

Original article

Ocular manifestations and complications of Stevens–Johnson syndrome and toxic epidermal necrolysis: an Asian series*

Background: To describe the acute and late ocular manifestations and complications in toxic epidermal necrosis (TEN) and Stevens–Johnson syndrome (SJS), and identify predictors for development of late complications.

Methods: Cases of TEN and SJS during a 9-year period were included. Patients with ocular involvement were reviewed for acute ocular complications. Patients with a minimum 6 months follow-up were reviewed for late complications. Records were reviewed for their demographics, etiology, and severity of ocular involvement.

Results: There were 117 patients with a mean age of 52.2 ± 18.6 years. Eighty-one of these (69%) had acute ocular involvement. This was mild in 40%, moderate in 25% and severe in 4%. Adverse drug reactions were the predominant cause. Patients with thrombocytopenia had more severe acute ocular involvement. Forty-four patients had a minimum 6 months of follow-up and half developed late complications. Severe dry eyes and trichiatric lashes were the commonest late complications. Patients treated with topical antibiotic were more likely to have late complications, particularly dry eyes. There was no difference in the severity of acute eye involvement or late complications when SJS and TEN patients were compared. The severity of the acute ocular disease and abnormal laboratory tests were not found to be the significant risk factors of late complications.

Conclusions: Ocular involvement is common in SJS and TEN and can be severe and blinding. The severity of acute ocular complications does not predict late complications. The diagnosis of TEN does not imply a more severe ocular involvement or increased frequency of late ocular complications compared with SJS. Care should be taken even in mild cases. Appropriate intervention during acute ocular disease may prevent late complications.

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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe acute adverse drug reactions. These drug reactions primarily affect the skin, but commonly involve ocular and orogenital mucous membranes as well. SJS is characterized by widespread macules or flat atypical target lesions with epidermal detachment involving <10% body surface area (BSA). In TEN, epidermal detachment involves >30% BSA. In a local study from Singapore, they were found to occur in 0.01% of hospital-based populations (1).

Ocular complications in SJS and TEN may occur acutely, together with or after the onset of skin involvement. Severe ocular complications may even result in permanent visual loss due to corneal scarring or vascularization. There is currently a paucity of literature on the

ocular manifestations of these diseases, particularly long-term ones. These have also mainly characterized ocular complications in predominantly Caucasian populations. Genetic differences in drug metabolism may turn up differences in the severity of disease in East Asian patients.

In SJS, the severity of systemic involvement is thought to determine the likelihood of late ocular complications (2). Erythema multiforme, SJS and TEN are viewed as a spectrum of systemic disease with increasing severity and mortality. The question is then if there is also a difference in the frequency and severity of ocular complications both acutely and in the long term.

A validated severity-of-illness score for TEN, severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was based on suspected important variables evaluated from patients with TEN (3). Clinical variables used in this included age above 40 years, malignancy,

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tachycardia > 120/min, initial skin epidermal detachment > 10% surface area, serum urea > 10 mmol/l, serum glucose > 14 mmol/l and serum bicarbonate < 20 mmol/l. There have been no published studies to date evaluating these prognostic factors in the assessment of outcomes in late ocular complications.

Our current study aims to describe acute and late ocular manifestations and complications in SJS and TEN, and to identify possible clinical predictors for the development of late complications.

Method

This retrospective study had the approval of the Ethics Committee of Tan Tock Seng Hospital, Singapore.

Consecutive patients admitted to Tan Tock Seng Hospital during the study period July 1, 1993–June 30, 2002 with the diagnosis of SJS or TEN were included. The classification criteria by Bastuji-Garin (4) were used to define SJS and TEN. Patients' records were reviewed for clinical and demographic data, laboratory results, causative drug as determined by the allergist-immunologist, and treatments. Patients with clinical evidence of acute ocular complications were reviewed by an ophthalmologist to determine the type, extent and severity of ocular involvement. Patients with a minimum follow-up period of 6 months were reviewed for late complications.

Acute ocular involvement was defined as previously described elsewhere (5). Briefly, mild ocular involvement comprised lid edema and/or mild conjunctival injection and/or chemosis only. Moderate involvement comprised membranous conjunctivitis and/or corneal epithelial defects, more than 30% healing with medical treatment and/or corneal ulceration and/or corneal infiltrates. Severe involvement comprised symblepharon formation and/or nonhealing corneal epithelial defects and/or visual loss and/or conjunctival fornix foreshortening.

The data were analyzed using SPSS statistical software (Version 14.0; Chicago, IL, USA).

Ordinal regression analysis (proportional odds model) was used to compare the severity of acute ocular involvement between SJS and TEN. Associations of late complications and categorical data were assessed using Chi-squared test, Fisher's exact test or Cochran–Armitage trend test; Mann–Whitney *U* test was performed for continuous data. The risk factors for late ocular complications with a *P*-value of <0.05 in the univariate analysis were identified and included in the logistic regression analysis for the disease group (SJS and TEN). *P*-values of <0.05 were considered statistically significant.

Results

There were 117 consecutive patients with SJS/TEN during the study period.

The mean age was 52.2 ± 18.6 years (range 19–91). Seventy-five percent of patients were Chinese, 17% Malay, 5% Indian and 3% of other races. There were 58 male patients and 59 female patients. The median follow-up duration by the ophthalmologist was 2 months (range 0.1–120 months). There were 10 (8.5%) deaths during the acute phase of disease. Three had a diagnosis of SJS and seven had a diagnosis of TEN. Fourteen

Table 1. Severity of acute ocular involvement in Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Severity (%)	None	Mild	Moderate	Severe
SJS (<i>n</i> = 85)	29 (34)	33 (39)	20 (24)	3 (4)
TEN (<i>n</i> = 32)	7 (22)	14 (44)	9 (28)	2 (6)
Total (<i>n</i> = 117)	36 (31)	47 (40)	29 (25)	5 (4)

(12%) patients were lost to follow-up, i.e. not having attended at least one outpatient review. Antibiotics were the most commonly implicated group of drugs in this series (27.4%). This was followed by antiepileptic drugs (26.5%). Co-trimoxazole was the most common antibiotic implicated (9%). The most commonly implicated nonantibiotic drugs were allopurinol (17%) and phenytoin (10%).

The severities of acute ocular involvement are presented in Table 1. Eighty-one (69%) of 117 patients had ocular involvement. The acute ocular involvement was mild in 40%, moderate in 25% and severe in 4%. The patients with TEN had a slightly but not significantly more severe acute ocular involvement compared with SJS (OR: 1.61, 95% CI: 0.76–3.40, *P* = 0.214) and this difference remained insignificant after adjusting for age and gender (OR: 1.67, 95% CI: 0.78–3.58, *P* = 0.185).

Forty-four (37.6%) patients had a follow-up period of more than 6 months and 22 (50%, 95% CI: 36–64%) developed late complications. The median follow-up duration by the ophthalmologist was 35.5 months (range 6–120 months). Severe dry eyes and trichiatric lashes were the two commonest late complications. Two patients developed visual loss. The first patient developed a perforated right corneal ulcer requiring penetrating keratoplasty and the other had a persistent epithelial defect requiring an amniotic membrane transplantation. Visual loss in this patient was because of total conjunctivalization of the cornea. The details of late ocular complications are displayed in Table 2.

Table 3 shows the demographic, disease groups, severity of the acute ocular involvement, number of mucosal surfaces involved and treatments used during the acute presentation of the systemic disease in 44 patients with at

Table 2. Late ocular complications found in 44 patients with at least 6 months of follow-up

Complication (%)*	Total of patients (<i>n</i> = 44)
Severe dry eyes	20 (46)
Trichiasis	7 (16)
Symblepharon	6 (14)
Distichiasis	6 (14)
Visual loss	2 (5)
Entropion	2 (5)
Ankyloblepharon	1 (2)
Lagophthalmos	1 (2)
Cornea Ulceration	1 (2)

* Percentages given refer to percentage out of total number of patients.

Table 3. Characteristics in 44 patients with at least 6 months of follow-up

Characteristic (%)	Late ocular complications		Total	P-value
	Yes (n = 22)	No (n = 22)		
Age				
Mean (SD)	50.6 (17.4)	50.1 (14.5)	50.3 (15.8)	0.907
Median (range)	52 (19 to 83)	47 (22 to 71)	51 (19 to 83)	
Gender				
Male	8 (36)	8 (36)	16 (36)	1.000
Female	14 (64)	14 (64)	28 (64)	
Disease groups				
SJS	14 (64)	19 (86)	33 (75)	0.082
TEN	8 (36)	3 (14)	11 (25)	
Severity of acute ocular involvement				
None	2 (9)	7 (32)	9 (21)	0.024*
Mild	8 (36)	8 (36)	16 (36)	
Moderate	9 (41)	7 (32)	16 (36)	
Severe	3 (14)	0 (0)	3 (7)	
Number of mucosal surfaces involved				
0	4 (18)	4 (18)	8 (18)	0.306*
1	9 (41)	13 (59)	22 (50)	
2	8 (36)	5 (23)	13 (30)	
3	1 (5)	0 (0)	1 (2)	
Systemic steroid				
Yes	15 (75)	17 (89)	32 (82)	0.407
No	5 (25)	2 (11)	7 (18)	
Topical corticosteroid				
Yes	14 (64)	11 (52)	25 (58)	0.455
No	8 (36)	10 (48)	18 (42)	
Topical antibiotic				
Yes	21 (95)	11 (52)	32 (74)	0.001
No	1 (5)	10 (48)	11 (26)	
Lubricant eye drops				
Yes	20 (91)	17 (81)	37 (86)	0.412
No	2 (9)	4 (19)	6 (14)	

* Cochran–Armitage trend test was used.

least 6 months of follow-up. Thirty-six (82%) patients had involvement of oral, anal or genital mucosa. Systemic steroids were used in 32 (82%) patients at doses equivalent to oral prednisolone 1 mg/kg body weight per day during the acute presentation of the systemic disease. High-dose IVIG (2 g/kg body weight over two consecutive days) was administered to 10 patients. Ocular treatments included topical corticosteroids, antibiotics (eye drops and ointment) and lubricants (preservative-free) and were used in 58%, 74% and 86% of patients respectively. Patients who had received topical corticosteroid ($P = 0.031$, Fisher's exact test, 95% CI: 1.28–26.90) and who had received lubricants ($P = 0.003$, Fisher's exact test, 95% CI: 2.54–262.39) were more likely to receive concurrent topical antibiotics.

The late ocular complications rates for patients with TEN was slightly but insignificantly higher than those with SJS (72% vs. 42%, $P = 0.082$, OR: 3.62, 95% CI: 0.81–16.15). The patients with more severe acute ocular involvement ($P = 0.024$) and those with topical antibiotic ($P = 0.001$, OR: 19.09, 95% CI: 2.16–169.09) were more likely to have late complications (Table 3). However, when adjusting for significant risk factors identified from

the univariate analysis (severity of acute ocular involvement, use of topical antibiotic and disease groups) in the logistic regression analysis, only the use of topical antibiotic ($P = 0.033$, OR: 14.90, 95% CI: 1.24–179.33) was found to be a significant risk factor for late ocular complications. Further analysis showed that the patients with dry eye were more likely to have used topical antibiotics. ($P = 0.004$, 95% CI: 1.66–128.43).

Laboratory tests reviewed during the acute admission included full blood counts, liver function tests, renal function and glucose levels. Neutropenia, lymphopenia, increased urea/ creatinine/ alkaline phosphatase/ serum protein/ aspartate aminotransferase/ glucose beyond the normal laboratory range were not associated with more severe acute ocular complications. However, patients with thrombocytopenia had significantly more severe acute ocular complications (OR: 3.79, 95% CI: 1.45–9.93, $P = 0.007$). Thrombocytopenia was however not associated with late ocular complications ($P = 0.299$).

Discussion

There have been few advances in the way we treat the acute ocular complications of SJS and TEN. Conventional management still remains unsatisfactory as long-term complications are not prevented. This is regrettable as patients with SJS and TEN do not develop sequelae except for ocular and genital complications. The current strategies of management with systemic and topical corticosteroids fail in preventing late ocular complications (5). This is also supported by data from our series. Moreover, we found that late ocular complications, in particular, severe dry eyes were associated with the use of topical antibiotics. This has not been described before. In our institution, chloramphenicol eye drops are sometimes prescribed during the acute setting. Their usage was empirical to prevent secondary bacterial infections. The antibiotics may also be administered as a topical chloramphenicol and dexamethasone 0.1% combination eye drop. Tetracycline ointment is also used and sometimes in combination with the above two formulations. We found that patients who receive topical corticosteroids and topical lubricants were also more likely to receive topical antibiotics. A possible explanation for more severe dry eye with topical antibiotic use could be further toxicity to the accessory tear glands from the preservatives contained in the topical antibiotics. Preservatives are chemicals that are meant to either destroy microorganisms or prevent their growth. Clinical, experimental and *ex vivo* studies implicate preservatives for allergic, toxic or inflammatory reactions induced by topical eyedrops rather than other excipients such as stabilizing agents (6). The preservatives among the excipients used in the eye drops mentioned above are Thiomersal and Phenylmercuric nitrate. These are of the mercurial chemical class of ophthalmic preservatives. *In vivo* and *ex vivo*

Table 4. Composition of antibiotic eye medications used in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis

Active ingredients	Preservative	Other excipients
Chloramphenicol 0.5% eyedrop	Phenylmercuric nitrate 0.02 mg/ml	Sodium borate, boric acid
Chloramphenicol 0.5%, dexamethasone sodium phosphate 0.1%, tetryzoline hydrochloride 0.025% eyedrop	Thiomersal 0.02 mg/ml	Macrogol 400, alpha-tocopherol acetate, methylhydroxypropylcellulose
Chlortetracycline HCl B.P. 1% Ointment	Ophthalmic ointment base q.s.	Sodium metabisulfite, distilled water, liquid paraffin, wool fat, ceresin, white petrolatum

studies have demonstrated their ability to cause ocular damage such as ocular acute and delayed hypersensitivity, stromal and endothelial cell edema (7). An alternative explanation is direct toxicity to the accessory tear glands from the topical antibiotic itself (8). In the setting of polypharmacy and already inflamed conjunctival tissue, the resulting tear gland damage leads to dry eyes as a sequelae. The judicious use and frequency of instillation of topical antibiotics and other topical treatments would thus seem necessary in all patients with SJS or TEN. Topical antibiotics should not be empirically administered unless there are clinical signs of concomitant ocular infection. The composition of the antibiotic eye medications that were used in our series are listed in Table 4. None were thought to be cross reacting with the cause of the adverse drug reaction.

Another major finding was that the severity of acute ocular complications is not associated with late complications after adjusting for the disease groups and use of topical antibiotic. This is an unexpected finding when considering the clinical course of two of our patients. In the first case, it appeared that severe inflammation led to corneal melting, necessitating keratoplasty. In the second case, limbal stem cell loss found in SJS (9) may have occurred during the acute phase in another patient. The clinical features of a nonhealing epithelial defect and subsequent corneal conjunctivalization could be explained by this insult.

We also found that there was no difference in the severity of acute ocular complications between the SJS patient group and the TEN patient group. There was a trend toward slightly higher late ocular complications rates in patients with TEN compared to those with SJS. This was however not statistically significant. We found this surprising as there is an ascending gradation of severity of disease manifestation, morbidity and mortality in SJS and TEN. This implies that SJS and TEN in the acute stages should be managed in a similar fashion with the main aim of preventing late ocular complications. If we were to give more weight to this trend to higher late ocular complication rates in TEN vs. SJS, possible reasons could be similar mechanisms of apoptosis in the skin and eye in TEN in contrast to SJS. The Fas–Fas ligand system is certainly expressed in the cornea and overexpression of CD95 receptors in ocular tissue during TEN may play a part in the observed increase trend to late ocular complications (10).

Other findings were that features of clinical presentation or indicators of severity of systemic disease were not a good guide to predicting late ocular complications, whether minor or sight threatening. One such clinical feature studied was the total number of mucosal surfaces involved by the disease. The mucosal surfaces that could be involved were conjunctival, oral, genital or anal mucosa. Two of several biochemical indicators studied were elevated glucose levels and serum urea nitrogen which are part of the SCORTEN (3). They are two of seven independent risk factors associated with mortality in TEN. Age of the patient greater than 40 used in SCORTEN also showed no relationship to the development of late complications. The one statistically significant finding was that of thrombocytopenia being associated with more severe acute ocular complications. This is likely to be a reflection of immune-mediated hypersensitivity.

The most common late complication was severe dry eyes, present in 46% of those with long-term follow-up. This finding is consistent with reports where the most common late complication was sicca syndrome (11). The true prevalence of dry eyes could be higher, given that patients with initial mild or moderate acute presentation may have been discharged from follow up.

Our study has several weaknesses. Firstly, ophthalmic evaluation would have been more complete had all patients been screened by an ophthalmologist for ocular involvement, rather than only those who were clinically suspected by the dermatologist or allergist-immunologist. This may have caused an underestimation of the ocular involvement. Secondly, when comparing the SJS and TEN groups for severity of ocular complications, bias may have been introduced by the higher mortality rate in the TEN group. This may have resulted in misclassification of the severity of the ocular complications, particularly if follow up was short. They would also be selectively excluded from analysis of long-term complications.

Thirdly, we have a low proportion of patients with follow up of more than 6 months. This is related to the weaknesses discussed above. There were 36 patients with no apparent ocular involvement and these therefore had no referral or follow up by an ophthalmologist. There were also 10 deaths during the acute phase of the disease. In addition, there were 14 patients who defaulted follow-up following discharge. The remaining 13 patients who were lost to more than 6 months of follow-up were those who were judged at early follow-up to have fully

recovered without complications. These were discharged from care.

Our knowledge of the disease mechanism in SJS and TEN is evolving with findings supporting the role of T cells in severe cutaneous acute allergic drug reactions (12). T-helper cells have also been found to be predominant in the conjunctival inflammatory cell infiltration of the chronic phase of SJS¹³ and in patients with recurrent episodes of inflammation.¹⁴

Novel immunomodulatory treatments such as intravenous immunoglobulin (IVIG) and cyclosporin A (CsA) have been used to treat TEN patients to improve morbidity and mortality. The clinical results of treatment are however still controversial. In addition, IVIG and CsA treatments appeared to exert no obvious effect on the inflammatory infiltrate, but abated the expression of the CD95 receptor in the skin of TEN patients. It was also inferred that IVIG and CsA did not completely abate the necrolytic process in TEN (15). It is not known if there is over expression of the CD95 receptor in conjunctiva during the acute phase of ocular inflammation in SJS and TEN.

Cyclosporin A works by reducing the expression of interleukin-2 by T-helper cells, thus reducing the proliferation of T cells. With the availability of a Food and Drug Administration approved topical preparation for treating dry eye in humans, topical cyclosporin A should be investigated to see if it is efficacious in reducing acute

and late complications. Our experience so far with IVIG in TEN where IVIG did not appear to reduce the severity of visually significant ocular complications warrants further study (16).

The clinical implication of our study is that both SJS and TEN patients should be carefully evaluated during the early acute stage for ocular involvement with timely intervention instituted. Furthermore, care should be taken to prevent late complications even in milder cases of acute ocular involvement. This would include the judicious use of topical antibiotics and other topical formulations that may lead to severe dry eyes. Unfortunately, current methods of treatment do not prevent long-term complications. Although there is growing knowledge of disease mechanisms in the skin, more research is required to elucidate the pathogenesis of ocular damage that may differ from the skin. Novel topical or systemic immunomodulatory treatments should be studied in well-designed multi-center trials to determine whether they better halt or downregulate ocular inflammation and damage in SJS and TEN.

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