Acute Ocular Manifestations and Long-term Ocular Complications of Stevens Johnson Syndrome Pattern in Thammasat University Hospital

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Objectives : The objectives of this study are to identify the acute and chronic ocular manifestations and severity of acute ocular involvement of Stevens-Johnson syndrome (SJS) and Toxic epithelial necrolysis (TEN) in Thammasat university hospital.

Methods: We did a retrospective study by chart review of patients with confirmed dermatological diagnosis of Stevens-Johnson syndrome and Toxic epithelial necrolysis with ocular involvement. The data were recruited from a database of Thammasat University Hospital. Thirty consecutive patients diagnosed between June 2013 and May 2018 were recruited. We reviewed age, sex, causes of the disease process, acute ocular complications, acute symptoms, visual acuity, and late ocular complication. We used Darren G Gregory's new grading system to identify the severity of acute manifestation of SJS and TEN.

Results: There were 30 consecutive patients. All were drug-induced. Antibiotics were the most commonly implicated group of drugs in this series (36.6%), followed by antiepileptic drugs (23.3%). The severity of acute ocular involvement was mild in 30%, moderate in 36.6%, severe in 13.3% and extremely severe in 20% of patients. Dry eye was the most common late complication (66.7%) followed by punctate epithelial erosion (58.3%) and trichiasis (41.7%). Two patients had visual loss (16.6%).

Conclusions : Ocular manifestations occurred in a high proportion of patients with SJS/TEN during both acute and late phases. The most common causes were antibiotic and antiepileptic drugs. A careful medication history should be obtained from these patients. Ophthalmic evaluation, and management are mandatory.

Keywords : Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; acute ocular manifestation; late ocular manifestation; severity

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Introduction

In 1922, Stevens and Johnson described two boys with Stevens-Johnson syndrome (SJS), a severe mucocutaneous

disease with ophthalmologic manifestations[1]. Later Lyell described a condition characterized by extensive epidermal ''scalding,'' naming it ''toxic epidermal necrolysis'' (TEN)[2]. The incidence of SJS and TEN are 9.2 and 1.9 per million person-years, respectively[2].

SJS and TEN are variants belonging in the same class and are defined based upon the amount of epidermal detachment; SJS, 10% or less of total body surface area involvement, TEN, 30% or greater involvement and SJS/TEN overlap, involvement between 10-30%.[3,4]

The pathogenesis of SJS/TEN is controversial. The genetic risk factors are drug-specific and vary among populations and/or ethnic groups. For the molecular pathogenesis of SJS/TEN, a cytotoxic T lymphocyte (CTL) immune-mediated reaction is known as the major immunologic component of SJS/TEN[5,6].

Clinical findings include a prodromal symptom of fever and malaise, followed by the development of a generalized, tender cutaneous eruption consisting of a variety of morphologic macules, papules, atypical target lesions and vesicles or bullae. Ocular manifestations in both SJS/TEN patients are common. More than 50-88% suffer from acute ocular manifestations, and 35−90% develop long-term sequelae[7].

Ocular involvement in the acute phase of SJS/TEN occurs due to rapid-onset keratinocyte apoptosis and secondary effects of inflammation and loss of ocular surface epithelium. Early involvement is highly variable and can range from self-limited conjunctival hyperemia to near total sloughing of the entire ocular surface epithelium, including the tarsal conjunctiva and eyelid margin. Ocular surface inflammation can be intense, with pseudomembrane or frank membrane formation, early symblepharon formation, fornix foreshortening, and corneal ulceration and perforation[8].

Chronic ocular complications of SJS/TEN are multifactorial in origin and occurred in up to 35% of SJS/TEN patients[9]. There are three categories of chronic ocular complications classified by Sotozono and colleagues[10]. The corneal complications included superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization. The conjunctival complications included hyperemia and symblepharon formation. The eyelid complications included trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal occlusion.

Fusion between the bulbar and forniceal surfaces due to conjunctival ulcerations or conjunctival membrane formation acutely, or persistent inflammation later, causes permanent symblepharon and ankyloblepharon, disrupting an already compromised tear film meniscus and inhibiting proper eyelid closure and blink, and at times restricting ocular motility. Tarsal conjunctival scarring can be associated with eyelid malpositions and other disorders, including ectropion, entropion, trichiasis, distichiasis, meibomian gland atrophy and inspissation, punctal occlusion, and keratinization of the eyelid margin, tarsal and bulbar conjunctival surfaces. These changes not only cause debilitating pain in affected patients, but also threaten vision and is related with the development of late corneal blindness[11], at least in part due to the chronic limbal stem cell dysfunction (LSCD). If not removed, misdirected and/or districhiatic lashes, the

latter from metaplastic meibomian glands, can mechanically abrade the corneal epithelium, leading to corneal epithelial defects, infection, and stromal scar. Repeated friction from a keratinized inner eyelid surface can lead directly to chronic corneal inflammation, neovascularization, scarring, and LSCD[12].

The aim of this study is to identify the acute and chronic ocular manifestations of Stevens-Johnson syndrome and TEN in Thammasat university hospital.

Method

This retrospective study was approved for ethical research in humans with the human research ethics committee of Thammasat university. (Certificate number 064/2562)

A chart review of patients with confirmed dermatological diagnosis of SJS and TEN with ocular involvement was performed, where patients were recruited from a database of Thammasat University Hospital. A total of 30 consecutive patients diagnosed between June 2013 and May 2018 were recruited for the study.

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.

Records were reviewed for age, sex, causes of the disease process, acute ocular complications, acute symptoms, visual acuity, and late ocular complications.

To identify the severity of SJS and TEN in the acute phase, we used the new grading system for the acute ocular manifestations of Stevens-Johnson syndrome, written by Darren G, Gregory[13].

SPSS version 23.0 has been used for statistical analysis in this study. The data was shown by using mean, standard deviation and percentage. Independent t-test and chi-square test were used for comparing the data between two groups. *P-value* less than 0.05 was statistically significant.

Result

There were 30 consecutive patients with SJS/TEN with ocular involvement during the study period. The mean age was 47.3 ± 20.6 years (range 10−89).

Table 1

Implicated group of drug		No. (%)
Antibiotics	Co-trimoxazole	3 (10%)
	Penicillin	3 (10%)
	Cephalosporin	1 (3%)
	Other	4 (13.3%)
Phenytoin		5 (16.6%)
Allopurinol		4 (13.3%)
NSAIDs		5 (16.6%)
Danazol		2 (6.6%)
Other		3 (10%)

There were 13 male patients (43.3%) and 17 female patients (56.7%). There were 1 (3.33 %) deaths during the acute phase of disease. Twenty-five (83.3%) had a diagnosis of SJS and five (16.7%) had a diagnosis of TEN. All cases of SJS/TEN were drug-induced. Antibiotics were the most commonly implicated group of drugs in this series (36.6%), followed by antiepileptic drugs (23.3%). Co-trimoxazole (10%) and Penicillin (10%) were the most common antibiotic implicated. The most commonly implicated non-antibiotic drugs were phenytoin (16.6%) , NSAIDs (16.6%) and allopurinol (13.3%). The details of the implicated drugs in this study were shown in Table 1.

Table 2 The severities of acute ocular involvement

Disease	Acute Ocular Involvement No. (%)			
	Mild	Moderate	Severe	Extremely Severe
SJS	9(36%)	7 (28%)	4 (16%)	5 (20%)
TEN	0 (0%)	4 (80%)	0 (0%)	1 (20%)
Total	9 (30%)	11 (36.6%)	4 (13.3%)	6 (20%)

The severities of acute ocular involvement were shown in Table 2. The acute ocular involvement was mild in 30%, moderate in 36.6%, severe in 13.3% and extremely severe in 20% of patients.

The treatment during the acute presentation of ocular involvement included topical corticosteroid eye drops, non-preservative lubricant eye drops, and topical antibiotic eye drops. These three types of eye drops were given to thirty (100%) patients who were diagnosed SJS/TEN with ocular involvement as a basic treatment in acute phase. Nineteen (63.3%) patients who developed conjunctival membrane underwent membrane peeling everyday until the membrane disappeared. Two (6.7%) patients who developed persistent epithelial defect underwent amniotic membrane patching.

Sixteen (53.3%) patients had a follow-up period of more than 6 months and twelve (75%) patients (75%) developed late complications. The demographic data, disease groups, severity of the acute

Table3 shows late ocular complications of SJS/TEN

Late ocular complications	No. (%)
Dry eye	8 (66.7%)
Punctate epithelial erosion	7 (58.3%)
Trichiasis	5 (41.7%)
Symblepharon	3 (25%)
Corneal ulcer	4 (33.3%)
Limbal stem cell deficiency	3 (25%)
Corneal perforation	2 (16.6%)
Conjunctival scar	4 (33.3%)
Visual loss	2 (16.6%)

Table 4 shows the demographic data, disease groups, severity of the acute ocular manifestation in 16 patients with at least 6 months of follow-up period.

Characteristic	Late ocular complications		Total	*P-value*
	Yes (N=12)	No (N=4)		
Age Mean (SD)	48.5 (18.2)	35.25 (25.84)	45.19	0.273+
Median (range)	48 (20-83)	30.5 (10-70)	43.50	
Sex				
Female	6	3	9	0.383++
Male	6	1	7	
Disease				
SJS	10	3	13	0.712++
TEN	2	1	3	
Severity				
Mild	1	0	1	0.242++
Moderate	4	3	7	
Severe			2	
Extremely severe	1	1	6	
	6	0		

+ One-way anova
++ Chi-square test

ocular manifestation of sixteen patients was shown in Table 4. There was no significant difference between two groups (twelve patients who developed late ocular complications and four patients who did not develop late ocular complications) in terms of age (*P-value* 0.273), sex (*P-value* 0.383), disease group (*P-value* 0.712), and severity of acute ocular manifestation (*P-value* 0.242). Dry eye was the most common late complication (66.7%) followed by punctate epithelial erosion (58.3%) and trichiasis (41.7%). Two patients had visual loss (16.6%). The first patient developed corneal ulcer of the right eye and finally developed corneal perforation. She underwent penetrating keratoplasty after that. The other developed total corneal conjunctivalization which caused visual loss. The details of late ocular complications are shown in Table 3.

Discussion

In our study, the most common causative drug in SJS/TEN was antibiotics (36.3%) followed by Phenytoin (16.6%), NSAIDs (16.6%), and Allopurinol (13.3%). Co-trimoxazole was the most common drug implicated (10%). This findings were similar to L.W.Yip et al[10].We found that the most common severity of acute ocular involvement in SJS/TEN was moderate severity (36.6%) whereas Darren G. Gregory reported that

the most common severity in his study was severe severity (35.4%)[13]. In Darren G. Gregory's grading system, he suggested that mild and moderate severity should be treated by medical treatment while severe and severely severe degree should be treated by amniotic membrane transplantation. In our study, every patient was initially treated by medically, but when the epithelial defect tended to persist, the amniotic membrane patching was used for treatment.

For the late complication of SJS/TEN, we found that severe dry eyes, which presented in 66.6% of our cases, was the most common late complication of those with long-term follow-up. This finding was consistent with the report by L.W.Yip et al. that the most common late complication was dry eye syndrome[14]. Other late complications such as punctate epithelial erosion, trichiasis, symblepharon, corneal ulcer, limbal stem cell deficiency, corneal perforation, conjunctival scar, and visual loss were also reported[15]. We also found that the severity of acute ocular manifestation did not predict late ocular complications. This finding was consistent with the report of L.W.Yip et al.

There are weaknesses in this study. Firstly, because of the retrospective method, there was the limitation of the quality of data that was collected. Secondly, almost half of the follow up period of patients were shorter than 6 months, so there were just 16 patients who were included for analysis of late complications.

Conclusions

Ocular manifestations occurred in a high proportion of patients with SJS/TEN during both acute and late phases. The most common causes were antibiotic and antiepileptic drugs. A careful medication history should be obtained from these patients. Good ophthalmic evaluation and management in the acute stages are mandatory for preventing or decreasing long-term ocular complications.

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