Original Article

Study of Ocular Manifestations of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Abstract

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent different ends of the spectrum of the same clinical entity causing severe mucocutaneous reactions, usually to drugs, characterized by intraepidermal cell death leading to blistering and epidermal sloughing. The severe cutaneous manifestations of this disease spectrum may often lead to overlooking of the ocular sequelae, which are very common and may lead to loss of visual acuity. **Aim:** The present research is an attempt to study the ocular manifestations seen in association with SJS/TEN. **Materials and Methods:** Patients having ocular manifestations of SJS/TEN attending the outpatient and inpatient department of skin and VD in a tertiary care hospital, were included in the study. Ophthalmologic examination of all patients was observed and recorded. **Results:** A total of 30 patients were included in the study. Among all, 27 patients had ocular involvement and among them 7 patients (25.9%) had mild, 17 patients (62.9%) had moderate, and 3 patients (11.1%) had severe ocular manifestations. Corneal involvement was found in 12 patients (44.4%), conjunctival involvement was found in 22 patients (81.4%), and eyelid involvement was found in 20 patients (74.0%). All patients were managed medically.

Keywords: *Ocular manifestations, Stevens-Johnson syndrome, toxic epidermal necrolysis*

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent different ends of the spectrum of the same clinical entity of severe mucocutaneous reactions, usually to drugs, characterized by intraepidermal cell death leading to blistering and epidermal sloughing. SJS is the milder variant with <10% of total body surface area involvement. TEN is the more severe form with >30% total body surface area involvement. An intermediate classification is the SJS-TEN overlap in which there is 10–30% involvement.

The incidence of SJS/TEN is low, approximating to about one to seven cases per million per year, the overall mortality rate is 20% to 25%.[1,2] The pathogenesis of SJS/TEN is controversial. The genetic risk factors are drug-specific and vary among different populations. Specific HLA subtypes A*0206 and DQB1*0601 carry increased risk for ocular complications secondary to SJS.[3,4] Moreover, the molecular pathogenesis of SJS/TEN is also largely unclear. Furthermore, up to 75% of cases are caused by delayed drug hypersensitivity reactions to a medication or its metabolites and appear to involve cell-mediated apoptosis of keratinocyte via the Fas signaling cascade and granulysin release.[5,6] Remaining 25% of cases are believed to have infectious etiology.

Initial presentation occurs in the form of a prodromal phase of malaise and fever followed by or may show concurrent development of generalized, tender cutaneous eruptions consisting of macules, papules, atypical target lesions and vesicles, or bullae. Epidermal detachment leaves off large raw weepy areas like that seen in severe burns. Denuded skin predisposes the patient to bacterial superinfection, most common being *Staphylococcus aureus*. Sepsis, therefore, serves as the main cause of death in SJS/TEN patients. At least two mucosal surfaces are affected. Painful oral erosions and crusts, conjunctivitis, and urogenital manifestations (e.g., urinary retention, urethritis, phimosis, and vaginal synechiae) accompany cutaneous manifestations in up to 90% of patients. The respiratory tract may be involved

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causing cough, dyspnea, respiratory distress, pneumonia, and pulmonary edema. Hepatitis and glomerulonephritis may develop.

The severe cutaneous manifestations of this disease spectrum may often lead to overlooking of the ocular sequelae, which are very common and may lead to loss of visual acuity. Most patients consult dermatologist or physician for skin lesions in the acute phase and consult ophthalmologist after the resolution of lesions. In the acute phase of SJS/TEN, ocular involvement has been reported to occur in 80% of patients. Chronic ocular sequelae secondary to SJS/TEN develop in 21–29% of pediatric cases and 27–59% of adult cases.[7] In this report, we attempt to study the acute and delayed ocular manifestations seen in patients of SJS/TEN.

Materials and Methods

30 patients of SJS/TEN, attending the outpatient/inpatient Department of Skin and VD, MGM Medical College and Hospital were included in the study. After obtaining informed consent, demographic information, detailed dermatologic, and systemic examination were done for all the patients. The causative drugs, if any, and details of treatment received were recorded. Patients were followed up regularly for a period of 6 months.

Ophthalmologic examination of all patients was conducted in association with the department of ophthalmology. Based on clinical parameters, observed on ocular slit-lamp examination, the severity of involvement at the time of presentation was determined as mild, moderate, and severe, as per the classification described by Power *et al*.[8] Mild ocular involvement comprised of eyelid skin involvement in the form of desquamation and denudation, eyelid edema, mild corneal involvement, mild conjunctival injection, mucous discharge, or chemosis. Moderate cases were the ones with membranous conjunctivitis, epithelial defects with more than 30% healing with medical treatment, corneal ulceration, or corneal infiltrates. Severe manifestations comprised of acquired eyelid malposition, formation of symblepharon, nonhealing corneal epithelial defects, complete or partial visual loss, or foreshortening of conjunctival fornix.

Results

A total of 30 patients were included in the study during the study period, of which 12 were males and 18 females. Out of these, 22 were SJS or SJS/TEN overlap and 8 were TEN patients. Ocular manifestations were observed in 27 patients (90%), with a male to female ratio of 10:17. All cases were drug-induced, except one, in which no history of any drug intake prior to the appearance of lesions could be elicited [Table 1]. All patients had bilateral ocular findings.

All the patients having ocular involvement, presented to us in the acute phase, with symptoms such as redness, burning, watering, discharge, swelling, and sloughing of skin over lids and so on. The acute manifestations were classified as mild, moderate, or severe using the classification system described above. About 25.9% (7 patients) had mild involvement, 62.9% (17 patients) had moderate involvement, and 11.1% (3 patients) had severe involvement [Table 2].

After performing a detailed ocular examination, the lid, conjunctival and corneal findings were observed in 20 (74.7%), 22 (81.48%), and 12 (44.44%) patients, respectively [Table 3]. The lid complications included discharge [Figure 1], lid margin ulceration and crusting [Figure 2], lid edema [Figure 3], matting of eyelashes [Figure 4], meibomitis, blepharitis, dystrichiasis, and peeling of skin over lids [Figure 5]. Conjunctival complications included conjunctivitis [Figures 1, 2 and 4], conjunctival membranes, subconjunctival hemorrhage, and symblepharon. Corneal complications included superficial punctate epithelial keratitis, corneal ulceration, and punctate epithelial erosions.

All patients were treated with topical antibiotics, topical corticosteroids, and tear substitutes in the acute phase.

At the end of the study period, 8 patients (29.6%) developed chronic sequelae of ocular manifestations [Table 4]. Out of these patients, 3 patients developed severe dry eye disease, 2 patients developed trichiasis, 2 patients had a diminution of vision, and 1 patient developed severe photophobia [Figure 6]. Patients of SJS and SJS-TEN overlap had mild-to-moderate whereas patients of TEN had moderate to severe ocular manifestations. It was observed that delayed complications are more common in patients with initial severe eye involvement. More diffuse cutaneous and oral mucous membrane damage was associated with a greater risk of ocular manifestations.

Table 1: Causative agents of SJS/TEN

Drug	Frequency	Percentage
Aceclofenac	5	18.5
Carbamazepine	4	14.8
Nimesulide	8	29.6
Ofloxacin	3	11.1
Phenytoin	6	18.5
No history of drug intake	1	7.4
Total	27	100

Table 2: Classification of ocular involvement based on severity

Ocular involvement	Frequency	Percentage
Mild	7	25.9
Moderate	17	62.9
Severe	3	11.1
Total	27	100

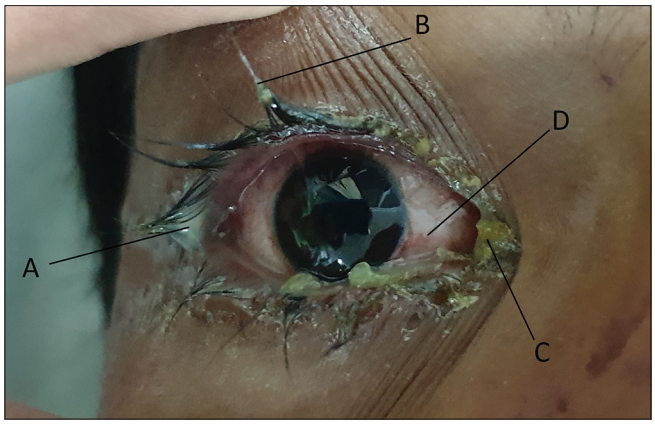

Figure 1: Acute ocular manifestations showing: A. Mucoid discharge B. Matting of eyelashes C. Crusting D. Congestion

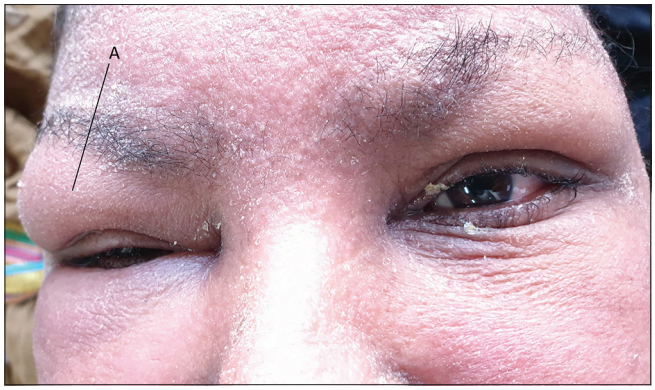

Figure 3: Acute ocular manifestations showing: A. Lid edema

Figure 5: Acute ocular manifestations showing peeling of skin over lids

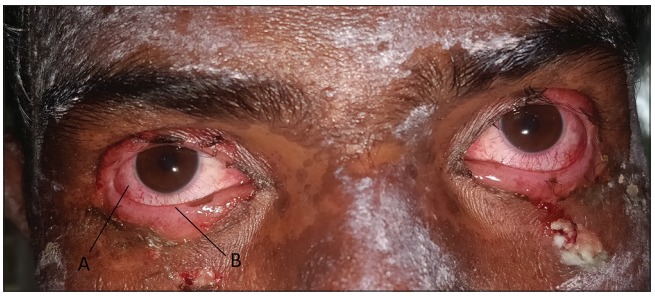

Figure 2: Acute ocular manifestations showing: A. Congestion B. Sloughing of skin over lid margin

Figure 4: Acute ocular manifestations showing: A. Congestion B. Matting of eyelashes

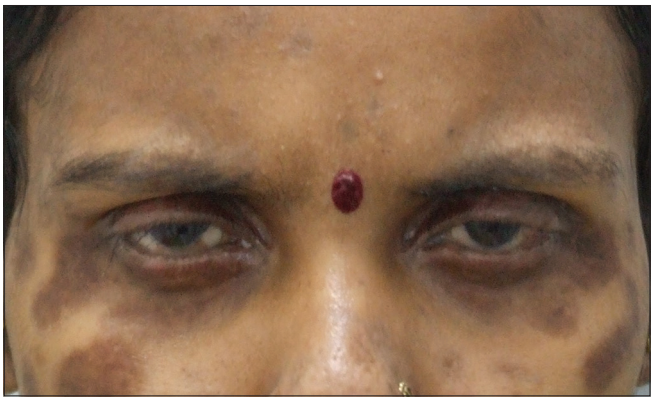

Figure 6: Chronic ocular sequalae showing development of photophobia

Discussion

SJS and TEN are an important cause of ocular morbidity. The reported incidence of ocular involvement in SJS/TEN is 72–90%. This is consistent with our findings, where 90% of the patients suffering from SJS/TEN had ocular findings. Most of the patients enrolled in our study (96.6%) had a drug-based etiology, with nimesulide being the most commonly implicated drug (26.6%). Another study by Devi *et al*. showed ciprofloxacin to be the most common etiological drug agent (23.1%) followed by paracetamol (17.3%), and sulphamethoxazole (15.4%).[7,9]

Based on severity, the ocular involvement in SJS/TEN can be classified into mild, moderate, or severe.[8,10] Mild ocular involvement is characterized by eyelid skin involvement in the form of desquamation and denudation, eyelid edema, mild corneal involvement, mild conjunctival injection, mucous discharge, or chemosis. Moderate cases present with membranous conjunctivitis, epithelial defects with more than 30% healing with medical treatment, corneal ulceration, or corneal infiltrates. Severe manifestations comprise of acquired eyelid malposition, formation of symblepharon, nonhealing corneal epithelial defects, complete or partial visual loss, or foreshortening of conjunctival fornix. Nearly 25.9% of our patients had mild involvement, 62.9% had moderate, and 11.1% of patients presented with severe ocular involvement. This is in contrast with another study by Yip *et al*., where mild involvement was seen in most patients (40%), followed by moderate involvement in 25%, and severe in 4%.[11]

Table 3: Ocular findings in the acute stage based on structures involved: Lids, Conjunctiva, and Cornea

Structure	Clinical findings	Number of patients
Lids	Discharge	20
	Edema/Thickening	12
	Meibomitis/Blepharitis	4
	Trichiasis	0
	Dystrichiasis	1
	Lid margin ulceration	7
Conjunctiva	Conjunctivitis	22
	Conjunctival membranes	1
	Subconjunctival hemorrhage	2
	Symblepharon	1
	Fornix foreshortening	1
Cornea	Punctate epithelial erosions	1
	Superficial punctate keratitis	6
	Corneal ulceration	4
	Corneal opacity	1

Table 4: Long-term ocular sequelae after the end of 6 months

Complication	Number of patients
Severe dry eye disease	3
Diminution of vision	2
Symblepharon	0
Trichiasis	2
Corneal opacification	0
Photophobia	1
Entropion	0
Ectropion	0
Ankyloblepharon	0
Lost to follow-up	5

Another classification of the ocular features can be done according to the clinical stages, into acute, subacute, and chronic. The acute stage is usually till 2 weeks after the onset of symptoms and comprises of conjunctivitis/conjunctival hemorrhage, conjunctival membrane or pseudomembrane formation, meibomianitis, symblepharon, and epithelial defects. Despite the resolution of skin lesions after the acute phase, persistent inflammation and ulceration of the ocular surface may lead to chronic cicatrizing conjunctivitis, trichiasis, or dystrichiasis and subsequently corneal epithelial defects, infection, and stromal scars. These comprise the subacute stage. The chronic ocular changes are seen in up to 35% of cases of SJS/TEN. The palisades of Vogt within the limbus and the meibomian glands are affected most commonly.[12,13] Other chronic ocular sequelae include permanent symblepharon and ankyloblepharon, cicatricial entropion and trichiasis, punctual occlusion, and keratinization of the eyelid margin, tarsal, and bulbar conjunctival surfaces. In the present study, we observed that all 27 patients (90%) presented to us in the acute phase of the disease, out of which 29.6% developed chronic sequelae at the end of the study period. In a study by Yip *et al*., acute ocular involvement was observed in 81 out of 117 patients (69%). Around 44 patients were followed up for more than 6 months, among which, 50% developed late complications.[11]

Early ophthalmic assessment and management, along with frequent follow-up are key factors to recovery and prevention of the ocular manifestations. In acute SJS/TEN, a combination of topical corticosteroids, topical cyclosporine, and broad-spectrum topical antibiotics with the concurrent use of preservative-free lubricants are commonly used. Early use of topical steroids may be associated with improved visual outcomes.[12] In cases of more severe involvement, early surgical intervention in the form of amniotic membrane transplantation greatly enhances the epithelialization and reduces the inflammation and scarring in the ocular surface.

The treatment strategy for chronic phase mainly aims at preventing continual ocular surface damage, managing the ocular sequelae, and visual rehabilitation. Structural abnormalities require surgical interventions such as keratoprosthesis and keratolimbal allografting (KLAL) which help in providing visual recovery. In the end-stage cases with corneal blindness and severe dry eye, limbal stem cell transplantation (LSCT) and cultivated oral mucosal epithelial transplantation (COMET) are recommended.

Conclusion

SJS/TEN is a fatal condition with a high incidence of ocular involvement. As observed in our study, ocular manifestations occurred in 90% of the patients suffering from SJS/TEN. Conjunctivitis was the most common acute ophthalmic manifestation (81.48%) whereas chronic sequelae developed in 29.6% of these patients. Chronic sequelae though severe can be avoided by proper care and early interventions. In conclusion, all patients with SJS/TEN should undergo initial ophthalmologic screening during the acute phase of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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