Original Article

Retrospective Analysis of Cases With Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis: A Case Series of 20 Patients

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Abstract

Background: Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) are rare, acute, severe cutaneous hypersensitivity reactions usually triggered by medications. They are classified by the extent of the detached skin surface area. **Objective:** We aimed to retrospectively evaluate the sociodemographic, clinical, therapeutic, and prognostic characteristics of SJS/TEN cases diagnosed between January 2015 and December 2020 in our centre. **Materials and Methods:** All the data regarding patient characteristics were obtained retrospectively. The SCORe of Toxic Epidermal Necrolysis (SCORTEN) was used to predict disease severity and mortality rates. **Results:** Out of 20 patients (14 females, 6 males), eight (40%) were evaluated as TEN, three (15%) as SJS/ TEN overlap, and nine (45%) as SJS. The mean age was 39.2 ± 27.92 years. A higher frequency of systemic antibiotic use was found in cases of SJS/ TEN overlap or TEN compared to SJS cases during patients' follow-up after the diagnosis ($P = 0.006$). The most common responsible drug was allopurinol (25%). While the estimated mortality in patients with SCORTEN values of 4 and 5 was 58.3% and 90.0%, the mortality observed in our cohort was 50% and 100%, respectively. In terms of complications, ocular problems were the most common ones. Ophthalmic sequelae were observed in 15 patients during the follow-up period, the most common belonging to the cornea. **Conclusion:** In conclusion, early diagnosis, immediate discontinuation of suspected drugs, and good clinical care are among the most crucial treatment steps in the treatment of SJS/TEN. In addition, multidisciplinary management of the disease is vital in preventing the development of long-term sequelae in survivors.

Keywords: Eye involvement, mortality, SCORTEN, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Introduction

Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrolysis (TEN) are rare, acute, and severe cutaneous hypersensitivity reactions usually triggered by medications.[1] They are associated with significant morbidity and mortality and clinically distinguished by atypical target-like lesions with a rapid course, diffuse purpura, epidermal detachment, and involvement of at least two mucosal surfaces.

SJS/ TEN spectrum is now classified by the extent of the detached skin surface area (SSA): SJS (<10%), SJS-TEN overlap (10–30%) and TEN (>30%).[2,3] The approximate incidence of the disease is 8.6–9.6/million cases for SJS, 1.4–1.8/million cases for SJS/TEN overlap, and 0.4–2.2/ million cases for TEN.[4,5] However, immunosuppressed, especially HIV-positive individuals and individuals with specific HLA alleles, constitute the higher risk group.[6] The mortality rate is related to the severity of epidermal

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separation; while it varies between 1–5% in SJS, it increases up to 25–35% in cases with TEN.[7]

Apart from the high mortality risk, patients with SJS/TEN have also high morbidity rates with the involvement of various organ systems. One of the most common involvement site often causing morbidity is ocular involvement. It could cause acute (conjunctional hyperaemia, dry eyes, foreign body sensation, ocular pain, photophobia, erosion or ulceration of the cornea) or chronic (conjunctivalization, neovascularization, opacification, keratinization, symblepharon) sequels even loss of eyesight. Thus, it is vital to monitor patients systematically by giving special attention to the common involvement sites.[5]

Given the rarity of SJS/ TEN, there is a lack of large-scale epidemiological studies. Therefore, current study aims to identify the characteristics of SJS/TEN in our cohort.

Materials and Methods

A retrospective cohort review of patients, treated at our dermatology inpatient clinic and/or intensive care unit (ICU) between January 2015 and December 2020, was undertaken. Patients were identified by requesting all files with coding for International Classification of Diseases (ICD) codes of L51 (erythema multiforme-EM), L51.8 (EM, other), L51.9 (EM, unspecified), L51.2 (TEN) and Y57 (The side effects caused by drugs and therapeutic substances). Ethics approval was granted (Ethics no: 70904504/489). All identified medical records were reviewed. Inclusion required documented evidence of epidermal detachment with involvement of at least two mucosal surfaces or a documented diagnosis of SJS, TEN or SJS/TEN overlap syndrome made by our dermatology clinic. To minimize the risk of possible misdiagnosis, only cases meeting the consensus definition proposed by Bastuji-Garin *et al.* were included.[2] Epidermal detachment is less than 10% in SJS and diffuse erythematous or purpuric macules, flat non-typical target-like macules are seen. In SJS/TEN overlap syndrome, the detachment of SSA is between 10–30%, and clinically widespread purpuric macules and flat non-typical target-like macules are observed. TEN diagnosis covers cases with epidermal detachment over 30% of SSA.[3] Patients with insufficient information to support the diagnosis of SJS/TEN and patients with an unconfirmed diagnosis were excluded. The SCORe of Toxic Epidermal Necrolysis (SCORTEN), a scale developed for TEN to evaluate disease severity and mortality, was obtained retrospectively from records.[8]

All patients were evaluated by a dermatologist, and the diagnosis was based on the initial diagnosis, history, clinical appearance, and physical examination. In some patients, a biopsy sample was not taken as the clinical examination was typical for the diagnosis. All patients with a suspicion of SJS/TEN diagnosis have always been examined by an ophthalmologist on the first day of their admission to outpatient or inpatient clinics routinely and they were also checked on the 3rd-5th day after initial examination.

The researchers collected demographic (age, gender) and clinical data (length of hospital stays, admission to ICU, culprit agent, clinical features, definitive diagnosis, comorbidities, ocular involvement and severity, progression of clinical findings, treatment history and morbidity/mortality data) from patient records and electronic databases.

Statistics

Data were analysed in SPSS software 23. P value 0.05 was set as a cut-off for statistical significance. To define the sample, descriptive analyses were used to characterize demographic and clinical factors; continuous variables were expressed as mean ± standard deviation and categorical variables as the number and percentage. Continuous variables were compared using the Mann-Whitney test and the Kruskall-Wallis test as adequate. The predicted mortality according to SCORTEN was compared to the actual mortality.[9]

Results

Twenty patients [14 (70%) females, 6 (30%) males], who were treated and followed up with the diagnosis of SJS/TEN between January 2015 and December 2020, were included [Table 1]. The mean age of 39.2 ± 27.92 years (range:1–87). Although the mean age of women (41.89 ± 26.91) was higher than men (15.80 ± 9.41), it was not significant (P = 0.08). Furthermore, no significant difference was found in other parameters between sexes.

Out of 20 patients, eight (40%) were evaluated as TEN, three (15%) as SJS/TEN overlap, and nine (45%) as SJS. The mean age of the subgroups was 50.88 ± 31.17, 35.33 ± 26.20, 19.67 ± 8.14, respectively (P = 0.25).

The average duration of lesions at the diagnosis was 4.7 ± 2.7 days (range:2–12). The mean SCORTEN on the admission day was 2.15 ± 1.66, and the 3rd day-SCORTEN was 1.86 ± 1.79. When the relationship between SCORTEN scores and admission to ICU was examined, a significant correlation was observed with the 1st-day score (P = 0.025), while no significant correlation was found with the 3rd-day SCORTEN (P = 0.11). When the relationship between SCORTEN and treatments were examined, no significant relationship was detected, but patients with high 1st-day SCORTEN used systemic antibiotics more often than others (P = 0.09).

The most common responsible drugs were allopurinol in five (25%) patients and lamotrigine in three (15%) patients. The average hospital stay was 19.5 days, and half of the patients (50%) needed ICU. Regarding the medical history, chronic renal failure was identified in three (15%) patients, while haematological malignancy in two (10%).

Table 1: Sociodemographic and clinical characteristics of patients

Patient no	Gender	Age	Symptoms (at the time of admission)	Duration of the rash (days)	Time between suspicious drug use and rash (days)	BSA (%)	Affected area	Causative drug	Pre-existing conditions (comorbidities)
1	F	44	Typical eruption, headache, fever	7	21	>%30	Total body, oral and genital mucosa, eyes	Allopurinol	CKD
2	M	19	Typical eruption	2	45	≤ %10	Limbs, oral mucosa, eyes	Lamotrigine	Hereditary spastic paraplegia
3	F	46	Typical eruption	2	7	>%30	Trunk, limbs, oral and genital mucosa, eyes	Moxifloxacin, diclofenac	No
4	F	9	Typical eruption, fever	2	25	≤ %10	Face, trunk, limbs, oral and genital mucosa, eyes	Amoxicillin clavulanate + ibuprofen	No
5	F	80	Typical eruption	5	30	≤ %10	Trunk, oral and genital mucosa, eyes	Allopurinol	HTN, Gout
6	F	16	Typical eruption, fever	4	30	%10-30	Total body, oral and genital mucosa, eyes	Lamotrigine, amoxicillin clavulanate	Mood disturbance
7	M	29	Typical eruption	8	30	%10-30	Total body, oral and genital mucosa, eyes	Dexketoprofen, metronidazole, clarithromycin	No
8	M	14	Typical eruption, fever	12	4	%10-30	Trunk, oral and genital mucosa, eyes	Mercaptopurine	Hematological malignancy
9	F	32	Typical eruption	7	30	≤ %10	Total body, oral and genital mucosa, eyes	Lamotrigine	Mood disturbance
10	F	42	Typical eruption	2	14	≤ %10	Trunk, limbs, oral mucosa, eyes	Antibiotic?	No
11	F	70	Typical eruption	2	30	≤ %10	Face, limbs, oral mucosa, eyes	Allopurinol	DM, HTN, Gout
12	F	79	Typical eruption	2	7	>%30	Trunk, neck, oral mucosa, eyes	Gemcitabine, vinblastine	Hematological malignancy
13	M	14	Typical eruption, fever	4	7	>%30	Total body, oral and genital mucosa, eyes	Vancomycin meropenem	Lung infection (aspergillosis)
14	F	78	Typical eruption	4	23	>%30	Neck, trunk, limbs, eyes	Allopurinol	DM, HTN, Gout, HD
15	F	1	Typical eruption	7	7	>%30	Total body, genital mucosa, eyes	Multiple antibiotic	Liver transplantation
16	F	42	Typical eruption	7	10	≤%10	Trunk, limbs, oral and genital mucosa, eyes	Herpes labialis, flurbiprofen	No
17	F	87	Typical eruption, fever	3	14	>%30	Trunk, genital mucosa, eyes	Multiple antibiotic	CKD Alzheimer Disease, Parkinson, HTN
18	M	58	Typical eruption	2	21	>%30	Total body, genital mucosa, eyes	Sulfamethoxazole-trimethoprim	Cancer (Liver transplantation)
19	F	21	Typical eruption, fever	5	10	≤%10	Face, limbs, oral mucosa, eyes	Sulfasalazine	Ankylosing spondylitis
20	M	3	Typical eruption	2	10	≤%10	Trunk, limbs, oral and genital mucosa	Allopurinol, ceftriaxone	CKD, epilepsy

M: Male, F: Female, BSA: Body surface area, CKD: chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, HD: heart disease.

Patients were treated with systemic corticosteroid (CS), cyclosporine A (CsA), CS + CsA, CsA + IVIG and CS + IVIG in dermatology inpatient clinic and/or in ICU [Table 2]. There was no relationship between SJS/ TEN subgroups and age ($P = 0.25$), acute ocular involvement ($P = 0.53$), CS therapy ($P = 0.89$), CsA ($P = 0.08$) and IVIG ($P = 0.64$). Although it did not reach a significant difference, CsA was used more in patients with TEN. A higher frequency of systemic antibiotic use was found in cases of SJS/TEN overlap or TEN compared to SJS cases during patients' follow-up after the diagnosis ($P = 0.006$).

Mortality showed a statistically significant relationship with 1st and 3rd-day scores of SCORTEN ($P = 0.004$,

Table 2: Clinical characteristics, treatments, and sequels of patients

Patient no	Biopsy	Diagnosis	Treatment	Hospitalization (days)	ICU admission	Sequelae
1	No	TEN	Systemic CS	22	No	Ophthalmic
2	No	SJS	CsA	16	No	Ophthalmic
3	Yes	TEN	Systemic CS+ CsA	25	Yes	-
4	No	SJS	Systemic CS+ IVIG	18	Yes	-
5	No	SJS	CsA	14	No	-
6	No	SJS/TEN overlap	Systemic CS+ IVIG	30	Yes	Ophthalmic
7	Yes	SJS/TEN overlap	Systemic CS+ CsA	60	Yes	Ophthalmic, atelectasis, dry mouth, nail damage, alopecia
8	Yes	SJS/TEN overlap	Systemic CS	18	Yes	Death
9	No	SJS	CsA	23	No	Ophthalmic
10	Yes	SJS	Systemic CS	9	No	-
11	Yes	SJS	Systemic CS	14	No	-
12	Yes	TEN	CsA	7	Yes	Death
13	No	TEN	CsA + IVIG	14	No	-
14	Yes	TEN	CsA	13	Yes	-
15	Yes	TEN	Systemic CS+ CsA	30	No	-
16	No	SJS	Systemic CS+ CsA	5	No	-
17	No	TEN	Systemic CS+ CsA	12	Yes	Death
18	No	TEN	Systemic CS+ CsA	16	Yes	Death
19	No	SJS	Systemic CS	14	No	Ophthalmic
20	No	SJS	Systemic CS+ IVIG	30	Yes	-

SJS: Steven Johnson Syndrome, TEN: Toxic epidermal necrolysis, CsA: Cyclosporine, CS: Corticosteroids, IVIG: Intravenous immunoglobulin,

Table 3: Predilected and observed mortality rates with SCORTEN values in our case series

SCORTEN	Cases (n)	Predicted mortality (%)	Observed mortality (%)
0	2	3,2	0
1	7	3,2	0
2	5	12,1	0
3	0	35,3	0
4	4	58,3	50
>5	2	90,0	100
Overall	20	25,2	20

$P = 0.025$, respectively). While the estimated mortality in patients with SCORTEN scores of 4 and 5 was 58.3% and 90.0%; the mortality observed in our study was 50% and 100%, respectively [Table 3]. No mortality was observed in patients with lower SCORTEN scores in this cohort.

In terms of complications, ocular problems were the most common ones. While 15 had acute ocular involvement, seven (31.5%) had severe ocular involvement (which is described as damage +formation of pseudomembranes in the ocular surface epithelium) and the amniotic membrane cover was applied in five patients [Supplementary Material 1]. Ophthalmic sequelae, which could be as corneal, conjunctival or eyelid complication, were observed in 15 patients during the follow-up period; the most common belonging to the cornea (loss of vogt palisade in five patients, epithelial defect in five, neovascularization in seven patients) and severe cornea involvement was usually associated with concomitant conjunctival and eyelid sequelae [Supplementary Material 2]. Although there were patients with sequelae in other mucous membranes, no comment was made since sufficient information could not be obtained retrospectively from patient records.

Discussion

Although TEN is more common in adults, SJS is mostly seen in children and young adults.[10] In our cohort, the mean age was 39.2 years which is in line with the average age reported (40–50 years) in the literature.[4] However, the mean age of patients in current study was lower than the previous study of our centre (52.75 years).[11] Furthermore, the rate of female patients was higher than male patients in most studies, as in this study, which was also different from our previous report.[11]

While culprit drugs are usually identified in 85% of SJS/TEN cases, they can only be detected in more than half of the SJS cases.[12] Therefore, the etiological relationship with drugs is most evident in TEN. In the literature, antiepileptics, allopurinol, trimethoprim/sulfamethoxazole (TMP-SMX), β-lactam antibiotics as medications and *Mycoplasma pneumoniae* among infections are reported as the most common triggers.[13-15] Allopurinol was the leading drug in this study, which was also the most common trigger in the European study conducted by Halevy *et al.*, unlike other reports showing different culprit drugs.[13-15] In a multicentre retrospective study from USA, the most frequent causative agent was

TMP-SMX (26.3%).[13] Antimicrobial drugs (37.2%) followed by antiepileptic drugs (35.7%) were also identified as the leading causes of SJS/TEN in a systematic review of Indian studies as well as the series [antibiotics (39%)] from Brazil.[5,15] However, antibiotics are one of the most used drugs both in inpatient and outpatient clinics. Therefore, in relative terms, antibiotics might be less relevant than other drugs. Furthermore, possible racial disparities, including genetic variations and susceptibility, as well as usage patterns and individual characteristics, might play an important role in the etiopathogenesis.[16] In the previous retrospective study of our centre, sulfasalazine and non-steroidal anti-inflammatory drugs followed by anticonvulsants were the most common causative medications.[11] However, our current study demonstrated allopurinol (25%) followed by anticonvulsants (lamotrigine) as the most common responsible drugs in the last 5 years.

The pathogenesis of SJS/TEN is not fully known. Drug-induced cytotoxic T lymphocytes are thought to initiate epithelial keratinocyte apoptosis and necrosis. Major histocompatibility complex class I drug presentation leads to clonal expansion of CD8+ cytotoxic T lymphocytes infiltrating the skin. In the study of Chung *et al.*, granulysin, a cytolytic protein secreted by cytotoxic T cells and natural killer (NK) cells, draws attention as an important mediator in keratinocyte apoptosis as well as increased interaction between FAS ligand and FAS death receptor on keratinocytes.[17] Granulysin levels in samples taken from the bulla content of patients with TEN were higher than other cytotoxic mediators and were found to be associated with disease severity.[18] On the other hand, Williams *et al.* suggested that a cytokine-mediated response contributes to the initial insult and an unresolved innate inflammatory process causes disease progression.[19]

Approximately half of the patients have prodromal symptoms like upper respiratory tract infections. These symptoms are usually accompanied by mucosal involvement. Approximately 1–3 days later, painful skin findings may appear, and systemic organ involvement can be seen in the course of the SJS/TEN. Therefore, early diagnosis and immediate discontinuation of suspicious medications are at utmost importance. Despite the various therapeutic options used in recent years, supportive therapy is still considered the most critical approach.[1] In our cohort, the number of patients requiring ICU was similar to the rates (55%) in the RegiSCAR cohort study by Sekula *et al.*[20]

Patients with SJS/TEN are suggested to be treated in an ICU/burn unit as severe fluid and electrolyte imbalance, temperature irregularities, nutritional and airway problems are common. Furthermore, special surveillance is needed for wound care, infection and other specialized care associated with systemic involvement of SJS/ TEN because of the rapid progress leading to death.[13,21] However, one third to half of the patients were often managed primarily in a nonspecialized medical ward, according to the retrospective data.[20]

Although supportive and intensive care is the most crucial approach, many systemic therapies were also used with inconsistent benefits.[21] Systemic treatment varies widely as a few evidence-based recommendations exist, and there is no clear consensus in acute or chronic management. CS, CsA and/or IVIG are the most used ones in the literature as in our study, along with supportive clinical care. Others include TNF-alpha inhibitors and plasmapheresis.[21] The published literature has shown mixed results. While some studies reported survival benefits, others showed no benefit or even increased mortality with systemic immunomodulatory treatments.[22-27] In our study, patients were treated with CS (25%), CsA (25%), systemic CS + CsA (30%), CsA + IVIG (5%) and CS + IVIG (15%). Due to a limited number of patients and variability of administered protocols, the current study has not shown any survival benefit for a specific treatment protocol. However, a possible reduction in mortality was shown with CS in many studies, including the results of a recent meta-analysis,[22] although other ones showed either no benefit or increased infection, prolongation of hospital stay, and higher mortality. IVIG is another therapeutic choice commonly used in the literature with uncertain efficacy. A systematic review and some case series suggested that IVIG, particularly high-dose IVIG (>2 g/kg total dose), improves survival.[23] However, many others showed no benefit on mortality.[22] Some studies also showed better outcomes in combination of IVIG and CS.[13,24] Thus, a combination of short-term CS and IVIG might be an alternative option, especially when used early in the disease course. In the last decade, improved outcomes, and lower mortality rates with CsA have also been published.[22,25] However, some studies showed no benefit with CsA, as well as acute renal insufficiency and common accompanying diseases such as hypertension and chronic renal problems are limiting factors for its use.[21,26] On the other hand, CsA demonstrates a benefit on actual mortality versus predicted mortality, according to the comparison of SCORTEN.[21] Another meta-regression analysis showed that CsA and IVIG plus CS were associated with fewer deaths than predicted by SCORTEN.[27] Zimmermann *et al.* suggested that CS and CsA are the most promising systemic immunomodulators in the treatment of SJS/ TEN.[22] Regarding anti-TNF-alpha agents, there are only limited case reports that are insufficient to draw any actual conclusion for their use and efficacy.

The mean SCORTEN score on day 1 was 2.15 ± 1.66, and on day 3 was 1.86 ± 1.79. When the relationship between SCORTEN scores and admission to ICU was

examined, a significant correlation was observed with the 1st-day score ($P = 0.025$), while no significant correlation was found with the 3rd-day score ($P = 0.11$). Previous data has shown reasonable predictability of mortality according to SCORTEN.[27] Furthermore, in multivariate meta-regression analysis, the mean age of patients and the ending year of the study were shown as significant influencers on the prediction of SCORTEN. Increasing age was associated with a significant increase in the observed/expected mortality ratio, whereas a progressive reduction in the observed/expected ratio was shown in recent years.[28] This study also revealed that there is a tendency to underestimate the mortality for SCORTEN values of 3 or less, and an opposite approach to overestimate the mortality for those above 3 (SCORTEN range: 0–7).[28] In SJS/ TEN, the mortality rate is related to the severity of epidermal detachment; while it varies between 1–5% in SJS, it increases up to 25–35% in cases with TEN. Patients with a relatively better prognosis with limited involvement (<30%) and symptoms who did not require hospitalization or had incomplete medical records, or no definitive diagnosis with a skin biopsy, were not included in many studies. Thus, patients treated in tertiary hospitals might not reflect the actual morbidity and mortality rates. Our study had %20 mortality among patients, which is similar to the literature. On any ground, prompt withdrawal of the suspected medication decreases mortality and progression of eruption.

In patients with SJS/ TEN, although antibiotics might be the cause of the eruption in some, they are also needed in patients with suspicious secondary infection. The most common infections were skin infections due to large-scale erosions and epidermal detachment, pulmonary infections being the second common one. In our cohort, systemic antibiotics were more commonly used in patients with SJS overlap and TEN versus patients with SJS. This suggests that increased skin surface involvement makes patients more prone to infections and/ or doctors to use prophylactic antibiotics early in the disease course. Diao *et al.* analysed a total of 125 patients diagnosed with SJS/ TEN between 2010–2017 and observed 75 (60%) patients with coinfections, of whom 44 had SJS (44/90, 48.9%) and 31 had TEN (31/35, 88.6%). *Staphylococcus aureus* (S. aureus) and *Escherichia coli* (E. coli) were the most frequently identified pathogenic organisms, and the most common antibiotics used in patients with coinfections were vancomycin, carbapenems, quinolones and macrolides.[29]

While it is vital to improve survival, a lack of multidisciplinary care can leave survivors with long-term sequelae in various organ systems. For example, significant acute (occurs in 60–100%) and chronic ocular involvement is well-documented among patients with SJS/TEN as well as in our study. Thus, ophthalmologic consultation upon admission is critical. Mederios *et al.* observed ophthalmic sequelae as the most prevalent (40%-75% of the total sequelae)[5] In our centre, ocular involvement was evaluated and classified with the ocular surface grading score defined by Jain *et al.*[30] Aggressive lubrication, judicious use of topical CS eye drops, prevention of infection with antibiotic eye drops, as well as amniotic membrane transplantation have significantly improved the outcomes of ocular disease in SJS/ TEN patients in our study, which is also the suggested approach in the literature.[30] Complications beyond the eye and skin are also described which are likely to reduce the quality of life for survivors.

Our study is in line with the previous literature regarding the association between SCORTEN scores and mortality. The presence of experienced consulting dermatologists and multidisciplinary teams, increased use of ICUs or burn units, high-level scientific research, and evidence-based recommendations on management are urgently needed.

Our study was limited by its retrospective nature and being a sample from a tertiary centre. Additionally, data retrieval also represented a possible limitation as, in some cases, we could not reach some information from the medical chart.

Prospective multicentre studies are necessary to identify epidemiologic and sociodemographic factors and develop evidence-based guidelines regarding SJS/ TEN.

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Conflicts of interest

There are no conflicts of interest.

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