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Conjunctival squamous metaplasia on amniotic membrane in Stevens-Johnson syndrome: a case report

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Abstract

Background To present a case of conjunctival growth on the amniotic membrane and subsequent pathology revealing conjunctival squamous metaplasia in a patient with Stevens-Johnson syndrome.

Case presentation A 21-year-old female presented with painful, blurred vision in both eyes for two weeks. She was diagnosed with Stevens-Johnson syndrome 5 weeks before. Due to bilateral corneal epithelial defects, ProKera®, an amniotic membrane corneal bandage with a polycarbonate ring, was placed in both eyes. However, three weeks later, a slit-lamp examination revealed vascularized tissue growth from the palpebral conjunctiva to the amniotic membrane, along with symblepharon formation in the left eye. The patient underwent conjunctival biopsy, amniotic membrane removal, and symblepharon release. Pathology report showed the growth of squamous epithelium on the acellular amniotic membrane. Immunohistochemistry further supported the diagnosis, revealing squamous markers through p40 staining and highlighting the presence of the amniotic membrane using trichrome stain. Three months later, the patient's visual acuity had improved to 20/25 and no symblepharon was noted.

Conclusions This is the first case of conjunctival squamous metaplasia on amniotic membrane associated with Stevens-Johnson syndrome. Our case indicates that, despite the anti-inflammatory properties of amniotic membrane, conjunctival squamous metaplasia may arise after amniotic membrane grafting due to intense inflammation in Stevens-Johnson syndrome. Clinicians should conduct regular monitoring before amniotic membrane dissolution to preclude the development of conjunctival squamous metaplasia on the membrane and potential invasion into the cornea.

Keywords Conjunctival squamous metaplasia, Amniotic membrane, Stevens-Johnson syndrome, ProKera

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Background

Conjunctival squamous metaplasia is a pathological transformation process from non-keratinized stratified epithelium to non-secretory squamous epithelium of the ocular surface [1]. This transformation is caused by chronic inflammation, with common etiologies including vitamin A deficiency, chemical burns, thermal burns, dry eye, mucous membrane pemphigoid, and Stevens-Johnson syndrome (SJS) [2]. Together with limbal stem cell deficiency, it represents a major cause of ocular surface failure, leading to significant visual impairment and blindness [3].

Amniotic membrane (AM) transplantation is provided in the acute stage of SJS to prevent chronic ocular complications, such as limbal stem cell deficiency, corneal ulceration, symblepharon and trichiasis [4]. Additionally, AM has demonstrated inhibitory effects on squamous metaplasia of conjunctival epithelium and facilitation of epithelial growth [5]. Although AM may dissolve in the short-term within the intense inflammatory environment of SJS, no cases have reported conjunctival squamous metaplasia on AM concurrent with symblepharon in SJS. Our case shows that early diagnosis and prompt removal of conjunctival squamous metaplasia on AM are crucial to prevent chronic complications, ensuring a favorable visual outcome.

Case presentation

A 21-year-old female with bipolar disorder was referred to our ophthalmology department due to bilateral red eye and painful blurred vision for 2 weeks. Five weeks prior, the patient received lithionate and aripiprazole to manage psychological symptoms. Gingival edema, red eye, and fever developed three weeks after the initiation of medication. She developed blisters on her face and trunk subsequently, which raised suspicion of SJS. Upon referral to our outpatient department, impaired visual acuity in both eyes was noted (OD: 20/630, OS: 20/320). Pupillary light reflex, extrinsic ocular motility, and intraocular pressure were within normal limits. Anterior segment biomicroscopy revealed lid margin ulceration, corneal epithelial defect, and conjunctival membrane OU (Fig. 1A). We initiated treatment with topical levofloxacin and betamethasone OU for infectious prophylaxis and anti-inflammation. We also performed placement of ProKera® (Bio-Tissue, Miami, Florida, USA), an AM corneal bandage with a polycarbonate ring, in both eyes due to its anti-inflammatory and anti-scarring properties. After two weeks of our management, corneal re-epithelization was observed in both eyes (Fig. 1B). However, conjunctival growth on AM and presence of symblepharon were observed on the upper lid margin of the left eye three weeks after the placement of ProKera® (Fig. 2).

To confirm the diagnosis of squamous metaplasia, a histopathology examination was performed. Symblepharon release was achieved through blunt dissection, accompanied by the removal of AM and the adhered vascularized tissue. No mucosal graft or AM transplantation was performed due to concerns about a previous adverse event related to the use of ProKera®. The pathology report revealed growth of squamous epithelium with goblet cell loss on an acellular amniotic membrane (Fig. 3). The immunohistochemistry study confirmed conjunctival squamous metaplasia through p40 staining (Fig. 4A) and highlighted the presence of amniotic membrane using trichrome stain (Fig. 4B).

Her best-corrected visual acuity reached 20/25 OD and 20/25 OS three months after the surgery. Corneal epithelial defect healed with minimal subepithelial fibrosis. Both fornices were deep without formation of symblepharon. This case represents the first instance of

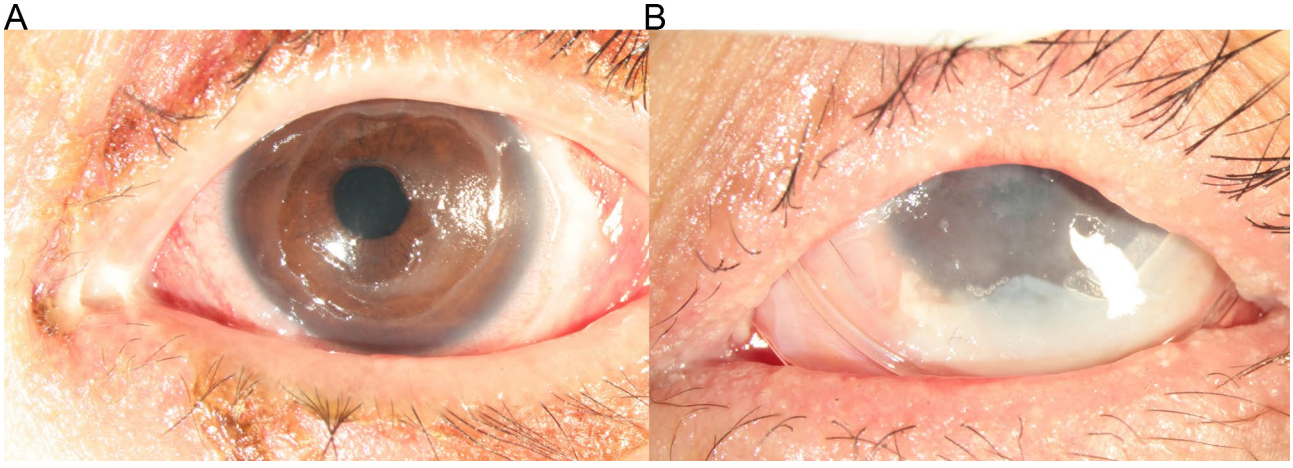

Fig. 1 Anterior-segment photograph of the left eye shows (**A**) subtotal corneal epithelial defect during the initial visit, and (**B**) healing of corneal epithelium with amniotic membrane covering after 2 weeks

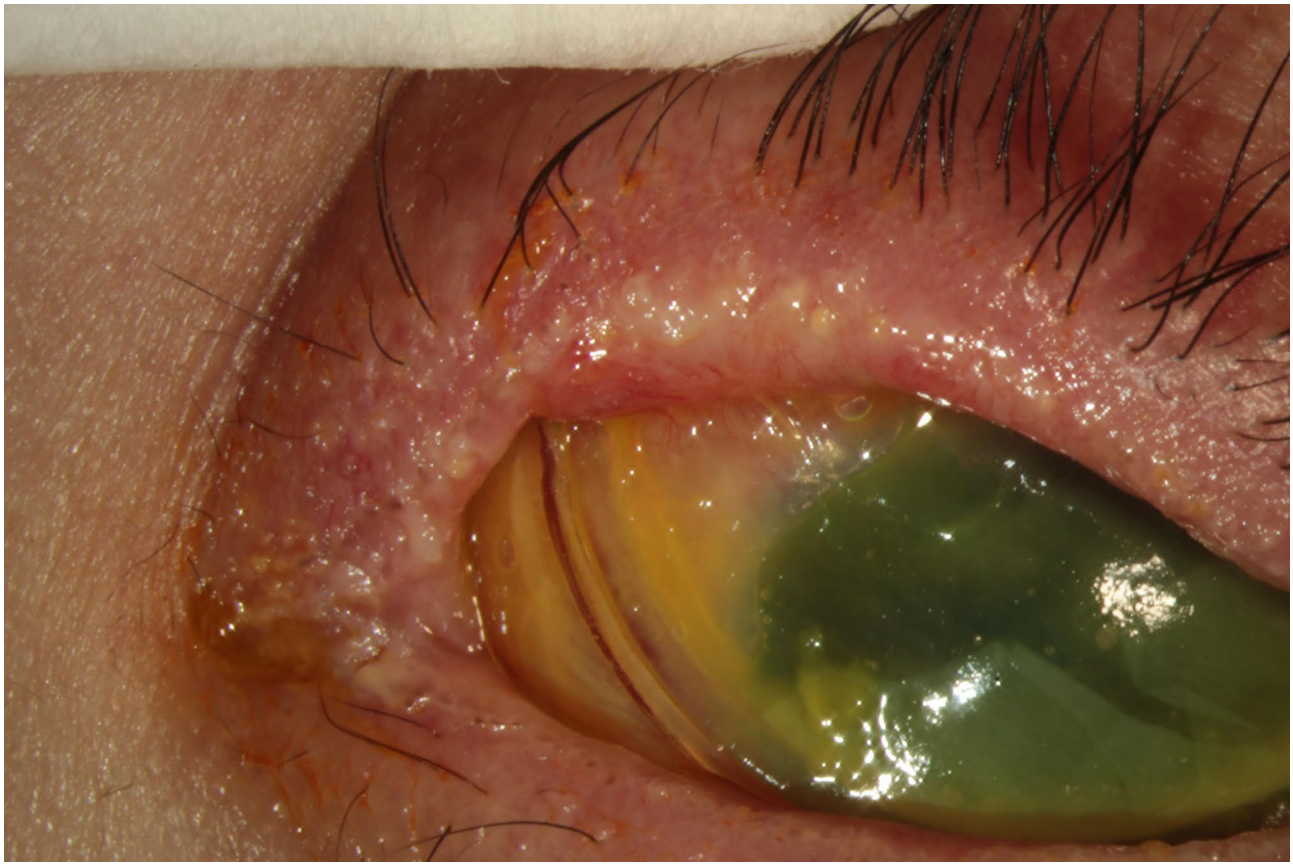

Fig. 2 Color slitlamp photograph shows conjunctival growth on the upper margin of amniotic membrane 3 weeks after the placement of ProKera®

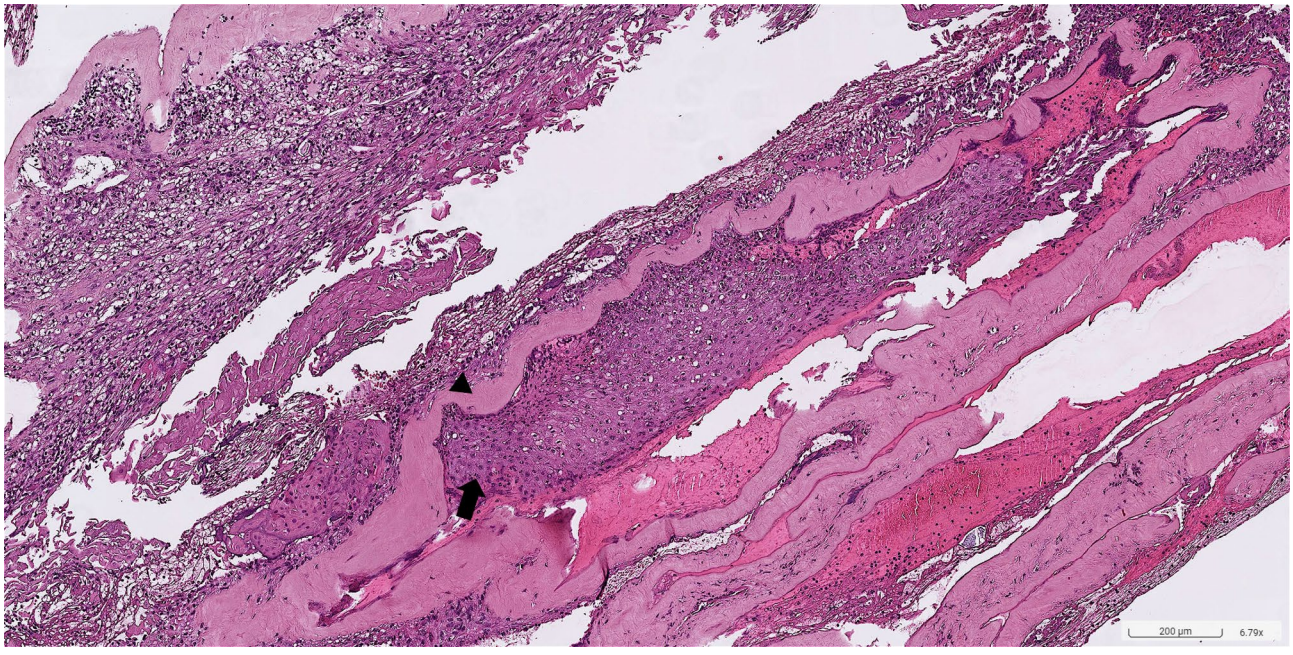

Fig. 3 Histopathology of excised conjunctiva on amniotic membrane reveals growth of squamous epithelium (arrow) lacking goblet cells on the amniotic membrane (arrowhead) (hematoxylin-eosin stain, original magnification x200)

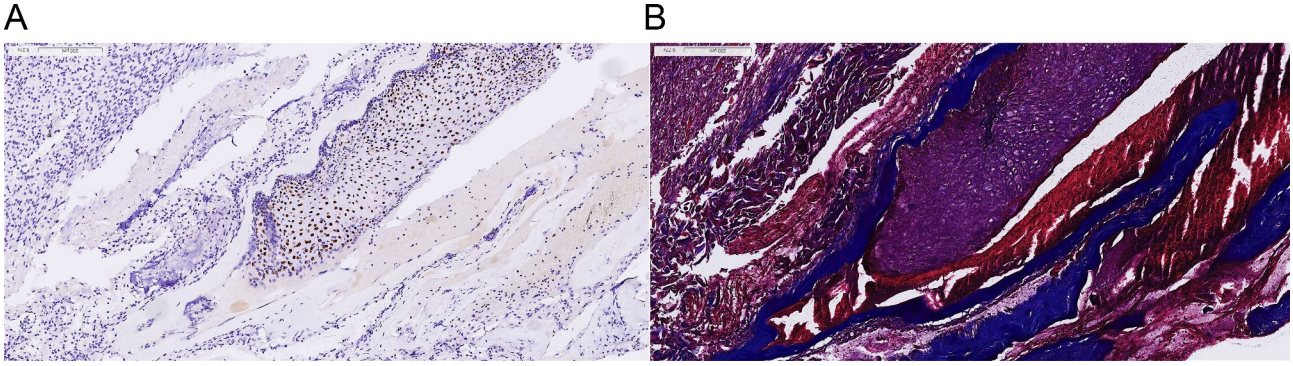

Fig. 4 The immunohistochemistry study demonstrates (**A**) diffuse conjunctival staining of the squamous cell marker p40, and (**B**) trichrome stain highlights the presence of amniotic membrane

conjunctival squamous metaplasia on AM, substantiated by pathological evidence.

Discussion and conclusion

Early recognition and timely treatment of SJS are imperative to prevent chronic ocular sequelae that lead to severe visual impairment [6]. AM has been shown to promote corneal epithelial healing and suppress inflammatory responses in SJS. However, our case underscores that ocular surface inflammation in SJS can overshadow the anti-inflammatory properties of AM, leading to squamous metaplasia that eventually encompasses the AM.

Conjunctival squamous metaplasia is mimicked *ex vitro* through airlift culture that induces inflammation of conjunctival tissue [7]. Upregulation of pro-inflammatory markers IL-1β, TNF-α, and MMP on the ocular surface in the airlift model parallels changes seen in dry eye disease linked to chronic inflammation. Consequently, abnormal mucin expression, abnormal differentiation and hyperproliferation of conjunctival epithelium ensued. The squamous metaplasia initiated a vicious cycle that exacerbated inflammation, damaged goblet cells, and reduced tear secretion. Current therapies, including serine protease inhibitor A3K, minocycline, or AM, have demonstrated effectiveness in inhibiting conjunctival squamous metaplasia in animal or cell models, yet their in vivo efficacy lacks substantial evidence [3, 7]. Given the uncertain etiology of the vascularized tissue on the AM in our case, confirmation of the diagnosis necessitates histopathological examination. Additionally, surgical excision and timely symblepharon release can arrest its extension to the cornea and restore fornix structure. These considerations underscore the important role of surgical removal and histopathological examination in managing such cases.

SJS is considered a drug-induced hypersensitivity triggered by cytotoxic T cells releasing cytotoxic molecules, Fas-Fas ligand interaction and activation of the tumor necrosis factor alpha pathway, ultimately causing keratinocyte cell death [8]. AM grafting is indicated for patients with severe ocular involvement during the acute stage of SJS, defined as having at least one of the following features: any corneal epithelial defect, staining of more than one-third of the length of the lid margin, or staining of the conjunctiva greater than 1 cm [9]. AM consists of simple epithelium, thick basement membrane and avascularized stroma. ProKera® offers advantages over AM grafting, such as reduced bulbar conjunctival sloughing, prevention of the retraction of the conjunctival cul-de-sac by the polycarbonate ring, and sutureless bedside procedures without general anesthesia. These features make it suitable for patients with poor general condition, such as SJS [10]. Early use of AM and ProKera® effectively promotes corneal epithelial healing and reduces scarring due to their anti-inflammatory properties [6]. Although in vitro studies suggest that AM inhibits squamous metaplasia of the conjunctiva, our case revealed that strong inflammation could still promote squamous metaplasia and the subsequent growth on the AM [5]. We propose that cell migration in the conjunctiva, prompted by damaged limbal stem cells, led to the growth of conjunctival tissue on the AM. Despite the absence of AM dissolution and the placement time adhered within the FDA-approved 30-day period, our case suggests the potential for inflammation in SJS to supersede the anticipated anti-inflammatory effects of AM. Additionally, directly suturing the AM onto both the bulbar and palpebral conjunctiva, rather than using ProKera®, might have prevented conjunctival squamous metaplasia. Although ProKera® can be used in patients without severe bulbar conjunctival inflammation, its outer diameter (21.6 mm) is inadequate for complete coverage from the upper to lower fornix [11]. Inflammation from uncovered areas might promote squamous metaplasia and subsequent symblepharon formation. Hence, consistent monitoring of conjunctival growth on AM and subsequent management are paramount to prevent chronic ocular complications in SJS.

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Author contributions
Research idea, study design, data interpretation: YKC; concept, data acquisition: PLW and CLC; YKC wrote the first draft of the manuscript; CHL supervised and discussed the work; PLW reviewed and approved the final version of the manuscript; all authors had full access to all the data and takes responsibility for the integrity of the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participants
Not applicable.

Consent for publication
Written informed consent for the use of personal details and associated images was obtained from the patient.

Competing of interest
The authors have declared that no potential conflict of interest relevant to this article exists.

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