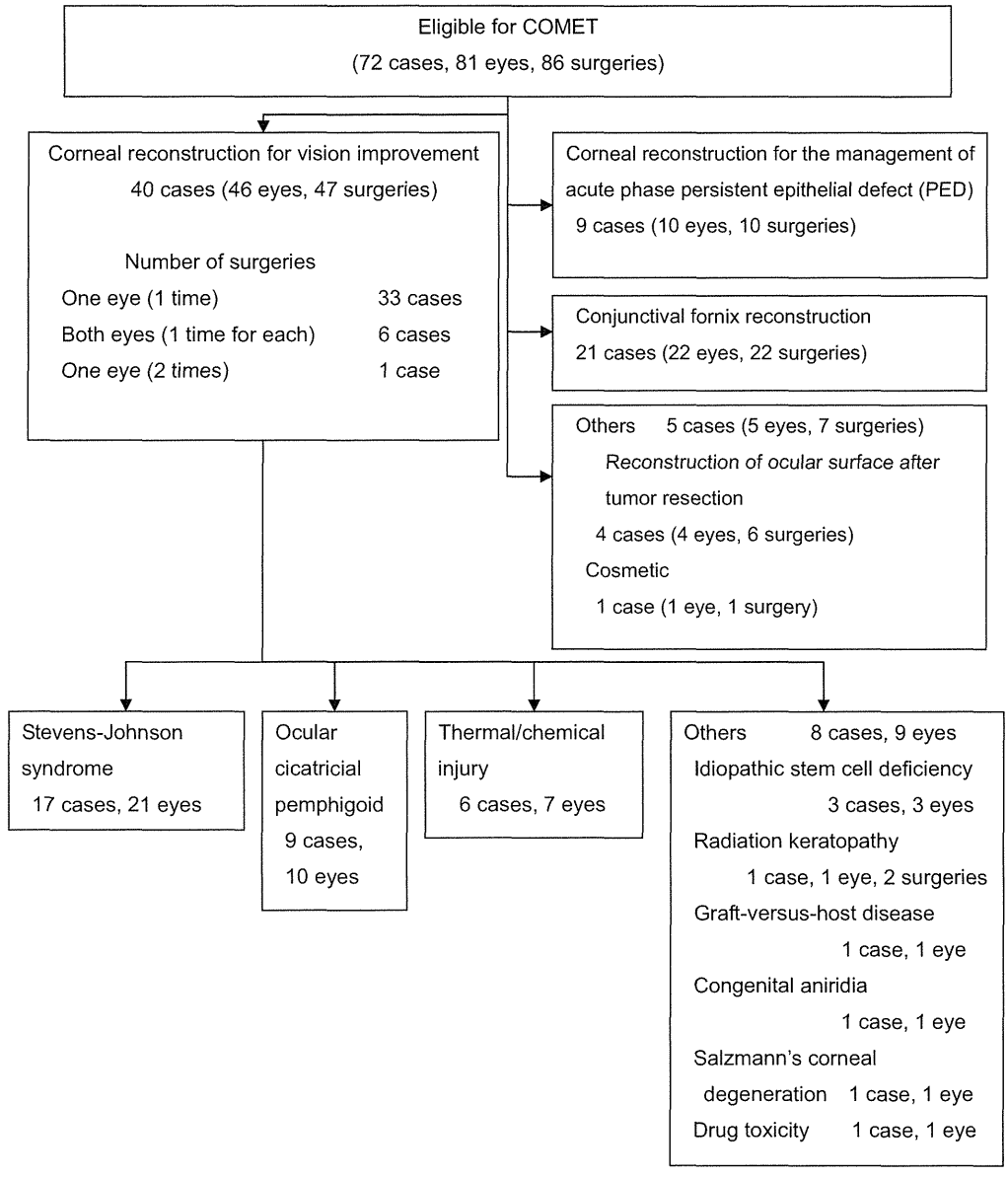



**Figure 1.** Diagram showing flow of study. Seventy-two patients (81 eyes) underwent cultivated oral mucosal epithelial sheet transplantation (COMET) between June 2002 and December 2008, and 40 patients (46 eyes) were analyzed for visual improvement in this study. Both corneal reconstruction and conjunctival fornix reconstruction were carried out in 3 cases, in the same eye in 1 case, and counted separately.

All statistical analyses were conducted at the Translational Research Informatics Center (Kobe, Japan) with the use of SAS software, version 9.1 (SAS Inc, Cary, NC) or JMP software, version 8.2 (SAS Inc). *P* values of less than 0.05 were considered statistically significant.

# Results

## Patient Characteristics

Between 2002 and 2008, 47 COMETs (46 eyes in 40 patients) were performed on 21 eyes with SJS, 10 eyes with OCP, 7 eyes with thermal or chemical injury, and 9 eyes with other causes of LSCD (Fig 1). Although 23 eyes (48.9%) previously had been treated with ocular surgery, all of these previous treatments had failed and recurrence of fibrovascular ingrowth on the cornea was observed. Of the 47 surgeries performed, symblepharon and keratinization of the cornea were present in 37 eyes (78.7%) and 10 eyes (21.3%), respectively, thus indicating that most of the eyes were inflicted with end-stage severe OSDs (Table 1).

## Outcomes of Cultivated Oral Mucosal Epithelial Sheet Transplantation

Cultivated autologous oral mucosal epithelial sheets were generated successfully from all patients. In all patients, COMET was performed successfully and no epithelial damage was observed during surgery. Cultivated oral mucosal epithelial sheet transplantation was combined with amniotic membrane transplantation in 34 (72%) of the 47 surgeries and with cataract surgery in 11 eyes (23%; Table 2, available at http://aaojournal.org). In 10 patients

Table 1. Baseline Characteristics in Patients Who Underwent Autologous Cultivated Oral Mucosal Epithelial Transplantation

| | Total | Stevens-Johnson Syndrome | Ocular Pemphigoid | Thermal/Chemical Injury | Others |
|---|---|---|---|---|---|
| No. of COMETs | 47 | 21 | 10 | 7 | 9 |
| Age (yrs) | | | | | |
| Median | 57.0 | 43.0 | 73.5 | 50.0 | 34.0 |
| Range | 9–86 | 14–71 | 62–86 | 27–79 | 9–75 |
| Duration of illness (yrs) | | | | | |
| Median | 12.3 | 17.9 | 3.5 | 6.0 | 5.08 |
| Range | 0.3–40.0 | 3.0–38.0 | 0.3–15.0 | 0.5–24.0 | 0.5–40.0 |
| Prior ocular surgery (%) | 23 (48.9) | 9 (42.9) | 4 (40.0) | 3 (42.9) | 7 (77.8) |
| Planned 2-step operations (%) | 10 (21.3) | 2 (9.5) | 0 (0) | 6 (85.7) | 2 (22.2) |
| Symblepharon (%) | 37 (78.7) | 18 (85.7) | 10 (100.0) | 6 (85.7) | 3 (33.3) |
| Keratinization (%) | 10 (21.3) | 8 (38.1) | 1 (10.0) | 0 (0) | 1 (11.1) |
| Preoperative visual acuity* | | | | | |
| Median | 2.40 | 2.4 | 2.70 | 2.70 | 2.40 |
| Range | 1.11–3.00 | 1.40–3.00 | 1.52–2.70 | 1.22–2.70 | 1.10–2.70 |
| Preoperative ocular surface grading score | | | | | |
| Median | 14.0 | 15.0 | 17.0 | 13.0 | 8.0 |
| Range | 5.0–21.0 | 8.0–21.0 | 10.0–21.0 | 7.0–17.0 | 5.0–19.0 |

COMET = autologous cultivated oral mucosal epithelial transplantation.
*Logarithm of the minimum angle of resolution units.

with severe corneal stromal opacity, a 2-step surgical approach was planned, with COMET followed by penetrating keratoplasty or deep lamellar keratoplasty.[25] Three patients underwent the second surgery before the 24th postoperative week and 5 patients underwent the surgery after the 24th week, but 2 patients did not undergo the second surgery during the study period.

The median preoperative logMAR BCVA was 2.40, and in 31 of the eyes (66%), visual acuity was poorer than 20/2000 (<0.01, logMAR >2). The median preoperative ocular surface grading score was 18.0 (range, 5 to 21). The median patient follow-up period with observation of the primary outcome was 28.7 months after transplantation (range, 6.2 to 85.6 months). Because of heterogeneous etiologic mechanisms, the outcomes in each category are described separately.

## Disease-Specific Outcomes

**Stevens-Johnson Syndrome.** Seventeen patients with SJS underwent COMET (Table 2, available at http://aaojournal.org). The BCVA improved significantly at 4, 12, and 24 weeks after surgery ($P = 0.0005$, $P = 0.0010$, and $P = 0.0117$, respectively; Fig 2A). The ocular surface grading score also improved significantly at 4, 12, and 24 weeks after surgery ($P<0.0001$ for each time point; Fig 2B).

**Ocular Cicatricial Pemphigoid.** Nine patients (10 eyes) with OCP underwent COMET (Table 1). All 9 patients were older than 60 years, older than many of the patients in this study with other diseases (Table 2, available at http://aaojournal.org). The BCVA was improved significantly at the 4th postoperative week ($P = 0.0156$), but this improvement later disappeared (Fig 2A). In contrast, improvement of the ocular surface grading score was sustained throughout the follow-up period ($P = 0.0020$, $P = 0.0020$, and $P = 0.0078$, respectively; Fig 2B).

**Thermal or Chemical Injury.** Seven patients (7 eyes) with thermal or chemical injury underwent COMET. Their BCVA did not change until the 24th postoperative week; however, the ocular surface grading score in all 7 patients improved significantly ($P = 0.0156$ for each visit; Fig 2A, B). Although penetrating keratoplasty or deep lamellar keratoplasty surgery was planned for 6 of these 7 patients, only 2 patients underwent this second surgery before the 24th postoperative week visit. Both the BCVA and ocular surface score improved in all 7 patients after the planned surgeries were performed.

**Others.** Eight other patients underwent COMET: 3 with idiopathic stem cell deficiency, 1 with radiation keratopathy, 1 with graft-versus-host disease, 1 with congenital aniridia, 1 with Salzmanns corneal degeneration, and 1 with drug-toxicity–induced LSCD. In 6 of these 8 patients, BCVA was improved significantly; however, no improvement was seen in 2 of these patients (Table 2, available at http://aaojournal.org; Fig 2A). The 2 patients with no improvement had severe dryness on the ocular surface and had the highest ocular surface grading score in this group. In addition, severe lagophthalmos was present in the 1 patient with radiation keratopathy because of severe lid scarring after irradiation for retinoblastoma. One other patient with graft-versus-host disease had longstanding inflammation on the ocular surface. In both of these 2 cases, keratinization and symblepharon progressed gradually after COMET. Six patients who demonstrated improvement had a low preoperative ocular surface grading score, yet this score was improved considerably in all patients at the 24th postoperative week (Table 2; Fig 2B).

## Critical Visual Improvement Rate

The critical visual improvement rate for SJS, OCP, and thermal or chemical injury was 50.0% (7/14), 42.9% (3/7), and 20.0% (1/5), respectively, although the second planned surgery[25] (penetrating or deep lamellar keratoplasty) had yet to be carried out at the 24th postoperative week in 7 of 10 eyes. The clinical observations on both preoperative and postoperative anterior segment slit-lamp photographs are shown in Figure 3 (available at http://aaojournal.org). All patients demonstrated an improvement in their BVCA to 0.01 or more, from a baseline condition of vision loss.

## Factors Influencing Visual Improvement

Multivariate stepwise logistic regression analysis was used to estimate the factors influencing postoperative visual acuity after COMET, and the following factors were chosen as variables:

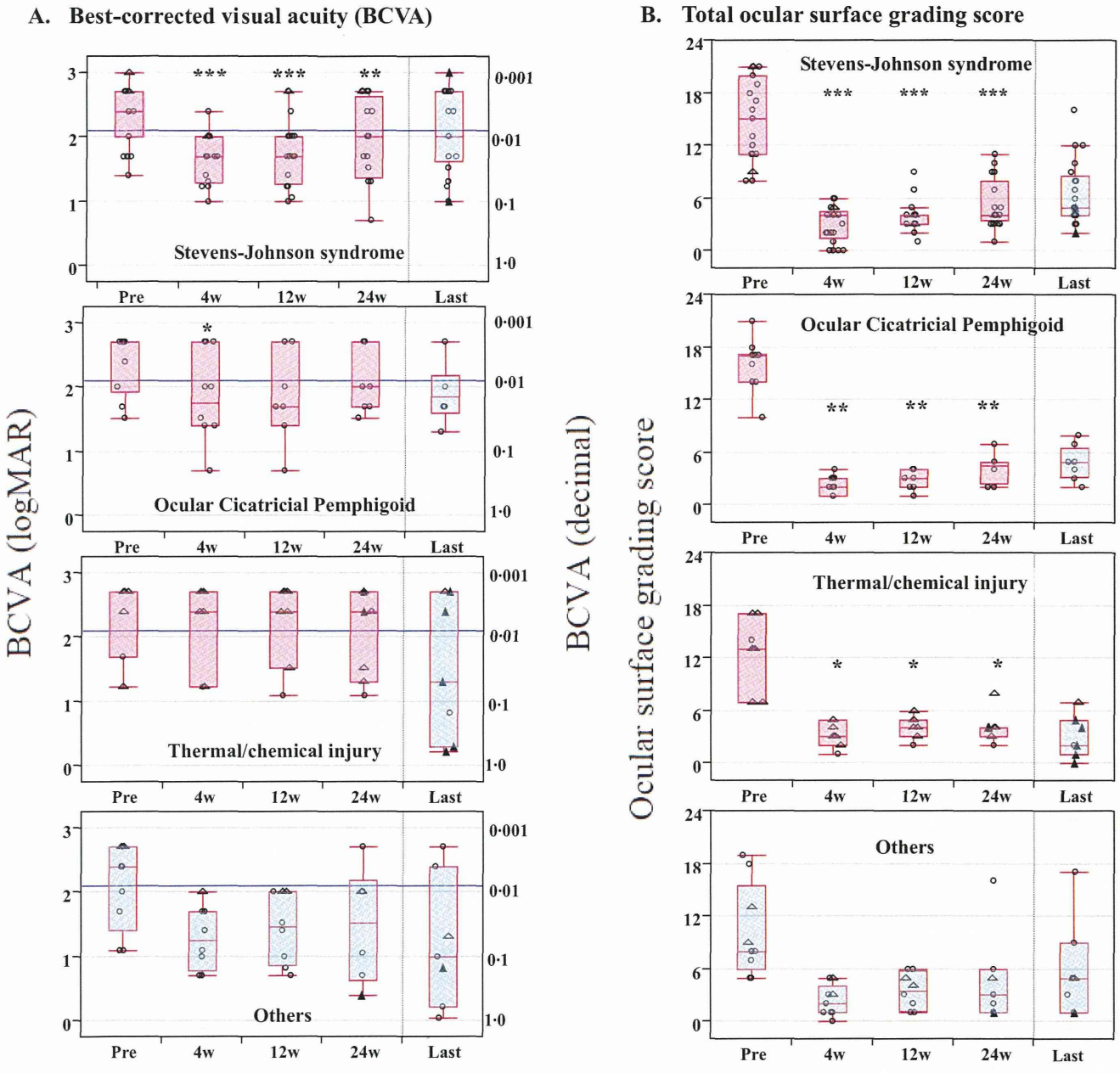



Figure 2. Graphs showing preoperative (Pre) and postoperative clinical outcomes. A, Best-corrected visual acuity (BCVA). The BCVA values for each patient are shown grouped according to the cause of corneal dysfunction: Stevens-Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP), thermal or chemical injury, and others. The change in BCVA from baseline at each visit, except for the last visit, was analyzed using the Wilcoxon signed-rank test in each disease category (SJS, OCP, thermal or chemical injury) except others. Open circles represent cases treated with autologous cultivated oral mucosal epithelial transplantation (COMET) only. Triangles represent cases treated with a planned 2-step surgical combination of COMET followed by penetrating keratoplasty (PK) or deep lamellar keratoplasty (DLKP). Open triangles are before the second operation, and closed triangles are after the second operation. The horizontal line within each box represents the median value, the bottom and top lines of the box represent the 25th and 75th percentiles, respectively, and the horizontal lines below and above the box represent the lowest and highest values, respectively (or are located 1.5 times the interquartile range away from the box). *$P$<0.05, **$P$<0.01, ***$P$<0.001 (2-sided). B, Total ocular surface grading score. Ocular surface grading scores for each patient were calculated and are shown according to each cause of corneal dysfunction: SJS, OCP, thermal or chemical injury, and others. Scores for 8 components of the ocular surface were calculated by the grading system. The total scores before surgery and at the 4th, 12th, and 24th postoperative weeks and at last follow-up examination were calculated. Open circles represent patients treated with COMET only. Triangles represent patients treated with a planned 2-step surgical combination of COMET followed by PK or DLKP. Open triangles are before the second operation, and closed triangles are after the second operation. The change in ocular surface grading score from baseline at each visit, except for the last visit, was analyzed using the Wilcoxon signed-rank test in each disease category (SJS, OCP, thermal or chemical injury) except others. The horizontal line within each box represents the median value, the bottom and top lines of the box represent the 24th and 75th percentiles, respectively, and the horizontal lines below and above the box represent the lowest and highest values, respectively (or are located 1.5 times the interquartile range away from the box). *$P$<0.05, **$P$<0.01, ***$P$<0.001 (2-sided). w = weeks.

Table 3. Summary of Adverse Events in Patients Who Underwent Autologous Cultivated Oral Mucosal Epithelial Transplantation

| Event | Total | Disease Category | | | |
|---|---|---|---|---|---|
| | | *Stevens-Johnson Syndrome* | *Ocular Cicatricial Pemphigoid* | *Thermal or Chemical Injury* | *Others* |
| Hepatic dysfunction | 1 | 1 | | | |
| Drug-induced allergy | 1 | | | | 1 |
| Persistent epithelial defect | 16 | 10 | 3 | 2 | 1 |
| Corneal stromal melting after the epithelial defect | 2 | | 1 | | 1 |
| Ocular infection (keratitis, endophthalmitis) | 2 | 2 | | | |
| Infiltration | 3 | 2 | 1 | | |
| Elevation of IOP resulting from steroid use | 4 | | 1 | 2 | 1 |

IOP = intraocular pressure.
No life-threatening serious adverse events were observed.

disease category, patient age, 2-step surgery, combination with amniotic membrane transplantation, combination with cataract surgery, preoperative logMAR BCVA, and the 8 components of the ocular surface grading system. Corneal neovascularization and symblepharon were found to be correlated significantly with logMAR improvement at the 24th postoperative week ($P = 0.0023$ and $P = 0.0173$, respectively). Visual prognosis was better in the eyes with slight symblepharon than in the eyes with severe symblepharon. In contrast, it was better in the eyes with severe neovascularization than in the eyes with slight neovascularization.

### Adverse Events

A summary of the adverse events in the 40 patients who underwent COMET is shown in Table 3. No life-threatening serious adverse events were observed in any of the transplantations. Systemically, moderate liver dysfunction occurred in 1 patient (2.5%; 95% confidential interval [CI], 0.1 to 13.2), but liver function normalized after the discontinuationof systemic drugs.

Postoperative persistent epithelial defects occurred in the eyes of 16 (40.0%) of the 40 patients (95% CI, 24.9 to 56.7), and rather frequently in the SJS eyes (60.0% of SJS patients). Corneal stromal melting after the epithelial defect occurred in 2 patients (5.0%; 95% CI, 0.6 to 16.9), but neither eye became perforated. All of these patients were treated successfully. Slight to moderate corneal infection occurred in 2 patients (5.0%; 95% CI, 0.6 to 16.9); however, both patients healed without scarring. A suspected infection with cell infiltration on the cornea[28] occurred in 3 patients, yet in each patient, it healed within 1 week after receiving a topical instillation of antibiotics. Although a slight elevation of intraocular pressure resulting from steroid use was seen in 4 patients (10.0%; 95% CI, 2.8 to 23.7), this returned to the normal range after reduction of the steroid dose. None of the patients required glaucoma surgery.

## Discussion

Severe OSD has proven to be one of the most difficult disorders to treat, and for many patients, vision loss is the end result.[29,31] Keratoprosthesis surgery is one possible way to obtain visual improvement in end-stage severe OSDs; however, serious complications such as endophthalmitis, glaucoma, and tissue melting can arise, especially in SJS or OCP, and can lead to permanent vision loss.[32,33]

At the beginning of 2002, the authors performed ocular surface reconstruction using tissue-engineered autologous oral mucosal epithelial sheets for the first time.[23] In a report of the initial results from the first 12 cases, the successful long-term engraftment of cultivated oral mucosal cells and their transparency was confirmed.[24] Since then, COMET has been used to treat OSD patients, with careful consideration of the surgical indications.[24–26,34] The authors performed 86 COMET operations between 2002 and the end of 2008 for visual improvement, epithelialization of persistent epithelial defects, or conjunctival reconstruction (Fig 1).

In this study, the clinical efficacy and safety of 47 COMETs were evaluated for visual improvement. In 23 eyes (48.9%), previous ocular surgery such as corneal transplantation or amniotic membrane transplantation already had been carried out unsuccessfully at other hospitals. Symblepharon was involved in 37 eyes (78.7%) and keratinization was involved in 10 eyes (21.3%). Symblepharon indicates conjunctival involvement, and pathologic keratinization means that the eye is at the end stage of a severe OSD with chronic inflammation.[3,35] Most of these eyes had severe tear deficiency, which is an important prognostic parameter for surgical outcome.[36] Although such eyes commonly are considered to have contraindications for ocular surface reconstruction, COMET offered substantial visual improvement even for patients with such advanced disease.

In more than half of the eyes, preoperative visual acuity was limited to counting fingers or hand movements. It is striking that such patients were able to come to the hospital without assistance during the 24 weeks after undergoing COMET. For this reason, critical visual improvement rate is proposed as a clear end point for measuring surgical outcome. Considering that most of the eyes in this study were at the end stage of a severe OSD, these results are very favorable and encouraging.

In this study, the preoperative ocular surface grading score was higher (more diseased) in patients with SJS and OCP than in those with thermal or chemical injuries or other

diseases. It should be noted that visual improvement was statistically significant in SJS. In contrast, visual acuity was not improved at the 24th postoperative week in patients with thermal or chemical injury, despite the improvement in total ocular surface grading score. The corneal stroma was damaged severely in most cases of thermal or chemical injury, and such patients obtained visual improvement after undergoing the planned second surgery with penetrating keratoplasty or deep lamellar keratoplasty. In general, the prognosis of penetrating or deep lamellar keratoplasty alone for severe OSDs is very poor.[2] However, the findings of this study show that patients with severe OSDs with corneal stromal opacity can obtain visual improvement after undergoing the surgical combination of COMET and penetrating or deep lamellar keratoplasty.

Best-corrected visual acuity was not improved at the 24th postoperative week in patients with OCP, despite significant improvement of the ocular surface grading score. Because OCP is a progressive autoimmune disease, pathologic keratinization or thickening of the epithelium occurred readily after COMET, thus disrupting visual acuity.

No serious systemic complications occurred in any of the patients. The incidence of postoperative persistent epithelial defects was relatively high, yet still similar to or lower than that reported with other therapies.[6,36–38] Considering that corneal perforation is a common complication after corneal reconstruction in severe OSDs,[38–40] it is noteworthy that no perforation occurred and that none of the eyes demonstrated vision loss after COMET. Ocular surface reconstruction with a combination of COMET and amniotic membrane transplantation was needed to achieve the total replacement of cicatrized tissue. Because cultured epithelial cells on amniotic membrane attach to a basement membrane with hemidesmosomes,[22] these cells can avoid being dropped off and actually survive, regardless of an unstable tear film and the mechanical trauma of blinking. When used as the substrate for oral mucosal cells, amniotic membrane may play a role in protecting the cornea from melting.

Multivariate stepwise logistic regression analysis showed that symblepharon and neovascularization are prognostic factors for visual improvement. Although disease-specific outcomes showed different patterns as described above, disease category was not related to visual prognosis. However, the sample size may be too small to perform such subgroup analyses. Multivariate stepwise logistic regression analysis also was performed for all 86 surgeries to determine the factors influencing persistent epithelial defects. Having SJS and a very low tear meniscus were the prognostic factors for persistent epithelial defects ($P = 0.0204$ and $P = 0.0388$, respectively). Thus, it is likely that both the disease category and dryness of the eye influenced the prognosis.

Long-term ocular surface appearance was examined in 17 of the 72 patients with a follow-up of more than 3 years.[34] No further surgery was carried out in these patients. The ocular surface in each case became stable from 6 months after COMET, with a gradual reduction in corneal neovascularization,[34] as others have reported in similar studies.[40] Moreover, postoperative invasion of conjunctival tissue and symblepharon formation was inhibited significantly for more than 3 years.[34] Deep lamellar or penetrating keratoplasty was performed for the patients with corneal stromal opacity after the stabilization of the ocular surface (as the second step of a 2-step surgical combination), in most cases from 24 weeks after COMET.

After COMET, upper or lower eyelid cicatricial entropion with various degrees of tarsal-plate atrophy sometimes was found. In cases with an eyelid abnormality, eyelid surgery was performed to correct entropion, trichiasis, or lagophthalmos. Eyelid condition is an important factor for maintaining ocular surface stability, as well as for avoiding complications such as infection or persistent epithelial defects.

In conclusion, the findings of this retrospective study showed that long-term visual improvement can be obtained in end-stage severe OSDs with complete LSCD and that COMET offered substantial visual improvement even for patients with severe tear deficiency. The findings also showed that patients with corneal blindness resulting from severe OSDs such as SJS benefited from critical improvement of visual acuity.

**Acknowledgments.** The authors thank Dr. Shin Kawamata of the Foundation for Biological Research and Innovation and Dr. Kazunori Takeda, Dr. Hiroaki Kato, Dr. Hiroshi Tanaka, Dr. Yuji Yamamoto, and Dr. Takahiro Yamawaki of Kyoto Prefectural University of Medicine for data collection.

## References

1. Kinoshita S, Adachi W, Sotozono C, et al. Characteristics of the human ocular surface epithelium. Prog Retin Eye Res 2001;20:639–73.
2. Tugal-Tutkun I, Akova YA, Foster CS. Penetrating keratoplasty in cicatrizing conjunctival diseases. Ophthalmology 1995;102:576–85.
3. Kawasaki S, Nishida K, Sotozono C, et al. Conjunctival inflammation in the chronic phase of Stevens-Johnson syndrome. Br J Ophthalmol 2000;84:1191–3.
4. Wall V, Yen MT, Yang MC, et al. Management of the late ocular sequelae of Stevens-Johnson syndrome. Ocul Surf 2003;1:192–201.
5. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. Ophthalmology 1989;96:709–22.
6. Tsubota K, Satake Y, Kaido M, et al. Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation. N Engl J Med 1999;340:1697–703.
7. Koizumi N, Inatomi T, Suzuki T, et al. Cultivated corneal epithelial transplantation for ocular surface reconstruction in acute phase of Stevens-Johnson syndrome. Arch Ophthalmol 2001;119:298–300.
8. Koizumi N, Inatomi T, Suzuki T, et al. Cultivated corneal epithelial stem cell transplantation in ocular surface disorders. Ophthalmology 2001;108:1569–74.
9. Nakamura T, Inatomi T, Sotozono C, et al. Successful primary culture and autologous transplantation of corneal limbal epithelial cells from minimal biopsy for unilateral severe ocular surface disease. Acta Ophthalmol Scand 2004;82:468–71.
10. Kinoshita S, Koizumi N, Nakamura T. Transplantable cultivated mucosal epithelial sheet for ocular surface reconstruction. Exp Eye Res 2004;78:483–91.
11. Kinoshita S, Koizumi N, Sotozono C, et al. Concept and clinical application of cultivated epithelial transplantation for ocular surface disorders. Ocul Surf 2004;2:1–33.
12. Nishida K, Yamato M, Hayashida Y, et al. Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. N Engl J Med 2004;351:1187–96.

13. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of autologous serum-derived cultivated corneal epithelial equivalents for the treatment of severe ocular surface disease. Ophthalmology 2006;113:1765–72.
14. Ang LP, Sotozono C, Koizumi N, et al. A comparison between cultivated and conventional limbal stem cell transplantation for Stevens-Johnson syndrome. Am J Ophthalmol 2007;143: 178–80.
15. Rama P, Matuska S, Paganoni G, et al. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med 2010;363:147–55.
16. Tseng SC, Espana EM, Kawakita T, et al. How does amniotic membrane work? Ocul Surf 2004;2:177–87.
17. Tseng SC, Prabhasawat P, Lee SH. Amniotic membrane transplantation for conjunctival surface reconstruction. Am J Ophthalmol 1997;124:765–74.
18. Solomon A, Espana EM, Tseng SC. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. Ophthalmology 2003;110:93–100.
19. Tsubota K, Satake Y, Ohyama M, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. Am J Ophthalmol 1996;122:38–52.
20. Tsai RJ, Li LM, Chen JK. Reconstruction of damaged corneas by transplantation of autologous limbal epithelial cells. N Engl J Med 2000;343:86–93.
21. Koizumi N, Inatomi T, Quantock AJ, et al. Amniotic membrane as a substrate for cultivating limbal corneal epithelial cells for autologous transplantation in rabbits. Cornea 2000;19:65–71.
22. Nakamura T, Endo K, Cooper LJ, et al. The successful culture and autologous transplantation of rabbit oral mucosal epithelial cells on amniotic membrane. Invest Ophthalmol Vis Sci 2003;44:106–16.
23. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of cultivated autologous oral mucosal epithelial cells in patients with severe ocular surface disorders. Br J Ophthalmol 2004; 88:1280–4.
24. Inatomi T, Nakamura T, Koizumi N, et al. Midterm results on ocular surface reconstruction using cultivated autologous oral mucosal epithelial transplantation. Am J Ophthalmol 2006; 141:267–75.
25. Inatomi T, Nakamura T, Kojyo M, et al. Ocular surface reconstruction with combination of cultivated autologous oral mucosal epithelial transplantation and penetrating keratoplasty. Am J Ophthalmol 2006;142:757–64.
26. Ang LP, Nakamura T, Inatomi T, et al. Autologous serum-derived cultivated oral epithelial transplants for severe ocular surface disease. Arch Ophthalmol 2006;124:1543–51.
27. Sotozono C, Ang LP, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. Ophthalmology 2007;114: 1294–302.
28. Sotozono C, Inagaki K, Fujita A, et al. Methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis* infections in the cornea. Cornea 2002; 21:S94–101.
29. Samson CM, Nduaguba C, Baltatzis S, Foster CS. Limbal stem cell transplantation in chronic inflammatory eye disease. Ophthalmology 2002;109:862–8.
30. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology 2002;109:1159–66.
31. Sotozono C, Ueta M, Koizumi N, et al. Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. Ophthalmology 2009;116:685–90.
32. Khan B, Dudenhoefer EJ, Dohlman CH. Keratoprosthesis: an update. Curr Opin Ophthalmol 2001;12:282–7.
33. Liu C, Okera S, Tandon R, et al. Visual rehabilitation in end-stage inflammatory ocular surface disease with the osteo-odonto-keratoprosthesis: results from the UK. Br J Ophthalmol 2008;92:1211–7.
34. Nakamura T, Takeda K, Inatomi T, et al. Long-term results of autologous cultivated oral mucosal epithelial transplantation in the scar phase of severe ocular surface disorders. Br J Ophthalmol 2011;95:942–6.
35. Tanioka H, Kawasaki S, Sotozono C, et al. The relationship between preoperative clinical scores and immunohistological evaluation of surgically resected tissues in chronic severe ocular surface diseases. Jpn J Ophthalmol 2010;54:66–73.
36. Shimazaki J, Shimmura S, Fujishima H, Tsubota K. Association of preoperative tear function with surgical outcome in severe Stevens-Johnson syndrome. Ophthalmology 2000;107:1518–23.
37. Turgeon PW, Nauheim RC, Roat MI, et al. Indications for keratoepithelioplasty. Arch Ophthalmol 1990;108:233–6.
38. Ma DH, Kuo MT, Tsai YJ, et al. Transplantation of cultivated oral mucosal epithelial cells for severe corneal burn. Eye (Lond) 2009;23:1442–50.
39. Shimazaki J, Aiba M, Goto E, et al. Transplantation of human limbal epithelium cultivated on amniotic membrane for the treatment of severe ocular surface disorders. Ophthalmology 2002;109:1285–90.
40. Satake Y, Higa K, Tsubota K, Shimazaki J. Long-term outcome of cultivated oral mucosal epithelial sheet transplantation in treatment of total limbal stem cell deficiency. Ophthalmology 2011;118:1524–30.

## Footnotes and Financial Disclosures

Originally received: March 10, 2012.
Final revision: July 17, 2012.
Accepted: July 18, 2012.
Available online: October 16, 2012. Manuscript no. 2012-353.

[1] Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

[2] Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan.

Presented at: American Academy of Ophthalmology Annual Meeting, October 2011, Orlando, Florida.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported in part by a Grant-in-aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare, Tokyo, Japan; and a Research Grant of the Coordination, Support and Training Program for Translational Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

Correspondence:
Chie Sotozono, MD, PhD, Department of Ophthalmology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Hirokoji-agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto 602-0841, Japan. E-mail: csotozon@koto.kpu-m.ac.jp.

特集 皮膚科 *and/or* 眼科　目のまわりの病気とその治療

総論

J Visual Dermatol 12: 110-112, 2013

# 眼科・皮膚科の境界領域となる疾患とともに診るべき疾患

外園　千恵

Key words　感染，悪性腫瘍，重症アトピー性皮膚炎，Stevens-Johnson 症候群

## はじめに

まぶたの疾患は，眼科・皮膚科の境界領域となる疾患であり，どちらの科にもかかりうる疾患である．また，アトピー性皮膚炎の眼合併症，Stevens-Johnson 症候群など，皮膚科と眼科が連携して治療にあたらねばならない疾患も存在する．本項では，眼科と皮膚科が知識を共有すべき疾患として，麦粒腫・涙嚢炎などの感染症，目のまわりの腫瘍性疾患，ヘルペス・帯状疱疹，皮膚粘膜症候群をとりあげる．

## 目のまわりの感染

目のまわりの感染は，涙嚢，涙小管，あるいはマイボーム腺といった眼付属器に生じやすい．麦粒腫が大きさの割に強い痛みを伴いやすいのに対して，涙小管炎と涙嚢炎は自覚症状に乏しく，慢性に経過することが多い．慢性涙嚢炎が，適切な治療がなされないままに放置されると突然に急性涙嚢炎を生じ，眼周囲のみならず顔面半分を腫らして救急受診し，感染の主体がどこであるかわかりにくいことがある．また涙小管炎は，「まぶたが腫れている」「軽い眼脂が続くが，抗菌点眼薬を使っても治らない」という症状で，確定診断されないままに漫然とした経過観察が行われがちである（図 1）．涙小管炎，涙嚢炎ともに，根治するには手術治療が必要であることから，的確に診断したい疾患である．

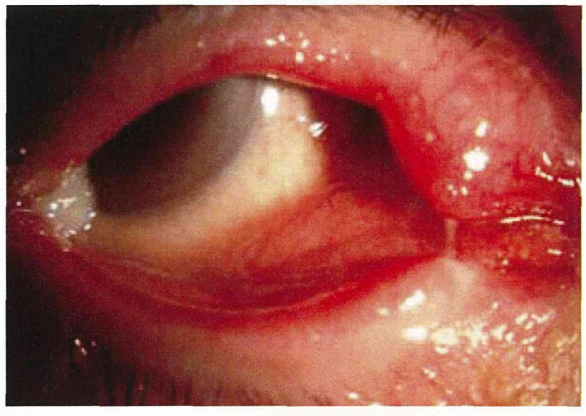


図 1　涙小管炎
慢性結膜炎として紹介受診．すべての抗菌点眼薬を中止して経過観察したところ，上涙点付近の発赤と腫脹を生じた．上涙点より膿と菌石を排出し，治癒した．

## 目のまわりの腫瘍

目のまわりの腫瘍にはさまざまなものがあるが，基底細胞癌と脂腺癌を見逃さないようにしたい．良性の慢性肉芽腫性炎症性疾患である霰粒腫と，悪性腫瘍である脂腺癌は，自覚症状，まぶたの所見のいずれも似ており，眼科医であっても両者の鑑別が困難であることが少なくない．脂腺癌は結節が明らかな nodular type（図 2）と，結節の境界がわかりにくい diffuse type（図 3）とがあり，diffuse type の方はさらに診断がむずかしい．まぶたを翻転して結膜側を観察すると，腫瘍の大きさと拡がりがわかる場合がある．悪性腫瘍の場合には緩徐に増大傾向を示す．丁寧に経過をみて，「もしかしたら悪性かも」と疑うことが大切である．

## 重症アトピー性皮膚炎の眼合併症

重症アトピー性皮膚炎はさまざまな眼合併症を生じ，それらの治療はあまりにもむずかしいことが多い．

アトピー性皮膚炎や春季カタルなど，高度アレルギー性結膜炎に伴う難治な角膜疾患としてシールド潰瘍（図 4a）があり，アレルギーに対する治療と，感染予防を必要とする．合併症である白内障，緑内障や網膜剥離などに対して眼科手術の回数が重なるうちに，角膜内皮細胞数が減少して水疱性角膜症となり，水疱性角膜症にさらに MRSA 感染を生ずる（図 4b）など，ドミノ倒し的に悪化していくことがある．

円錐角膜は通常は角膜移植の予後が良好であるが，重症アトピー性皮膚炎では角膜移植後の眼表面の炎症をコ

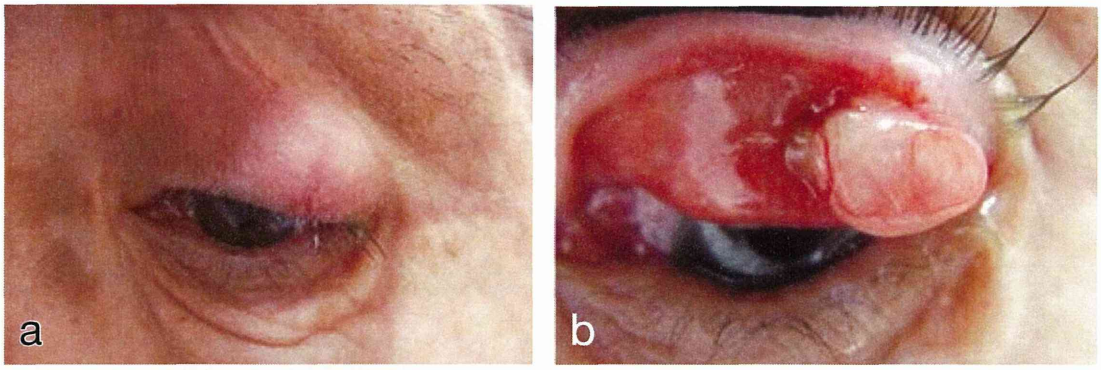



図2 脂腺癌，nodular type
(a) 皮膚側．上眼瞼の軽度発赤と腫脹を認める．
(b) 結膜側．結節性の隆起が明らかであり，凹凸強い硬結であることから悪性が疑われる．

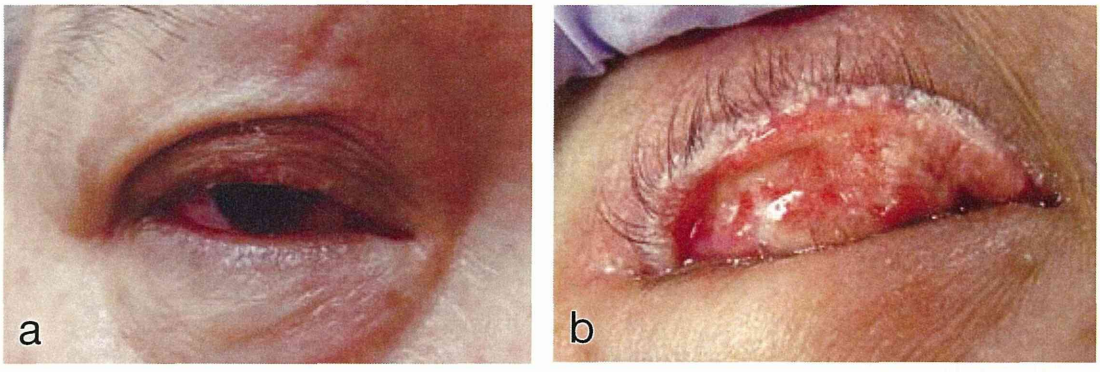



図3 脂腺癌，diffuse type
(a) 皮膚側．上眼瞼の軽度発赤と瞼縁不整を認める．
(b) 結膜側．びまん性に拡がる多数の小結節を認め，健常部分との境界は不明瞭である．

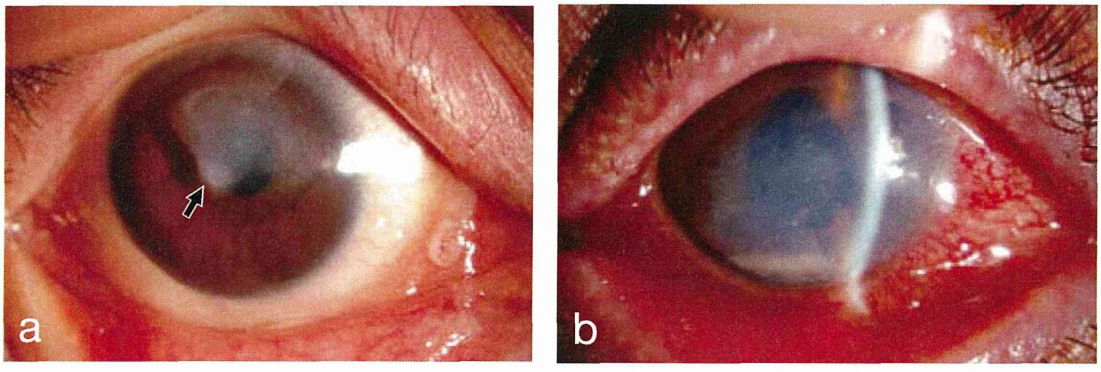



図4 重症アトピー性皮膚炎に伴って生じた角膜障害
(a) シールド潰瘍．眼瞼結膜と接する角膜中央から上方にかけて潰瘍を認める（➡の白い部分）．
(b) 水疱性角膜症．MRSA 角膜炎を合併し，前房蓄膿がみられる．

ントロールしにくく，拒絶反応や感染を合併しやすい．眼合併症が重症であるほど，眼科治療に加えて，皮膚科専門医によるアトピー性皮膚炎の管理が重要となるが，患者に尋ねると自己判断で皮膚科通院を止めていたり，民間療法に多額を費やしていたりする．皮膚科と眼科が連携して，重症アトピー性皮膚炎に伴う眼障害の予後を向上させたい．

## 帯状疱疹

帯状疱疹は皮膚科ではよく診る疾患であり，眼合併症は少ないという印象ではないかと思われる．実際に眼科紹介を受けても，何も問題なく経過することも多いが，眼球運動障害や角膜ヘルペス，虹彩毛様体炎を生じ，長びくことがある．皮疹消褪後にも注意を要する．

## 皮膚粘膜症候群— Stevens-Johnson 症候群と眼類天疱瘡

角膜疾患のうちもっとも難治な部類に属するのが，皮膚粘膜症候群であり，具体的には Stevens-Johnson 症候群と眼類天疱瘡がある．いずれも角膜上皮ステムセル疲弊を生じて，まぶたと眼球の癒着（瞼球癒着）と高度の角膜混濁を来すが，通常の角膜移植では治すことができない（図 5）．

Stevens-Johnson 症候群は発症時から眼科も治療に加わり，角膜上皮欠損や偽膜の有無をチェックし，これ

特集 皮膚科 *and/or* 眼科　目のまわりの病気とその治療

# 総論　眼科・皮膚科の境界領域となる疾患とともに診るべき疾患

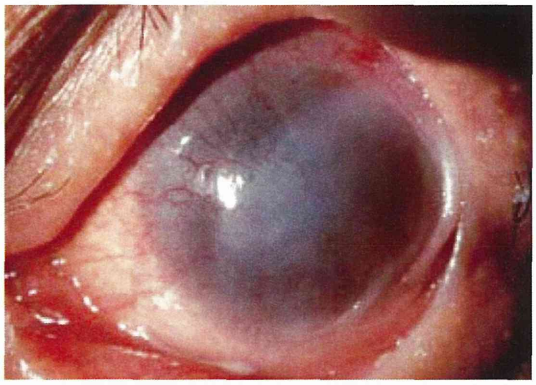
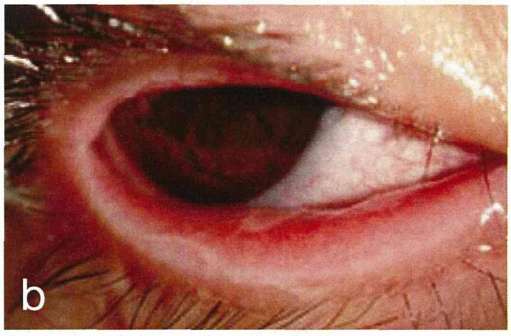


図5　Stevens-Johnson 症候群慢性期の眼障害
高度ドライアイに対して人工涙液の頻回点眼を要し，高度角膜混濁のために視力障害が著しい．このような眼障害が後遺症となる患者は，重症薬疹であることの確定診断が遅いか，全身状態が重篤などの理由で発症初期に眼科受診されていないことが多い．

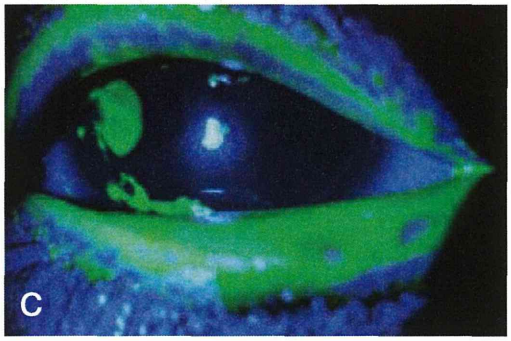




図6　Stevens-Johnson 症候群 急性期の眼障害
10歳，女児．高熱と皮疹を生じた翌日に眼科を受診し，Stevens-Johnson 症候群を疑われて当院に紹介された．
(a) 眼周囲の所見．結膜充血は軽度である．
(b) 細隙灯顕微鏡での所見．高熱のため診察がむずかしいが，何とか細隙灯顕微鏡で観察．皮膚粘膜移行部である眼瞼縁に軽度の偽膜を認める．
(c) フルオレセイン染色像．角膜びらんを認めた．眼表面に病変を伴うことがわかり，ステロイドパルスとベタメタゾン頻回点眼を実施し，眼後遺症を伴わず治癒した．

らがあれば全身に加えて眼局所の消炎と感染予防を行うことが，予後向上のために重要である．

SJS 発症時に肉眼的にみた結膜充血が軽度であっても，角膜びらんを伴うことがある（図6）．角膜びらんを伴う場合には，急速に眼所見が悪化する可能性があり，眼障害を後遺症としないように全身と眼局所の両方の治療を必要とする．全身が重篤なほどに，眼合併症に注意を払いにくいが，皮膚科初診日から眼科に紹介いただきたい．

また眼類天疱瘡（眼型粘膜天疱瘡）は本人の気づかぬうちに，粘膜の癒着が進行し，白内障手術が契機で急性増悪を来すことがある．他の粘膜症状が内科や耳鼻咽喉科で加療され，総合的に診断されていない場合もあり，関連診療科の連携と早期発見が今後の課題である．

## おわりに

その他におさえておかねばならないのが，眼瞼に限局する浮腫・紅斑であり，接触皮膚炎や皮膚筋炎，粘液水腫などがあげられるが，本特集では，とくに接触皮膚炎と，薬剤が皮膚あるいは眼粘膜におよぼす影響についてとりあげた．

また，皮膚外用薬と点眼薬にはさまざまな種類があるが，それらの効果的な使い方や副作用については，科間で意外と知識が共有されていない．とくに新しい薬剤は，名称を聞いても何の薬剤がわからないことがある．局所溶剤について，各科エクスパートにまとめていただいた．

本著の企画，編集を通じ，眼科と皮膚科の連携を要する疾患は，日常的な疾患から難治あるいは稀な疾患まで，広く存在することを再認識した．本特集を診療現場の傍らに置いていただき，ご活用いただければ幸いである．

外園　千恵　Sotozono, Chie

京都府立医科大学眼科
〒602-0841　京都市上京区川原町通広小路上ル
FAX：075-251-5663

Visual Dermatology Vol.12 No.2 2013

特集 皮膚科 *and/or* 眼科　目のまわりの病気とその治療

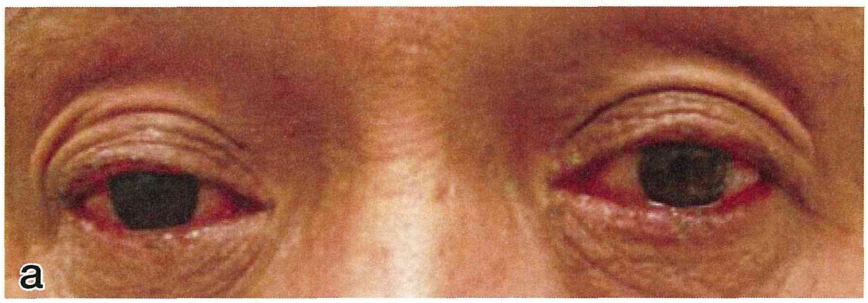
case 16 Part4. 知っておきたい合併症

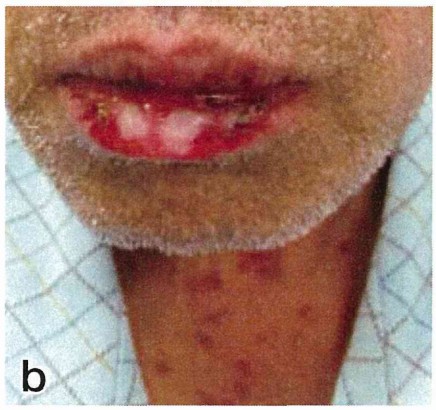
J Visual Dermatol 12: 172-174, 2013

# Stevens-Johnson 症候群の眼障害

上田　真由美，外園　千恵

Key words Stevens-Johnson 症候群（SJS），中毒性皮膚壊死融解症（TEN），眼障害




64 歳，男性．2012 年 11 月初診
結膜炎と感冒様症状，発熱を生じ，それに対して抗菌薬ならびに解熱鎮痛薬等を処方されて，その翌日に SJS を発症した．(a) 充血と (b) 口唇・口腔内のびらん，発疹を認める．

重症薬疹には，重篤な眼合併症を生じ，最悪の場合，失明に至る疾患が存在する．それは，Stevens-Johnson 症候群（SJS）とその進行型である中毒性表皮壊死融解症（TEN）である．SJS/TEN における眼合併症率は，約 60％と報告されており，SJS と TEN による眼所見に違いはない．

本症例は，発症 2 日前に，充血・眼脂と咽頭痛を認め，眼科を受診し，結膜炎と診断を受けた．翌日，37.6℃の発熱を生じ内科を受診，抗菌薬と解熱鎮痛薬を処方され内服した．その翌日夕方に，腹部を中心に水疱を伴う紅斑および口腔内びらんを認め，SJS と診断された．

## 鑑別疾患

偽膜形成，角膜上皮欠損の眼所見から，ウイルス性結膜炎の一つである流行性角結膜炎と診断されることがある．しかし，熱発，発疹や口腔内びらんより鑑別は可能である．

SJS/TEN と診断される症例には，眼合併症を伴わない症例も含まれるが，皮膚に発疹が生じた時点で，重篤な両眼性の結膜炎（充血）を認める場合は，眼後遺症を生じる可能性が高く，眼科医と連携して治療を進めていく必要がある（TEN では SJS 進展型で眼合併症を伴うことが多い）．

## 臨床診断

重篤な眼合併症を伴う SJS/TEN の特徴は，発症時に，偽膜を伴う両眼性の急性結膜炎（偽膜性結膜炎），口唇・口腔内のびらん，爪囲炎を認めることである．また，感冒様症状が薬剤投与に先行することが多い（表 1，2）．

## 治療と経過

本症例では，発疹の悪化に伴い眼所見も悪化した．ステロイドパルス療法後も眼所見（偽膜性結膜炎ならびに角膜上皮欠損）は軽快しなかった．そのため，眼局所のベタメタゾン点眼を昼間 1 時間毎（夜間以外）まで回数を増やし，その結果，偽膜性結膜炎ならびに角膜上皮欠損は軽快傾向となった．

## 本症例のポイント

本症例では，発症時は結膜炎はそれほど重篤ではなかったが，ステロイドパルス療法にもかかわらず重症化した．眼所見を観察しながら，眼局所のベタメタゾン点

表 1　Stevens-Johnson 症候群（SJS）診断基準

**概念**
発熱を伴う口唇，眼結膜，外陰部などの皮膚粘膜移行部における重症の粘膜疹および皮膚の紅斑で，しばしば水疱，表皮剥離などの表皮の壊死性障害を認める．原因の多くは，薬剤である．

**主要所見（必須）**
1. 皮膚粘膜移行部の重篤な粘膜病変（出血性あるいは充血性）がみられること．
2. しばしば認められるびらんもしくは水疱は，体表面積の 10% 未満であること．
3. 発熱（38℃以上）．

**副所見**
4. 皮疹は非典型的ターゲット状多形紅斑．
5. 角膜上皮障害と偽膜形成のどちらかあるいは両方を伴う両眼性の非特異的結膜炎．
6. 病理組織学的に，表皮の壊死性変化を認める．

ただし，TEN への移行があり得るため，初期に評価を行った場合には，極期に再評価を行う．
主要項目の 3 項目をすべて満たす場合 SJS と診断する．

表 2　中毒性表皮壊死症（TEN）診断基準

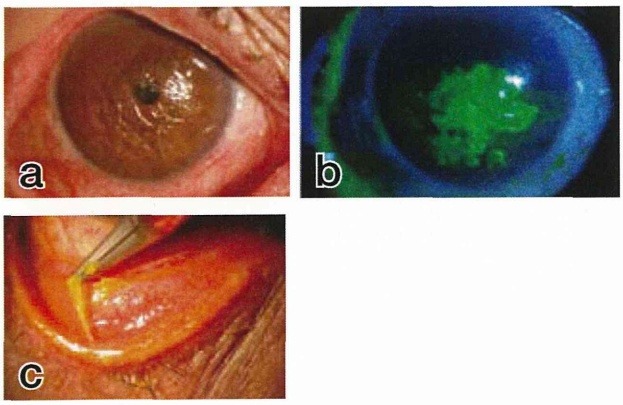
**概念**
広範囲な紅斑と，全身の 10% 以上の水疱，表皮剥離・びらんなどの顕著な表皮の壊死性障害を認め，高熱と粘膜疹を伴う．原因の大部分は薬剤である．

**主要所見（必須）**
1. 体表面積の 10% を越える水疱，表皮剥離・びらんなどの表皮の壊死性障害．
2. ブドウ球菌性熱傷様皮膚症候群（SSSS）を除外できる．
3. 発熱（38℃以上）．

**副所見**
4. 皮疹は広範囲のびまん性紅斑および斑状紅斑である．
5. 粘膜疹を伴う．眼症状は，角膜上皮障害と偽膜形成のどちらかあるいは両方を伴う両眼性の非特異的結膜炎．
6. 病理組織学的に，顕著な表皮の壊死を認める．

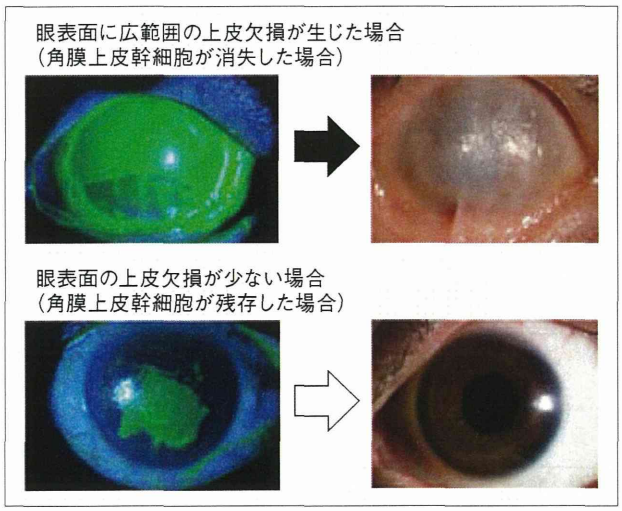
主要 3 項目のすべてを満たすものを TEN とする．

○サブタイプの分類
1 型：SJS 進展型（TEN with spots）*1
2 型：びまん性紅斑進展型（TEN without spots）*2
3 型：特殊型
*1　SJS 進展型 TEN（TEN with spots あるいは TEN with macules）：顔面のむくみ，発熱，結膜充血，口唇びらん，咽頭痛を伴う多形紅斑様皮疹
*2　びまん性紅斑型 TEN（TEN without spots あるいは TEN on large erythema）：発熱を伴って急激に発症する広汎な潮紅とびらん




入院翌日の眼所見
(a) 眼球結膜の高度な充血，角膜の不整な反射は角膜上皮欠損によるものである．
(b) 蛍光色素により染色し，フィルターを通してみると黄色に染まった角膜上皮欠損が確認できる．
(c) 眼瞼結膜に偽膜を伴った高度な充血を認める（写真では蛍光色素の染色により黄色く染まった偽膜を除去している）．

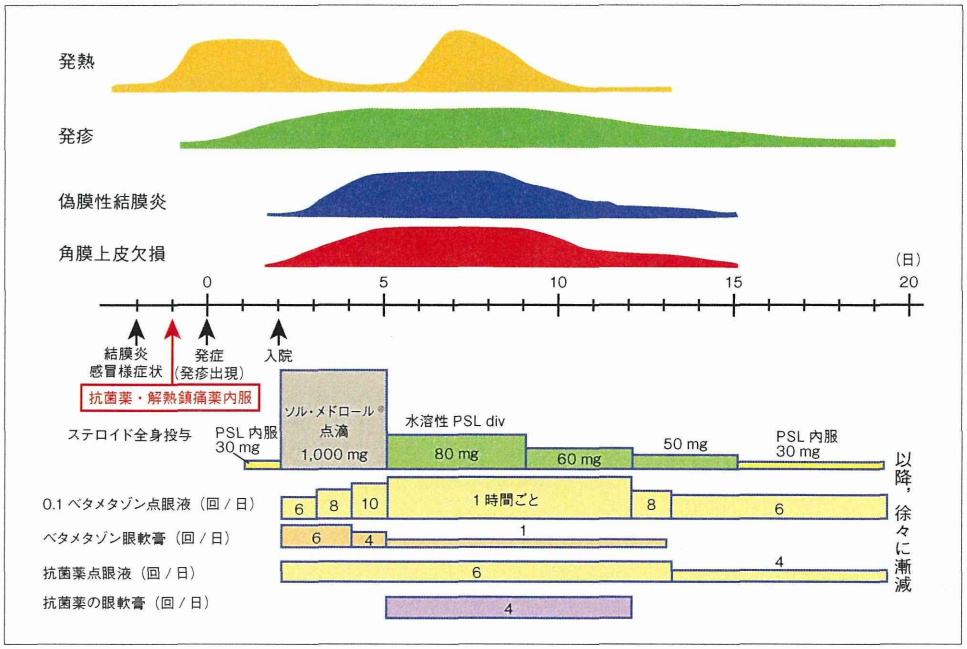
眼回数を増やすことで角膜上皮びらんが治癒し，眼後遺症としてはドライアイを残すのみで落ち着いた．しかし，十分に眼表面の消炎ができなかった場合，重篤な視力障害が生じた可能性もある．




急性期における眼表面の上皮欠損
上：急性期に眼表面に広範囲の上皮欠損が生じた場合，角膜上皮幹細胞は消失し，角膜は結膜組織に覆われて，著しい視力障害を生じる．
下：急性期の眼表面の上皮欠損が少ない場合は，角膜上皮幹細胞は残存し，角膜は透明な角膜上皮で修復されれ，視力障害は生じない．

特集 皮膚科 *and/or* 眼科　目のまわりの病気とその治療

# case 16 Stevens-Johnson 症候群の眼障害




治療ならびに発熱・発疹・偽膜性結膜炎・角膜上皮欠損の経過

急性期に眼表面に広範囲の上皮欠損が生じた場合，角膜上皮幹細胞は消失し，最終的には角膜は結膜組織に覆われて，著しい視力障害を生じる．一方，急性期の眼表面の上皮欠損を最小限に抑え，角膜上皮幹細胞を残存させることができた場合は，角膜は透明な角膜上皮で修復され，角膜の透明性は維持され視力障害は生じない．急性期における眼表面の十分な消炎は，角膜上皮幹細胞の残存，つまり視力障害の防止に，きわめて重要である．

本論文は厚生労働科学研究費補助金（難治性疾患克服研究事業）の援助を受けた．

**皮膚科からのコメント**

**Q**：SJS/TEN では，発症初期からの皮膚科医と眼科医との連携が必須である．薬疹で皮膚科を受診した患者の SJS/TEN を疑うべき眼所見について，皮膚科医にも可能な問診や診察での所見について教えて下さい．（加藤 則人）

**A**：結膜充血を認めれば，眼合併症を伴う SJS ならびに SJS 進展型 TEN の可能性がありますので，躊躇せずに眼科医へご紹介ください．結膜充血があっても眼表面の上皮欠損を認めなければ，眼合併症を伴う SJS/TEN ではない可能性が高いですが，これについては，眼科専門医でなければ判断がむずかしいと思います．結膜充血を認めれば，ぜひ眼科医への紹介をお願いいたします．（上田 真由美）

上田　真由美　Ueta, Mayumi

京都府立医科大学眼科
〒 602-8566　京都市上京区河原町通広小路上ル梶井町 465
FAX：075-251-5663

外園　千恵　Sotozono, Chie

京都府立医科大学眼科