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H．知的財産権の出願・登録状況
(予定を含む。)

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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Presumed stromal graft rejection after automated lamellar therapeutic keratoplasty: case report

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Abstract

Purpose: To describe the development of presumed immune-mediated stromal rejection after automated lamellar therapeutic keratoplasty (ALTK) and its reversal after initiation of intensive topical corticosteroid therapy.

Methods: Observational case report.

Results: Stromal edema localized in the graft developed 42 days after ALTK for Avellino corneal dystrophy in a 65-year-old man. After one week of intensive topical corticosteroids, complete reversal of graft edema occurred, with full recovery of visual function.

Conclusion: The clinical appearance and response to therapy in this case supported the diagnosis of immune-mediated stromal rejection. Ophthalmologists should be aware that stromal rejection may occur in lamellar corneal grafts.

Background

Lamellar keratoplasty was the first form of corneal transplantation ever attempted, and now has a history of over a century. Occasionally, it is employed in the rehabilitation of thinned corneas or those with anterior opacification[1]. However, the use of lamellar keratoplasty has been limited by difficulties such as irregularity and scarring of tissue interfaces, leading to poor visual outcomes compared with penetrating keratoplasty, as well as technical difficulties and prolonged operating time[1]. The thickness and contour of the transplanted tissue are difficult to control, which causes problems with optical clarity.

Automated lamellar therapeutic keratoplasty (ALTK) is a new approach to lamellar keratoplasty which avoids some of these problems[2]. In ALTK, an automated keratome is used to cut partial-thickness sections through the anterior surfaces of both the donor and host corneas. These sections are very similar to the flaps cut in LASIK surgery, and allow a very precise surface to be obtained. Thus, ALTK offers advantages over traditional lamellar keratoplasty, as it reduces astigmatism, thereby resulting in better potential visual outcomes and shorter operation time.

Lamellar grafting offers several advantages over penetrating keratoplasty, including elimination of allograft rejec-

tion and avoidance of intraocular complications. Although there is still the possibility of rejection at either the donor epithelium or stroma, the avoidance of endothelial rejection is an exceptional advantage. Irreversible loss of vision after lamellar keratoplasty due to presumed stromal rejection has occurred in only 1.4%–1.9% of patients according to previous reports[3,4]. This lower rate of stromal rejection may due to the small number of lamellar keratoplasties performed compared to penetrating keratoplasties, and an increased number of lamellar keratoplasties may, therefore, result in an increased number of stromal rejection. Here, we report a case of presumed immune-mediated stromal rejection after ALTK that was completely reversed with prompt initiation of intensive steroid therapy.

Case presentation

A 65-year-old Japanese man was referred to the National Tokyo Medical Center because of blurred vision in both eyes. The patient was diagnosed with Avellino corneal dystrophy, and had a history of keratectomy in both eyes at the age of 60. Corrected visual acuity was 20/100 in the right eye, and 20/50 in the left eye. Examination by slit-lamp microscopy revealed gray-white granular opacities in the anterior stroma of both eyes, which was compatible with the diagnosis of Avellino corneal dystrophy. The patient's medical history was otherwise unremarkable. His daughter also had Avellino corneal dystrophy.

Additional PTK was ruled out because of insufficient corneal thickness due to previous keratectomy, and ALTK was performed in the right eye to remove anterior stromal deposit in October, 2004. Using the "Moria LSK Evo-II MircoKeratome Evo II Micro Keratome (Moria Japan, Tokyo, Japan), a 9.5-mm-diameter, 200 μm-depth flap was cut out from the recipient cornea. In same way, a 9.5-mm-diameter, 300 μm flap was obtained from a donor cornea maintained in an artificial chamber (Moria Japan). The donor cornea was transported from an eye bank in the United States, and met the criteria of the Eye Bank Association of America for donor quality. Fresh, full-thickness graft material preserved in Optisol GS (Bausch & Lomb, Rochester, NY) for 7 days was used for the lamellar keratoplasty. The lamellar graft was sutured in place with 9 interrupted 10-0 nylon sutures. Topical betamethasone phosphate 0.1% (Shionogi Pharmateutical Co., Osaka, Japan) and levofloxacin 0.5% (Santen Pharmateutical Co., Osaka, Japan) were applied three times daily in the postoperative periods. Visual acuity improved to 20/40 with correction at 4 weeks after the operation.

Forty-two days postoperatively, the patient returned to our clinic with the sensation of a foreign body and blurred vision in the right eye. Slit-lamp examination revealed a diffuse stromal edema limited to the graft (Fig. 1). The posterior half of the corneal stroma, which was the recipient bed, remained clear. There were no epithelial defects, and no keratic precipitates or inflammation were seen in the anterior chamber. Intraocular pressure was 12 mmHg. A diagnosis of presumed immune-mediated stromal rejection was made based on these findings. On an hourly regimen of betamethasone phosphate 0.1%, the stromal edema began to improve immediately, completely clearing within 1 week (Fig. 2). Corrected visual acuity in the right eye improved to 20/25 at 10 days after treatment. Topical corticosteroids were tapered and discontinued over 3 months, and the graft remained clear at the last follow-up.

Discussion

The patient developed stromal edema localized in the graft 42 days after ALTK. Differential diagnoses might have included diffuse lamellar keratitis (DLK) and herpetic keratitis, as well as allograft rejection. DLK is usually a postoperative complication of LASIK in early phase (within 1–6 days after surgery), and is defined as an inflammatory condition in which white blood cells migrate along the stromal interface[5]. The etiology of DLK remains to be clarified, and it is generally thought that the cause of this inflammatory reaction may be multifactorial [6].

In this case, DLK could be excluded due to the lateness of onset (42 days after the operation) and involvement of the entire graft, not just the interface. Herpetic infection

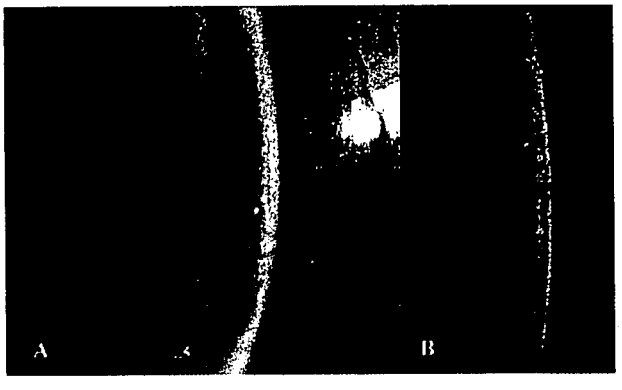

Figure 1
Day 42 after surgery. A. Diffuse edema of lamellar graft was apparent, whereas there were no epithelial defects, keratic precipitates, or inflammation in anterior chamber. Gray-white granular opacities were observed in the graft bed, which were residual deposits of Avellino corneal dystrophy. B. High-magnification slit-lamp photograph demonstrated marked anterior stromal thickening (graft edema). In contrast, posterior half of corneal stroma, which was recipient bed, remained clear.

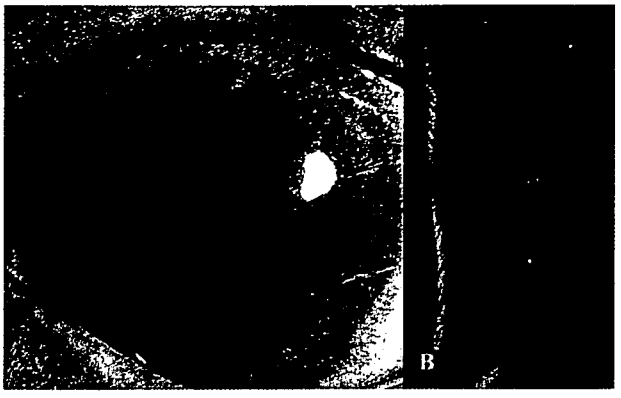

Figure 2
One week after treatment with topical corticosteroids. Corneal stroma cleared completely.

could also be excluded due to the localization of the stromal edema in the graft and negative history of herpetic eye infection. Although stromal edema has been reported to sometimes occur following LASIK, such as in eyes with uveitis and elevated intraocular pressure[7], this possibility was also excluded due to the maintenance of normal range (around 12 mmHg) throughout the follow-up period. The absence of associated ocular abnormalities and the prompt response to intensive corticosteroid therapy indicated a diagnosis of stromal allograft rejection after ALTK. Stromal rejection involves infiltration rather than edema of the stroma[8], and recently Watson et al reported that the stroma became opaque and edematous in 2 stromal rejection cases after deep lamellar keratoplasty[4], which also supported our diagnosis. In our case, one contributing factor to stromal rejection could be the large graft size in ALTK

Three different types of allograft rejection have been identified after penetrating keratoplasty: endothelial rejection, epithelial rejection, and subepithelial infiltrates [9]. Theoretically, lamellar grafts are free from endothelial rejection, but not from other types of rejection. Alldredge and Krachmer[9] reported that frequencies of epithelial rejection and subepithelial infiltrates after penetrating keratoplasty were 10% and 15%, respectively. However, the true frequencies of these two types of rejection are hard to determine because they can easily take place without symptoms between examinations. In our case, the patient developed a diffuse stromal edema localized in the graft, with no epithelial involvement, which ruled out epithelial rejection or subepithelial infiltrates.

Our case appears to resemble the case of stromal rejection after deep lamellar keratoplasty described by Al-Torbak and associates[10]. In their case, diffuse stromal edema of the entire graft developed 16 months after surgery for keratoconus. Although such stromal rejection is not included in reported criteria of allograft rejection after penetrating keratoplasty[9], it might be overshadowed by endothelial rejection in penetrating keratoplasty.

Conclusion

In this case, the clinical appearance and response to therapy supported the diagnosis of immune-mediated stromal rejection. This case suggests that stromal rejection can occur after lamellar keratoplasty and that it usually goes unrecognized. We propose that ophthalmologists should be aware of stromal rejection as a potential complication of lamellar corneal grafts.

Abbreviations

ALTK; automated lamellar therapeutic keratoplasty, PTK; phototherapeutic keratectomy, DLK; diffuse lamellar keratitis, LASIK; Laser in situ keratomileusis.

Authors' contributions

MK drafted the manuscript. TK and JS helped to draft the manuscript. SH and HM participated in the data collection and treat this case. MY performed surgery and treat this case. All authors read and approved the final manuscript.

Acknowledgements

That patient consent was received for this case report to be published.

The author has no proprietary interest in any of the materials described in this manuscript.

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Quantitative Evaluation of Tear Meniscus Height From Fluorescein Photographs

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Purpose: To describe a method of quantifying the tear meniscus height (TMH) and using these values to diagnose patients with dry eye.

Methods: Thirty-eight eyes of 19 healthy subjects and 14 patients diagnosed with dry eye were studied. Each eye received 2 μL of 1% fluorescein-sodium solution in the conjunctival sac, and digital photographs were taken of the external surface of the eye with a fundus camera. The tear meniscus was extracted from the digitalized image and used to measure the TMH with NIH image software. The correlation between the mean TMH and Schirmer test values or cotton-thread test values was evaluated.

Results: The means of the upper and lower TMH in healthy subjects were 0.22 ± 0.06 and 0.24 ± 0.08 mm, respectively. The comparable values in patients with dry eye were 0.17 ± 0.04 and 0.17 ± 0.07 mm (upper TMS, $P = 0.01$; lower TMH, $P = 0.04$; unpaired t test). A significant correlation was found between the TMH and Schirmer test values ($r = 0.72$, $P = 0.01$) but not with cotton-thread test values.

Conclusions: Fluorescein photographs of the eye can be used to quantify the upper and lower TMH separately and simultaneously without specialized equipment. This technique can be used for the diagnosis of dry eye.

Key Words: dry eye, fluorescein, fundus camera, tear meniscus

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An adequate volume of tears is essential to prevent desiccation of the exposed ocular surface. The tear meniscus is a part of the precorneal tear film and results from the reservoir of tears.[1] The clinical importance of measuring the tear meniscus has not been stated clearly,[2,3] although it has been suggested that quantifying the size of the tear meniscus may be useful for the diagnosis of dry eye.[4,5]

The tear meniscus height (TMH) has been measured by slit-lamp examination with a scale attached to the objective lens,[1] a digital photographic system with a slit-lamp equipped with a digital camera,[6] and a meniscometer that measures the radius of curvature of the tear meniscus.[7–9] The measurement of the radius of curvature of the tear meniscus might be a useful method, but the instrument to do this is not available commercially.

We hypothesized that TMH is correlated with the degree of dry eye. To test this hypothesis, we calculated the coefficient of correlation between TMH and other more conventional measures of dry eye.

MATERIALS AND METHODS

Healthy Subjects and Patients With Dry Eye

The upper and lower TMH of 38 eyes of 19 healthy subjects (8 men and 11 women; age range, 18–79 years) with no abnormalities of the cornea, conjunctiva, lacrimal system, or meibomian glands were studied. Fourteen right eyes of 14 patients with dry eye (3 men and 11 women; age range, 28–74 years), who had a Schirmer test value of <5 mm (Schirmer 1 test with anesthesia) or a value of a cotton-thread wetting test of <10 mm, were compared with the 19 right eyes of healthy subjects. The principles of the World Medical Association Declaration of Helsinki were followed. Each subject received a full explanation of the study and all procedures involved in the study, and they provided written informed consent before enrollment. Approval for this study was granted by the Committee for the Protection of Human Subjects at the Keio University School of Medicine.

Meniscus Photographs and TMH Analyses

A 10 × 2-mm paper strip that had been stained with sodium fluorescein was placed on the inferior eyelid as a calibration marker (Fig. 1A). Then, 2 μL of 1% fluorescein sodium solution was dropped into the lower conjunctival sac with a micropipette. After 3 minutes, the anterior segment of the eye was photographed with a fundus camera (TRC-50LX; Topcon, Tokyo, Japan) equipped with blue light for excitation and a fluorescence filter for detection of the tear meniscus. Only the tear meniscus and paper strip were highlighted under these conditions (Fig. 1B). These images were uploaded to the IMAGENET system (IMAGE NET 2000;

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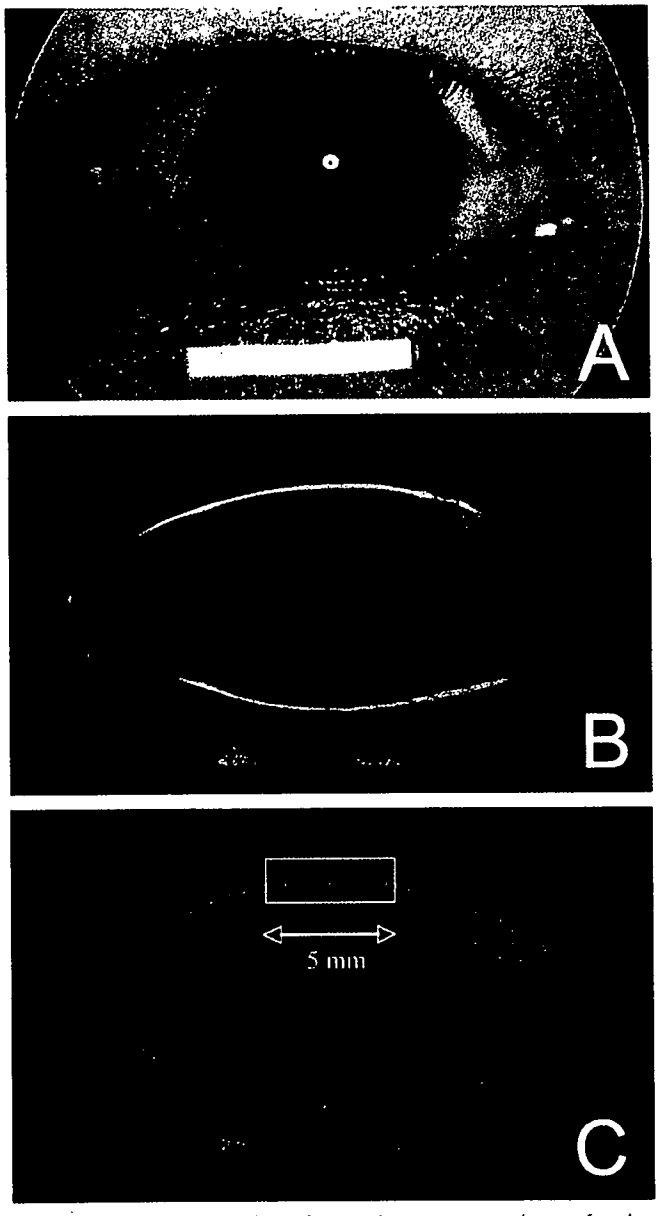

FIGURE 1. Photographs of anterior segment by a fundus camera. A, Under white light illumination with a 10 × 2-mm strip as a calibration scale on the lower lid. B, Photograph with a scale under blue light through a fluorescein filter showing the area of the tear meniscus. C, Area corresponding to tear meniscus is shown in red, and the average height of a selected area of 5 mm width was calculated.

Topcon). The area corresponding to the tear meniscus was outlined (Fig. 1C), and the number of pixels in the selected central 5-mm-wide region was counted to calculate the TMH by NIH image software (NIH, Bethesda, MD). To reduce the bias, 1 masked examiner (MK) performed the whole image analysis. The upper and lower TMH was measured, and the values for healthy subjects were compared with those for patients diagnosed with dry eye. The Pearson correlation coefficient was calculated between mean TMH (upper and lower TMH) and values of the Schirmer test (Schirmer 1 test with anesthesia) or the cotton-thread tests to determine whether they were related in normal subjects and patients with dry eye.

RESULTS

TMH Values in Healthy Subjects

The TMH of the upper tear meniscus (upper TMH) and that of the lower meniscus (lower TMH) was measured on the same image in all subjects. The means of the upper and lower TMH in both eyes of healthy subjects were 0.22 ± 0.06 and 0.24 ± 0.08 mm, respectively. The mean upper TMH in the right eyes was 0.24 ± 0.06 (SD) mm, and the lower TMH was 0.25 ± 0.07 mm (Fig. 2). The comparable values for the left eyes were 0.20 ± 0.04 and 0.23 ± 0.09 mm, respectively. The upper TMH was significantly higher than the lower TMH in each eye (right eye, $P = 0.03$; left eye, $P = 0.02$; paired t test).

TMH Values in Patients With Dry Eye

The mean upper TMH was 0.17 ± 0.04 mm and the mean lower TMH was 0.17 ± 0.07 mm in the patients with dry eye. The difference between the upper and lower TMH was not significant in patients with dry eye ($P = 0.85$, paired t test). However, both of these values were significantly lower than the comparable values in healthy subjects (Fig. 3; upper TMH, $P = 0.01$; lower TMH, $P = 0.04$; unpaired t test).

Correlation Analysis

The coefficient of correlation between mean TMH (upper and lower TMH) and the Schirmer test values in patients with dry eye was significant ($r = 0.72$, $P = 0.01$; Fig. 4), but the correlation between TMH and the cotton-thread test values in dry eye patients was not significant ($r = 0.10$; $P = 0.75$; Fig. 5). In healthy subjects, the correlations of the mean TMH to these 2 values were also not significant.

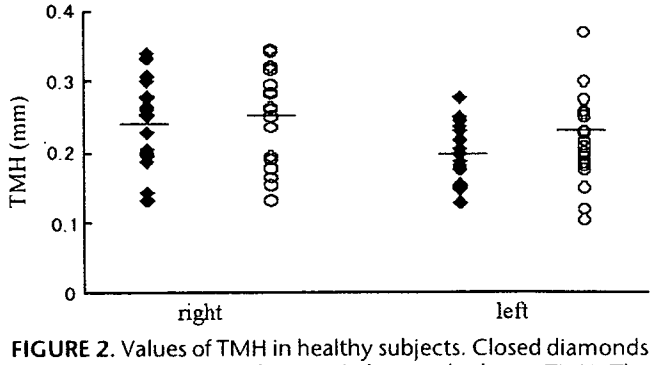

FIGURE 2. Values of TMH in healthy subjects. Closed diamonds are the upper TMH, and open circles are the lower TMH. The mean upper TMH is 0.24 ± 0.06 (SD) mm, and the lower TMH is 0.25 ± 0.07 mm in right eyes of healthy subjects and 0.20 ± 0.04 and 0.23 ± 0.09 mm in left eyes, respectively. These mean TMH values are not significantly different.

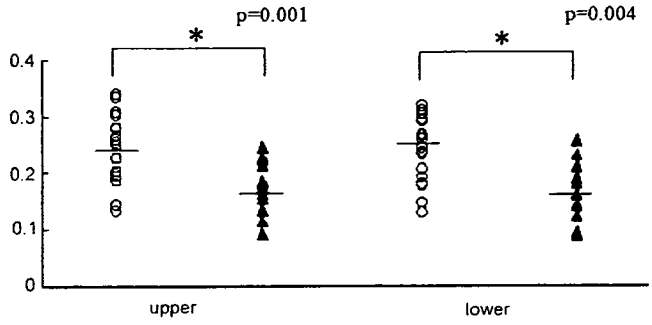

FIGURE 3. Comparison of TMH in healthy subjects and in patients with dry eye. ○, values of TMH in healthy subjects; ▲, TMH in patients with dry eye. The upper and lower TMHs in healthy subjects are significantly higher than those in patients with dry eye.

DISCUSSION

The results of this study showed that the mean upper and lower TMHs in patients with dry eye were significantly smaller than those in healthy subjects, and the TMH values were correlated significantly with the Shirmer test values in patients with dry eye. This simple method is valuable to evaluate dry eye because values of the Schirmer test with anesthesia represent the volume of tear reservoir and basic tear secretion. In addition, the upper and lower TMHs can be measured individually on the same photograph, and all subjects and patients can be measured to allow the quantification of the entire meniscus, not only the lower TMH as in earlier studies.[1–9] Another advantage of this technique is that it requires only a conventional fundus camera to photograph the anterior ocular surface and a personal computer without any specialized equipment.

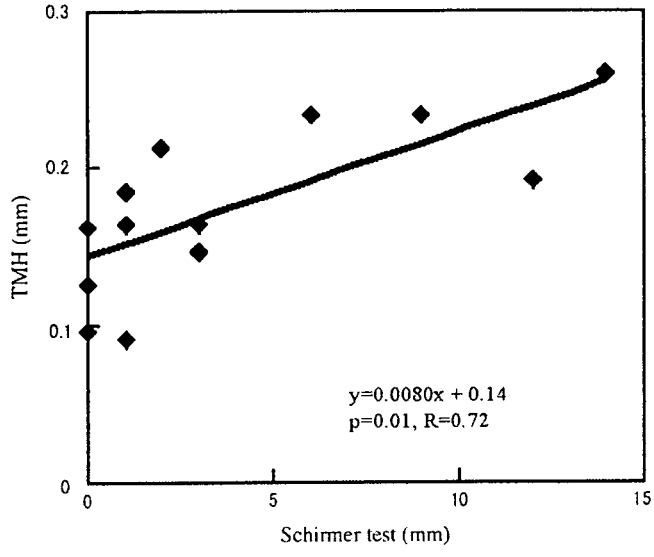

FIGURE 4. Correlation between mean TMH and values of the Shirmer test in patients with dry eye. A significant correlation was observed between mean TMH and values of the Schirmer test in patients with dry eye.

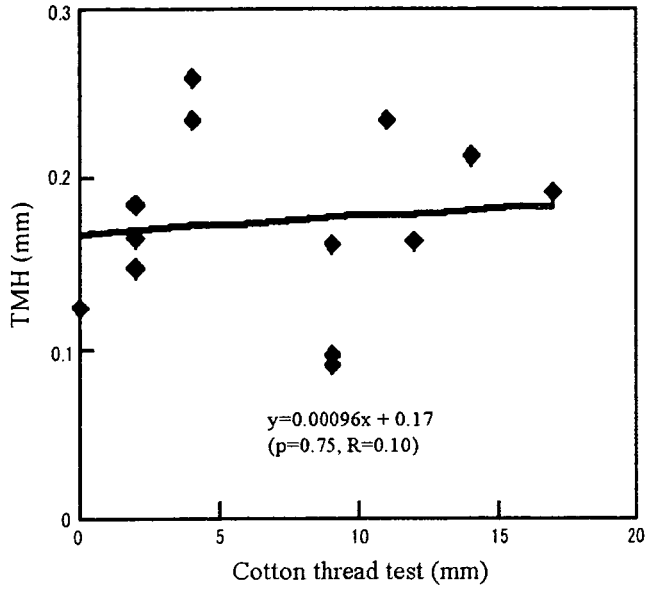

FIGURE 5. Correlation between mean TMH and values of the cotton thread test in patients with dry eye. There was a lower, but not significant, correlation between mean TMH and values of the cotton-thread test in patients with dry eye.

A low supply of tears has been suggested to play a role in certain types of dry eye. For example, patients with superior limbic keratoconjunctivitis (SLK) have been reported to have a low level of tears. The degrees of Rose Bengal and fluorescein staining are reduced, accompanied by an improvement of subjective symptoms after lacrimal punctal occlusion in the upper and lower sides or even after upper lacrimal punctal occlusion without lower occlusion.[10] Thus, it was suggested that SLK might be caused by lack of upper tear meniscus. Our method should be able to quantify the therapeutic values before and after lacrimal punctal occlusion by evaluating the upper or lower TMH separately.

This method also has disadvantages; it requires topical fluorescein solution, which may alter the characteristics and volume of the tear film. However, Oguz et al[9] evaluated the tear meniscus of the lower central lid with a meniscometer with and without fluorescein, and they concluded that there was a minimal effect of the small amount of fluorescein. Another disadvantage is that the TMH values cannot be obtained immediately but require offline analysis with a personal computer.

This technique probably will be valuable in the diagnosis of dry eye and determining the effectiveness of treatment of dry eye. In addition, this technique can be used to define the role played by the upper and lower TMHs in patients with dry eye.

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New Grading System for the Evaluation of Chronic Ocular Manifestations in Patients with Stevens–Johnson Syndrome

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Purpose: To evaluate and grade the extent and severity of chronic ocular manifestations in Stevens–Johnson syndrome (SJS).

Design: Prospective multicenter case series.

Participants: We enrolled 73 patients (138 eyes) with SJS seen between April 2003 and March 2005 at 3 tertiary referral centers.

Methods: Patients with a confirmed history of SJS and chronic ocular complications that persisted for at least 1 year from the onset of SJS were included. Their detailed medical history and ophthalmic examination results were recorded on an itemized data collection form. Complications were categorized as corneal, conjunctival, and eyelid complications, and 13 components were evaluated and graded on a scale from 0 to 3 according to their severity.

Main Outcome Measures: These were broadly classified as corneal (superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, keratinization), conjunctival (hyperemia, symblepharon formation), and eyelid (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, punctal damage) complications.

Results: The most severely affected complication components were loss of the palisades of Vogt (114 eyes; 82.6%) and meibomian gland involvement (102 eyes; 73.9%). Visual acuity in 74 of the 138 eyes (53.6%) was worse than 20/200. The severity of corneal, conjunctival, and eyelid complications was significantly correlated with visual loss. All 13 complications were correlated significantly with logarithm of the minimum angle of resolution (logMAR) visual acuity; the correlation coefficient (R) ranged from 0.359 to 0.810 ($P<0.0001$); for corneal epithelial defects, R was 0.169 ($P = 0.0473$). Eyes with a higher total score for the 3 complication categories had poorer vision ($R = 0.806$; $P<0.0001$). Multivariate regression analysis showed that corneal neovascularization, opacification, keratinization, and cataracts significantly affected logMAR visual acuity ($P<0.0001$, $P<0.0001$, $P = 0.0142$, $P = 0.0375$, respectively).

Conclusions: The authors describe a new method for grading the extent and severity of ocular involvement in patients with SJS and demonstrate that the severity of ocular involvement is correlated significantly with the final visual outcome. This new grading system provides a more objective method for evaluating SJS patients and may be adapted for use in other cicatricial ocular surface diseases. *Ophthalmology 2007;114:1294–1302 © 2007 by the American Academy of Ophthalmology.*

Stevens–Johnson syndrome (SJS) is an acute, self-limiting disease of the skin and mucous membranes that predisposes patients to life-threatening complications such as sepsis, respiratory dysfunction, and multiorgan failure. In the acute stage, more than 50% of patients experience ocular complications ranging from minimal (e.g., mild conjunctival hyperemia) to very severe (e.g., corneal melting and perforation).[1–4] Inflammation and epithelial erosion of the ocular surface often persist beyond the acute stage and the resolu-

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tion of skin eruptions, leading to ocular complications and scarring in the chronic stage. Severe ocular surface disease arising from SJS encompasses a spectrum of ocular manifestations and complications that often is associated with significant visual morbidity. Visual impairment and ocular discomfort continue throughout life and patients usually require long-term medication for disease control.

Over the past 40 years, it has been widely accepted that erythema multiforme (EM), SJS, and toxic epidermal necrolysis (TEN) are part of a single EM spectrum.[5–7] However, because no clear diagnostic criteria have been established, reaching a definitive diagnosis can be difficult. Roujeau,[6] who performed a retrospective analysis of the type and distribution of skin lesions and the extent of epidermal detachment, concluded that EM major (EMM) and SJS were 2 separate clinical entities that differed with respect to histopathologic changes and cause. A large international case-control study, called the Severe Cutaneous Adverse Reaction study, prospectively evaluated the validity of this clinical distinction; its results strongly support the hypothesis that EMM is different from SJS and TEN, and that SJS and TEN are severity variants of a single entity.[5] The classification was based on the clinical appearance and pathologic results of skin lesions present in the acute stage. However, patients often seek treatment from ophthalmologists in the late stage of the disease with chronic cicatricial complications, after resolution of the dermatologic changes, and it can be difficult to elicit the original clinical manifestations used to distinguish between EMM and SJS or TEN from patients seen many years after disease onset. Therefore, from the ophthalmologist's perspective, ocular surface diseases arising from EM, SJS, or TEN often are regarded collectively as SJS.

Corneal transplantation in SJS patients with severe ocular surface disease is associated with a poor prognosis. Persistent epithelial defects occurring after penetrating or lamellar keratoplasty often progress to corneal melting and perforation. Transplanted limbal stem cells or keratoepithelioplasty in these chronically inflamed eyes often elicit graft rejection and loss of donor epithelial cells, resulting in progressive conjunctivalization, scarring, and visual loss.[8,9] Over the past decade, new ocular surface reconstructive procedures such as amniotic membrane and cultivated epithelial transplantation have yielded promising results for the treatment of SJS.[10,11] However, despite its potentially devastating nature and the increasing indications for ocular reconstructive surgery, there is currently no standardized method for evaluating the spectrum of ocular manifestations and the severity of ocular complications in this blinding disease.

The aims of this study were to elucidate the profile of chronic ocular manifestations in SJS patients and to develop an objective method for grading the extent and severity of ocular complications in patients with cicatricial ocular surface diseases. Three large tertiary referral ophthalmic centers participated in this multicenter study; to our knowledge, it represents the largest series of SJS patients with ophthalmic complications studied to date. Because it provides a common platform for the discussion and management of these patients, this study has important clinical implications for the diagnosis, treatment, and the prediction of visual outcomes in patients with SJS.

Patients and Methods

Patients

The 3 ophthalmic centers that participated in this multicenter study are Kyoto Prefectural University of Medicine, Keio University, and National Tokyo Medical Center. All patients with chronic ocular complications from SJS who were referred to these centers between April 2003 and March 2005 were evaluated prospectively in this study. Patients with a confirmed history of SJS and chronic ocular complications that persisted for at least 1 year from the onset of SJS were included. The diagnosis of SJS was based on 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. Eyes with a past history of ocular surface surgery were excluded from this study. The study was approved by the ethics committee and institutional review boards of each institution; the guidelines of the Declaration of Helsinki in Biomedical Research Involving Human Subjects were followed, and written informed consent was obtained from each patient.

The symptomatology, physical findings, detailed ophthalmic examination results, and ocular complications were recorded on an itemized data collection form. The detailed ophthalmic examination included an assessment of visual acuity, tonometry, slit-lamp examination, fluorescein staining, and anterior segment photography. A careful drug history also was obtained by the attending physician. A drug was considered a possible etiologic agent if it had been taken shortly before the onset of symptoms, that is, within 2 weeks of disease onset. If the reaction showed signs of regression during the continued administration of the drug, a causal relationship was considered unlikely.

Classification and Grading of Ocular Involvement

We considered 13 components of 3 categories of ocular complications to be important in the assessment of the 138 eyes; each component was graded on a scale from 0 to 3, depending on the severity of involvement. The complications were classified broadly as corneal complications, comprised of superficial punctate keratopathy (SPK), epithelial defect, loss of the palisades of Vogt (POV), conjunctivalization, neovascularization, opacification, and keratinization components; conjunctival complications with hyperemia and symblepharon formation as the components; and eyelid complications consisting of trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage as the evaluated components. The following classification and grading systems were used to evaluate the nature of the ocular complications in these patients.

Corneal Complications

Severity of Superficial Punctate Keratopathy. We used fluorescein staining and a simplified method of Miyata et al[12] to grade SPK based on the area and density of the lesions. The area was graded as A0 when there was no punctate staining and as A1, A2, or A3 when the area occupied less than one third, one third to two thirds, or more than two thirds of the cornea, respectively. Density was graded as D0 when there was no punctate staining and as D1,

D2, or D3 when density was sparse, moderate, or high and the lesions overlapped, respectively. Although Miyata et al used the sum of the grades assigned to the area and density to obtain the final grade for the eye, we simplified their grading system and assigned scores of 0 through 3: A1D1 was scored as 0; A1D2 or A2D1 was scored as 1; A1D3, A2D2, or A3D1 was scored as 2; and A2D3, A3D2, or A3D3 was scored as 3.

Corneal Epithelial Defect. The extent of corneal epithelial defect was scored from 0 through 3, where 0 = no epithelial defect, 1 = epithelial defect involving less than one quarter of the corneal surface, 2 = defect involving one quarter to one half, and 3 = defect involving more than one half of the corneal surface.

Loss of the Palisades of Vogt. The extent of the loss of the limbal POV was graded from 0 through 3, where 0 = presence of the entire POV, 1 = loss of less than half of the entire circumference of POV, 2 = loss of more than half of the entire circumference of POV, and 3 = total loss of POV.

Conjunctivalization. The extent of conjunctivalization was graded clinically from 0 through 3 as follows: 0 = absence of conjunctivalization, 1 = conjunctivalization involving less than one quarter of the corneal surface, 2 = conjunctivalization involving one quarter to one half, and 3 = conjunctivalization involving more than one half of the corneal surface (Fig 1).

Corneal Neovascularization. The extent of corneal neovascularization was scored from 0 through 3, where 0 = no neovascularization, 1 = neovascularization confined to the corneal periphery, 2 = neovascularization extending up to the pupil margin, and 3 = neovascularization extending beyond the pupil margin into the central cornea (Fig 1). In eyes where significant opacification or extensive symblepharon formation made it difficult to evaluate corneal neovascularization, a score of 3 was assigned.

Corneal Opacification. The severity of corneal opacification was graded from 0 through 3, where 0 = clear cornea with iris details clearly visualized, 1 = partial obscuration of the iris details, 2 = iris details poorly seen with pupil margin just visible, and 3 = complete obscuration of iris and pupil details (Fig 1).

Corneal Keratinization. The extent of keratinization was graded from 0 through 3, where 0 = no corneal keratinization, 1 = keratinization involving less than one quarter of the corneal surface, 2 = keratinization involving one quarter to one half, and 3 = keratinization involving more than one half of the corneal surface (Fig 1).

Conjunctival Complications

Conjunctival Hyperemia. Conjunctival hyperemia was graded from 0 through 3 based on the following clinical features: 0 = absence of hyperemia, 1 = mild (mild or sectoral engorgement of the conjunctival vessels), 2 = moderate (diffuse engorgement of the conjunctival vessels), and 3 = severe hyperemia (significant engorgement of the conjunctival vessels).

Symblepharon Formation. The extent of symblepharon formation was scored from 0 through 3, where 0 = no symblepharon, 1 = symblepharon formation involving only the conjunctival surface, 2 = symblepharon formation involving less than half of the corneal surface, and 3 = symblepharon formation involving more than half of the corneal surface (Fig 1).

Eyelid Complications

Trichiasis. The extent of trichiasis for the total area of the upper and lower eyelids combined was scored as 0 through 3, where 0 = no trichiasis, 1 = trichiasis involving less than one quarter of the lid margin, 2 = trichiasis involving one quarter to one half of the lid margin, and 3 = trichiasis involving more than one half of the lid margin.

Mucocutaneous Junction Involvement. The severity of mucocutaneous junction involvement was scored from 0 through 3, where 0 = normal mucocutaneous junction, 1 = mild irregularity of the mucocutaneous junction, 2 = moderate irregularity of the mucocutaneous junction, and 3 = severe irregularity of the mucocutaneous junction (Fig 2). Fluorescein staining of the conjunctiva was helpful in evaluating the involvement of the mucocutaneous junction. Normal mucocutaneous junction showed the linear staining at the end of the conjunctiva, and either mild, moderate, or severe irregularity of this line was observed in the eyes with mucocutaneous junction involvement. In eyes where significant keratinization of the lid margin or extensive symblepharon formation made it difficult to evaluate mucocutaneous junction involvement, a score of 3 was assigned.

Meibomian Gland Involvement. The severity of meibomian gland involvement was determined clinically by the nature of the meibomian gland secretion expressed manually at the center of the upper lid and was scored from 0 through 3, where 0 = clear oily fluid expressed, 1 = yellowish-white oily fluid expressed, 2 = thick cheesy material expressed, and 3 = inability to express any fluid from the meibomian glands.

Punctal Involvement. Punctal damage and occlusion were graded from 0 through 3, where 0 = normal patent puncta, 1 = iatrogenic punctal occlusion (e.g., punctal plugs or suture), 2 = either superior or inferior puncta occluded by scarring, and 3 = both superior and inferior puncta occluded by scarring.

Overall Total Score

Each eye was evaluated and graded by at least 2 trained corneal specialists. When the scores varied from one corneal specialist to another, the scores were averaged or determined after a discussion. The results then were added together to give an overall score from 0 to 39, with 39 representing the most severely affected eyes.

Visual Acuity

We categorized the 138 eyes from the 73 patients according to their visual acuity. In group 1 (n = 28 eyes), visual acuity was 20/20 or better, in group 2 (n = 36 eyes), it was worse than 20/20 and up to and including 20/200, in group 3 (n = 32 eyes), it was worse than 20/200 and up to and including 20/2000, and in group 4 (n = 42 eyes), it was worse than 20/2000.

Eye Complications Independent of Ocular Surface Disorders

Cataract, glaucoma, retinal diseases, or other eye diseases independent of ocular surface disorders also were evaluated and their presence, absence, or the inability to diagnosis because of ocular surface abnormalities was recorded.

Statistical Analysis

Spearman correlation coefficients (2-tailed) were used to evaluate whether the scores of the 13 components were correlated with logarithm of the minimum angle of resolution (logMAR) visual acuity. The correlation between the total score and logMAR visual acuity and the correlations between the subtotal scores of 3 problem categories and the total score also were evaluated. Using a logistic regression model, the scores for each of the 13 components

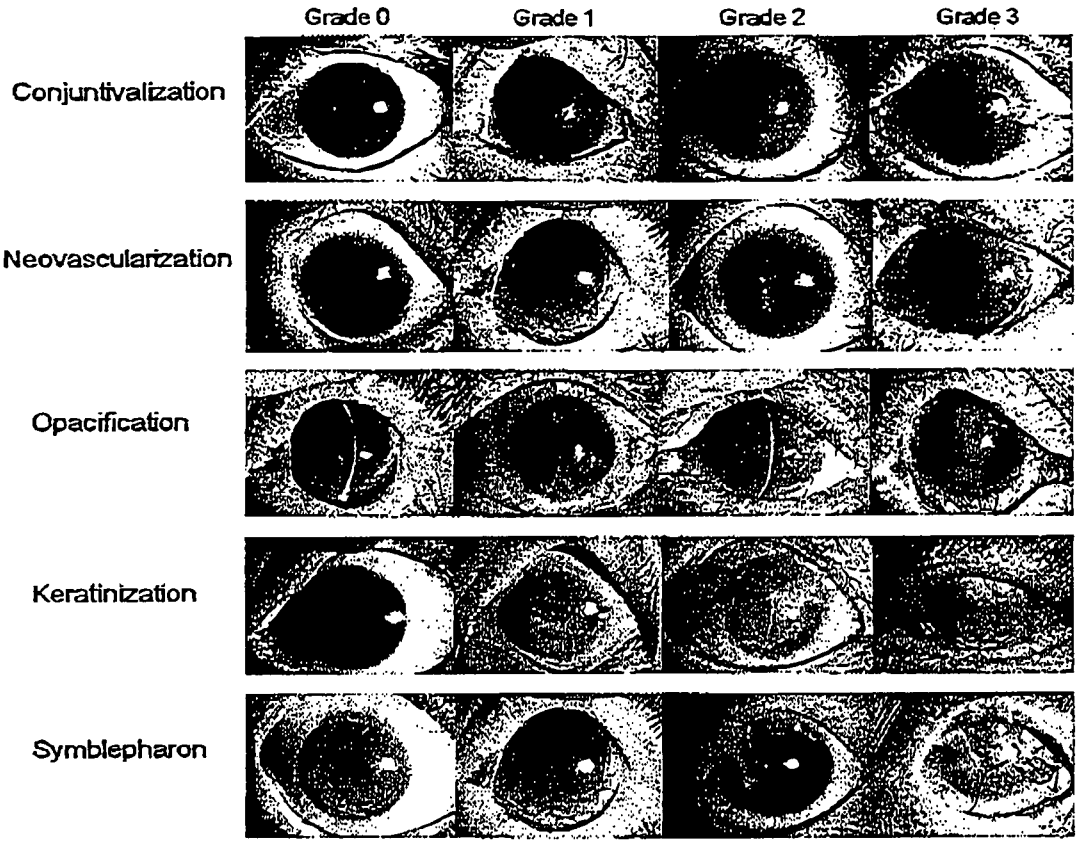

Figure 1. Grading scores of corneal and conjunctival complications.

in eyes with better visual acuity (20/200 or better; i.e., groups 1 and 2) were compared with the scores obtained for eyes with poorer visual acuity (worse than 20/200; i.e., groups 3 and 4). The statistical model for predicting logMAR visual acuity was calculated using a linear model with stepwise variable selection (multivariable regression analysis). In multivariable regression analysis, cataract and glaucoma were graded as follows: with cataract, 1; without cataract or lens invisible, 0; with glaucoma, 1; and without glaucoma or unable to diagnosis glaucoma, 0. All statistical tests were conducted at a 5% level of significance ($P = 0.05$).

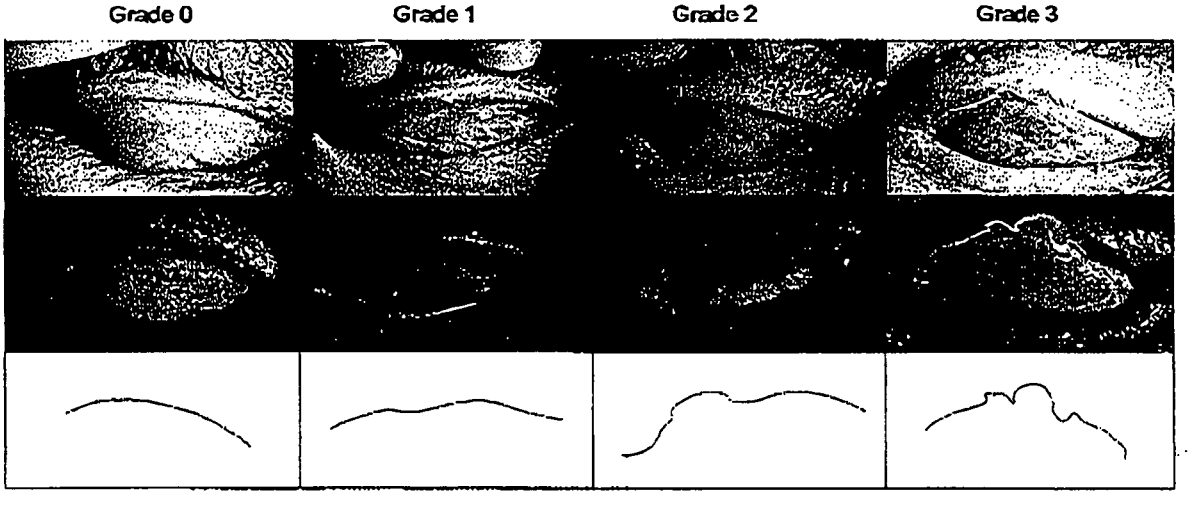

Figure 2. Grading scores of mucocutaneous junction involvement. Top, Grade 1 was assigned for normal mucocutaneous junction, and grades 1, 2, and 3 were assigned for mild, moderate, and severe irregularity of the mucocutaneous junction, respectively. Middle, Bottom, Fluorescein staining of the conjunctiva was helpful in evaluating the severity of the involvement of mucocutaneous junction.