Egyptian Dermatology Online Journal
Volume 8 Number 2

Ocular Manifestation of Steven Johnson Syndrome and Toxic Epidermal Necrolysis in Rural Karnataka

Sujatha Vijayalekshmi; M S Padmajothi

Department of Ophthalmology MVJMC &RH, kolathur post, Hoskote, Karanataka, India

Egyptian Dermatology Online Journal 8 (2): 3

Corresponding author: Dr. Sujatha Vijayalekshmi

E-mail: drsujatha2006@yahoo.co.in

Submitted: June 2, 2012
Accepted: November 20, 2012

Abstract

Background: To study the ocular manifestation, complications and treatment of SJS & TEN in Rural Karnataka.

Method: We studied the ocular manifestation and complications of SJS & TEN from March 2007 to October 2011. The details of the ocular examination and treatment were collected and examined to determine the pattern of presentation, complications, and treatment response.

Results: A total of 33 patients, 10 males (30.31%) and 23 females (69.69%), were identified during the 4-year period. A majority of the patients (n=22; 66%) were between 20 and 40 years of age. All patients had bilateral involvement and most (n=33; 97.89%) had bilateral symmetrical presentation. The duration from the onset of symptoms to the time of presentation at the institute varied from 6 days to 1 year. 15 (45.45%) presented with in 10 days, 13(39.40%) presented within 2-6 months, five (15.15%) presented between 7-12 months. Intake of drugs was the most commonly identified possible etiology (n=20; 60.61%.8 patients (24.24%) had a prior history of viral infection with no history of drug ingestion. No definitive cause could be ascertained in 5 (15.15%) patients. The best corrected visual acuity (BCVA) was 6/12 or better in 14 (42.42%) patients. In the early presenters the main complications were lid edema (16.67%), conjunctival congestion (72.2%), and superficial punctate keratitis (83.3%). The late presenters had lid thickening (53.34%), entropion (26.67%), conjunctival xerosis (60%), symblepharon

(20%), and there was scaring (33.33%), vascularization (33.33%) and thinning of cornea (6.67%).

Conclusion: Ocular manifestations occur in a high proportion of patients with SJS/TEN. The most frequent causes were sulfonamide and nimesulide. A careful medication history should be obtained from these patients. Ophthalmic consultation, evaluation, and management are mandatory. Early diagnosis and intervention can prevent long-term squeal.

Keywords: Steven Johnson Syndrome, erythema multiforme major, complications, management.

Background

Toxic Epidermal Necrolysis (TEN) and Steven Johnson Syndrome (SJS) are severe, rare skin reactions, usually to drugs, and are associated with widespread destruction of the epidermis. The 2 diseases are closely related: SJS is a limited form characterized by mucous membrane erosions and blisters on limited areas of the skin (<10% of the total body surface area), and TEN resembles superficial burns because of the confluence of blisters and erosions on more than 30% of the total body surface area. Overlapping cases are defined by an intermediate extent of the skin lesions [1]. The incidence of SJS and TEN is approximately 2 cases per million persons per year [2] and the overall mortality rate is 20% to 25%.[3] Ocular complications in SJS and TEN may occur acutely along with or after the onset of skin involvement. Severe ocular complications may even result in permanent visual loss due to corneal scarring or vascularization [4-6]. Little is currently known about the ocular symptoms of these diseases, particularly the long-term manifestations. SJS and TEN are viewed as a spectrum of systemic diseases with increasing severity and mortality. SJS & TEN predominantly involve the oral mucosa and conjunctiva. Various studies have shown conjunctival involvement varying from 49% to 81% [7,8]. A wide range of factors has been suggested to precipitate SJS & TEN but only in a few instances could it be convincingly established. A variety of drugs are thought to cause up to 60% of the cases of SJS&TEN, but there is no conclusive evidence except with long-acting sulfonamides [9,10]. Management of patients with SJS & TEN is a challenge and is often frustrating. Acute medical intervention involves both local and systemic measures for care of lids, conjunctiva and cornea. In the later part of the disease process, medical therapy aims at reducing the sequela of cicatrization. Surgical therapy aims to correct structural abnormalities.

This retrospective review of patients presenting with SJS & TEN at our institute aims to evaluate the presentation characteristics, possible etiological factors, ocular complications and their management.

Materials and Methods

Medical records of patients with SJS and TEN who presented were retrospectively reviewed. The classification criteria of Bastuji- Garin et al [1] were used to define SJS overlap, and TEN. An ophthalmologist examined patients with clinical evidence of acute ocular complications during the initial hospitalization to determine the type, extent, and severity of the ocular involvement. The inclusion criterion was acute ocular involvement, as defined by Power et aI., [11] described below.

1. A serious mucocutaneous illness with characteristic target-like lesions
2. Bullae and extensive areas of necrosis
3. A prominent acute prodromal period
4. Involvement of at least 2 mucosal sites.

Mild ocular involvement consisted of eyelid edema, and/or mild conjunctival injection, and/or chemosis only. Moderate involvement consisted of membranous conjunctivitis, and/or corneal epithelial defects, more than 30% healing with medical treatment, and/or corneal ulceration, and/or corneal infiltrates. Severe involvement consisted of symblepharon formation, and/or non healing corneal epithelial defects, and/or visual loss, and/or conjunctival fornix foreshortening.

In all cases, a detailed clinical history pertaining to the diagnostic criteria was taken or the referring physician's prescription at the initial episode was sought. The patients who met the above criteria were included in the analysis. The hospital records were reviewed to obtain detailed demographic data; details of laterality, symmetry, duration of initial insult to time of presentation to the institute and possible etiological factors were noted.

Use of any oral or systemic drug was considered a possible etiological factor, if the drug had been taken within two weeks of onset of prodromal symptoms. If the patient showed signs of regression in the clinical condition despite continuing to take this drug, then it was not considered as the possible etiological agent. All patients were asked to narrate important events that preceded the onset of SJS/TEN/overlap.

Detailed slit lamp examination included the ocular findings of lids, conjunctiva and cornea. Lid abnormalities included lid thickening, discharge, blepharitis, entropion and Conjunctival pathologies included congestion, xerosis, symblepharon and corneal abnormalities included superficial punctate keratitis, thinning, scarring, and vascularization. The patients in the early stage presented with lid edema, conjunctival congestion, and superficial punctate keratitis. The patients in the later stage presented with thickening of lids, entropion, symblepharon, xerosis of conjunctiva, scarring, vascularization and thinning of cornea.**(Table 1)**

The best-corrected visual acuity in the better eye was noted at presentation. All patients received medical treatment with topical tear

substitutes, topical corticosteroids or topical broad-spectrum antibiotics either alone or in combination. Patients who had some structural abnormalities were treated surgically. All patients were informed about the chronicity of ocular disease.

Results

There were 20 cases of SJS, 5 cases of overlap and 8 cases of TEN. There were 10 (30.31%)males and 23(69.69%) females. .There were two patients between 1 -10(06.06%) years of age, eight patients(24.24%) were between 11-20, 22(66.66 %) patients were between 21-40 years and one(03.14%) patient was more than 40 years of age . All patients had bilateral involvement and 30 (90.02%) patients had symmetrical involvement in both eyes. The duration from initial onset of symptoms to the time of presentation to the institute varied from 6 days to 1 year, 15 (45.45%)presented with in 10 days, 13(39.40%) presented within 2-6 months, five (15.15%) presented between 7-12 months. Intake of drugs was the most commonly identified possible etiology (n=20; 60.6%). Sulfonamides, under various trade names, comprised the most frequently identified agent before the onset of SJS/TEN/overlap (n= 5.25%) nimesulide (n=3.15%), dapsone and anticancer drugs. We thus identified 12 different drugs that led to SJS in our study patients. 8 patients (24.24%) had a prior history of viral infection with no history of drug ingestion. No definitive cause could be ascertained in 5 (15.16%) patients.

The best corrected visual acuity (BCVA) at presentation in the better eye was as follows: 14 (42.42%) patients had acuity of 6/12 or better; 12 (36.36%) patients had acuity between 6/12-6/60; 7(21.22%) patients had acuity of 6/60 to counting fingers close to face. The extent of ocular involvement is given in **Table 1**

In the early presenters the main complications were lid edema (16.67%), conjunctival congestion (72.2%), and superficial punctate keratitis (83.3%). The late presenters had lid thickening (53.34%), entropion (26.67%), conjunctival xerosis (60%), symblepharon (20%), and there was scaring (33.33%), vascularisation (33.33%) and thinning of cornea (6.67%) **(Table1-1)**.

All patients presenting with ophthalmic complications received topical medications. This included antibiotics, tear substitute and topical corticosteroids. Three (9.09%) of them underwent surgery for symblepharon release and fornix reconstruction.

	Ocular structure	Early Presenters	Late Presenters
1	Lid		
	Edema	12(16.67%)	-
	Thickening	-	8(53.34%)
	Entropion	-	4(26.67%)
2	Conjunctiva		
	Congestion	13(72.2%)	-
	Xerosis		9(60%)
	Symblepharon	-	3(20%)
3	Cornea		
	SPK	15(83.33%)	-
	Scaring		5(33.33%)
	Vascularisation		5(33.33%)
	Thinning		1(6.67%)

Table 1: Extent of ocular involvement.

Discussion

SJS and TEN are the most severe variants of the spectrum of erythema multiforme, an acute immunological mucocutaneous disorder with high morbidity and mortality, and an incidence of 1.89 per million inhabitants per year [2]. Approximately 80% of hospitalized patients develop acute ocular complications that are similar for both SJS and TEN, with severe involvement in 25% [11,12] .The morbidity of the disease may be due to the acute corneal complications, but is more usually due to the results of conjunctival scarring [13], with chronic sequelae occurring in approximately 35% of patients [14]. This analysis aimed at studying the presenting features, possible etiological factors, ocular complications and their management in a tertiary center in a rural set up. Most patients who develop SJS /TEN consult a physician or a dermatologist in the acute phase. They consult ophthalmologists only after being referred by a dermatologist or physician.

Studies have shown that drugs are responsible in up to 60% of cases of SJS [11,15,16]. In our study drugs were the cause in 48.48%and sulfonamides and nimesulide were the most common (49.09%) etiological agents. Despite the advent of newer antibiotics, sulfonamides continue to be used by some physicians. This remains a cause of concern. Definite cause could not be ascertained in 8 (24.24%) patients, similar to the observation in another study [11].

After the acute vesicular phase, within hours to days, a concomitant conjunctivitis typically develops. A more severe conjunctival lesion results in pseudo-membrane or membranous conjunctivitis [18,19] which may often lead to cicatricial conjunctivitis [19]. The severity of the consequences of conjunctival scarring ranges from mild to severe. Some

patients in this series presented with mild ocular involvement, caused by mild dry eye and showed no progression towards the more severe stages. Others presented with severe complications early after the acute stage.

Late complications result from scarring of lids leading to ectropion, entropion, trichiasis and lagophthalmos. Tear film deficiency is often troublesome and leads to late phase complications [20], which in turn lead to conjunctival and corneal xerosis with ocular surface problems. Late phase corneal complications develop due to corneal exposure leading to punctate epithelial keratitis, [21] recurrent epithelial defects, ingrowth of abnormal new blood vessels (corneal neovascularization), opacification in the visual axis and blindness. Finally, the impairment of host defense system due to alteration in lid structure, composition of tear film, loss of integrity of epithelium lead to more serious complications such as corneal and scleral infections. Uncontrolled infection may lead to perforation, endophthalmitis and pan-ophthalmitis [1,22] that may finally need evisceration or enucleation.

In our series, since most patients presented within the critical 6-week period, it was expected that a majority had acute-onset complications of conjunctiva and cornea leading to minimal visual impairment (VA >6/12) in 42.05%. In the critical acute phase, local measures play an important role. Measures advocated include tear substitutes, frequent irrigation of both superior and inferior conjunctival fornices with preservative-free solutions, removal of pseudomembranes and lysis of symblepharon using a glass rod or symblepharon ring. Topical antibiotics to prevent secondary infections, topical corticosteroid to prevent scar formation and topical cycloplegics can be used to relieve pain, photophobia and ciliary spasm. The integrity of corneal epithelium could be maintained by bandage contact lens, but this should be used with extreme caution. Surgical therapy at this stage only aims to correct structural defects of lids, conjunctiva and cornea.

Amniotic membrane transplantation, which is known to have anti-inflammatory effects and to favor wound healing, is already used to treat ocular burns [23-25]. Encouraging preliminary results have been obtained for the use of this technique in isolated cases of ocular complications of SJS/TEN [26,27]

It is very disturbing to know that despite the advent of newer antibiotics sulfonamides are still used by some physicians. The drugs that are banned like nimesulide, a NSAID, have been prescribed by many physicians. These problems need to be addressed.

Our study has several weaknesses. During the acute phase, the ophthalmologist screened only patients with suspected ocular involvement identified by the treating physician, which may have resulted in an underestimation of ocular involvement. Although we intended to analyze the outcome, as most of the patients came from a rural background, it was not possible to contact these patients, despite an extremely thorough

search by telephone and address.

Despite its retrospective nature, this study is useful to understand some of the presenting features, possible aetiological factors, ocular complications and management in SJS, TEN & overlap syndrome.

References

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Steven Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993; 129(1):92-96.

2. Rzany B, Mockenhaupt M, Baur S; et al. Epidemiology of erythema exsudativum multiforme majus, STEVEN JOHNSON syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. J Clin Epidemiol. 1996;49(7):769-773.

3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-1285.

4. Sotozono C, Ang LP, Koizumi N; et al. New grading system for the evaluation of chronic ocular manifestations in patients with STEVEN JOHNSON syndrome. Ophthalmology. 2007;114(7):1294-1302.

5. Koizumi N, Inatomi T, Suzuki T, Sotozono C, Kinoshita S. Cultivated corneal epithelial transplantation for ocular surface reconstruction in acute phase of STEVEN JOHNSON syndrome. Arch Ophthalmol. 2001;119(2):298-300.

6. Nordlund ML, Holland EJ, Kersten RC. Ocular surface reconstruction in a patient with complete ankyloblepharon resulting from STEVEN JOHNSON syndrome. Arch Ophthalmol. 2004; 122(6):934-935.

7. Arstikatis MJ. Ocular aftermath of Stevens Johnson syndrome: review of 33 cases. Ophthalmology 1973;90:376-79.

8. Rasmussen JE. Erythema multiforme in children. Response to treatment with systemic corticosteroids. Br J Dematol 1976;95:181-86.

9. Biancine JR, Macaraeg PV Jr, Lasagna L, Azarnoff DL, Brunk SF Hvidberg EF, et al. Drugs as etiological factors in Stevens Johnson syndrome. Am J Ophthalmol 1968;44:390-405.

10. Bottinger LE, Strandberg I, Westernholm B. Drug-induced febrile mucocutaneous syndrome: With a review of literature. Acta Med Scand 1975;198:229-33.

11. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute

ophthalmic manifestations of erythema multiforme/Stevens Johnson syndrome/ toxic epidermal necrolysis disease spectrum. Ophthalmology 1995;102:1669-76

12. Pleyer U, Haberle H, Baatz H, et al. Acute manifestations of oculo-cutaneous disorders: erythema multiforme major, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Pleyer U, Hartmann Chr, Sterry W, eds. Oculodermal diseases. Buren, The Netherlands: Aeolus Press, 1997:169-91.

13. Leonard J N, Dart J K G. The skin and the eyes. In: Burns, ed. Rooke's dermatology. Oxford: Blackwell Scientific, 2004:64.1-64.38

14. Yetiv JZ, Bianche JR, Owen JA. Etiologic factors of the Stevens-Johnson syndrome. South Med J 1980;73:599-602.

15. Honavar SG, Bansal AK, Sangwan VS, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction in STEVEN JOHNSON syndrome. Ophthalmology 2000;107:975-79.

16. Schopf E, Stuhmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol 1991;127:839-42.

17. Foster CS, Fong LP, Azar D, Kenyon KR. Episodic conjunctival inflammation after Stevens Johnson syndrome. Ophthalmology 1988;95:453-62.

18. Prendiville JS, Herbert AA, Greenwald Mj, Esterly MD. Management of Stevens Johnson syndrome and toxic epidermal necrolysis in children. J Pediatr 1989;115:881-87.

19. Mondino B. Cicatricial pemphigoid and erythema multiforme. Ophthalmology 1990;97:939-52.

20. Baum J. Clinical manifestations of dry eye states.Trans Ophthalmol Soc UK 1985;104:415-23.

21. Wright P, Collin JR. The ocular complications of erythema multiforme (Stevens Johnson syndrome) and their management. Trans Ophthalmol Soc UK 1983; 103: 338- 41.

22. Tabbara K, Shammas H. Bilateral corneal perforations in Steven Johnson syndrome. Can J Ophthalmol 1975;10:514-17.

23. Giasson CJ, Bouchard C, Boisjoly H, Germain L. Amnion and ocular surface problems [in French]. Med Sci (Paris). 2006;22(6-7):639-644.

24. Muraine M, Gueudry J, Toubeau D; et al. Advantages of amniotic membrane transplantation in eye surface diseases [in French]. J Fr

Ophtalmol. 2006;29(9):1070-1083.

25. Muraine M, Descargues G, Franck O; et al. Amniotic membrane graft in ocular surface disease: prospective study with 31 cases [in French]. J Fr Ophtalmol. 2001;24(8):798-812.

26. Kobayashi A, Yoshita T, Sugiyama K; et al. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. Ophthalmology. 2006;113(1):126-132.

27. John T, Foulks GN, John ME, Cheng K, Hu D. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. Ophthalmology. 2002;109(2):351-360.