMT in which AM did not cover the cornea.[70] Only two of 12 eyes showed focal symblepharon, which was located in the inferior fornix. Two of the six eyes with corneal involvement healed with fine peripheral vascularization.

Collectively, these results demonstrate that AMT, when performed within two weeks after the onset of the disease, effectively aborts inflammation and facilitates rapid healing in AM-covered areas, thus preventing pathogenic cicatricial complications at the chronic stage. When performed at a later stage, AMT might still recover the corneal surface, but cannot prevent progressive conjunctival scarring. Further studies may be necessary to determine the optimal timing of AMT.

Conclusion

Persistent inflammation and ulceration of the conjunctiva or cornea invariably results in cicatricial complications in many types of chronic cicatricial keratoconjunctivitis. Herein literature evidence strongly demonstrates that lesions for SJS/TEN tend to be hidden in the fornix and tarsus in the acute stage and frequently evolve into sight-threatening corneal complications in the chronic stage. For the first time, the literature data also reveal an encouraging trend: AMT performed in the first two weeks after the onset of ocular involvement facilitates rapid epithelial healing and reduces inflammation and scarring of the ocular surface. As a result, this novel therapy can potentially avert the otherwise doomed visual outcome at the chronic stage of this disease. Therefore, although SJS/TEN is relatively rare, the high rate and typically severe ocular morbidity requires prompt diagnosis and early intervention with AMT at the acute stage. Further investigation may elucidate how AMT exerts such anti-inflammatory and anti-scarring actions and help unravel new therapeutic modalities that will promote regeneration rather than repair in SJS/ TEN as well as other mucous membrane inflammatory and ulcerative diseases.

Method of Literature Search

Literature search was performed in Medline using the following keywords: *epidemiology, pathogenesis, Stevens-Johnson syndrome, toxic epidermal necrolysis*, as well as relevant references cited in those articles. For foreign language publications, no translation was obtained, however, abstracts of relevant non-English articles were used. For the first section focusing on a short review of SJS and TEN and its ocular morbidity, we chose key review articles or studies with large series dealing with these topics back to 1860. For the second and third sections describing the clinical significance of ocular SJS/TEN including epidemiology, pathogenesis, and natural history, we focus on the literature connecting cicatricial complications and blindness. For the medical treatments of acute SJS detailed in the fourth section, studies of the treatments as well as recent reviews were chosen from 1990. Regarding action mechanism and ocular applications of AMT, we only cite recent key reviews dated after AMT was introduced for ocular surface reconstruction in 1995. For the statements that are frequently mentioned by others but have not changed from time to time, we chose the earliest publication and other important articles. For surgical outcome, we conducted a Medline search with the keywords acute, *Stevens-Johnson syndrome*, and *amniotic membrane*. All articles dealing with AMT in the acute management of SJS and TEN were reviewed and succinctly summarized as a Table for meta-analysis.

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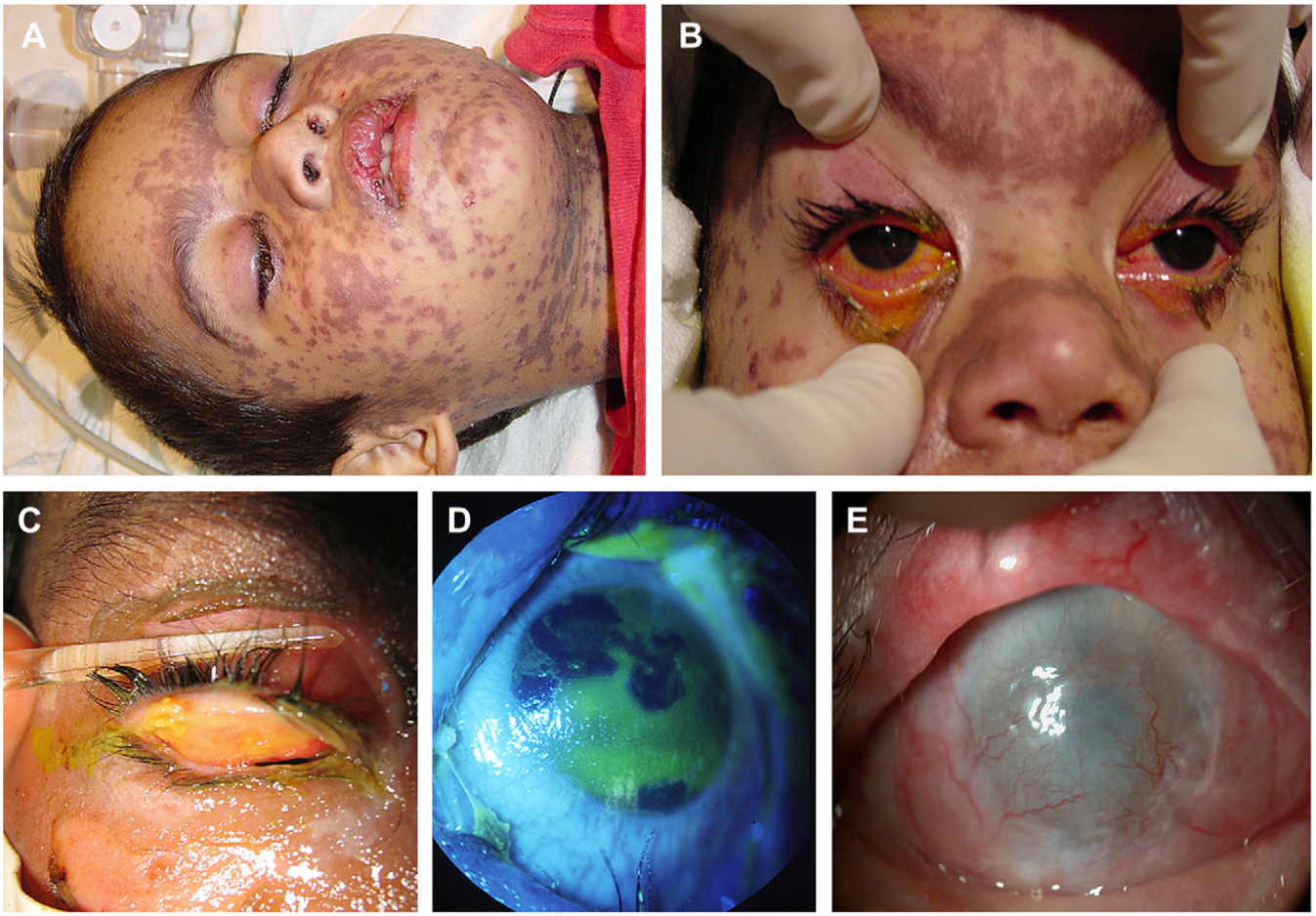

Fig. 1.

Acute ocular manifestation of SJS/TEN. A: External appearance of a SJS patient shows diffuse skin rashes, oral mucosal ulceration, and closure of both eyes with crust. *B*: External examination at the bedside reveals only ulcers involving the lid margin skin and conjunctival redness. (Reproduced from Di Pascuale et al[16] with permission of Ophthalmology.) *C*: Eversion of the eyelids reveals diffuse ulcers involving the tarsus and fornix. *D*: Acute ocular involvement manifesting a geographical corneal epithelial defect. (C and D are reproduced from Kobayashi et al[31] with permission of Ophthalmology.) *E*: Limbal stem cell deficiency can occur acutely, resulting in conjunctivalization and formation of an extensive fibrovascular scar, causing blindness.

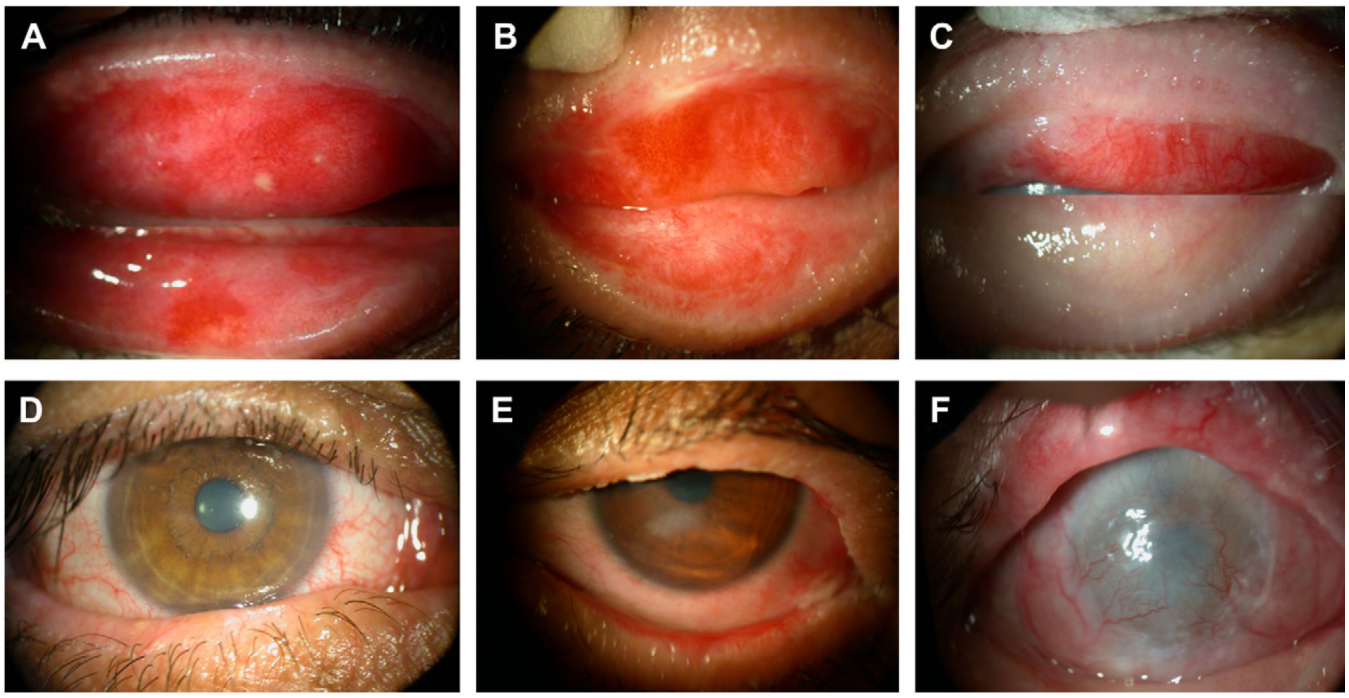

Fig. 2.

Significant correlation between lid margin or tarsal keratinization and scarring with corneal scarring and vascularization. The severity of grade 1 (*A*), grade 2 (*B*), and grade 3 (*C*) of lid margin and tarsal scarring and keratinization of representative cases is correlated well with their corneas, which showed clear (*D*), mild scarring (*E*), and severe scarring and vascularization (*F*). (Reproduced from Di Pascuale et al[16] with permission of *Ophthalmology*.)

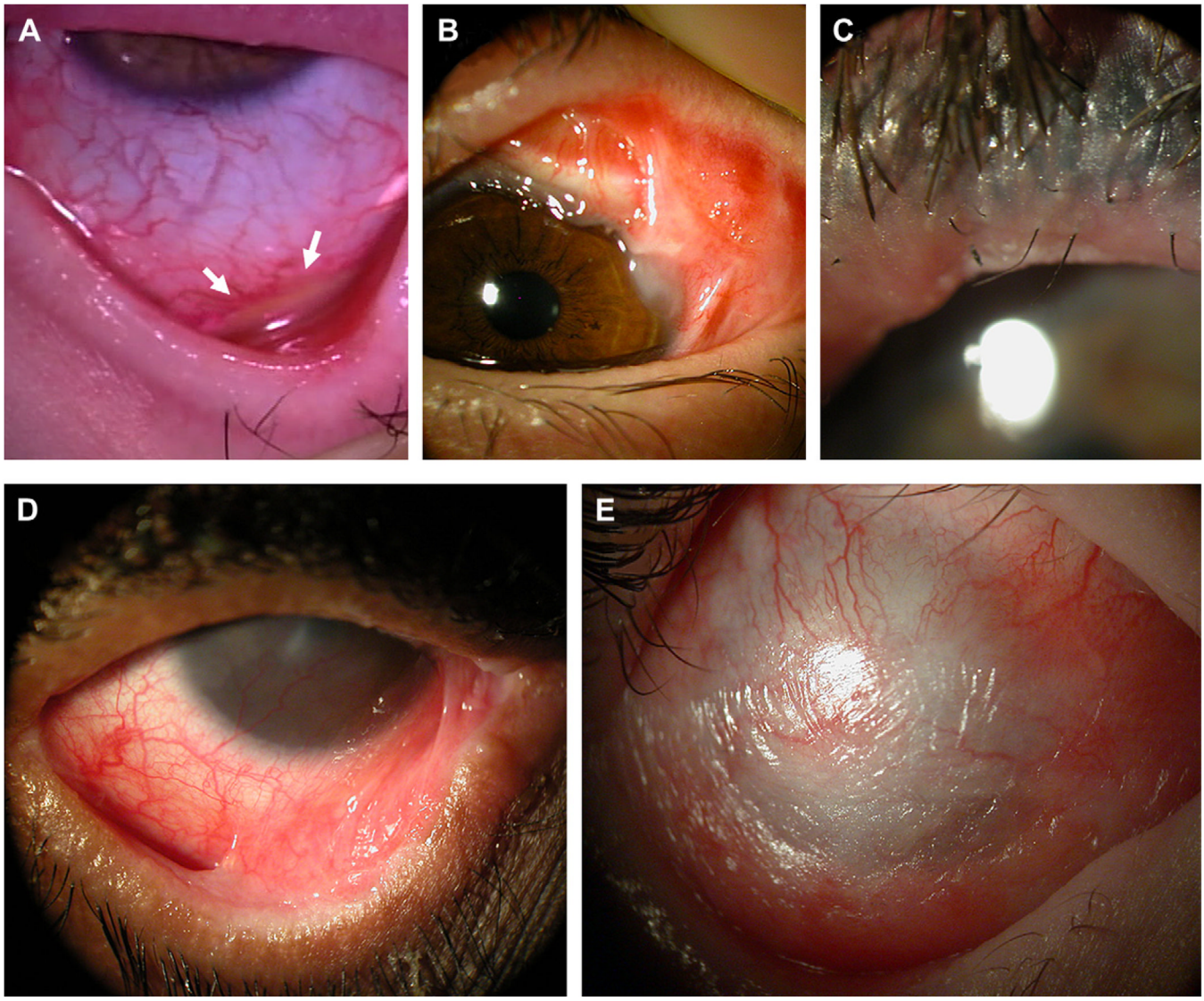

Fig. 3.

Chronic cicatricial complications of SJS/TEN. *A*: Progressive conjunctival inflammation and non-healing fornix ulcer (marked by arrows) in the chronic stage, seen when the eyelid was everted by a muscle hook. *B*: Persistent conjunctival inflammation and scarring involves the superotemporal fornix, obstructing the lacrimal ductules. *C*: Lid margin keratinization and scarring leads to distichiasis and meibomian gland obstruction. *D*: Inferior symblepharon obliterates the tear meniscus, interfering with aqueous tear flow and spread to the ocular surface *E*: Diffuse squamous metaplasia due to severe dry eye and exposure.

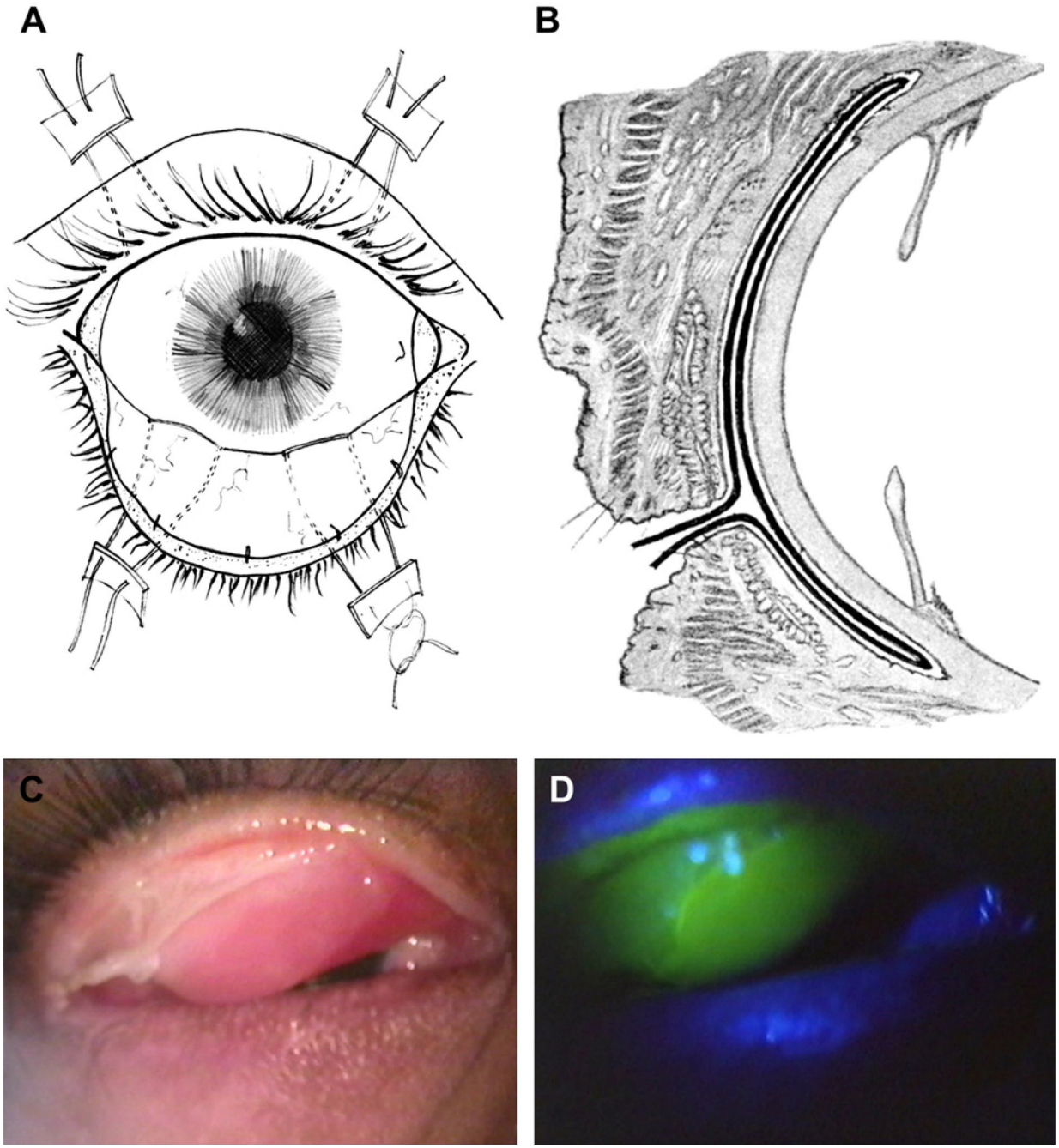

Fig. 4.

Schematic depiction of the sutured method of AMT for SJS/TEN. AM covers the entire ocular surface, secured by four 4-0 silk double-armed sutures from the fornix to the skin (*A*: front view; *B*: side view.) (*A* and *B* are reproduced from Meller et al[41] with permission of *Ophthalmology*.) *C*: AM is attached to the ulcerated tarsus while dissolving in other areas. *D*: Fluorescein staining confirms that AM has covered the tarsus. This membrane facilitates conjunctival epithelialization while preventing epidermal migration from the lid margin. (*C* and *D* are reproduced from Di Pascuale et al[16] with permission of *Ophthalmology*.)

TABLE 1

Literature Summary of AMT for Acute SJS/TEN

Case Number	1	2	3	4	5	6
Age	6	8	4	6	12	10
Sex	M	F	M	M	F	F
Offending Agent	SMZ	Mycoplasma	Ibuprofen	Phenobarbital	Infection	Drug
Diagnosis	TEN	TEN	SJS	TEN	TEN	SJS
Initial Presentation						
Lid						
Margin ulceration	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)	No
Adhesion to globe	Yes (OU)	Yes (OU)	No[a]	Yes (OU)	Yes (OU)	Yes (OU)
Conjunctiva						
Inflammation	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)
Tarsal/fornix ulceration	NA	NA	Yes (OU)	Yes (OU)	Yes (OU)	Yes (OU)
Corneal involvement						
Inflammation	No	Yes (OU)	No	Yes (OU)	No	No
Epithelial defect	No	Total (OU)	No	Total (OD), Geographical (OS)	No	Geographical (OU)
Limbal involvement	No	No	No	Yes (OS)	No	No
Timing of AMT (days)[b]	<14	<14	7	5	3	3
Follow-up (months post-operative)	36	34	12	4	3	6
Outcome						
Persistent conjunctival inflammation	No	No	No	No	No	No
Cicatricial						
complications						
Lid margin	No	No	Mild (OU)	No	Mild (OU)	No
Tarsal conjunctiva	No	Mild (OU)	Mild (OU)	Mild (OD)	Mild (OU)	No
Symblepharon	No	No	No	Focal (OD)	Focal (OD)	No
Corneal complications						
Epithelial defect	No	No	No	No	PEE (OU)	No

Case Number	**1**	**2**	**3**	**4**	**5**	**6**
Opacity	No	No	No	Peripheral (OD)	No	Slight central haze (OS)
Vascularization	No	Peripheral (OS)	No	Peripheral (OD)	No	No
Limbal stem cell deficiency	No	No	No	No	No	No
Other morbidity	No	Madarosis (OU)	No	No	Trichiasis (OU)	Trichiasis (OU)
VA	20/20	20/30 (OD), 20/40 (OS)	20/20[a]	20/16	20/20	20/16
Literature source	(26)	(26)	(16)	(31)	(70)	(44)

AMT = amniotic membrane transplantation; NA = not available; OD = right eye; OS = left eye; OU = both eyes; PEE = punctuate epithelial erosions; SJS = Stevens-Johnson syndrome; SMZ = sulfamethoxazole; TEN = toxic epidermal necrolysis; VA = uncorrected visual acuity.

[a]This data do not appear in original paper, but are instead obtained from personal communication with the author.

[b]After onset of eye symptoms.