Severe Dry Eye With Combined Mechanisms is Involved in the Ocular Sequelae of SJS/TEN at the Chronic Stage

Chie Sotozono, Mayumi Ueta, and Norihiko Yokoi

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Sweeney-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory diseases of the skin and mucous membranes that predispose patients to life-threatening complications such as sepsis, respiratory dysfunction, and multi-organ failure. Although the incidence of SJS and TEN is very low, both can affect anyone at any age, usually as a consequence of adverse drug reactions. After the acute-stage impairments subside, cicatrization of the ocular surface progresses. Serious visual impairment and severe dry eye remains as ocular sequelae. At the acute stage, ocular complications occur in 77% of SJS/TEN patients. In cases with pseudomembranous formation and/or epithelial defects, the risk of ocular sequelae increases. Among 13 slit-lamp microscopy images that we obtained of SJS/TEN patients at the chronic stage, the loss of corneal epithelial stem cells and severe meibomian gland involvement were found to be the most common disorders. Severe dry eye in SJS includes three important mechanisms: (1) aqueous tear deficiency, (2) decreased wettability of corneal surface, and (3) increased evaporation. Dry eye severity in SJS patients is often underestimated when the meniscus is first observed, as the punctum is closed due to scarring or surgery. In SJS patients with severe dry eye, the dryness results in immense eye pain, and unstable tear film related to dry eye result in a change/loss of vision. For the treatment of dry eye in SJS, it is important to suppress chronic inflammation on the ocular surface, and 2% rebamipide ophthalmic solution reportedly helps to obtain ocular surface stabilization. Scleral contact lenses, as well as the newly developed limbal-rigid contact lenses, improve the patients’ visual acuity and reduce symptoms related to severe dry eye. Further studies and new therapeutic methods are needed to more effectively treat dry eye in patients afflicted with SJS/TEN.

Keywords: Stevens-Johnson syndrome, tear deficiency dry eye, meibomian gland dysfunction, evaporative dry eye, limbal rigid contact lens

Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are life-threatening diseases of the skin and mucous membranes. After the acute-stage damage subsides, serious visual impairment and severe dry eye remains as ocular sequelae. The clinical features at the acute stage and ocular sequelae of SJS/TEN are discussed.

CLINICAL FEATURES AT THE ACUTE STAGE AND OCULAR SEQUELAE

In 77% of SJS/TEN patients, ocular complications are involved at the acute stage of the disease. Bilateral acute conjunctivitis is known to occur prior to, or simultaneously with, acute fever and systemic eruption. Extensive inflammation arises on the ocular surface with extreme upregulation of inflammatory cytokines, accompanied by pseudo-membranous formation and corneal and/or conjunctival epithelial defects.

Recently, we proposed a simple grading system to evaluate acute ocular severity of SJS/TEN, with the grades ranging from 0 to 3 based on the presence of conjunctivitis, corneal or conjunctival (ocular surface) epithelial defect, and pseudo-membrane formation. Bilateral conjunctival hyperemia was assessed as grade 1. Eyes with pseudomembrane formation or an ocular-surface epithelial defect were assessed as grade 2. Eyes with both pseudomembrane formation and an ocular surface epithelial defect were assessed as grade 3. In both SJS and TEN, the chronic ocular sequelae more frequently occur in patients with severe, or very severe, ocular involvement (grades 2 and 3 of the acute ocular severity score) than in patients with no or mild ocular involvement (grades 0 and 1). We found that the prevalence of dry eye at the chronic stage increases according to the increase of acute ocular severity (SJS: \( P = 0.001 \); TEN: \( P = 0.014 \); Fig. 1). We consider ocular surface inflammation and epithelial necrosis or apoptosis to be the initial ocular pathologic changes.

Keywords: Stevens-Johnson syndrome, tear deficiency dry eye, meibomian gland dysfunction, evaporative dry eye, limbal rigid contact lens
processes of SJS/TEN. Secondary processes include persistent epithelial defects, ulceration and perforation, fornix shortening, symblepharon formation, and vision loss. Both SJS and TEN are self-limited diseases, and the systemic condition improves within 2 months after the onset. However, in cases with prolonged ocular surface inflammation, the secondary process can progress even after the systemic findings subside.

**Objective Findings at the Chronic Stage**

Previously, we developed a new grading system to evaluate chronic ocular complications in SJS/TEN. In our new grading system, corneal complications (i.e., superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt [POV], conjunctivalization, neovascularization, opacification, and keratinization), conjunctival complications (i.e., hyperemia and symblepharon formation), and eyelid complications (i.e., trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage) were graded on a scale from 0 to 3 according to their severity (Fig. 2). The severity of meibomian gland involvement was determined clinically by the decreased quantity of the meibomian gland secretion expressed manually at the central-third of the upper lid margin. Of the above-described complications, the loss of the POV and severe meibomian gland involvement were most common ocular complications at the chronic stage (i.e., 82.6% and 73.9%, respectively).

In SJS/TEN cases, limbal stem cell destruction, evidenced by the loss of the POV, may occur at disease onset, thus resulting in conjunctivalization, neovascularization, and opacification of the cornea. Meibomian glands may also be involved in the injury after the onset of SJS. In addition, the ocular pathologic process is often accompanied by the destruction of goblet cells. Since the meibomian glands and goblet cells play a crucial role in tear-film stabilization, this is likely to contribute to the evaporative effect of dry eye via the instability of tear film. In the clinical setting, it is important to first understand that both “aqueous-tear-deficient” and “evaporative” dry eye are involved in the ocular sequelae of SJS/TEN at the chronic stage.

**Meibomian Gland Dysfunction in SJS**

The differences of meniscus tear volume, the condition of the precorneal tear film, and the structure of the meibomian glands in eyes with severe ocular surface disorders and in normal healthy eyes are shown in Figure 3. The study involved 69 eyes of 37 cases with SJS (mean age: 47.1 ± 21.3 [SD] years), 32 eyes of 17 cases with ocular cicatricial pemphigoid (OCP; mean age: 63.6 ± 18.9 years), 22 eyes of 16 cases with chemical/thermal injury (mean age: 42.6 ± 15.8 years), and 42 eyes of normal healthy control subjects (mean age: 49.3 ± 20.5 years). The meniscus tear volume was evaluated by measurement of the tear meniscus radius (TMR) via video meniscometry. For evaluation of the pre-corneal tear film condition, a video-interferometer (DR-1; Kowa, Tokyo, Japan) was used to observe the specular image of the reflected light from the tear-film lipid layer (TFLL) at the central part of the cornea (2 mm circular area), with the images being graded from 1 to 5 based on our previously reported novel grading system. Using a video-meibography system, the structure of the meibomian glands was evaluated from the point of the gland...
dropout of the meibomian glands of the lower eyelid, which was classified into one of the following 3 grades: 1) normal, 2) mild dropout, and 3) severe dropout.

Our findings revealed that the TMR values, as evaluated by meniscometry, did not differ among the 4 groups (i.e., 0.30 ± 0.26 mm in the SJS group, 0.25 ± 0.20 mm in the OCP group, 0.27 ± 0.18 mm in the chemical/thermal injury group, and 0.26 ± 0.19 mm in the normal healthy control group). On the other hand, the mean (±SD) grades of the TFLL, in which greater grades imply an abnormal tear film, were significantly greater in the SJS (4.1 ± 1.2; ±SD) and OCP (3.7 ± 1.1) groups than in the chemical/thermal injury (2.5 ± 1.0) and normal healthy control (2.3 ± 0.5) groups ($P < 0.05$). From these findings, it is important to note that among the 63 SJS eyes in which the TFLL could be examined, 31 eyes demonstrated a grade 5, the corneal condition uncovered by the complete tear film. This finding implies that in those SJS cases with grade 5, although the tear volume was maintained and compatible with that of normal controls, sufficient aqueous tears were not reflected upon the corneal surface, being uncovered by the tear film. This discrepancy might possibly be explained by the abnormal corneal surface in SJS patients. Grade 5 signifies the decrease of wettability of the epithelium; less water holding capacity of epithelium resulting in the decreased thickness of aqueous tear film on the surface of the cornea leading to the arrest of spreading of TFLL. In SJS eyes, it is reported that abnormal epithelial differentiation such as keratinization occurs on the ocular surface epithelium. Taking into consideration the fact that normal corneal epithelium is known to have remarkably high wettability, abnormal epithelial differentiation in SJS may result in a decreased wettability of the corneal surface, thus leading to an inability to establish complete precorneal tear film (grade 5).

**Figure 2.** Ocular surface grading scores at chronic stage in SJS/TEN (A) Grading scores of corneal and conjunctival complications. (B) Grading scores of mucocutaneous junction involvement.
Video-meibography showed high rates of severe dropout in meibomian glands in SJS and OCP (i.e., 66.7% and 53.1%, respectively). Since, severe meibomian gland dropout is known to be related to evaporative dry eye via the dysfunction of meibomian glands, the evaporative mechanism in SJS and OCP is also thought to be involved in the associated dry eye.

When considering the possible association of aqueous tear deficiency in SJS due to the involvement of the lacrimal gland duct in subconjunctival scarring, the results described above suggest that in SJS at the chronic phase, three important mechanisms are likely to be involved, (i.e., aqueous tear deficiency, decreased wettability due to corneal surface change via squamous metaplasia/keratinization, and increased evaporation due to meibomian gland dysfunction).

**SUBJECTIVE SYMPTOMS RELATED TO DRY EYE IN SJS**

Severe dryness of the ocular surface causes eye pain, foreign body sensation, photophobia, and visual disturbance, and patients often experience difficulty in opening their eyes. Sometimes, SJS patients present complaining of severe dryness of the eye despite frequent instillation of artificial tears. Thus, it is important to understand that severe dry eye with the combined mechanisms of aqueous tear deficiency, decreased corneal surface wettability, and increased evaporation may be involved in cicatrizied cases with SJS. In eyes in which the superior and/or inferior punctum is closed due to scarring or surgery (e.g., punctal plugs or cauteryization), tear deficiency can often be underestimated when the meniscus is first observed. SJS complications such as trichiasis, cicatrical entropion, and scarring of the mucocutaneous junction (lid margin) can be the cause of blink-related microtrauma, and enhance the symptoms related to dry eye.

It should be noted that a stable tear film over the cornea is needed for consistent good vision, and that unstable tear film related to dry eye can result in a fluctuation of vision. In fact, SJS patients at the chronic stage often complain of fluctuating visual acuity, especially in the eye with severe dry eye, depending on the time after blinking. Using the functional visual acuity (FVA) measurement system, dynamic visual changes can be continuously measured under a 30-second blink-free period in one eye. Kaido et al. examined the dynamic visual changes in SJS using the FVA system and reported that the time-related decline of FVA was greater in patients with SJS compared to normal subjects. In addition, the visual maintenance ratio (VMR) was found to be markedly lower in patients with SJS compared to patients with Sjögren syndrome (SS) and controls.

**TREATMENT FOR DRY EYE IN SJS**

For the proper treatment of dry eye in SJS cases, it is vital to pay attention to not only dry eye, but also to ocular surface inflammation. In SJS eyes at the chronic stage, persistent conjunctival inflammation exists. Recently, we discovered chronic inflammation in the follicles of eyelashes. To increase tear volume, the administration of artificial tears is necessary, and preservative-free artificial tears are recommended. Moreover, autologous serum/plasma is widely used for the treatment of dry eye or persistent corneal epithelial defects. The use of a punctal plug or surgical punctal occlusion is also effective. Low-dose topical steroids decrease the patients’ symptoms. However, when topical steroids are used, strict attention should be paid to adverse events such as infectious keratitis and the elevation of intraocular pressure.
It should be noted that 2% rebamipide ophthalmic suspension, which was specifically developed for the treatment of dry eye, suppresses inflammatory cytokine production in human corneal or conjunctival epithelial cells. In a multicenter, open-label, 52-week study, five cases of SJS were included, and rebamipide was found to be safe and effective for SJS dry eye. In that study, ocular surface stabilization was surprisingly obtained without steroids after the use of 2% rebamipide. Thus, it is highly possible that rebamipide ophthalmic suspension works to suppress ocular surface inflammation. In fact, in many SJS cases, we have successfully switched treatment from topical steroids to 2% rebamipide ophthalmic solution.

Recent reports have demonstrated the therapeutic benefits of scleral contact lenses (CLs) in the management of severe ocular surface diseases such as SJS and TEN. However, scleral CLs are too large to use for severely cicatrized eyes with conjunctival fornix shortening. A newly developed limbal rigid CL (limbal CLs) with a 13.0- or 14.0-mm diameter size can be used in eyes with a short fornix and/or symblepharon. Limbal CLs allow for tear exchange under the CL at the time of blinking, and their use improves the patients' visual acuity and reduces symptoms related to severe dry eye. Due to the decrease of tear evaporation, and possible improvement of wettability of the corneal surface covered by the limbal CL, eye pain dramatically decreases during limbal CL wear. It should be noted that the use of limbal CLs has been found to improve the patient's general health and overall wellbeing (Fig. 4).

As a surgical treatment for severe ocular disorders, amniotic membrane transplantation in the acute phase works to prevent late complications. Moreover, oral mucus membrane grafts can be used for fornix reconstruction and tarsal conjunctival scarring. Minor salivary glands transplantation was found to improve dry eye in SJS. We also developed autologous cultivated oral mucosal epithelial transplantation (COMET). COMET is a novel therapeutic method that is used for reconstruction of the ocular surface in eyes afflicted with severe conjunctivalization, keratinization, and symblepharon. The use of limbal CLs after COMET promises both the improvement of visual acuity and the decrease of dry eye symptoms in severely affected SJS eyes.

**FUTURE DIRECTIONS**

At the acute stage, ocular involvement is often easily overlooked because of high mortality rates associated with serious systemic diseases. Thus, strict attention must be paid to ocular involvement at the acute stage. In cases treated with steroid pulse and intensive topical betamethasone at the early stage post disease onset, none of the eyes showed ocular sequelae. Hence, recognition of ocular involvement at the acute stage of SJS/TEN may reduce the rate of ocular sequelae. Although a variety of ophthalmic solutions are currently available, and scleral CLs or limbal CLs are known to effectively reduce dry-eye-related symptoms, it is still difficult to treat and manage dry eye in SJS/TEN patients. Thus, further studies and new therapeutic methods are needed to more effectively treat dry eye in patients with SJS/TEN.

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