Challenges in managing Steven Johnson Syndrome with chronic ocular and extraocular abnormality.

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Background: *Stevens-Johnson syndrome (SJS) is one of the most debilitating adverse drug reactions which can lead to ocular complications, making management more challenging with multiple options for surgical approaches.*

Case report: *A 10-year-old girl with a history of SJS presented with difficulty opening both eyes after a symblepharon release surgery twice in other hospital. Unfortunately, there was still recurrence of symblepharon in both eyes followed with trichiasis and entropion. The multistep surgical approaches for ocular restoration were symblepharon lysis surgery, followed by amnion membrane transplant and conformer shell placement on both eyes. The shells were released one month after the initial surgery. After being treated for several months, the patient underwent eyelid reconstruction surgery for trichiasis and entropion to provide better ocular surface. Nevertheless, these approaches still showed recurrence of symblepharon in the left eye 6 months after the initial surgery.*

Conclusion: *Surgical approach should be patient-tailored based on complexity and severity of the ocular complications of SJS. Comprehensive management in treating SJS is required since the presence of systemic processes and complications are always possible.*

Conflict of interest: *none.*

Keywords: *Stevens-Johnson syndrome, amnion membrane transplant, recurrence of symblepharon.*

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Background

Stevens-Johnson syndrome (SJS) is a rare skin reaction, usually related to drugs. It is one of the most debilitating adverse drug reactions to be recognized. SJS is a life-threatening reaction and if left untreated, can result in death with mortality rates ranging from 1-5%.[1,2] Ocular complications are quite common in SJS which usually involve the cornea, conjunctiva, and eyelids. It has been reported that 50% of patients developed late ocular complications including severe dry eyes (46%), trichiasis (16%), symblepharon (14%), distichiasis (14%), visual loss (5%), entropion (5%), ankyloblepharon (2%), lagophthalmos (2%), and corneal ulceration (2%).[3] Other mucous membranes could also be affected such as genitourinary, nasopharyngeal, rectal and the respiratory tract.[4]

Symblepharon is one of many ocular sequelae, it is a condition that refers to any adhesion between the bulbar and tarsal conjunctiva that occurs following various etiologies. Its pathogenic effects include dry eye resulting from interruption of tear flow and spread; blockage of lacrimal gland ducts; blink-related microtrauma resulting from irregular tarsal surface, cicatricial entropion, or misdirected lashes; untoward exposure because of inadequate blinking and closure or limitation of Bell's phenomenon; and interference with the vision resulting from restriction of the ocular motility and ptosis. Cumulative insults from these pathogenic elements may lead to ocular surface failure.[5,6]

There are several surgical techniques for managing symbepharon. Tissue substitutes such as conjunctiva, oral mucosa graft or amnion membrane have been used for ocular surface reconstruction after symblepharon lysis in conjunction with additional material to keep the potentially adhesive surface apart after surgery.[5]

This case illustrates how chronic SJS could develop multiple complications, not only related to the skin and eye but also systemic complications which makes the management more challenging with multiple surgical approaches. Treatment was initiated using amniotic membrane transplant for symblepharon lysis, followed by eyelid surgery to reconstruct the eyelid that hopefully will provide a healthy environment for ocular surface. Besides the consideration of the ocular involvement, the extra-ocular tissue involvement can be one of complicating factors that should be monitored for comprehensive management.

Case Report

A 10 year old girl presented with a history of SJS and underwent symblepharon release surgery twice in another hospital. After the first surgery, which was performed 3 years ago, both eyes were covered with conformer shells. Systemic immunosuppressive medication was given during acute phase. Upon follow up after 6 months, there was a recurrence of the symblepharon in both eyes, which prompted plans for a second surgery. After the second surgery, the conformer shells were not used to cover both eyes. One year later, she came to our hospital with a complaint of difficulty in opening both eyes involuntary. She needed to use her hands to open it forcefully. She had already been treated with artificial tears for both eyes. There was no history of red eye, infection and other eye diseases before she was diagnosed with SJS.

Ocular examination revealed visual acuity of right eye was hand movement with good projection and left eye was light perception with good projection.

Intraocular pressure was difficult to be obtained due to difficulties opening both eyes. There was cicatricial entropion and trichiasis on both eyes followed by madarosis in both inferior palpebral. Tarsal conjunctiva was hard to be evaluated due to difficulties in performing the eversion of the lower eyelid while the bulbar conjunctiva showed symblepharon for both eyes. The cornea showed a hazy appearance that defined as a keratopathy for both eyes followed by neovascularization (figure 1). Any further examinations were difficult to perform. We suggested the patient to undertake a symblepharon release surgery with amniotic membrane graft and everting sutures both for lower eyelids and anterior lamellar recession (ALR) with tarsal splitting for left upper eyelid.

Figure 1: Pre-operative picture showing both eyes with symblepharon, madarosis on inferior eyelid followed with conjuntival injection, ciliary injection and corneal haziness.

While preparing for the surgery, the patient was consulted with the pediatric department for pre-operative evaluation. Laboratory and radiology examination showed a pathologic condition related to her lung based on her thorax radiograph. She developed an atelectasia of her left lung, confirmed by thorax Multi-slice computer tomography which showed lung agenesis with left hemithorax herniation that has been compensated with mediastinum organ in left hemithorax. According to these findings, the pediatric department planned for further investigation related to the pulmonary condition.

The symblepharon release surgery was subsequently performed followed by amniotic membrane graft using a cryopressed amnion membrane (figure 2) and closed with conformer shell placement (figure 3). After the first step was done, the next step was eyelid reconstruction. Post-operative medications were chloramphenicol eye ointment (EO), levofloxacin eye drop (ED), prednisolone acetonide ED, artificial tears ED, ibuprofen, and amoxicillin.

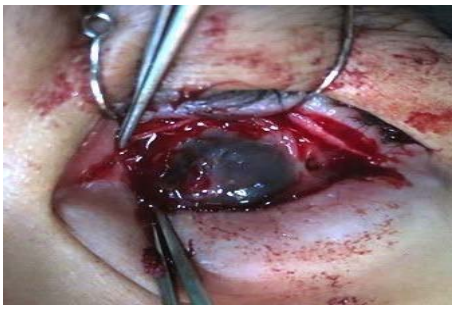

Figure 2: Symblepharon release surgery with amniotic membrane transplant.

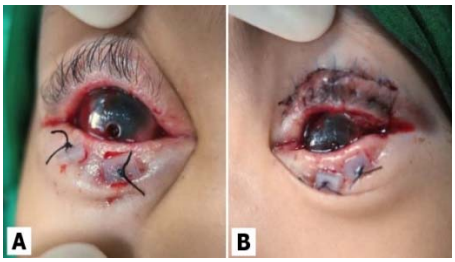

Figure 3: (A) Right eye with conformer shell and tarsorraphy on the inferior eyelid and everting suture on inferior eyelid. (B) Left eye with conformer shell followed with stitches on the superior eyelid after ALR with tarsal splitting procedure and everting suture on the inferior eyelid.

One month after the first surgery, the conformer shells were removed. There was no symblepharon, entropion and trichiasis. Nevertheless, both eyes still

showed conjunctival and cilliary injections (figure 4). The post removal medications were chloramphenicol EO, fluometholone ED and polyvinylpyrolidone ED. The pediatric department planned to perform bronchoscopy.

Figure 4: Both eyes after conformer release one month after the first surgery showing minimal sign of inflammation, no sign of symblepharon and dissolving of amnion membrane.

Six months after the first surgery, she complained of having red eyes followed by difficulties while opening her eyelid. After further examination, both palpebras were spasms and shows cicatrical entropion at inferior part of right eyelid and cicatrical entropion at superior and inferior part of left eyelid. Trichiasis were found in both eyelids (figure 5). Regarding to these findings, we performed the second surgery which include tarsal fracture at inferior eyelid followed with lamellar division superior eyelid and levator advancement on left eye (figure 6). Post-operative medications were amoxicillin, paracetamol and chloramphenicol EO.

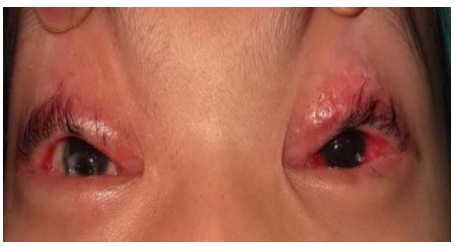

Figure 5: Six months after the first surgery, both eyes showing entropion with recurrence of symblepharon.

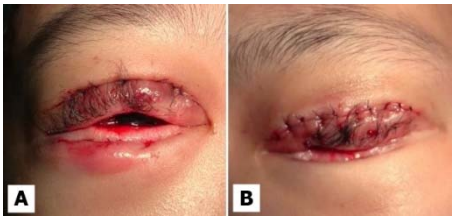

Figure 6: Post-operative picture after tarsal fracture on inferior eyelid followed with lamellar division on superior eyelid and levator advancement on the left eye. (A) right eye (B) left eye

One month after second surgery, there was no complaint regarding the eyes except dazzled and blurry vision. From clinical examination, the right eye was in good condition, with madarosis on inferior palpebral without any entropion and trichiasis and there was no lagophtalmos. However, on the left eye, there was a recurrence of the symblepharon especially in inferior part. Other examinations were difficult to perform due to uncooperativeness of the patient. At the time, we planned further treatment regarding her ocular surface and decided to consult her case with Cornea and Refractive Surgery Division for a full corneal evaluation under anesthesia. However, this could be done after the dry eye symptoms on both eyes were managed.

Discussion

SJS and its severe variant, toxic epidermal necrolysis (TEN) defined as severe and life-threatening mucocutaneous diseases that is characterized by acute skin blisters and mucous membrane erosions, the condition is nearly always drug-related and is consider a medical emergency. It was a rare disease with an incidence of between 1 to 6 cases per million annually worldwide meanwhile the incidence of SJS/TEN in South East Asia is largely undetermined.[7, 8]

This patient first came to our hospital with history of SJS having underwent two similar procedures with the same complaint of difficulty in opening both eyes. At the beginning, the patient had an allergic reaction on her body after she took medical treatment for her respiratory disease. She developed a fever with uncomfortable sensation around both superior palpebral regions at the beginning, followed by some redness with peeled skin around her head and upper trunk, which continued to lower trunk, genitalia and anus. With further examination, we found the same features on her genitalia and anus. The prodromal phase of SJS and TEN frequently consists of influenza-like symptoms, including fever, cough, myalgias, arthralgias, and malaise, which may last between one day to two weeks. These symptoms were followed by the appearance of skin lesions, mostly seen on the trunk and face, but can also occur on the neck and proximal extremities. The characteristics were flat skin lesions, irregular, atypical target lesions or diffuse purpuric macules that frequently have necrotic centers and tend to coalesce over the course of time. As a result of cell death in the basal layer and stratum spinosum, the epidermis will detaches from the dermis, giving rise to flaccid blisters. Reepithelialization usually begins after a few days, at a time when lesions are still spreading, and is generally complete within 2 to 3 weeks. In almost 90% of patients, there was involvement of the mucous membranes. Erythematous, painful erosions occur most commonly on the buccal mucosa, but can also be found on the ocular and anogenital mucosa. SJS and TEN are primarily diagnosed clinically, with high suspicion usually raised with a good initial history and physical examination alone and best support by the histological examination. In this patient, diagnosis were made just based on history of the disease that matched with SJS/TEN clinical features.[7,9] Therefore, the symblepharon on both eyes were caused by SJS. Based on literature, more than 100 drugs have been identified being related with SJS/ TEN. The most frequent implicated drugs primarily allopurinol, antibiotics, nonsteroidal anti-inflamatory drugs and anticonvulsant. Among the antibiotics, sulfonamide most strongly associated with SJS followed by aminopenicilins, quinolones, cephalosporins, tetracycline and anti fungals. Furthermore, drugs with longer half life are most likely to cause drug reactions.[2] Unfortunately, the patient's parents could not remember the name of medications that she was taken.

SJS effects on the ocular surface can be devastating, leaving survivors with permanent, severe dry eye problems and debilitating photophobia.[10,11] Damage to the ocular surface appears to be caused by apoptosis and necrosis in the epidermal layers, as well the intense inflammation that can followed. Ocular problems may occur acutely in conjunction with skin involvement or after the skin eruption. It has been reported that 50% of patients develop late ocular complications including severe dry eyes (46% of cases), trichiasis (16%), symblepharon (14%), distichiasis (14%), visual loss (5%), entropion (5%), ankyloblepharon (2%), lagophthalmos (2%), and corneal ulceration (2%).[3] Mild cases are manifested by a conjunctivitis, which can produce localized conjunctival epithelial defects. Severe cases yield a diffuse, destructive inflammation with pseudomembranous and membranous conjunctivitis. The raw surfaces can lead to adhesion formation between the palpebral and bulbar conjunctiva,

known as symblepharon. The intense inflammation can destroy goblet cells and accessory lacrimal glands, as well as the secretory ductus of the main lacrimal gland. The normal mucosal structure of the conjunctiva is eventually replaced by a cicatricial epithelium and subconjunctival scar tissue. The eyelids themselves can also suffer significant damage. Contracture of the palpebral conjunctiva can yield cicatricial entropion. Lid margin inflammation can cause widespread destruction of meibomian gland orifices and the glands themselves. Eyelash architecture can also be affected, resulting in trichiasis and distichiasis. The abnormally directed lashes can abrade the compromised ocular surface and lead to discomfort, corneal abrasions, and corneal ulceration. Keratinization of the lid margins and palpebral conjunctiva further contributes to discomfort and corneal damage via blink-related microtrauma to the corneal epithelium. Destruction of the corneal limbal stem cells is perhaps the hardest consequence of the aforementioned pathologies and can lead to vascularization and thickening of the corneal epithelium. This "conjunctivalization" of the cornea, accompanied by the abnormal tear film, produces severe visual loss. Additionally, it creates a poor prognosis for any future corneal transplantation.[12]

This case showed the difficulties to open both eyes due to symblepharon and had been treated twice with surgical intervention. Reccurence of the disease was caused by progression of the disease or inadequate treatment option. The eyelid had shown a cicatrical entropion on both eyes. Meanwhile, the cornea showed conjunctivalisation followed by neovascularization, indicative of an inflammatory process was present on this site. These clinical features were mentioned as a chronic ophthalmologic sequelae of SJS.

Certain forms of surgical technique have been reported for the treatment of symblepharon. Tissue substitutes such as conjunctiva, oral mucosa graft or amniotic membrane has been used for ocular surface reconstruction after symblepharon lysis. Some materials have been evaluated to retain the potentially adhesive surfaces apart after surgery such as symblepharon ring, silicone sheet implant, mitomycin C, bevacizumab or applicaton of beta-irradiation. Amongst all efforts, the recurrence rate remain highly variable from 6.2% to 40%.[6] This patient showed symblepharon recurrence twice after surgery. We planned to perform symblepharon lysis surgery followed by amniotic membrane transplant with hope for an improved outcome. The aim of this option was to prevent the recurrence of symblepharon and restore the ocular surface.

The amniotic membrane, which is the innermost layer of the placenta, is now widely used in the treatment of nonhealing corneal ulcers, persistent epithelial defects and ocular surface reconstruction. Histologically, it closely resembles the basement membrane of conjunctiva. Pathologically, amniotic membrane has several beneficial properties including the suppression of the innate immunity by trapping both mononuclear and polymorphonuclear granulocytes within its stromal matrix and inducing them into rapid apoptosis, in addition to modulation of acquired immunity by suppression of alloreactive responses and downregulation of production of Th1 and Th2 cytokines. The stromal matrix of amniotic membranes exert a powerful direct anti-scarring action on ocular surface fibroblasts by suppression of TGF-β signaling at the transcriptional

level, leading to downregulation of several downstream genes that are responsible for scar formation. These properties made amniotic membrane an ideal substitute for ocular surface reconstruction following chemical injuries, cicatricial ocular surface disorders, pterygium and ocular surface growth excisions. This promotes epithelization of raw surfaces and therefore prevents recurrence of symblepharon.[13]

Literature review of amniotic membrane transplantation (AMT) on acute stages of SJS/TEN showed good clinical outcome and revealed that AMT performed in the first two weeks after onset of ocular involvement facilitates rapid epithelial healing and reduces inflammation and scarring of the ocular surface.[6,14] In our case, the challenge was that we decided to use AMT after two previous surgeries, in which the patient was already at a later stage. Additional conformer shells were placed to prevent recurrence after unpredictable degradation of amniotic membrane.

Our case showed a symblepharon recurrence 6 months after treatment with AMT. Currently, there are no useful biomarkers for the diagnosis and monitoring the disease progression of SJS/TEN. Clinically we often see SJS patients with slowly progressive conjunctivalisation of cornea and visual acuity degradation even years after the initial attack.

The immunopathological features of conjunctivalised corneas in SJS were not appreciably different from those with chemical injury. Also, the pattern of immunoreactivity to antibodies examined was consistent with no clear correlation having emerged between the immunopathological findings of an individual patient and the patient's clinical histories. The results revealed that inflammatory cells in the substantia propria of conjunctivalised cornea of SJS patients composed of CD4+ T cells, CD8+ T cells, and/or macrophages. Additionally, the predominance of IFN-γ suggesting that CD4+ T cells were mainly Th1 cells that can promote cellular immunity. Interestingly, some immunohistochemical study of patients with SJS who experienced recurrent episodes of inflammation, found that the predominant T cells in conjunctiva were T helper cells, rather than suppressor T cells which usually outnumber T helper cells in normal conjunctiva. However, the difference between patients with SJS who experienced recurrent episodes of conjunctival inflammation and those who do not is not readily established.[15]

Regarding the recurrence of ocular sequelae, other options should be considered. Oral mucosa graft is commonly used to restore ocular surface. For reconstruction of the lid margin, it used to correct trichiasis and entropion. Some studies showed oral mucosa graft not only to correct districhiasis, but also incomplete closure caused by severe cicatrical ocular surface disease. Oral mucosa are thought to be at a lower stage of differentiation than epidermal keratinocytes. Their short cell turnover time requires shorter cultures and they can be maintained in culture for prolonged periods without keratinization. Moreover, the oral cavity is an ideal location for tissue biopsy as the resulting scar is inconspicuous. Finally, keratin 3 is a reliable marker for corneal type differentiation and is positive for epithelial cells of normal in vivo oral mucosa. Due to these characteristics, oral epithelial cell was recommended as an ideal substitute for corneal epithelial in ocular surface reconstruction.[16]

After dealing with ophthalmic sequelae, the chest radiology examination showed a pulmonary atelectasis of the left lung, with SJS being the suspected cause. We consulted the pediatric department for further examination and treatment. The pediatric department planned to perform bronchoscopy to determine the pathological event in the lung. The incidence of pulmonary involvement in SJS/TEN has not been examined in literature. Pulmonary involvement in SJS/TEN is divided into two types: interstitial pneumonia during the course of SJS/TEN, and obliterative bronchitis/bronchiolitis after the resolution of SJS/TEN. According to one report, pulmonary sequelae tend to occur in relatively young patients. A few cases of obliterative bronchitis/bronchiolitis after SJS/TEN has been documented, as well as respiratory tract obstruction and bronchiectasis. The interval from the onset of SJS/TEN to development of pulmonary sequelae is unclear because some reported cases show persistent respiratory symptoms from the onset of SJS/TEN. Obliterative bronchitis/bronchiolitis is diagnosed using imaging and respiratory function tests, with findings of bronchiectasis on high resolution computed tomography (CT) of the chest, occlusion of the bronchus on bronchoscopy, and a severe obstructive pattern in the flow-volume curve. Although the pathomechanism remains unknown, immunological pathways, infection, and remodeling of the bronchial mucosa are implicated in the pulmonary sequelae of SJS/TEN. If patients suffered from recurrent respiratory symptoms after the resolution of SJS/TEN, they should be closely monitored using respiratory function tests and CT. No effective treatment is available for permanent obstructive pulmonary changes in obliterative bronchitis/bronchiolitis. In severe cases, mechanical ventilation is required, and living-donor lung transplantation may be necessary.[17] Patients with pulmonary sequele after resolution of SJS/TEN tend to have a poor prognosis.

Conclusion

The management of ocular surface restoration for chronic SJS sequelae was a challenge due to the risk of recurrence and failure. The recurrence of ophthalmic sequelae in our case was unavoidable although it has been treated with multiple step approaches and showed good progression at the beginning. Every surgical approach should be individually chosen and patient tailored according to the severity of the ocular complications. Comprehensive management on treating SJS is needed since every patient is at risk of systemic complications resulting in poor prognosis.

Acknowledgement

N/A

Conflict of Interest

The authors affirm there is no conflict of interest in this study.

Consent

The patient's mother in this study has given her consent for her daughter's anonymized photograph and case history to be published.

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