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This is the first report of the expression of T_H17-related cytokines in the airway tissues in severe asthma. Although we did not perform colocalization studies, the pattern of the immunoreactive cells in the submucosa suggests that this new subset of T cells may be involved in the inflammatory process in severe asthma. IL-17 has been associated with the activation of epithelial cells *in vitro* and the induction of IL-6 and IL-8 with downstream effects on neutrophil recruitment and activation.[7] We and others have reported an upregulation of IL-8 in severe asthma.[8] Neutrophils were also shown to be increased in severe asthma by many groups,[9] and this phenomenon may be IL-17–driven. We have also previously reported that IL-17 is increased in chronic sinusitis and that its expression is resistant to steroids.[4] Steroid unresponsiveness in severe asthma has been attributed to the presence of neutrophilic inflammation and an upregulation of the glucocorticoid receptor β isoform. T_H17-related cytokines have been implicated in the pathogenesis of a number of diseases that do not respond well to corticosteroids. Recently McKinley et al[10] have shown in a murine model that T_H17 cells not only are proinflammatory cells but also may induce steroid resistance. It is possible that steroid hyporesponsiveness in subjects with severe asthma may also relate to the presence of IL-17A and IL-17F. IL-17 has also been reported to affect structural cells and to stimulate the production of profibrotic cytokines and extracellular matrix proteins. This feature of airway remodeling in severe asthma may be attributable to an excess of these cytokines. If so, targeting IL-17 cytokines may be of value in the therapy of severe asthma, in which steroid resistance, neutrophilic inflammation, and airway remodeling are substantial.

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Toll-like receptor 3 enhances late-phase reaction of experimental allergic conjunctivitis

To the Editor:

Toll-like receptors (TLRs) are well-known key receptors of the innate immune system. *TLR3* recognizes double-stranded RNA, a component of the lifecycle of most viruses, mimicking polyinosinic:polycytidylic acid (polyI:C). Although a relationship between viral infection and allergic inflammation has been reported, the function of *TLR3* in allergic inflammation remains to be defined. Allergic conjunctivitis is an ocular surface inflammation associated with type I hypersensitivity reactions; the degree of eosinophil infiltration in the conjunctiva reflects the degree of its late-phase reaction.[1,2] Using our model of murine experimental allergic conjunctivitis (EAC)[1] and *TLR3* knockout (KO) and *TLR3* transgenic (Tg) mice (*TLR3*KO and *TLR3*Tg mice, respectively), we assessed directly the role of *TLR3* in conjunctival eosinophil infiltration.

BALB/c mice purchased from CLEA (Tokyo, Japan) were sensitized at 6 to 12 weeks of age. *TLR3*KO and *TLR3*Tg mice were generated as previously described,[3,4] back-crossed more than 7 generations to BALB/c mice, and subjected to EAC at 9 to 15 weeks of age. Age-matched wild-type BALB/c mice were used as control animals. The experiments were conducted with a protocol approved by the Institutional Animal Care and Use Committee of Kyoto Prefectural University of Medicine. Short ragweed pollen (RW) was purchased from Polysciences, Inc (Warrington, Pa), and aluminum hydroxide (alum) was purchased from Sigma-Aldrich Corp (St Louis, Mi). The mice were immunized with an intracutaneous injection into the left hind footpad of RW adsorbed on alum (200 μg of RW and 2.6 mg of alum) on day 0. On day 7, they received an intraperitoneal injection of RW adsorbed on alum, and on day 18, their eyes were challenged with RW in PBS (500 μg in 5 μL per eye) or with PBS alone (5 μL per eye).[1] Their eyes, including the conjunctiva, were harvested 24 hours after the last challenge, fixed in 10% neutral buffered formalin, and embedded in paraffin blocks for histologic analysis. Vertical 6-μm-thick sections were mounted on microscope slides, deparaffinized, and stained with Luna stain,[1,2] which identifies erythrocytes and eosinophil granules. Using the entire section from the central portion of the eye, including the pupil and optic nerve head, we counted infiltrating eosinophils in the lamina propria mucosae of the tarsal conjunctiva. Cell counts were expressed as the number of infiltrating eosinophils per unit area (0.1 mm^2) measured with image software (Scion Corp, Frederick, Md).[1,2] Quantitative RT-PCR

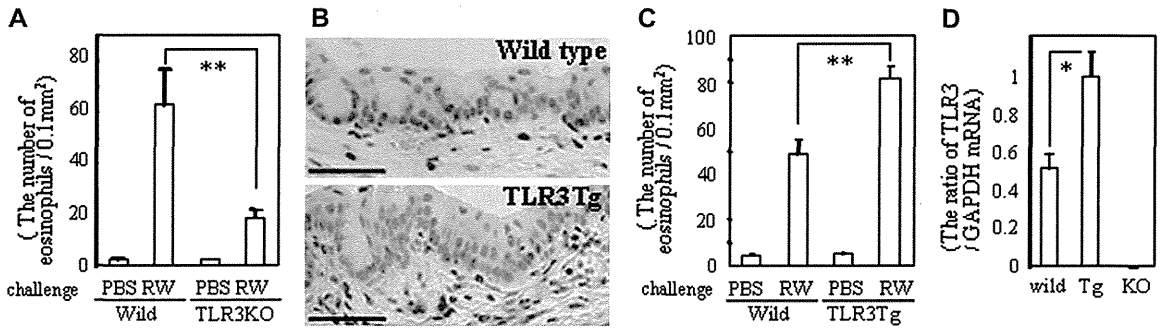

FIG 1. **A**, Eosinophil infiltration in *TLR3*KO mice. **B**, Eosinophil infiltration into the conjunctiva of ragweed-challenged wild-type and *TLR3*Tg mice was detected with Luna's method. Scale bars = 50 μm. **C**, Eosinophil infiltration in *TLR3*Tg mice. **D**, *TLR3* mRNA expression in eyelids. Data are shown as the means ± SEMs of samples from 3 mice. $*P < .05$. In Fig 1, *A* and *C*, data are shown as the means ± SEMs of samples from all 12 mice examined in 3 groups of 4 mice each. $**P < .01$.

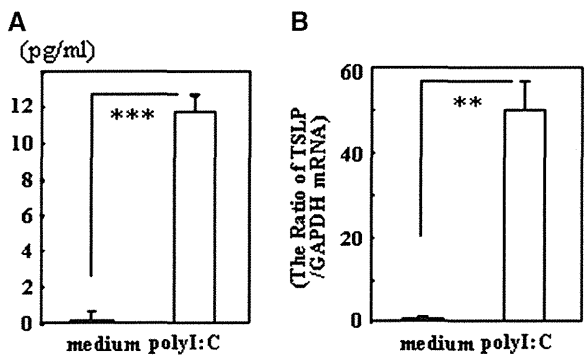

FIG 2. **A**, TSLP production. **B**, *TSLP* mRNA expression. The *y-axis* shows the increase in specific mRNA over that seen in medium samples. Primary *human conjunctival epithelial cells were either left untreated or stimulated* with 10 μg/mL polyI:C and then incubated for 24 (Fig 2, *A*) or 6 (Fig 2, *B*) hours. The data are representative of 3 independent experiments and shown as the means ± SEMs of 4 samples. $***P < .0005$, $**P < .01$.

of *TLR3*-specific mRNA in the eyelids was performed as previously reported.[1,2] Briefly, the upper and lower lids were collected 6 hours after the last RW challenge and homogenized in liquid nitrogen. Total RNA was extracted with the RNeasy mini kit (Qiagen, Tokyo, Japan). ReverTraAce (TOYOBO, Otsu, Japan) was used for reverse transcription. The primers and probes for mouse *TLR3* and *glyceraldehyde-3-phosphate dehydrogenase* were from Applied Biosystems (Foster City, Calif). The results were analyzed with sequence detection software (Applied Biosystems). Data were expressed as the mean ± SE, and statistical analyses were performed by means of ANOVA or the Student *t* test, as appropriate.

First, we compared eosinophil infiltration in *TLR3*KO and wild-type mice. Although sensitization without challenge did not affect the number of eosinophils, after sensitization and challenge, their number in the lamina propria mucosae of the conjunctiva was significantly increased in both *TLR3*KO and wild-type mice; however, it was significantly lower in *TLR3*KO than in wild-type mice (Fig 1, *A*). Next we compared eosinophil infiltration in *TLR3*Tg mice and wild-type mice. The numbers of eosinophils in TLR3Tg mice after sensitization and challenge were significantly greater than in wild-type mice (Fig 1, *B* and *C*). Furthermore, we have confirmed that *TLR3* mRNA expression in the eyelids of *TLR3*Tg mice was greater than that of wild-type mice after sensitization with challenge and that *TLR3* mRNA expression in the eyelids of *TLR3*KO mice was undetectable (Fig 1, *D*). These results suggest that TLR3 positively regulates late-phase reaction of EAC, which causes reduced eosinophilic conjunctival inflammation in *TLR3*KO mice and increased it in *TLR3*Tg mice.

We also examined whether sensitization with RW induced RW-specific immune responses equally in wild-type, *TLR3*KO, and *TLR3*Tg mice. It produced an increase in IgE and IgGl antigen–specific antibody responses equally in all 3 groups of mice (data not shown), suggesting that their sensitization to RW was equivalent.

Our results showed that TLR3 could regulate allergic inflammation in the absence of an exogenous viral infection or TLR3 ligand. It is reported that in the absence of viral infection, TLR3 can amplify immune responses during acute inflammatory processes, which might involve stimulation of TLR3 by endogenous RNA from necrotic cells.[5] It is also possible that endogenous RNA from tissue or cells might stimulate TLR3 in our allergic conjunctivitis model. On the other hand, there is a report that a TLR3 ligand can suppress allergic inflammation.[6]

Although the function of TLR3 in allergy remains to be defined, the expression of thymic stromal lymphopoietin (TSLP), which plays a key role in allergic inflammation, is reportedly induced by stimulation with the TLR3 ligand in airway epithelial cells and keratinocytes.[7] TSLP is highly expressed by airway epithelial cells of asthmatic patients and keratinocytes in skin lesions of patients with atopic dermatitis. We previously reported that human ocular surface epithelium expressed TLR3[8,9] and that cytokine production was upregulated by polyI:C, a TLR3 ligand.[9] We also confirmed that TSLP is induced by means of stimulation with the TLR3 ligand polyI:C in human conjunctival epithelial cells (Fig 2 and see the Methods section and Fig E1 in this article's Online Repository at www.jacionline.org). It is possible that TLR3 positively regulates the late-phase reaction of EAC through the induction of TSLP. Further investigations are required to identify the precise molecular mechanisms of allergic conjunctivitis in the murine model.

Elsewhere, we showed that EP3 is expressed in the ocular surface and that the prostaglandin E_2–EP3 pathway in

conjunctival epithelium works as a negative regulator for allergic conjunctivitis.[1] It is evident that ocular surface epithelial cells regulate the inflammation of allergic conjunctivitis. The actual role of TLR3 in conjunctival inflammation must be further investigated.

In summary, we demonstrated that TLR3 positively regulates late-phase reaction of EAC, which caused reduced eosinophilic conjunctival inflammation in *TLR3*KO mice and pronounced it in *TLR3*Tg mice.

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The carbohydrate galactose-α-1,3-galactose is a major IgE-binding epitope on cat IgA

To the Editor:

Cross-reactive carbohydrate determinants are widely occurring IgE epitopes. Glycan-related IgE reactivity has been demonstrated in most allergen sources, especially in the plant kingdom.[1] The clinical effect of these cross-reactive carbohydrate determinants is debated.

TABLE I. Comparison of monoclonal antigalactose reactivity to solid phase bound α-gal, cat IgA, and recombinant Fel d 1 (rFel d 1) by ELISA

Antigen	OD (450 nm)
α-gal	0.69
Cat IgA	0.67
rFel d 1	0.05

We were recently able to show that IgE Abs to the cat IgA, present in cat-sensitized patients, are mainly directed to a glycan moiety localized on the α-chain.[2] In addition, we have reported that these carbohydrates are present on IgM Abs from cat, as well as on IgM from many different mammalian species, but not human immunoglobulins.[3] Interestingly, IgE antibodies to cat IgM and cat IgA show a complete cross-reactivity, whereas cat IgG does not, suggesting an identical oligosaccharide on the 2 former immunoglobulin classes. Because this is the first mammalian carbohydrate IgE epitope found, it is of major interest to identify the carbohydrate structure responsible for the broad cross-reactivity.

Chung et al[4] have recently investigated subjects with anaphylactic reactions after treatment with the drug cetuximab, a chimeric mouse–human IgG_1 mAb against the epidermal growth factor receptor, which is approved for use in colorectal cancer and squamous-cell carcinoma of the head and neck. The authors found that a carbohydrate epitope on the mouse Fab portion, galactose-α-1,3-galactose, a part of the Galα1,3Galß1,4GlcNAc-R (α-gal) epitope, was responsible for the IgE binding. Furthermore, in most subjects, the IgE antibodies against cetuximab were present in serum before therapy.

The α-gal epitope is expressed on many different glycoproteins in mammals, except for old world monkeys, apes, and human beings. Species lacking the α-gal residues produce large quantities of IgG antibodies to this epitope.[5] Studies have demonstrated that approximately 1% of antibodies in all healthy subjects are directed to α-gal.[6] These antibodies also react with closely related carbohydrate structures in the ABO blood group and are one of the major obstacles in xenotransplantation.

Here we investigated whether α-gal is present on cat IgA and whether it is a major epitope responsible for IgE binding to cat IgA.

Cat IgA was purified from cat serum,[3] and α-gal–human serum albumin was obtained from Dextra Laboratories, Reading, United Kingdom. To investigate the presence of α-gal on cat IgA, a monoclonal anti-Gal antibody was used in ELISA. Plates were coated with 5 μg/mL α-gal, cat IgA, or recombinant Fel d 1,[7] which was included as negative control. Incubation with monoclonal anti-Gal antibodies (Alexis Biochemicals, Lausen, Switzerland), diluted 1:25, was followed by antimouse–IgG-alkaline phosphatase (Dako, Glostrup, Denmark) and substrate solution (Sigma, Steinheim, Germany). We found that the anti-Gal reactivity to α-gal and cat IgA was almost identical, whereas no reactivity was detected to recombinant Fel d 1 (Table I).

Twenty sera from the United States, 9 from patients who were found to have IgE antibodies to the α-gal epitope on cetuximab by using the streptavidin CAP technique,[8] (range, 0.79 to >100 kilo

METHODS

Primary human conjunctival epithelial cells

This study was approved by the institutional review board of Kyoto Prefectural University of Medicine, Kyoto, Japan. All experimental procedures were conducted in accordance with the principles set forth in the Declaration of Helsinki. The purposes of our research and the experimental protocol were explained to all patients, and their prior written informed consent was obtained.

For ELISA and real-time quantitative PCR, we harvested primary human conjunctival epithelial cells from conjunctival tissue obtained at the time of conjunctivochalasis surgery. Cells were cultured by using a modification of previously described methods.[E1] Briefly, conjunctival tissues were washed and immersed for 1 hour at 37°C in 1.2 U/mL purified Dispase (Roche Diagnostic Ltd, Basel, Switzerland). Epithelial cells were detached, collected, and cultured in low-calcium k-SFM medium supplemented with 0.2 ng/mL human recombinant epidermal growth factor (Invitrogen, Carlsbad, Calif), 25 mg/mL bovine pituitary extract (Invitrogen), and 1% antibiotic-antimycotic solution. Cell colonies usually became obvious within 3 or 4 days. After reaching 80% confluence in 7 to 10 days, the cells were seeded, and after reaching subconfluence, they were used in subsequent procedures.

ELISA

Primary human conjunctival epithelial cells were either left untreated or stimulated with 10 μg/mL polyI:C and then incubated for 24 hours. The amount of TSLP proteins was determined by using ELISA. TSLP release into culture supernatants was quantitated by using the Human TSLP DuoSet (R&D Systems, Inc, Minneapolis, Minn), according to the manufacturer's instructions.

Real-time quantitative PCR

Real-time quantitative PCR was performed on an ABI-prism 7700 (Applied Biosystems), according to previously described procedures.[E2] The initial amount of RNA used for reverse transcription to cDNA was approximately 1 μg. The cDNA was used at the original concentration for quantitative PCR. The primers and probes for human *TSLP* and human *glyceraldehyde-3-phosphate dehydrogenase* were from Perkin-Elmer Applied Biosystems. Quantitative PCR was used to measure the expression of *TSLP* mRNA in primary human conjunctival epithelial cells treated for 0, 1, 3, or 6 hours with 10 μg/mL polyI:C. The quantification data were normalized to the expression of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase.

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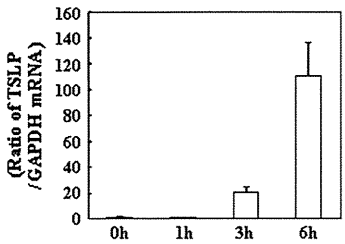

FIG E1. Increased *TSLP* mRNA expression by TLR3 stimulated with polyI:C. The *y-axis* shows the increase in specific mRNA over 0-hour samples or medium samples. The x-axis shows the time after stimulation. The data are presented as the means ± SEMs of 3 samples.

Examination of *Staphylococcus aureus* on the Ocular Surface of Patients With Catarrhal Ulcers

Mayumi Ueta, MD, PhD,† Chie Sotozono, MD, PhD,* Junko Takahashi, MD,* Kentaro Kojima, MD,* and Shigeru Kinoshita, MD, PhD**

Purpose: The purpose of this study was to investigate the role of *Staphylococcus aureus* in the onset of ocular catarrhal ulcers.

Methods: We examined the colonization by *S. aureus* of the ocular surface (conjunctival sac, upper and lower lid margins) of 3 patients with catarrhal ulcers and analyzed the *S. aureus* isolates by pulsed-field gel electrophoresis.

Results: *S. aureus* organisms were found on the lid margin of all eyes affected by catarrhal ulcers. The contralateral eye without ulcers harbored *S. aureus* exhibiting a pulsed-field gel electrophoresis pattern identical to that of the affected eye.

Conclusions: Although *S. aureus* on the lid margin plays an important role in the onset of catarrhal ulcers, its presence is one among several risk factors.

Key Words: *Staphylococcus aureus*, catarrhal ulcer, pulsed-field gel electrophoresis (PFGE)

(*Cornea* 2009;28:780–782)

INTRODUCTION

Catarrhal ulcers are usually a complication of long-standing staphylococcal blepharitis, conjunctivitis, or meibomitis,[1,2] which might sometimes be subclinical, and cultures from the lid margins of affected patients usually yield colonies of *Staphylococcus aureus*,[2] although lid margins of normal eyes also sometimes, but not usually, have *S. aureus*.[3,4] Because corneal cultures are usually negative for the organisms, it has been suggested that catarrhal ulcers are not the result of direct infection of the cornea, but rather derive from an antigen–antibody reaction with complementary activation and neutrophil infiltration in patients sensitized to staphylococcal antigens.[1,5,6]

Catarrhal infiltrates and ulcers are frequently seen by ophthalmologists and because they readily respond to adequate treatment, they do not attract much attention in the literature. To the best of our knowledge, this is the first pulsed-field gel electrophoresis (PFGE) analysis of the relationship between catarrhal ulcers and the presence of *S. aureus*.

MATERIALS AND METHODS

The diagnosis of catarrhal ulcer in our 3 patients was based on ocular surface manifestations. The patients were 15- (Case 1, Fig. 1A), 81- (Case 2, Fig. 1B), and 55-year-old (Case 3, Fig. 1C) females. In all patients, the right eye was involved. Clinical examinations revealed oval infiltrates and ulcers separated from the limbus by a distinct lucid border and adjacent conjunctival inflammation. We examined 3 ocular sites (the conjunctival sac and the upper and lower lid margins) for the presence of bacteria; in cases 1 and 2, we examined both eyes and in case 3 only the affected eye. Using PFGE analysis, we analyzed and compared the *S. aureus* organisms isolated from 2 or more sites in each patient.

The isolates obtained were stored (–20°C) in ANAport BIKEN culture medium (BIKEN, Osaka, Japan) at the Department of Ophthalmology of Kyoto Prefectural University of Medicine; they were sent to The Research Foundation for Microbial Diseases of Osaka University the next day. The isolates were cultured in both methods, direct culture and enrichment culture, as previously reported.[3,7]

We used the GenePath system (Bio-Rad Laboratories, Hercules, CA) to perform PFGE according to the manufacturer's instructions (GenePath Group I Reagent Kit; Bio-Rad) and visually compared the DNA banding patterns as described by Tenover et al.[8]

RESULTS

The colonization by *S. aureus* is shown schematically in Figure 2A. In case 1, *S. aureus* was detected in the lower lid margin of the affected and the conjunctiva of the unaffected eye. The PFGE patterns of the organisms from both eyes were identical (Fig. 2B-1), suggesting that they derived from the same clone. In case 2, *S. aureus* was detected in the upper lid margin and conjunctiva of the affected and in the lower lid

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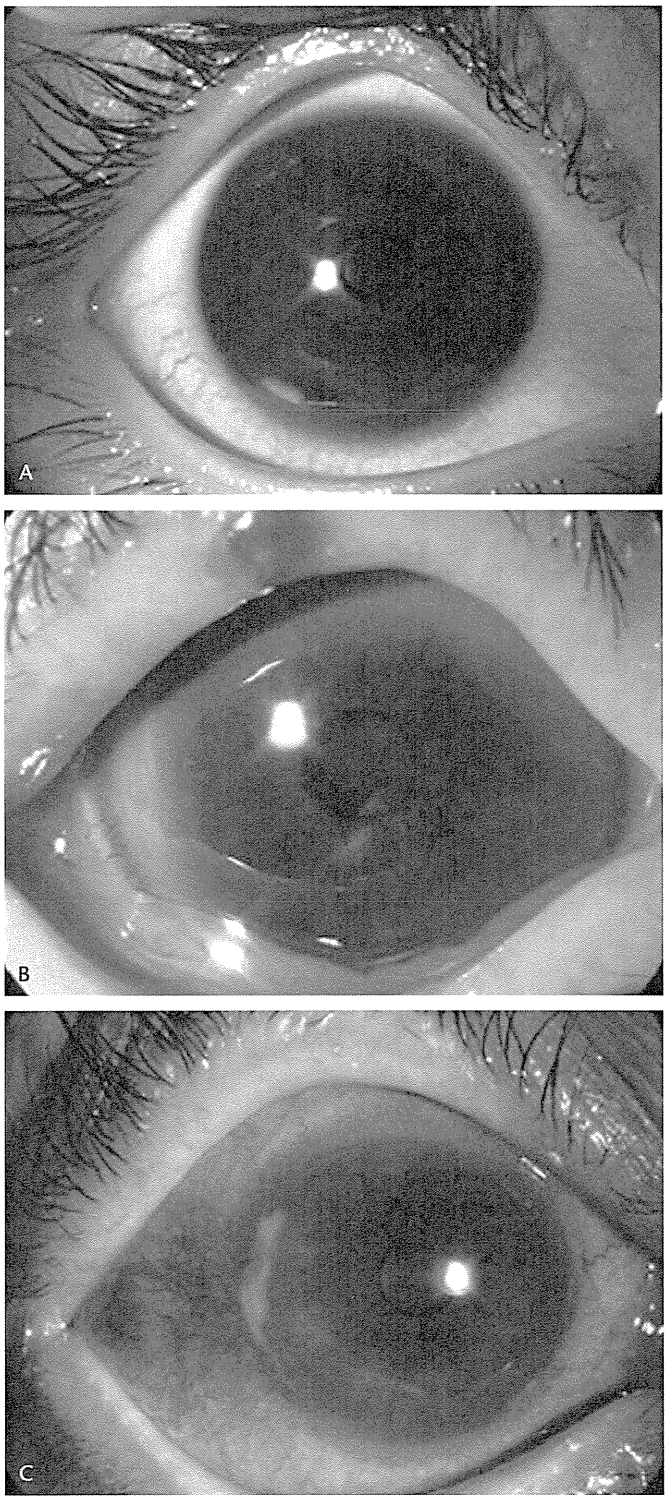

FIGURE 1. Photographs of the affected eyes of patients with catarrhal ulcers. (A) Case 1: The right eye of a 15-year-old girl. (B) Case 2: The right eye of an 81-year-old woman. (C) Case 3: The right eye of a 55-year-old woman.

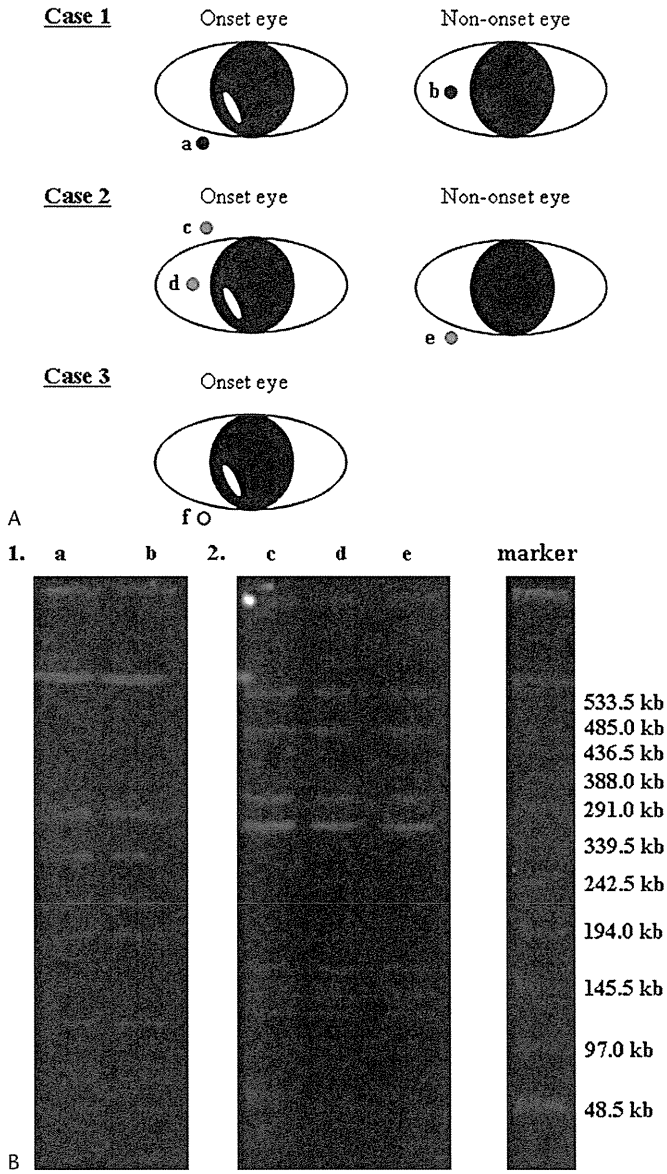

FIGURE 2. Colonization by (A) and pulsed-field gel electrophoresis (PFGE) analysis of (B) *Staphylococcus aureus*. Case 1: *S. aureus* was detected in the lower lid margin (A) of the affected and the conjunctiva (B) of the unaffected eye. The organisms from the 2 sites showed identical PFGE patterns (Fig. 2B-1). Case 2: *S. aureus* was detected in the upper lid margin (C) and the conjunctiva (D) of the affected eye and in the lower lid margin (E) of the unaffected eye. These organisms from the 3 sites exhibited identical PFGE patterns (Fig. 2B-2). Case 3: *S. aureus* was detected in the lower lid margin of the affected eye (F). We used the GenePath System for PFGE. Bacterial chromosomal DNA was cut with SmaI. The PFGE patterns were obtained by running digested DNA on 1% agarose gels in a CHEF-DR Mapper. A lambda ladder was used as the molecular size marker.

margin of the unaffected eye. They also manifested identical PFGE patterns (Fig. 2B-2), suggesting that they originated from the same clone. In case 3, *S. aureus* were detected in the lower lid margin of the affected eye; the unaffected eye could not be examined because the patient gave consent to examine only the affected eye.

DISCUSSION

Although our study included only a small number of patients, we found *S. aureus* to be present in the lid margin of the eyes affected by catarrhal ulcers. This might suggest that their presence in the lid margin, rather than the conjunctival sac, is important for the development of catarrhal ulcers. Because we were able to detect all *S. aureus* organisms in enrichment cultures, it appears that the development of catarrhal ulcers does not require the presence of large amounts of the bacterium.

Interestingly, in case 2, we also found *S. aureus* in the lid margin of the unaffected eye. It means that if the patient, who was sensitized to staphylococcal antigens, has *S. aureus* on both eyes, the catarrhal ulcer may occur on only one eye but not the fellow eye. Moreover, our PFGE analysis showed that *S. aureus*, which was detected in both eyes, might be derived from the same clone, suggesting that the kind of clone of *S. aureus* is not necessarily important for the initiation of the catarrhal ulcers.

Although our study included only a small number of patients, our findings might suggest that other factors may be necessary for the initiation of the catarrhal ulcers in addition to the existence of *S. aureus* on the lid margin and the patients' sensitivity to staphylococcal antigens. One possible factor may be an immune abnormality of the ocular surface of the affected eye. A second possible factor may be the condition of contact between the cornea and the lid margin such as a subtle difference of pressure and/or angle of the lid margin, although it is not apparent in clinical findings. A third possible factor may be a difference in the amount of bacterium between the affected eye and unaffected eye, although the development of catarrhal ulcers does not require the presence of large amounts of the bacterium. Investigations are underway to shed light on the pathogenesis of catarrhal ulcers.

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Diagnosis and Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis with Ocular Complications

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Purpose: To present a detailed clarification of the symptoms at disease onset of Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), with ocular complications and to clarify the relationship between topical steroid use and visual prognosis.

Design: Cross-sectional study.

Participants: Ninety-four patients with SJS and TEN with ocular complications.

Methods: A structured interview, examination of the patient medical records, or both addressing clinical manifestations at disease onset were conducted for 94 patients seen at Kyoto Prefectural University of Medicine. Any topical steroid use during the first week at the acute stage also was investigated.

Main Outcome Measures: The incidence and the details of prodromal symptoms and the mucosal involvements and the relationship between topical steroid use and visual outcomes.

Results: Common cold-like symptoms (general malaise, fever, sore throat, etc.) preceded skin eruptions in 75 cases, and extremely high fever accompanied disease onset in 86 cases. Acute conjunctivitis and oral and nail involvements were reported in all patients who remembered the details. Acute conjunctivitis occurred before the skin eruptions in 42 patients and simultaneously in 21 patients, whereas only 1 patient reported posteruption conjunctivitis. Visual outcomes were significantly better in the group receiving topical steroids compared with those of the no-treatment group ($P<0.00001$).

Conclusions: Acute conjunctivitis occurring before or simultaneously with skin eruptions accompanied by extremely high fever and oral and nail involvement indicate the initiation of SJS or TEN. Topical steroid treatment from disease onset seems to be important for the improvement of visual prognosis.

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Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory disorders that affect the skin and mucous membranes.[1–4] Although the incidence of SJS and TEN is very low, approximately 0.4 to 1 case per 1 million persons and 1 to 6 cases per 1 million persons, respectively, both can affect anybody at any age, usually as a consequence of adverse drug reactions.[5–7] A variety of drugs including antibiotics, nonsteroidal anti-inflammatory drugs, and antiepileptic medications, that is, any of the popularly used drugs, have been reported to cause severe drug reactions and to induce SJS or TEN.

The mortality rates for SJS and TEN are high: 1% to 5% and 25% to 35%, respectively.[8,9] Ocular complications occur in more than 50% of the patients, and ocular surface inflammation develops rapidly at the acute stage.[10,11] Extensive inflammation of the ocular surface often is accompanied by pseudomembranous formation and corneal or conjunctival epithelial defects, or both. The common pathway after the acute stage includes persistent epithelial defects, ulceration, and perforation, finally developing into corneal cicatricial changes such as neovascularization, opacification, keratinization, and symblepharon.[12,13] Even after the acute-stage impairments subside, permanent visual impairment or blindness remains and conjunctival inflammation prolongs at the chronic stage.[14] Patients with SJS or TEN require life-long management for ocular discomfort and morbidity. Stevens-Johnson syndrome or TEN accompanied by ocular complications, at both the acute and chronic stage, are 2 of the most devastating ocular surface diseases, and both are extremely difficult to treat.

The loss of corneal epithelial stem cells, which are located in the limbal region,[15–18] evidenced by the loss of palisades of Vogt, is the most common ocular feature of SJS.[13] As soon as the corneal epithelial stem cells are lost at the acute stage of SJS or TEN, the corneal epithelium does not regenerate, thus resulting in conjunctival epithelial invasion into the cornea (conjunctivalization) and cicatricial changes of the ocular surface. In contrast, the regeneration of the epidermis develops rather smoothly at the remission of the diseases.

Penetrating keratoplasty (PK) generally is contraindicated for eyes with SJS or TEN because PK does not supply the limbal region of the eye with corneal epithelial stem

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cells. Moreover, PK-initiated, immunologically driven ocular surface inflammation may induce persistent epithelial defects and corneal melting, perforation, or both, ultimately resulting in blindness.[12] Allograft transplantation of healthy limbal tissue is useful for the reconstruction of the ocular surface. However, long-term outcomes are poor in eyes with SJS or TEN.[19] Groundbreaking surgical procedures have been developed over the past 12 years. We first reported the usefulness of cultivated corneal epithelial transplantation for SJS with persistent epithelial defects after the acute stage.[20–23] In another report, we clarified the efficacy of ex vivo expanded autologous oral mucosal epithelial cells to the ocular surface.[24] Cultivated oral mucosal epithelial transplantation and the 2-step surgical combination of cultivated oral mucosal epithelial transplantation and PK have provided the patients with SJS or TEN with a surgical pathway toward restoration of their visual function.[25–27] However, it is impossible for the ocular surface of those patients to be restored to its previously normal state.

Diagnosis of SJS or TEN at disease onset is complex, often confusing, and very difficult. Moreover, the use of steroids for treatment remains controversial.[10,28–30] Our recent reports and those of others indicated the influence of genetic endowment in SJS and TEN.[31–40] For instance, there are statistically significant differences in single nucleotide polymorphisms of toll-like receptor 3, interleukin (IL)-4R/IL-13, and Fas ligand in SJS and TEN; thus, genetic screening may help to deliver a more rapid diagnosis in the future. At present, however, the understanding of the typical clinical picture of SJS and TEN is still a vital aspect of early diagnosis and the initiation of treatment. Therefore, this study investigated the clinical manifestation at disease onset of SJS and TEN with ocular complications and evaluated the relationship between ophthalmic management at the acute stage and the visual outcomes.

Patients and Methods

From November 2005 through May 2008, extensive interviews were conducted with 94 patients (45 males and 49 females) with SJS or TEN with ocular complications seen at the SJS outpatient service at Kyoto Prefectural University Hospital. Of those patients, 88 cases were referral patients from the greater Japan area who had come to the SJS service at the acute stage (n = 14) or at the chronic stage (n = 74). Their ages ranged from 1 to 83 years (mean age±standard deviation, 41.6±18.5 years). At disease onset, the patients' ages ranged from 0 to 77 years (mean age±standard deviation, 26.2±18.8 years), and the duration of the illness ranged from 1 to 48 years (mean±standard deviation, 16.1±15.2 years). The questionnaires used in this study were structured as follows: (1) age of the patient at disease onset; (2) causative drugs; (3) the presence of prodromal symptoms; and (4) the episodes of high fever, conjunctivitis, skin eruptions, fingernail loss, and associated mucous membrane involvements. Medical records also were examined or the patients were asked directly regarding any ophthalmic management, especially the use of topical steroids, during the first week from disease onset. Then, the Mann–Whitney *U* test was used to analyze the correlation between the use of topical steroids and the visual outcomes. This study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan.

The diagnosis of SJS or TEN at the acute stage was based on the acute onset of high fever, serious mucocutaneous illness with skin eruptions, involvement of at least 2 mucosal sites, and the pathologic findings of a skin biopsy that demonstrated necrotic changes of the dermis. The diagnosis of SJS or TEN at the chronic stage was based on ocular cicatricial findings such as symblepharon, severe dry eye, corneal neovascularization, opacification, and conjunctivalization, and a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites including the ocular surface. In the patients where disease onset occurred before age 10 years or in those who had lost consciousness at the acute stage because the illness, specific details were obtained by directly interviewing members of the immediate family.

Results

Of the 94 patients, drugs were the most commonly associated etiologic factor in 84 patients (89.4%). The causative drugs were cold remedies in 30 patients, antibiotics in 23 patients, nonsteroidal anti-inflammatory drugs in 19 patients, anticonvulsants in 5 patients, and others (anticancer agents, antirheumatic drugs, antimalarial, Chinese medicine, etc.).

Best-corrected visual acuity obtained at the chronic stage was 20/20 or better in 34 eyes (18.3%; Fig 1A), worse than 20/20 and up to and including 20/200 in 55 eyes (29.6%; Fig 1B), worse than 20/200 and up to and including 20/2000 in 53 eyes (28.5%; Fig 1C), and worse than 20/2000 in 44 eyes (23.7%; Fig 1D). Two eyes of 1 boy who was 1 year or age were excluded from the results because his visual acuity could not be assessed.

Characteristics of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis with Ocular Complications

Of the 94 patients, common coldlike symptoms (general malaise, fever, sore throat, etc.) preceded skin eruptions in 75 patients. Extremely high fever (more than 39° C) was reported by 86 patients, whereas 1 patient reported no fever and the remaining 7 patients could not remember the extent of the fever. Acute conjunctivitis and oral involvements (blisters, erosions, and bleeding of the mouth and lips) occurred in all patients who could recollect their symptoms in detail. Fingernail loss at the acute stage or deformation at present existed in all patients (Table 1; Fig 2). Other mucous membrane involvements included those of the pharynx, respiratory tract, or ear canal.

Forty-two patients reported episodes of acute conjunctivitis several hours to 4 days before the skin eruptions, and 21 patients reported that skin eruptions and conjunctivitis occurred simultaneously. Only 1 patient reported posteruption conjunctivitis (Table 2).

Topical Steroid Instillation and Visual Outcomes

Thirty-three patients (13 males and 20 females; mean age±standard deviation at disease onset, 31.5±18.6 years) began topical steroid treatment during the first week from disease onset, whereas 31 patients (14 males and 17 females; mean age±standard deviation, 27.9±19.5 years) received no topical steroid treatment or any other treatment for their eyes. The remaining 30 patients could not recall the details of ocular management during the first week from disease onset. Visual outcomes were significantly better in the group that received topical steroids at the acute stage compared with those of the no-treatment group ($P<0.00001$; Fig 3).

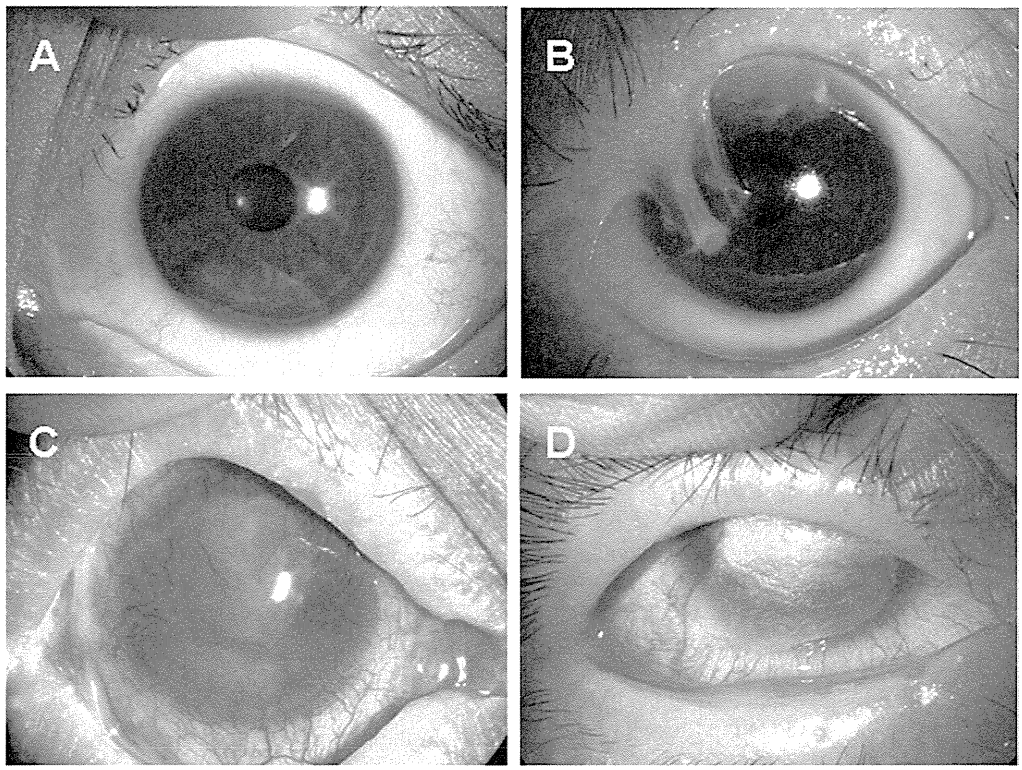

Figure 1. Photographs showing representative ocular manifestations at the chronic stage, with corresponding visual acuity. **A**, Clear cornea and best-corrected visual acuity of 20/20 or better: 34 eyes (18.3%). **B**, Moderate conjunctivalization and visual acuity worse than 20/20 and up to and including 20/200: 55 eyes (29.6%). **C**, Severe conjunctivalization and neovascularization and visual acuity worse than 20/200 and up to and including 20/2000: 53 eyes (28.5%). **D**, Keratinization, severe opacification, and visual acuity worse than 20/2000: 44 eyes (23.7%).

Diagnosis at the Acute Stage

Eleven patients were diagnosed with acute conjunctivitis by ophthalmologists before the development of systemic eruptions. An additional 12 patients were misdiagnosed as having measles (n = 4), chickenpox (n = 2), herpetic infection (n = 2), rubella (n = 1), or other diseases by physicians in other fields.

Among 94 patients, only 37 patients were diagnosed as having SJS or TEN at disease onset. Seven patients were diagnosed properly at several weeks (range, 2–8 weeks) after the onset, and surprisingly, 6 patients obtained the diagnosis at 2 to 45 years after the onset. For the remaining patients, when they received a proper diagnosis could not be ascertained.

Table 1. Symptoms and Mucosal Involvements of the 94 Patients at the Acute Stage

Symptoms	Experienced	Did Not Experience	Unknown
Prodromal common cold-like symptoms	75	17	2
Extremely high fever (>39° C)	86	1	7
Ocular involvement	94	0	0
Oral involvement	82	0	12
Genital involvement	46	18	30
Fingernail loss or deformation	94	0	0

Discussion

Stevens-Johnson syndrome and TEN are rare but potentially fatal skin disorders. Ocular involvement is common and often results in long-term complications such as serious visual impairment with ocular discomforts.[13,28] Although much has been learned over the past 50 years about the management of SJS and TEN, the following 3 important problems still remain: (1) the difficulty of obtaining a prompt and accurate diagnosis of SJS or TEN at disease onset, (2) ocular involvement often is overlooked easily because of the serious general symptoms and high lethality of these 2 diseases, and (3) a universally accepted treatment regimen for SJS and TEN has yet to be adopted and treatment with corticosteroids remains controversial.[10,28–30] There is also no standardized ophthalmologic treatment for the prevention of ocular complications.

In this study, 12 patients were misdiagnosed as having chickenpox, measles, herpetic infection, or other diseases. For early diagnosis, the clinical pictures of SJS and TEN need to be well understood, and to that end, the results of this study provided new and important data. Common cold-like symptoms (general malaise, slight fever, sore throat, etc.) preceded skin eruptions in 82% of the cases, and in all but 1 patient, the disease was accompanied by very high fever (more than 39° C) at the onset. It should be emphasized that acute conjunctivitis occurred before or simulta-

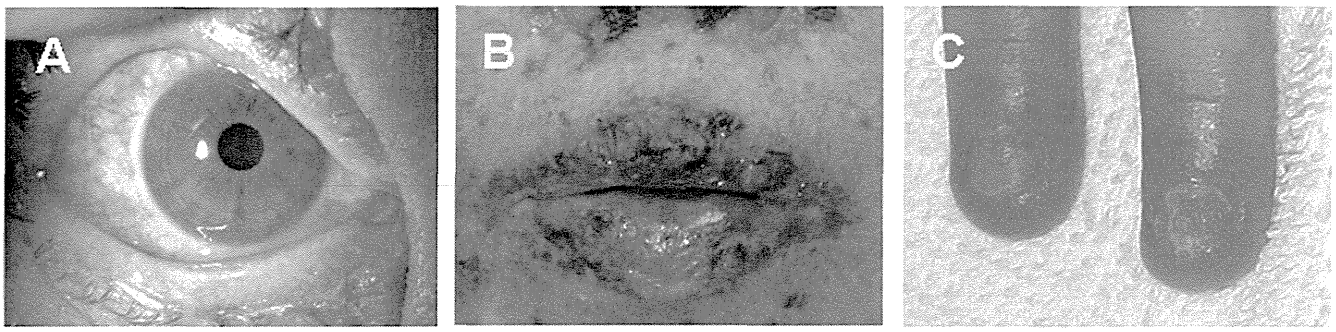

Figure 2. Representative photographs showing Stevens-Johnson syndrome/toxic epidermal necrolysis-associated ocular and oral involvement and fingernail loss at the acute stage. **A**, Conjunctivitis, which was accompanied by extensive loss of bulbar conjunctival epithelium. **B**, Swollen and crusted lips. **C**, Fingernail loss and deformation with paronychia.

neously with skin eruptions and that the involvement of oral mucosa was observed in 100% of the cases who could remember the details. Fingernail loss at the acute stage, deformation at the time of the writing of this report, or both also occurred in all of the patients, suggesting that paronychia occurred in all patients at the acute phase.

Visual outcomes were significantly better in the patients who received treatment with topical steroids during the first week from disease onset compared with those of the patients who received no topical steroid treatment. However, those outcomes may be because of the presumed fact that patients who fail to receive treatment with topical steroids are highly likely not going to receive systemic steroids as well. Thus, treatment with topical steroids, systemic steroids, or both at the early stage of the disease helps to decrease the incidence of chronic ocular complications. At the onset of the diseases, both necrotic changes of the skin and the destruction of the ocular surface progress rapidly. Prompt use of topical steroids, and presumably systemic steroids, from disease onset may prove to be important for preventing the loss of corneal epithelial stem cells. Unfortunately, a detailed history concerning the systemic therapy during the acute stage could not be obtained in most instances. Additional studies are needed to confirm the safety and efficacy of those medications.

Of the 94 patients, the mean duration of the illness was 16.1 years, and more than 50% of the eyes manifested visual acuity worse than 20/200. Considering the fact that patients with SJS or TEN experience ocular complications for an extended period, it is vital that strict attention be paid to any ocular involvement. When dermatologists, physicians, and healthcare professionals suspect SJS or TEN, prompt referral to an ophthalmologist is vital for the prevention of permanent loss of vision. Ophthalmologists have to find distinctive appearances such as pseudomembrane formation and corneal or conjunctival epithelial defects, or both.

Table 2. Order of Conjunctivitis and Skin Eruptions of the 94 Patients at Disease Onset

Conjunctivitis	Period Preceding Eruption	No. of Patients
Occurred before skin eruption	4 days	1
	3 days	3
	2 days	11
	1 day	12
	Several hours	9
	Unknown	6
		Total = 42
Occurred simultaneously		21
Occurred later		1
Unknown		30
Total		94

In the first report by Stevens and Johnson, 2 boys reported eye pain before skin eruptions and manifested a purulent conjunctivitis. Visual prognosis was total blindness in one case and severe corneal scarring in the other case. Both cases had the typical clinical picture clarified in the present study.[1] If their eyes had been treated with topical steroids from disease onset, the visual outcomes might have been different.

To date, the pathophysiologic mechanisms underlying the onset of SJS and TEN have yet to be fully elucidated. The rarity of these diseases has led us to speculate that patients with SJS or TEN genetically are susceptible to specific environmental precipitants. A report from the United States showed an increase of human leukocyte antigen (HLA)-B12 (HLA-Bw44) antigen in white patients with SJS with ocular involvement.[31] Analyses of TEN patients in France also disclosed an association with HLA-B12 (HLA-Bw44).[32] In Han Chinese, there was a very strong association between carbamazepine-induced SJS and the HLA-B*1502 allele.[33] The authors also reported that in Japanese persons, HLA-A*0206 was strongly associated with SJS and TEN with ocular surface complications.[34,38] These findings suggest that SJS and TEN are associated with a complex genetic inheritance background.

The prodromal symptoms occurred in 82% of the cases in this study. Given the association between the onset of SJS and TEN and infections and the opportunistic infection of ocular surfaces by bacteria such as methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis*,[41] it is highly possible that there is an association between SJS and TEN and a disordered innate immune response. Recently, the association of the polymorphisms in the toll-like receptor 3 gene with SJS and TEN in the Japanese population were reported.[36] Also, an association between SJS and TEN and the IL-4R gene polymorphism and combined IL-13/IL-4R signaling pathway gene polymorphism was reported.[35,39]

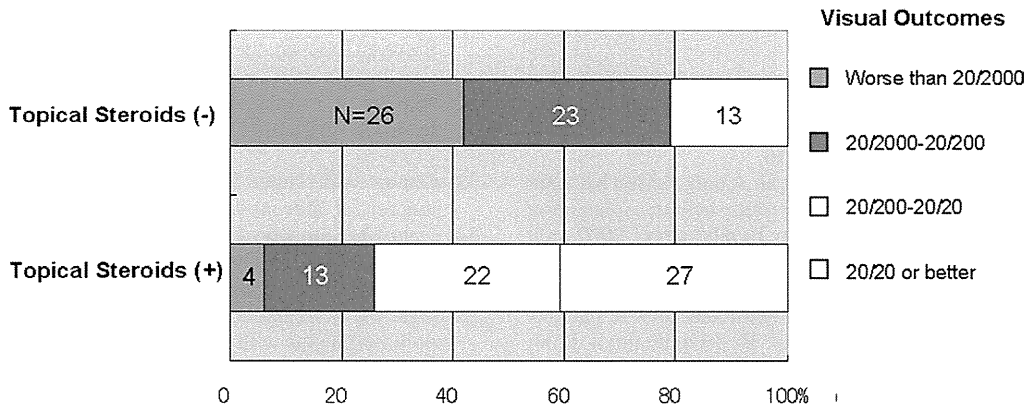

Figure 3. Graph showing the relationship between topical steroid use during the first week from disease onset and visual outcomes. Sixty-six eyes of 33 patients began topical steroid treatment during the first week from disease onset, whereas 62 eyes of 31 patients received no topical steroid treatment or any other treatment. Visual outcomes were significantly better in the group receiving topical steroids at the acute stage compared with those of the no-treatment group ($P<0.00001$).

Thus, both innate immunity and host–defense mechanisms may play a critical role in the development of SJS and TEN.

In conclusion, ocular involvement at disease onset is a helpful symptom for the diagnosis of SJS and TEN. Acute conjunctivitis before or occurring simultaneously with skin eruptions accompanied by very high fever and blisters on the mouth greatly implies the initial signs of SJS and TEN, and prodromal symptoms and genital involvements support that diagnosis. Initiating treatment with topical steroids from the onset seems to be important for the improvement of visual prognosis. A prompt and accurate diagnosis as assisted by the clinical manifestation offers a breakthrough against the historically poor visual outcomes associated with patients with SJS or TEN.

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Successful Treatment of Stevens-Johnson Syndrome with Steroid Pulse Therapy at Disease Onset

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• PURPOSE: To evaluate the visual prognosis of patients with Stevens-Johnson syndrome (SJS) and its severe variant, toxic epidermal necrolysis (TEN), followed by general and topical high-dose corticosteroids administration from disease onset.

• DESIGN: Prospective, observational case series.

• METHODS: Between May 1, 2003 and June 30, 2005, we enrolled 5 patients with SJS or TEN with ocular complications at the acute stage. Intravenous pulse therapy with methylprednisolone (steroid pulse therapy; 500 or 1000 mg/day for 3 to 4 days) was initiated within 4 days from disease onset. Topically, 0.1% betamethasone was applied over 5 times daily for at least 2 weeks. Visual acuity (VA) and slit-lamp microscopic appearance 1 year from disease onset were evaluated.

• RESULTS: At the first examination, corneal or conjunctival epithelial defects and pseudomembranous conjunctivitis were present in all cases. Skin eruptions dramatically improved after steroid pulse therapy. Although ocular inflammation increased for several days, pseudomembranes disappeared and corneal and conjunctival epithelium regenerated within 6 weeks. At the chronic stage, all eyes had clear corneas with the palisades of Vogt (POV), implying the presence of corneal epithelial stem cells. Best-corrected VA was 20/20 or better in all eyes. Five eyes showed superficial punctate keratopathy. No eye had cicatricial changes except for 1 with slight fornix shortening. No significant adverse effects of steroid occurred during all clinical courses.

• CONCLUSIONS: Steroid pulse therapy at disease onset is of great therapeutic importance in preventing ocular complications. Topical betamethasone also shows great promise for preventing corneal epithelial stem cell loss in the limbal region and cicatricial changes. (Am J Ophthalmol 2009;147:1004–1011. © 2009 by Elsevier Inc. All rights reserved.)

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STEVENS-JOHNSON SYNDROME (SJS), FIRST REPORTED in 1922, is an acute inflammatory disease that predominantly affects the skin and mucosal membranes, including the ocular surface.[1] In 1956, Lyell described a clinical condition characterized by extensive epidermal loss, termed *toxic epidermal necrolysis* (TEN).[2] Recent reports suggest that SJS and TEN are the same disorder, but of different severities.[3–5] In the acute stage, these diseases predispose patients to life-threatening complications such as sepsis, respiratory dysfunction, and multiorgan failure. Mucosal sites including the ocular surface and oral membrane commonly are involved at the onset of acute fever and skin eruptions. Although skin usually heals without dysfunction, severe corneal opacity and dry eye often persist during the chronic stage. Patients with SJS or TEN require life-long management for ocular discomfort and morbidity.[6–9] Recently, it was reported that amniotic membrane transplantation (AMT) onto the ocular surface is effective for reducing the destructive inflammation in acute SJS or TEN and for preventing cicatricial change.[10–12] However, safe and effective medical treatment for the prevention of ocular complications has yet to be established.

Although the pathogeneses of SJS and TEN has not been elucidated fully, it has been indicated that soluble FasL-mediated apoptosis plays a crucial role in the pathogeneses of SJS and TEN.[13] Drug-specific cytotoxic CD8+ T lymphocytes were detected in blister fluids of SJS and TEN patients and in cytotoxic lymphocyte cytolytic pathways, including major histocompatibility complex class I.[14] It also has been reported that tumor necrosis factor and interferon-γ also are involved in the mechanisms of epidermal necrosis.[15] Therefore, it is highly possible that medication at the acute stage to downregulate such immunologic reactions is useful for the treatment of SJS and TEN.

The use of systemic corticosteroids for the care of patients with acute SJS and TEN is controversial.[16,17] Although the beneficial effects of corticosteroid therapy during the acute stage has been reported,[18–20] high mortality rates in patients receiving corticosteroids has been shown.[21,22] The timing, dose, formulation, and route of administration of the steroid differ in these reports. At disease onset, skin involvement and ocular involvement progress rapidly, and facial manifestation and general condition became worse from morning to evening. Considering the pathogenesis described above and the rapid progression of SJS and TEN at disease onset, we hypoth-

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esized that the timing and dose of the administered steroid are both key to obtaining beneficial effects.

In patients with SJS- or TEN-induced chronic ocular complications, the total loss of the palisades of Vogt (POV) commonly is observed.[23] POV in the limbal area implies the presence of corneal epithelial stem cells.[24] At the acute stage, corneal epithelial defect or corneal ulceration occur in more than 50% of the patients with SJS or TEN.[25] In cases with limbal stem cell loss, conjunctivalization and neovascularization of the cornea progress, leading to severe visual impairment or blindness.[6–9] Loss of the POV occurs during the acute stage of SJS and TEN and can be accompanied by severe inflammation. The administration of high-dose general and topical corticosteroids from disease onset may downregulate the immunologic reactions described above and may prevent the loss of corneal epithelial stem cells.

The aim of this study was to evaluate the ophthalmic efficacy of high-dose corticosteroid therapy at the acute stage of SJS or TEN. All patients in this study were administered high-dose systemic methylprednisolone (steroid pulse therapy) and topical betamethasone for SJS or TEN with ocular involvement from the onset of the disease. Side effects of the steroids were monitored carefully over the duration of this study, and a great amount of attention was paid to systemic and ophthalmic infections. We then evaluated visual acuity (VA) and the slit-lamp microscopic appearance in these patients at the chronic stage.

METHODS

BETWEEN MAY 1, 2003 AND JUNE 30, 2005, WE ENROLLED 5 consecutive patients (2 males and 3 females, 23 to 49 years of age at disease onset; mean age, 32.8 years) referred to us during the first 4 days from the onset of SJS or TEN accompanied by ocular complications (ocular surface epithelial defects, pseudomembranous formation, or both). The diagnosis of SJS or TEN was confirmed by dermatologists based on clinical and histopathologic classification.[26,27] Prior informed consent to participate in the study was obtained in written form from all patients, their families, or both.

We initiated therapy with intravenous high-dose methylprednisolone and intensive topical betamethasone immediately after the dermatologic and ophthalmologic diagnosis. For initial treatment, the protocol used in this study was as follows: intravenous methylprednisolone at a dosage of 500 to 1000 mg/day was used for 3 to 4 days (steroid pulse therapy) and 0.1% betamethasone was applied topically more than 5 times daily for at least 2 weeks. The topical antimicrobial agent was applied prophylactically.

Signs of systemic and ophthalmic infection were monitored by the culture of blood, conjunctival swab, and the swab of other mucous membranes. The body temperature and the patient's symptoms and biochemical parameters also were monitored carefully.

Patient-related ocular findings and the complications during the acute stage were recorded fully until the remission of the ocular surface inflammation. As for ocular complications, corneal complications (superficial punctate keratopathy [SPK], epithelial defect, loss of the POV, conjunctivalization, neovascularization, opacification, and keratinization), conjunctival complications (hyperemia and symblepharon formation), and eyelid complications (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage) were recorded according to a new grading system for SJS that we previously reported.[23] Tear secretion was assessed by the Schirmer 1 test, and meibomian gland morphologic features were evaluated using meibography.[28,29] VA and ocular findings at the chronic stage were evaluated after 1 year from the onset of the disease.

RESULTS

• **OCULAR FINDINGS AND THERAPY DURING THE ACUTE STAGE:** Five patients were referred to us within 4 days (0 to 4 days; mean, 1.2 days) from the onset (the initiation of skin eruptions accompanying mucocutaneous illness) of the disease (Table). All patients had rapidly progressing skin eruptions, mucous membrane erosions, and a very high fever (more than 39 C) at presentation. Those symptoms were preceded by common cold-like symptoms (general malaise, fever, sore throat, or a combination thereof) in 4 patients. The causative drugs were cold remedies (Cases 1 and 5), antibiotics (Cases 3 and 5), and nonsteroidal anti-inflammatory drugs (Cases 3, 4, and 5). In 1 patient, high fever and erythematous macules developed after vaccination for measles (Case 2). All 10 eyes had pseudomembranous conjunctivitis. Corneal or conjunctival epithelial defects were present in all cases. Corneal epithelial defects existed in 5 eyes, and severe SPK was present in the other 5 eyes. Conjunctival epithelial defects were observed in 6 eyes (Figures 1 and 2). Skin biopsy specimens of the erythematous macules from all patients showed necrotic keratinocytes and liquefaction degeneration that were consistent with the diagnosis of SJS or TEN (Figure 3).

In all patients, steroid pulse therapy was initiated immediately after confirming ocular involvement, except 1 case (Case 5) in which steroid pulse therapy already had been initiated previously by a dermatologist. Thereafter, systemic steroids were changed to prednisolone or betamethasone (Table). Topically, 0.1% betamethasone (0.1% betamethasone solution, 0.1% betamethasone eye ointment, or both; 5 to 8 times daily) was used from the day we confirmed ocular involvement. An ophthalmic fluoroquinolone solution (0.3% gatifloxacin or 0.3% ofloxacin; 4 times daily) was used for the prevention of ocular infec-

TABLE. Dosage and Duration of Systemic Corticosteroid Administration during the Acute Stage of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

				Steroid Pulse Therapy (Methylprednisolone)			Steroid Administration after Pulse Therapy (Prednisolone Equivalent)		
Case	Diagnosis	Age (yrs)	Gender	Elapsed Time from Onset to Initiation of Therapy (days)	Steroid Dose (mg/day)	Duration (days)	Initial Dose (mg/day)	Total Duration (days)	Total Amount (mg)
1	SJS	23	M	1	500	3	40	85	1045
2	SJS	27	F	0	1000	3	40	35	510
3	SJS	31	F	4	500	3	60	20	425
4	SJS	34	F	1	1000	3	40	72	570
5	TEN	49	M	0	500	4	60	9	420
Mean		32.8		1.2				44	594

F = female; M = male; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; yrs = years.

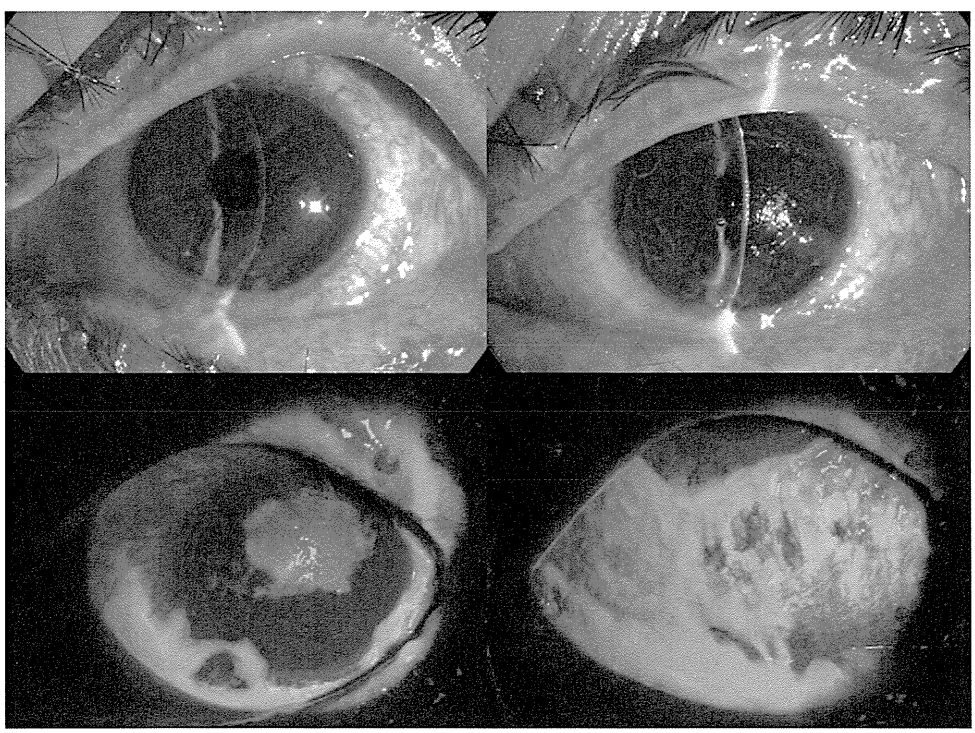

FIGURE 1. Images demonstrated Stevens-Johnson syndrome (SJS) at the acute stage (Case 1). (Top left) Two days after disease onset, pseudomembranous conjunctivitis with conjunctival epithelial defect was present around the limbus. The cornea was clear without defect and superficial punctate keratopathy. (Top right) At the most inflamed phase, 9 days after disease onset and 8 days after the start of steroid pulse therapy, the ocular surface was most inflamed with increased eye discharge, and the pseudomembrane and cilia fell out partially in the lower eyelid. (Bottom left) Corneal epithelial defect. (Bottom right) Conjunctival epithelial defect extending to almost the entire bulbar and palpebral conjunctiva.

tions. Prophylactic systemic antibiotics were not used, because all 5 cases were associated with drug reactions.

Skin eruptions dramatically improved after initiation of the steroid pulse therapy (Figure 4). Despite intensive use of systemic and topical corticosteroids, pseudomembranous formation increased and epithelial defects enlarged during the first several days, peaking at 1 to 9 days (mean, 4.0 days) from their onset. Thereafter, corneal epithelial defects improved day by day and disappeared within 2 to 13 days (mean, 5.2 days). Conjunctival epithelium regenerated completely within 1 to 38 days (mean, 13.0 days).

The administration of systemic steroids was tapered off gradually according to the patient's general and ophthalmic conditions. Whereas cutaneous involvement was quickly eliminated after initiation of steroid pulse therapy, ocular surface inflammation tended to persist longer than cutaneous inflammation. The total amount of steroids was 420 to 1045 mg (changed to prednisolone) during 9 to 85

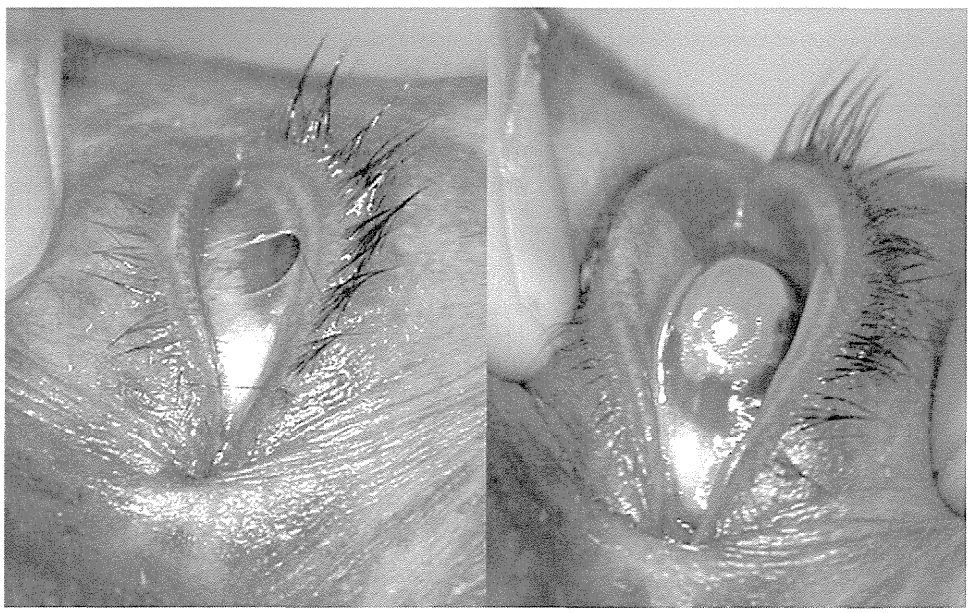

FIGURE 2. Images showing toxic epidermal necrolysis at the acute stage (Case 5). Because the general condition was still critical, the patient was examined on his bed. (Left) Pseudomembrane was present between the upper and lower eyelids. (Right) After removal of the pseudomembrane, corneal epithelial defect was observed.

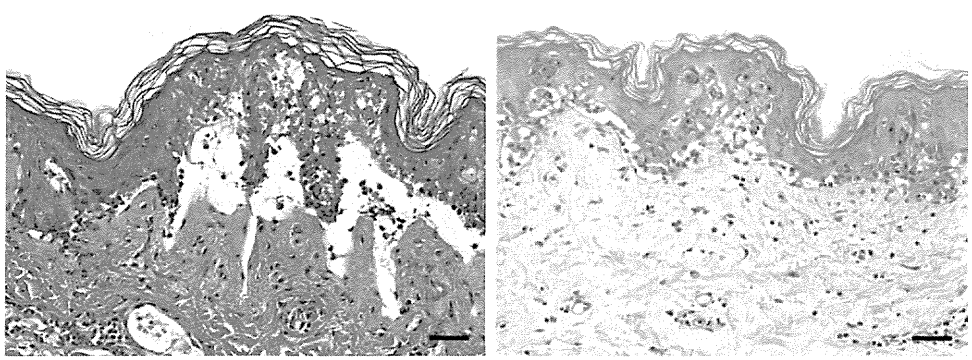

FIGURE 3. Photomicrographs showing sections from a skin lesion of SJS or toxic epidermal necrolysis at the acute stage. (Left) Case 1 with SJS (Right) Case 5 with toxic epidermal necrolysis. These sections show liquefaction degeneration producing a subepidermal cleft. The epidermis contains numerous necrotic keratinocytes with vacuolated cytoplasm or pyknotic nucleus (hematoxylin and eosin, bars = 100 mm).

days from disease onset (Table). One patient with TEN received plasmapheresis[30,31] for 3 days after steroid pulse therapy. Topical 0.1% betamethasone was used for a total of 40 to 165 days (mean, 91.4 days), then switched to 0.1% fluorometholone.

We observed no significant adverse effects from steroid pulse therapy, such as sepsis, pneumonia, or other infections. No cardiac arrhythmia or kidney or liver dysfunction occurred. We continued the culture of the conjunctival swabs during the use of topical or systemic steroids, or both. Methicillin-resistant *Staphylococcus aureus* was detected from the culture of the conjunctival swab in 2 eyes of 1 case at 1.5 months from disease onset, and coagulase-negative *Staphylococci* was observed in 2 eyes of another case at 10 days from disease onset. However, both cases showed no infectious ocular manifestations.

• VISUAL OUTCOMES AND OCULAR FINDINGS AT THE CHRONIC STAGE: In all eyes, best-corrected VA at 1 year from disease onset was 20/20 or better. No eyes had the appearance of an epithelial defect, the loss of the POV, conjunctivalization, neovascularization, opacification, or keratinization. As for corneal complications, only mild SPK was present in 5 eyes. As for conjunctival complications, fornix shortening with mild symblepharon was present only in 1 eye (Case 4). In contrast, all eyes manifested mild lid complications and mild irregularity of the mucocutaneous junction (Figure 5). All patients ex-

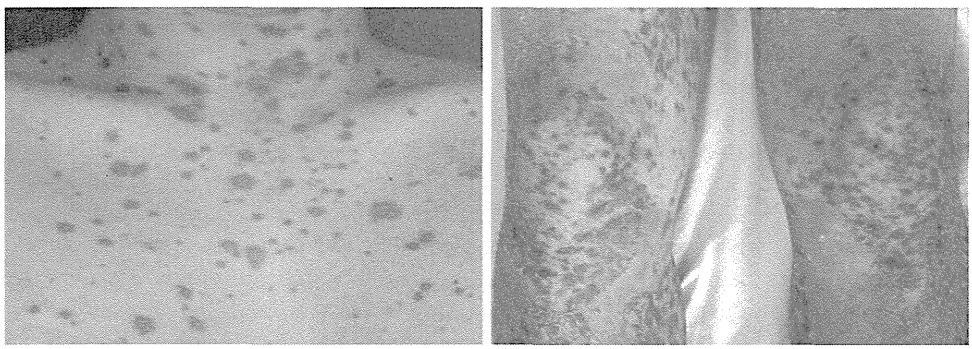

FIGURE 4. Photographs showing skin eruptions of SJS or toxic epidermal necrolysis after steroid pulse therapy. (Left) Case 1 with SJS. (Right) Case 5 with toxic epidermal necrolysis.

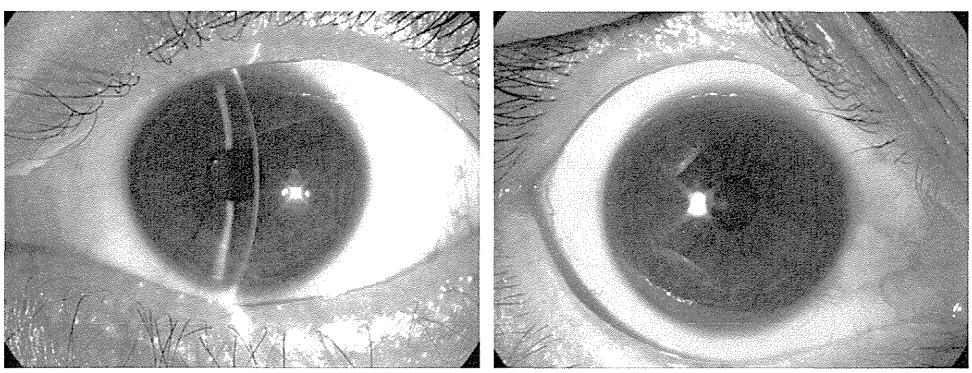

FIGURE 5. Photographs showing the ocular appearances of SJS or toxic epidermal necrolysis at the chronic stage. (Left) Case 1 with SJS. (Right) Case 5 with toxic epidermal necrolysis. The corneas were clear and the ocular surfaces were not inflamed 1 year after disease onset. Mucocutaneous junction involvements were mild.

perienced slight discomfort from irritation to their ocular surface, thus requiring the instillation of artificial tears. The Schirmer 1 test measured less than 5 mm in 4 eyes of 3 cases and 5 mm or more in the other eyes. There was no punctal damage in all eyes. Meibomian gland morphologic features were normal in 8 eyes and mild to moderately dropout in 2 eyes. No increase of intraocular pressure and no infectious keratitis occurred during all clinical courses.

• CASE 1: A healthy 23-year-old man (Case 1) presented to our hospital on October 14, 2004. He had erythematous skin eruptions on the trunk and extremities after taking cold remedies. The body temperature increased to more than 39 C and the erythematous macules increased rapidly and became blisters. Extensive hemorrhagic erosion on the lips and oral mucosa were also observed when he visited our hospital. He was aware of bilateral red eyes just before the skin eruptions. Eye discharge appeared with skin rashes and markedly increased as the skin and oral site worsened. At first examination, both eyelids were edematous, and pseudomembranous conjunctivitis was noted. The tarsal and bulbar conjunctivae were affected severely, and extensive epithelial defect was observed in both eyes. Lid margins also were ulcerated with the partial loss of cilia (Figure 1). A skin biopsy was performed and histopathologic findings were compatible with the clinical diagnosis of SJS (Figure 3).

Immediately after the diagnosis, steroid pulse therapy (methylprednisolone; 500 mg/day for 3 days) was initiated. Topically, betamethasone was instilled 8 times daily (eye drop and ointment each administered 4 times daily). The improvement was dramatic. First, the development of new lesions stopped after the initiation of steroid pulse therapy. Thereafter, skin eruptions decreased and systemic conditions improved day by day (Figure 4). However, ocular inflammation increased with pseudomembranous formation, bilateral epithelial defects in the center of the cornea, and large conjunctival epithelial defects extending to nearly the entire bulbar and palpebral conjunctiva. After the peak of ocular surface inflammation at 9 days from disease onset, corneal and conjunctival epithelium began to regenerate.

Steroid pulse therapy was switched to intravenous betamethasone at a dosage of 4 mg/day for 5 days and then gradually tapered off. The total amount of systemic steroid was 1045 mg of a prednisolone equivalent, administered for a total of 85 days. Topically, betamethasone was initially administered for 31 days, with a total duration of 165 days. The pseudomembrane was removed daily and