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CASE REPORT

Use of amniotic membrane at outpatient conditions for acute ocular surface involvement of Stevens-Johnson syndrome

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Abstract

The purpose of the study is to present a case of Stevens-Johnson syndrome (SJS) with acute ocular surface involvement, who was managed by amniotic membrane application in outpatient clinic conditions. A 68-year-old female patient with a diagnosis of acute SJS, under topical skin therapy as well as intravenous steroid and immunoglobulin treatment at the Dermatology Service, was consulted for ocular involvement with red eyes and secretion in both eyes. At the initial examination, her visual acuities were counting fingers from 1 m in the right eye and from 10 cm in the left eye. In addition to bilateral pseudomembranous conjunctivitis, corneal epithelial irregularity and an epithelial defect of approximately 4 mm × 6 mm were present in the right and left eyes, respectively. Amniotic membrane was applied to the left eye with a sutureless ring (Amnioring®) that fits at the fornices, at outpatient clinic conditions. Topical treatment with steroids, cyclosporine, and hyaluronic acid eyedrops was commenced. During follow-up, a dramatic improvement in ocular surface inflammation was observed; chemosis regressed. The cornea was epithelialized preserving the stromal transparency. Keratinization at the eyelid ciliated margin, symblephora formation, corneal vascularization, and cicatrization was not observed. Topical steroid therapy was tapered; the patient was followed-up by reducing the doses of cyclosporine and hyaluronic acid. SJS has a poor prognosis in terms of corneal transplantation and keratoprosthesis surgeries. In patients at the acute stages of the disease, who cannot be admitted to operating room conditions, sutureless amniotic membrane application in outpatient clinic or even intensive-care unit conditions should be considered. This is a promising method, to prevent both short- and long-term complications of the ocular surface and irreversible corneal blindness.

Keywords: Amniotic membrane; Amnioring; Stevens-Johnson syndrome.

Stevens-Johnson syndrome (SJS), also known Erythema Multiforme Major, is a systemic disease with extensive and severe mucosal involvement that can be fatal if not treated. When dealing with severe systemic disease, ocular involvement can be missed in early stages leading to devastating consequences, including permanent corneal blindness. In those cases, full-thickness corneal grafting may lead to epithelization problems and melting of the cornea. As such, following Boston Keratoprosthesis surgery in SJS patients, extrusion of the prosthesis with permanent

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loss of vision has been reported.[1–3] Similar to those cases of chemical burns, ocular and systemic complications can be prevented with early diagnosis and prompt management in SJS patients.

Amniotic membrane transplantation is a promising tool in acute stages of SJS, with its low immunogenic, highly anti-inflammatory, anti-angiogenic, anti-fibrinogenic, anti-microbial, and anti-apoptotic properties. Its application does not require general anesthesia and can be easily performed even in outpatient clinics or in inpatient services and intensive care units at the bedside.[4–6] In this case report, we aim to present the clinical outcome of a case with acute SJS ocular surface involvement, to whom we performed amniotic membrane transplantation at outpatient clinic conditions, along with a review of the relevant literature.

Case Report

A 68-year-old female patient with a diagnosis of acute SJS, who had been under topical skin treatment as well as intravenous steroid and immunoglobulin (IVIG) therapies at dermatology department inpatient services, was consulted for bilateral ocular involvement with red eyes and secretion. At the initial examination, her visual acuities were counting fingers from 1 m and 10 cm, in the right and left eyes, respectively. In addition to bilateral pseudo-membranous conjunctivitis, corneal epithelial irregularity was noted in the right eye. In the left eye, there was an epithelial defect of ~ 4 mm × 6 mm in size, along with a fluorescein uptake in the lower palpebral conjunctiva (Fig. 1a and b). No shallowing or symblepharon formation was observed in upper and lower fornices, bilaterally.

Immediately after initial biomicroscopic examination, at outpatient clinic conditions, amniotic membrane was applied to the left eye with a sutureless ring (Amnioring®). After written consent was obtained from the patient for this procedure, the amniotic membrane was fixated at the fornices with Amnioring, to promote rapid corneal epithelization and to avoid ocular surface complications in the chronic period of SJS. Amniotic tissue had been obtained under sterile conditions during elective cesarean-section birth, with confirmed consent of a donor mother, who was tested seronegative for human immunodeficiency virus, Hepatitis B surface antigen, Hepatitis C virus, and syphilis. Membranes (amnion and chorion) were detached from the placenta and cleaned with saline and processed with gentamycine. Under topical anesthesia with proparacaine eye drops (Alcaine®, Alcon, USA), one layer of amniotic mem-

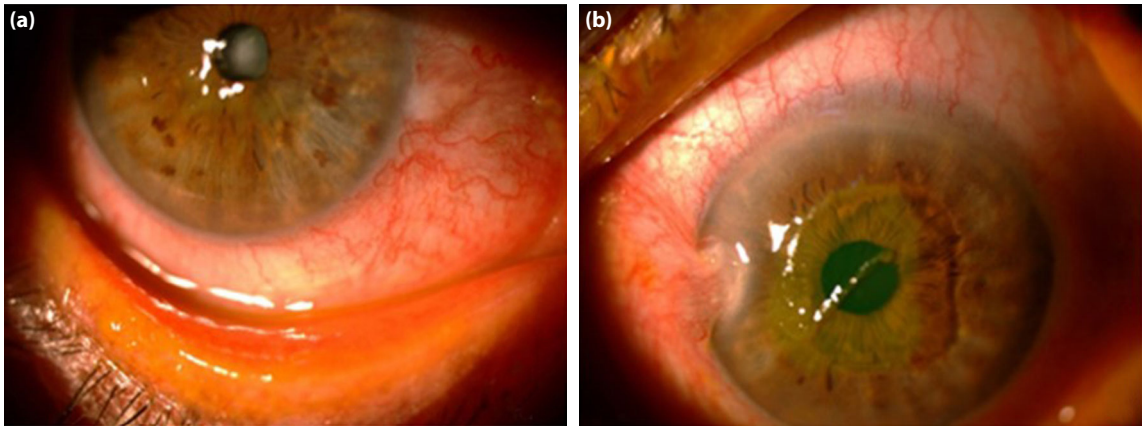

Fig. 1. **(a, b)** Bilateral conjunctival hiperemia, chemosis, and mild pseudo-membraneous conjunctivitis due to SJS. Corneal epithelial irregularities are seen in the right eye. Corneal epithelial defect is seen in the left eye.

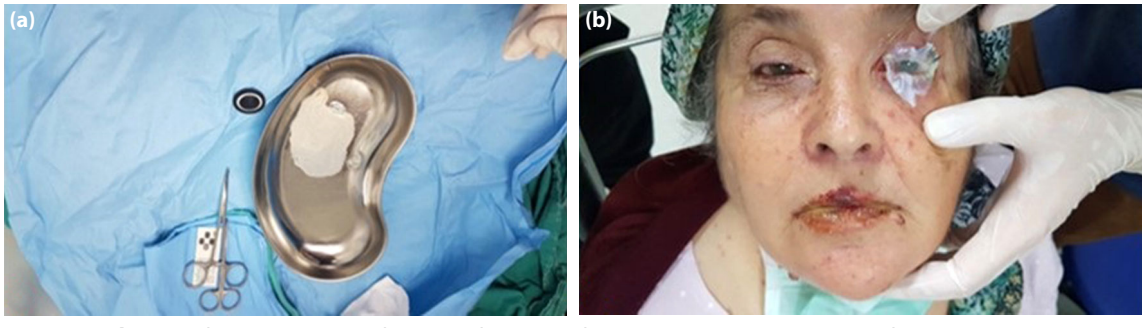

Fig. 2. **(a, b)** Sutureless amniotic membrane application with AmnioRing® in outpatient conditions.

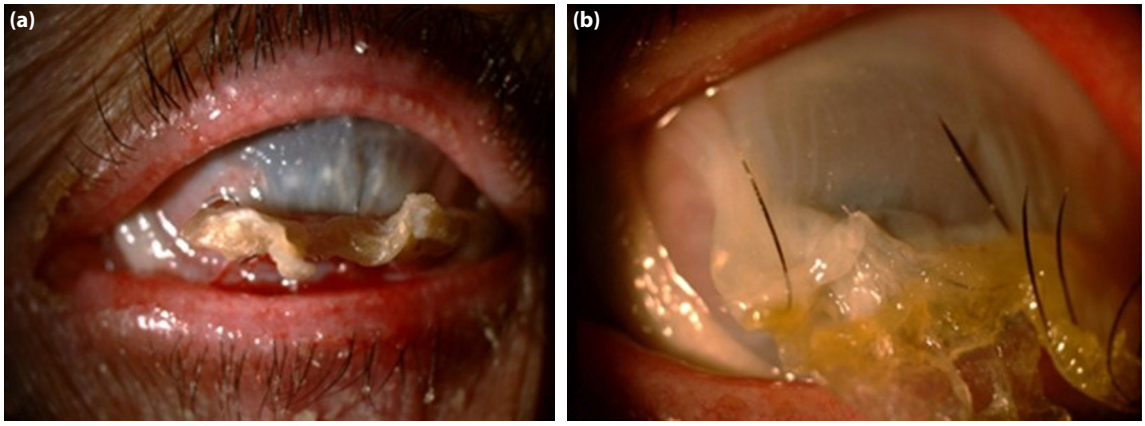

Fig. 3. **(a, b)** In the left eye, amniotic membrane remained on the surface of the eye for 1 month after it was applied to lining the fornix. The dried eyelashes were cleaned daily with a warm dressing.

brane, which was ~ 3.5 cm × 3.5 cm in size, was placed on the ocular surface with basement membrane side facing away from the corneal surface. It was gently fixed to the ocular surface with Amnioring® which fits safely on the superior and inferior fornices. Excess membrane was resected and removed with Westcott scissors; remaining edges were folded over Amnioring® at the fornices (Fig. 2).

After the procedure, a topical treatment regimen including moxifloxacin, preservative-free dexamethasone, cyclosporine 0.05% and trehalose-sodium hyaluronate qid, and preservative-free polyvinyl alcohol-povidone eye drops hourly was commenced to relieve ocular surface inflammation. The thickened amniotic membrane and meibomian gland secretions at the ciliated edge of the eyelashes were cleaned daily with a warm dressing (Fig. 3).

In the following days, a dramatic improvement in ocular surface inflammation was observed. Conjunctival edema regressed. Keratinization of the ciliated edge at eyelid margin, symblepharon formation, corneal vascularization, and scarring was prevented. After 1 month, remaining amniotic membrane residues were removed from the left eye surface (Fig. 4). Minimal punctate epithelial defect was seen in the epithelialized and clear cornea. Topical steroid therapy was tapered; short-term topical carbomer gel 2 × 1 and Vitamin A ointment 2 × 1 were added until punctate epithelial defects disappeared.

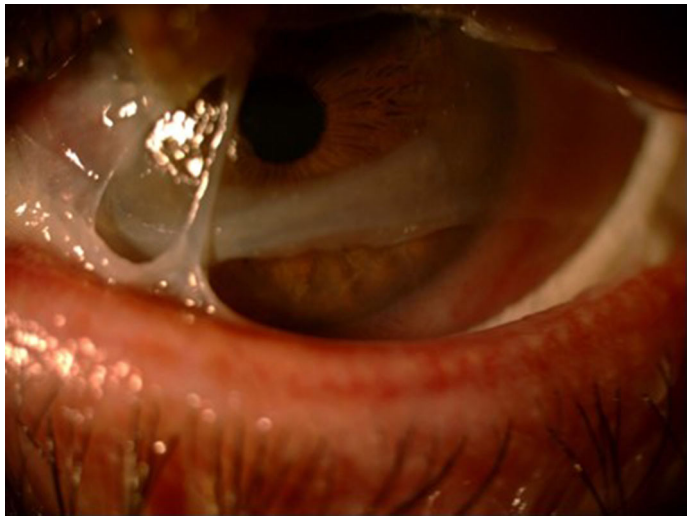

Fig. 4. Amniotic membrane residues that did not dissolve after 1 month were removed and AmnioRing® was removed.

Both ocular surfaces of the patient healed without complications. Treatment was continued with topical cyclosporine 0.05% bid and preservative-free polyvinyl alcohol/povidone qid. Visual acuity improved to 1.0 and 0.5 Snellen lines, in the right and left eyes, respectively (Fig. 5a and b). Stage 2 nuclear cataract in the left eye limited further visual enhancement.

Discussion

SJS is a rare exfoliative disease of the skin involving at least two mucosal areas. It is a life-threatening inflammatory hypersensitivity reaction of the skin, as well as eye involvement, which can develop against antibiotics, anticonvulsant medications, non-steroid anti-inflammatory drugs, or less commonly infectious species. The incidence of ocular involvement varies between 50% and 80%,[7] which may present in a spectrum ranging from mild dry eye to cicatricial keratoconjunctivits and bilateral permanent corneal blindness.

Acute ocular involvement includes inflammation in the whole all ocular surface. In case of persistence of inflammation, chronic period of ocular SJS ensue including fornix foreshortening and sympblephora formation. In addition to damage to the mucin-producing goblet cells, keratinization of the tear ducts and meibomian glands and subsequent problems such as entropion and trichiasis take place.[4] Mul-

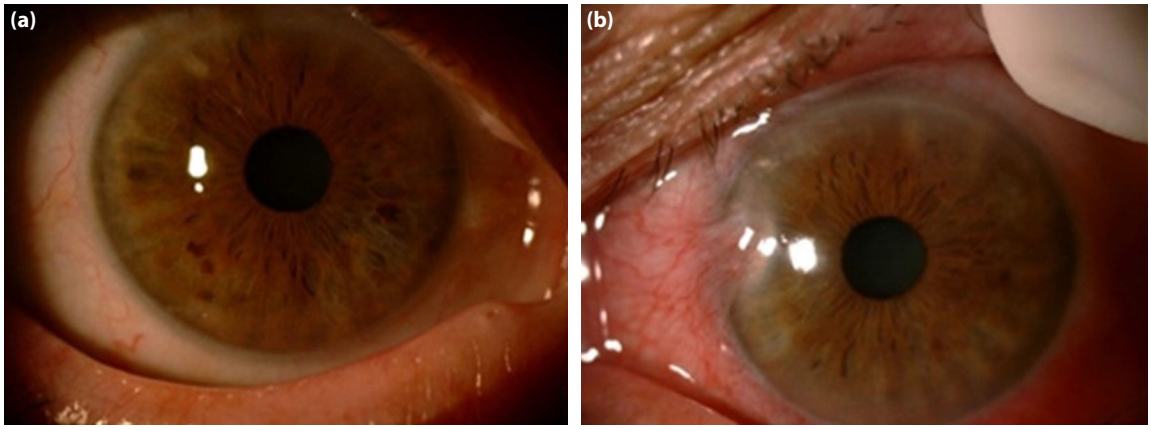

Fig. 5. **(a, b**) At the end of the treatment, the corneal epithelium of the both eyes were intact without any complications. The ocular surface inflammation has subsided.

tidisciplinary approach involving dermatologists and ophthalmologists should be adopted with appropriate topical, as well as systemic treatment. Ocular therapy differs in acute and chronic phases (Table 1).

The most common ocular presentation in the acute phase is bilateral conjunctivitis, seen in 15–75% of all patients. Approximately 25% of hospitalized SJS patients develop conjunctival and corneal ulcers. When patient struggles to survive and more attention is directed to systemic manifestations of acute SJS, it is important not to miss performing a careful examination of the tarsal and bulbar conjunctiva by everting the eyelids and using fluorescein staining, to detect any subtle ocular surface involvement.[7]

Various agents have been used in the treatment of acute SJS; including corticosteroids, IVIG, plasmapheresis, granulocyte stimulating factor, cyclosporine, tumor necrosis factor-alpha inhibitors, and cyclophosphamide.[8] Topical ocular treatment includes steroids, steroid-sparing immunomodulatory agents, antibiotics, and artificial tears. Successful results of amniotic membrane application in acute phase of SJS have been reported to suppress inflammation, prevent ulcer formation, and avoid other vision-threatening ocular surface complications.[7] This method is particularly promising in the prevention of cicatrizing ocular surface and lid margin complications.[9–12] Recently, amniotic membrane application has been strongly recommended in the first 7–10 days of acute SJS involvement of the ocular surface, if there is fluorescein staining of more than one-third of the lid margin in at least 1 eyelid, or any epithelial defect that is greater than punctate staining of the cornea, or fluorescein staining of greater than 1 cm size, in the bulbar or palpebral conjunctiva.[13] Likewise, we performed amniotic membrane transplantation upon the occurrence of ocular involvement with decreased visual acuity, conjunctival and eyelid ciliated edge inflammation with staining and significant corneal epithelial defect, despite systemic treatment of SJS.

The amniotic membrane is anatomically the innermost layer of the placental membrane. It consists of an avascular membrane on a thick basement membrane and used to suppress inflammation and accelerate healing in many corneal and ocular surface diseases.[14–17] Potential anti-inflammatory and anti-cicatricial effects of amniotic membrane application in addition to its stimulating effect on limbal epithelial stem cell expansion have been demonstrated.[18,19] The amniotic membrane is known to sup-

Table 1. Treatment in SJS ocular surface involvement

Ocular treatment in the acute phase	Ocular treatment in the chronic phase
Ensure ocular hygiene	Surgical methods after controlling inflammation for the lid sequale such as distichiasis, trichiasis, and entropion
Clean accumulated mucus and debris with sponges	Dry eye treatment (medical therapy, tarsoraphy, punctate occlusions in severe cases)
Topical steroids for control of inflammation	Surgical removal of extensive keratinization and conjunctival grafting
Topical antibiotics for infection prophylaxis	Removal of cicatricial structures, amniotic membrane application
Preservative-free artificial tears and lubricants	Penetrating keratoplasty (poor prognosis)
Amniotic membrane application	Boston keratoprosthesis (poor prognosis)

SJS: Stevens Johnson syndrome.

press natural immunity by capturing both mononuclear and polymorphonuclear granulocytes within its stromal matrix and promoting their rapid apoptosis. In addition, it has been shown to have anti-scarring effect by suppressing the transforming growth factor-b signaling within the stromal matrix.[20] Sharma et al.[7] have shown that among SJS patients, eyes that underwent amniotic membrane application had better corrected visual acuities, tear break-up time and Schirmer test results as compared the those that received only medical treatment. In the same study, corneal epithelial defects, limbal stem cell insufficiency, symblepharon formation, and lid-related complication rates were also reported at very low rates as compared to the eyes that were only medically treated.

It is known that the mortality risk of general anesthesia is high in patients with acute SJS and the technique of suturing the amniotic membrane to the ocular surface at bedside and later removing those sutures inherit various challenges. Therefore, sutureless techniques have been described in the literature, for patients with acute SJS.[22–26] Amniotic membrane can be applied to the ocular surface in the from graft, dressing, or a combination of both, with or without sutures (i.e., use of commercial amniotic membranes, tissue glue, or modified methods).[27] Modified methods include the application with the symblepharon ring, the feeding catheter or the AmnioRing®.[28,29] AmnioRing consists of 2 components; a white ring and a black bed. The White ring which can be manually separated from the black bed is spongy and the amniotic membranes adheres tightly to this ring without the need for suturing. It is applied directly to the eye, in the form of a wide contact lens with a central amniotic membrane (Fig. 2). AmnioRing can remain in the eye until the amniotic tissue dissolves. In our case, the amniotic membrane was applied to the ocular surface immediately after the initial eye exam, in outpatient conditions, using the AmnioRing, to suppress inflammation as soon as possible and prevent possible complications. This was accompanied by intensive topical eye treatment. This approach could be successful in preventing permanent loss of vision, due to corneal complications of SJS.

Conclusion

In summary, in addition to intensive topical treatment for ocular mucosal involvement of SJS, amniotic membrane transplantation has a role in suppressing inflammation in the acute phase, preventing loss of goblet cells and cicatrization in the chronic phase, and subsequent complications such as dry eye, formation of symblepharon, ankyloblepharon, conjunctival epithelial squamous neoplasia, trichiasis, entropion, lagophthalmos, corneal ulcer, neovascularization, and conjunctivalization. Sutureless amniotic membrane application can be performed in any patient who cannot be admitted to the operating room, even in the outpatient clinic or at bedside in inpatient or intensive care unit conditions. It is crucial that the dermatologists be aware of importance of ocular involvement of SJS and ask for early ophthalmologists' consultation for appropriate topical treatment including the use of amniotic membranes. Since "SJS corneas" have a poor prognosis in terms of corneal transplantation and keratoprosthesis surgeries,[1–3,30,31] amniotic membrane application in the acute period should be kept in mind as an important tool to prevent ocular surface complications and permanent corneal blindness.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: C.A.U., Z.O.; Design: C.A.U., Z.O.; Supervision: Z.O.; Resource: C.A.U., Z.O.; Data Collection and/or Processing: C.A.U., Z.O., D.O.; Analysis and/or Interpretation: D.O., C.A.U., Z.O.; Literature Search: C.A.U., Z.O.; Writing: D.O.; Critical Reviews: C.A.U., Z.O.

Conflict of Interest: None declared.

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