International Journal of Research in Dermatology
Rahima S et al. Int J Res Dermatol. 2017 Mar;3(1):134-139
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20170802

Original Research Article

A clinical study of Stevens-Johnson syndrome and toxic epidermal necrolysis in a tertiary centre, South India

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Received: 30 December 2016
Accepted: 02 February 2017

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ABSTRACT

Background: Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered as the severest end of spectrum of erythema multiforme. Various etiologies like infections, drugs and malignancies have been proposed. The aim of the present study was to know the incidence, common causes, clinical course of SJS and TEN and to estimate the morbidity and mortality.
Methods: A 2 year study of patients presenting with SJS and TEN was carried out. A detailed examination to know the cutaneous and mucosal involvement was done. Biopsy was done in 3 patients.
Results: There were fifty patients of SJS-TEN spectrum. Of which 31 were SJS, 3 had SJS-TEN overlap and 16 had TEN. Anticonvulsants were implicated in causing these reactions in 24 patients (48%) with carbamazepine being the most common i.e. in 16 patients (32%). Sparing of pressure areas like the strap area of brassier and waist was noticed in two patients (4%). The most common complication was due to eye involvement seen in 20 patients (40%). 46 patients were treated with steroids and of the remaining, 3 were children and one was HIV positive. Only three patients with TEN (6%) died.
Conclusions: To conclude, TEN was less common than SJS, had more sequelae and more mortality compared to SJS.

Keywords: Stevens Johnson syndrome, Toxic epidermal necrolysis, Treatment

INTRODUCTION

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are life threatening disorders.[1] They are considered as the severest end of spectrum of erythema multiforme. Erythema multiforme (EM) is an acute self-limiting mucocutaneous disorder characterized by unique iris or target lesions. It represents an ill-defined syndrome with a spectrum of manifestations and myriads of causes. Erythema multiforme minor differs from SJS in duration, severity and extent of mucosal damage. SJS manifest with severe systemic symptoms and should have one or more mucosal involvement. TEN is an acute life threatening syndrome characterized by extensive erythema, cutaneous tenderness and peeling of necrotic epidermis in sheets leaving a scalded appearance.[2] When it starts as SJS and progresses to TEN, it is called Stevens Johnson syndrome – toxic epidermal necrolysis overlap (SJS-TEN overlap) with 10-30% of cutaneous desquamation.

A better understanding of the clinical pattern will help us to improve the recovery of these patients and to reduce the morbidity and mortality. Further, knowing the common causative drugs will caution us from using these drugs indiscriminately.

METHODS

All patients of Stevens-Johnson syndrome and toxic epidermal necrolysis admitted in our department during a two year period from August 1999 to July 2001 were included in the study. An approval from the ethics committee was obtained. A careful and complete clinical

history with emphasis on possible etiological factors especially ingestion of drug and infection were elucidated. Indication for the drug and the time period between ingestion of drug and onset of disease was sought. Percentage of body surface area involved at the maximum, was taken for classification into SJS-TEN spectrum. A complete haematological profile, urine analysis, renal function tests, liver function tests, serum electrolytes, skin and blood cultures were done in all patients. Skin biopsy was done in 3 patients who were willing.

Patients with severe denudation were made to lie on sterile plaintain leaves. All suspected drugs were stopped and if necessary substituted with chemically unrelated drugs. Patients were started on injection dexamethasone (8 mg) on the day of admission and tapered off. Meticulous eye care was advised and daily ophthalmology review was done. All patients were followed up for at least 3 months to identify the sequelae.

RESULTS

There were fifty patients of SJS-TEN spectrum during this 2 year study period. 31 were SJS, 3 had SJS-TEN overlap and 16 had TEN. The average age of SJS, SJS-TEN overlap and TEN were 38.9, 20.3 and 35.0 years respectively. Maximum incidence with SJS was noted in the 6th decade and TEN in the 3rd decade. The overall average age was 36.5 years with peak incidence in the 3rd decade. Youngest in the series was 2.5 year old and the oldest 80 years. Twenty nine (58%) were females and twenty one (42%) males, the male: female ratio being 1:1.38.There was history of taking various drugs in forty six (92%), mumps in one patient (2%), food additive in one (2%) patient, ayurvedic drugs in one (2%) patient and no specific cause could be found in one patient (2%). Drugs implicated in causing these reactions are depicted in Table 1.

Maximum number of cases was due to carbamazepine (32%). The period between consumption of causative drug and onset of lesions varied from a minimum of 1 hour to a maximum of 72 days with an average of 14.2 days. Most common drugs used were for neurological disorders in 24 patients (48%), followed by medication for respiratory infections (24%).

Two of the patients who died had rapid progression of skin lesion within 24 hours and had 100% involvement. Purpuric macules were the predominant lesion in SJS cases, whereas TEN cases presented with vesicles, bullae and with charred appearance as shown in Figure 1. Typical target lesions as seen in Figure 2 were seen in five patients in which 4 were SJS cases and one SJS-TEN overlap. One finding which was impressing in this study was the sparing of pressure areas like the brassier strap area and waist in 2 patients (4%) as seen in Figure 1 and 3.

Table 1: Drugs implicated in SJS, TEN patients.

S. no	Drugs implicated	No. of cases	Percentage
1	Carbamazepine	16	32
2	Phenytoin	8	16
3	Antimicrobials	8	16
	a) Cotrimoxazole	3	6
	b) Chloroquine	1	2
	c) Dapsone	1	2
	d) Ciprofloxacin	1	2
	e) Erythromycin	1	2
	f) Amoxycillin	1	2
4	Analgesics, Antipyretics	7	14
	a) Paracetamol	6	12
	b) Diclofenac	1	2
5	ATT	2	4
6	Multiple drugs	2	4
7	Amlodipine	1	2
8	Promethazine	1	2
9	Allopurinol	1	2

Figure 1: Shows charred appearance, bullae and sparing of pressure areas in a patient with–TEN.

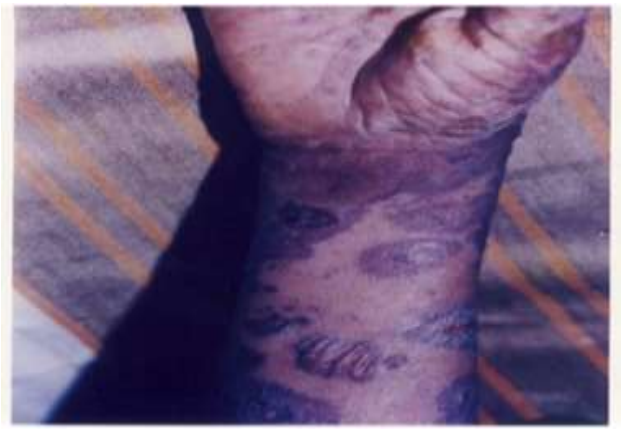

Figure 2: Shows target lesion in a patient with SJS.

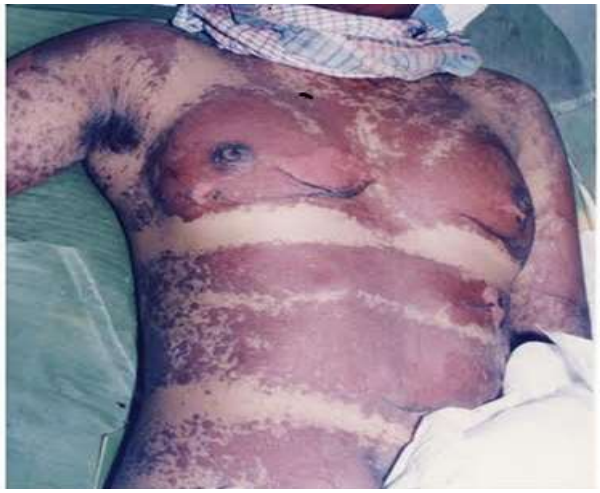

Figure 3: Shows sparing of the pressure areas in a TEN patient.

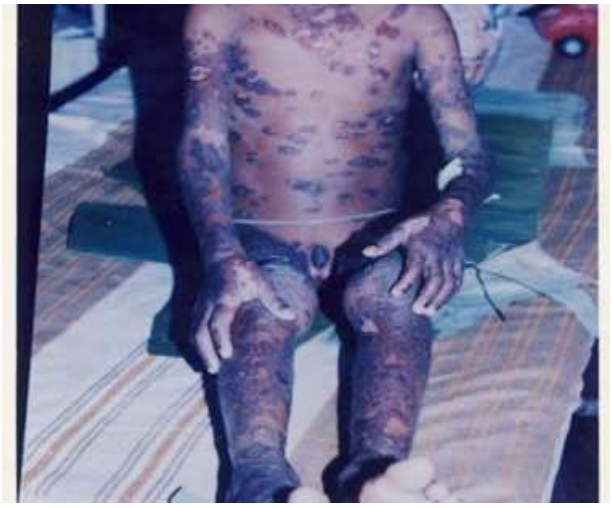

Figure 4: Shows a child with SJS TEN overlap.

Mucosal involvement was seen in all patients, varying from two to five mucosal sites as in Table 2. Most common finding was hemorrhagic crusting of the lips. Erythrocyte sedimentation rate was increased in 15 patients (30%) closely followed by haematuria (24%). Cultures from blood and skin erosion revealed *Staphylococcus aureus*. Skin biopsy was done only in 3 patients (6%) and was consistent with the clinical findings.

Table 2: Mucosal involvement in SJS, TEN patients.

No.	Mucosal involvement	No. of patients	Percentage
1	Oral	50	100
2	Eyes	43	86
3	Genitalia	40	80
4	Urethra	12	24
5	GIT	7	14
6	Nasal	2	4

The most common complication was due to eye involvement seen in 20 patients as given in Figure 4. Two patients developed bronchopneumonia, one patient who died had of adult respiratory distress syndrome as in Table 3.

Table 3: Various complications in SJS, TEN patients.

No.	Complications	No. of patients	Percentage
1	Eye complication	20	40
2	Jaundice	5	10
3	Psychiatric	4	8
4	Diabetic ketoacidosis	2	4
5	Broncho pneumonia	2	4
6	Septicemia, DIC	2	4
7	ARDS	1	2
8	Phimosis	1	2

Figure 5: Shows symblephron in a patient with TEN.

Of the 4 patients not treated with steroids, 3 were children as seen in Figure 4 and one was HIV positive. One patient had to undergo evisceration for panophthalmitis. Patient with phimosis underwent circumcision. In most of the patients, skin lesions healed with hyperpigmentation as shown in Figure 6. Details of sequelae are charted in Table 4.

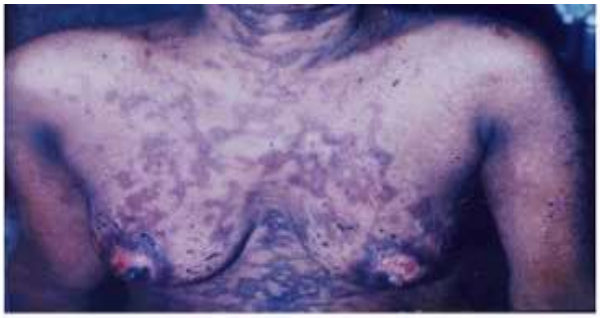

Figure 6: Shows TEN patient with erosion of nipple, cutaneous pigmentation and panophthalmitis.

Table 4: Sequalae in SJS, TEN patients.

No.	Sequelae	No. of patients	Percentage
1	Pigmentary disturbance	50	100
2	Dryness of eyes	4	8
3	Alopecia	3	6
4	Blindness	2	4
5	Corneal opacity	2	4
6	Keloidal formation	2	4
7	Trichiasis, Ectropion	1	2
8	Onychomadesis	1	2

Three (6%) out of fifty cases died, all of them were TEN cases. Two of them had rapid progression of the skin lesion within 24 hours. One died due to septicemia and the other two due to cardiorespiratory failure. Average duration of stay in hospital was 15.84 days. Maximum duration of stay was found in patients with TEN.

DISCUSSION

This two year study had revealed a total of fifty patients with SJS-TEN spectrum which accounted for 0.003% of total admissions in this institution and 2.5% of the total admissions in the dermatology ward. The incidence of SJS was reported to be 0.8 per million per year. Studies in France and Germany during 1981-85 period had an incidence of 0.93-1.30 cases of TEN/million.[1] In a review of ninety eight cases of TEN, Lyell found that 22% had features of both SJS and Lyell's syndrome.[2] Kumar et al had reported an eighty year old woman who was diagnosed as SJS but later progressed to TEN, which supports that SJS and TEN are of the same spectrum.[3]

The mean age of our patients was 36.85 years ranging from 2½ years to 80 years. Revuz et al and Roujeau had observed a slightly higher age of involvement of 45.8 years and 46.8 years indicating higher incidence of TEN in older individual.[5,6] Kaur et al recorded a lower average of 23 years which along with our finding indicate that TEN may affect lower age group in our population.[7] We had 6 children in our study which was also reported in other studies.[4]

In this study, SJS was found more in females while TEN was more in males. Male to female ratio being 1:1.38 similar to a study by Maldonado et al (1:1.47).[4] However, Kaur et al also reported slight male preponderance for TEN in Indian population.[7] Sarkari et al, Shah et al found male predominance in their series of SJS cases compared to our study where female outnumbered males.[9,10]

Drugs as the cause for these reactions is easy to postulate but difficult to prove. In this study, there was history of taking drugs in forty six cases (92%). Food additive caused the reaction in one patient which has also been noticed by Roujeau et al and Ayurvedic Medicine in another patient which has also noted by Fogh et al.[6,11]

Anticonvulsants were the commonest drug causing these reactions which was also reported by others.[4,6] Carbamazepine was found to be the most frequent culprit which was also noted by Revuz et al, Sharma et al.[5,12] In a case series by Ruiz et al, phenytoin topped the list followed by carbamazepine and the finding is also at par with other studies by Heng et al.[4,13] Sarkari et al in his study of 20 cases found sulfonamides to be the commonest compared to 3 cases in our study.[9] This may be because of the widespread use of this drug in the past and restriction of its use nowadays due to fear of reaction. ATT was found to be the culprit in two of our patients which were also found to be the commonest offender by others.[7] Chan et al and Roujeau et al found NSAIDS to be the commonest cause in their series.[1,6] The drugs implicated reflect the wide variation in drugs prescribed from place to place.

We had a case of TEN due to allopurinol which was also reported by others. We also had cases following intake of paracetamol. Roujeau et al and Shah et al has also reported incidence of cases due to paracetamol.[6,10] The period between consumption of drug and onset of lesion was with an average of 14.2 days which is also comparable with 13.6 days reported by Guillame et al in 77% of his TEN patients.[13]

The most frequent underlying disease for which the drug was taken was CNS disorder, of which seizures and neuralgia were found in 6 cases each. Prophylactic antiepileptics for head injury accounted for 3 cases, probably head injury patients are more prone for these reactions because of release of cytokines. Two of the CNS tumor cases had undergone cranial irradiation. Roujeau et al, and Eralp et al also have reported similar cases.[6,14] Probably there is suppression of suppressor T cells by irradiation.

We had one patient of SLE with seizures. Chan et al have also reported similar cases.[1] Roujeau et al feels that it might be coincidental or due to more exposure to drugs.[6] There were three (6%) patients with tuberculosis and one with AIDS. Sarkari et al and Sharma et al observed tuberculosis in 40% and 11.7% of their patients respectively.[9,12] But in these studies, the most implicated drug was thiacetazone, which is known for drug reactions. But none of our patients were on thiacetazone. Saiag et al also have reported cases with HIV infection.[15,16] This may be because of the following reasons that they are frequently exposed to various drugs, the viral infection sensitizing the patients to certain drugs, systemic glutathione deficiency and reduced ability to scavenge drug metabolites.

Fever as a prodromal symptom was reported by almost all patients which had been reported by others also.[4,6]

Fever may be due to release of pyrogens from extensive tissue necrosis, or due to the drugs itself like sulfonamides, phenytoin or due to the underlying infection. The extent of involvement had a significant effect on prognosis of the patient, because two of our patients who died had 100% cutaneous involvement within 12-24 hours. But in others, the skin lesions had progressed over a period of 3-5 days. Revuz et al also had observed one of his seven patients with 100% involvement.[5] One characteristic finding which was noticed in two female patients with TEN in this study was the typical sparing of the brassier strap areas and waist areas, i.e. in pressure areas. This finding was also noticed by Roujeau et al. [6]

Revuz et al found lymphopenia in 90% of his TEN patients, which he attributes to selective and transient depletion of CD_4 positive helper T lymphocytes.[5] We did not find any significant change in leucocytes. Abnormal renal functions in the form of proteinuria were seen in 10% of our patients which was also noted by Kaur et al (23.3%) and Ting and Adam (50%) in their patients.[7,17]

Six percent of our patients had signs of pneumonitis on chest X-ray, which was also reported by others.[18] Cultures from skin revealed *Staphylococcus aureus* to be the commonest pathogen which was also noted by others.[1] Blood culture was positive in 6% of our cases compared to 16% as reported by Maldonaldo et al, 16 of his 60 patients.[4] Blood culture positivity was more seen in TEN patients.

Most common complication was due to eye involvement (40%), which was comparable with a study by Revuz et al.[5] Complications were more common with TEN. Commonest eye complication was symblepharon which was also observed by others.[5,6] Dryness of eyes seen in 8% of patients is attributed to destruction of mucin secreting cells in conjunctiva or due to blockade of lacrimal duct.

Three (6%) of our patients had expired, all of them having TEN. Mortality rate was 30% in a French series, 34% in a German study and 20% in a Singapore study. [1,6] Cause of death in one was ARDS and other was septicemia. Both these patients had died on the 5th day of illness. Revuz et al also reported most of their deaths occurring at the initial days, thus necessitating intensive nursing care and monitoring during first few days.[5] Kaur et al, Maldonaldo et al also found septicemia in 36.7% and 17% of their cases.[4,5] All the three patients who died had been treated with steroids. This indicates that steroid therapy need not reduce mortality of this disease. Ting and Adam et al also have reported 13% mortality in their patients who were also on steroids.[18]

The hospital stay was longest for TEN which was comparable to Maldonado's et al study with total stay of 14 days for ADEN-1 and 20 days for ADEN-type 3.[4] In our study, mucosal lesions were slow to heal and accounted for longer hospital stay.

Most common sequelae was cutaneous dyschromia both hypo and hyperpigmentation. Onychomadesis noted by us also was reported by Acharya et al.[8] This is probably due to bullous lesion involving nail matrix. Nail changes were seen in higher proportion in other studies.[4,5] Two of our patients had become blind due to corneal opacity, symblepharon and panophthalmitis, which was also reported by others.[7]

Patients who died had rapid peeling of skin in 24 hours, all being TEN cases. Two of the males were of older age group. According to Revuz et al, prognostically significant factors were number of drugs taken, percentage of denuded skin, blood glucose, blood urea and platelet count.[5] Kaur et al found septicemia to be the worst prognostic factor for fatal outcome. [7]

Role of corticosteroids remain controversial. Owing to the small number of patients in the latter group and the fact that the patients were not satisfactorily matched in terms of age, sex etc., it is not possible to make any direct comparison which are statistically significant. All the patients with ocular and other sequelae were from the steroid group and all the three deaths were also from steroid group. This suggests that steroid treatment need not completely prevent long term complication and reduce mortality of disease. A retrospective study comparing the efficacy of corticosteroids finally came to a conclusion that steroid therapy does not shorten the course of the disease.[19] IV Ig was also found to be useful in healing mucosal lesion. It also reduces the hospital stay.

To conclude, in this study from South India, SJS was more commoner than TEN. Carbamazepine was the most commonly implicated drug. Sequelae, mortality was more with TEN. Extensive cutaneous involvement with rapid progression and septicemia were the bad prognostic factors. Another unique feature was the sparing of pressure areas suggesting a negative koebnerisation.

ACKNOWLEDGEMENTS

I am grateful to my professor late Dr. Thomas Koshy for his help and guidance.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Rahima S, Abdul Latheef EN, Pavithran K, Saleem PM. A clinical study of Stevens-Johnson syndrome and toxic epidermal necrolysis in a tertiary centre, South India. Int J Res Dermatol 2017;3:134-9.