Acta Derm Venereol 2016; 96: 525–529

CLINICAL REPORT

Long-term Sequelae of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Che-Wen YANG[1], Yung-Tsu CHO[1], Kai-Lung CHEN[1], Yi-Chun CHEN[1,2], Hsiang-Lin SONG[3] and Chia-Yu CHU[1]
Departments of Dermatology, [1]National Taiwan University Hospital and National Taiwan University College of Medicine and [2]Cathay General Hospital, Taipei, and [3]Department of Pathology, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions characterized by different extents of epidermal necrosis and mucosal breakdown. A limited number of studies have reported the long-term patterns of SJS and TEN complications in patient populations over long follow-up periods. The aim of this retrospective study was to collect data on long-term sequelae in patients admitted for SJS, SJS/TEN overlap, or TEN between 1998 and 2012. Among all 102 patients eligible for analysis, the 2 most common sequelae were cutaneous and ocular problems, both with incidences of 44.1%. Visceral organ involvement was observed in 2 patients with irreversible deterioration of chronic kidney disease and in one patient with interstitial lung disease. Autoimmune disease was present in 6 patients: Sjögren's syndrome or Sjögren-like syndrome in 5 patients and concomitant systemic lupus erythematosus and Hashimoto thyroiditis in 1 patient. *Key words: complication; sequelae; Sjögren's syndrome; SJS; Stevens-Johnson syndrome; TEN; toxic epidermal necrolysis*.

Accepted Nov 18, 2015; Epub ahead of print Nov 19, 2015

Acta Derm Venereol 2016; 96: 525–529.

Chia-Yu Chu, Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, No. 7, Chung-Shan South Road, Taipei, Taiwan. E-mail: chiayu@ntu.edu.tw

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions characterized by different extents of epidermal necrosis and mucosal breakdown. Even though they account for only a small proportion of adverse drug reactions, physicians should seek to increase their awareness of the accompanying mortality and morbidity. In a previous study, disease severity was determined according to the area of epidermal detachment in affected individuals, ranging from SJS (< 10% of the body surface area) to SJS/TEN overlap (10–30% of the body surface area) to TEN (> 30% of the body surface area) (1). The chronic sequelae of SJS have been discussed in a number of studies published over the past decade (2–8). Well-known long-term complications include ocular and cutaneous sequelae (2). Mucosal involvement consisting of oral frenulum-like fibrotic bands or vulvovaginal synechiae has also been noted previously (3, 4). Although rare, chronic pulmonary complications, including bronchiolitis obliterans, chronic bronchitis, and interstitial lung disease (ILD), have also been reported previously (5). Most of the past research discussing the long-term complications of SJS and TEN has focused on specific organ systems. Prior to the present study, little was known about the pattern of different complications encountered during long-term follow-up of patients. The aim of this retrospective study was to determine the incidence of various sequelae related to SJS/TEN among patients at a single medical centre.

METHODS

Patients

Patients who were admitted and treated for SJS, SJS/TEN overlap, or TEN at National Taiwan University Hospital between 1 January 1998 and 31 December 2012 were included in this study. The diagnoses of SJS, SJS/TEN overlap and TEN were confirmed by using the RegiSCAR criteria (1). Among all the patients, 35 cases that were diagnosed after 2007 had consented to participate in the RegiSCAR study. We retrospectively reviewed the medical records of these patients to collect their demographic data as well as data on the causative drugs, length of hospitalization, treatments, and mortality. This study was approved by the research ethics committee of National Taiwan University Hospital.

Definition of long-term sequelae and data collection

Long-term sequelae were defined as the onset of clearly diagnosed diseases, observed end-organ failure after resolution of SJS/TEN, or the onset of a disease during the acute stage that was still not resolved at least one month after the resolution of SJS/TEN. We designed a questionnaire regarding each patient's clinical visits and diagnosed long term-complications (Table SI[1]). We then used the questionnaire to conduct phone interviews with the patients as a means of evaluation and medical chart review to evaluate patients who were followed up for at least one year after the diagnosis of SJS/TEN. Patients who died during hospitalization were excluded from the study population. In contrast, patients who died within the first year after discharge with sequelae, or who had not died within one year after discharge, were included in the follow-up study population. For these patients, we noted the cause of death and health status before death by using medical records and by conducting interviews with family members.

[1]https://doi.org/10.2340/00015555-2295

Statistical analysis

Measurement data for each group are shown in terms of means ± SDs. Statistical comparisons between the groups were performed by SPSS (Version 19, IBM Corp, Armonk, NY, USA). Statistical significance was defined as p-values <0.05.

RESULTS

A total of 151 patients who received a diagnosis of probable or definite SJS, SJS/TEN overlap, or TEN during the study period were identified (Fig. 1). Of those patients, we excluded 28 who were lost to follow-up. Of the remaining 123 patients (91 probable cases and 32 definite cases), 90 were diagnosed with SJS, 11 were diagnosed with SJS/TEN overlap, and 22 were diagnosed with TEN. Because of the small sample size of the SJS/TEN overlap group, we divided the patients into only 2 groups; a SJS group and a group including both the SJS/TEN overlap and TEN patients (overlap-TEN group) for further analysis (Table I). There was no significant difference in age and sex distribution among the SJS and overlap-TEN groups. Assessment of drug causality was performed by using Naranjo score before 2010 (9) and ALDEN score (10) after 2010. Among the common causative drugs were carbamazepine, allopurinol and phenytoin, with the causes being similar in both groups. The mean number of hospitalization days for the overlap-TEN patients was higher than the mean for the SJS patients, but the difference did not reach statistical difference. The overall mortality rate for the overlap-TEN group was higher than that for the SJS group (45.5% vs. 20.0%, $p=0.01$), but this was largely due to the higher in-hospital mortality rate among the overlap-TEN patients (30.3% vs. 8.9%, $p=0.007$). There was no significant difference in mortality rates between the 2 groups after discharge.

Table I. *Demographics of patients with Stevens-Johnson syndrome (SJS) and SJS/toxic epidermal necrolysis (TEN) overlap + TEN*

	SJS ($n=90$)	SJS/TEN overlap + TEN ($n=33$)	p-value
Age, years, mean ± SD	55.7 ± 19.8	55.8 ± 20.9	0.948
Male sex n (%)	45 (50.0)	14 (42.4)	0.603
Hospital days, mean ± SD (median)	20 ± 33.1 (12.5)	27 ± 21.7 (19)	0.193
Common culprits, n (%)			
Carbamazepine	19 (21.1)	3 (9.1)	0.123
Allopurinol	14 (15.6)	3 (9.1)	0.357
Phenytoin	10 (11.1)	4 (12.1)	0.876
Trimethoprim-sulphamethoxazole	8 (8.9)	2 (6.1)	0.611
Diclofenac	5 (5.6)	3 (9.1)	0.481
Mortality, n (%)	18 (20.0)	15 (45.5)	**0.010**
In-hospital death	8 (8.9)	10 (30.3)	**0.007**
One-year mortality	3 (3.3)	2 (6.1)	0.610
Mortality after one year	7 (7.8)	3 (9.1)	0.727

Significant values are shown in bold.

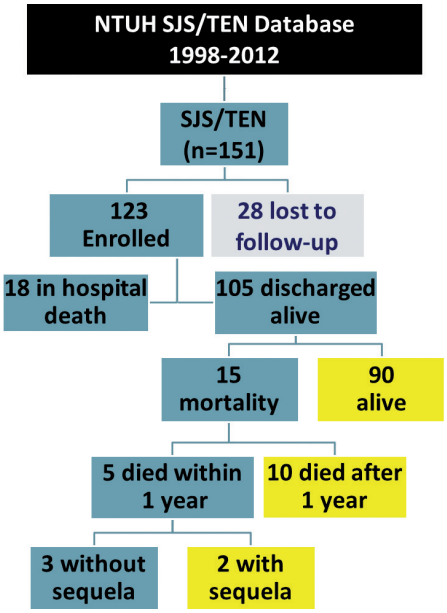

Fig. 1. Study flow diagram. Follow-ups were completed in 105 patients, 90 of whom were still alive at the end of the follow-up period. Among the 15 patients who died after being discharged, 10 died after the first year. Two of the 5 patients who died within the first year had Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)-related sequelae. Finally, a total of 102 patients were eligible for analysis (*yellow background*). NTUH: National Taiwan University Hospital.

Out of all 123 patients, 18 died during hospitalization. Therefore, we completed follow-up for 105 patients, 90 of whom were still alive at the end of the follow-up period. Among the 15 patients who died after being discharged, 5 died within the first year. Three of these 5 patients died without any SJS/TEN-related sequelae. Finally, a total of 102 patients were eligible for analysis (Fig. 1). Sixty-eight patients were found to have at least one complication, with an overall incidence of 66.7%. The incidence of sequelae was 63.0% among the SJS group patients and 81.0% among the overlap-TEN group patients ($p=0.119$). Cutaneous and ocular problems were the 2 most common sequelae. Other less frequent complications included connective tissue diseases and visceral organ involvement (Table SII[1]).

Cutaneous sequelae

Skin or nail problems were the most frequent sequelae noted in this study (45/102, 44.1%; Table SII[1]). Common cutaneous sequelae were chronic eczema (31.4%), persistent skin pigmentary changes, including hyperpigmentation and hypopigmentation (13.7%, Fig. 2A–D), and chronic nail changes, such as anonychia, dystrophic nails, longitudinal nail ridges, and pterygium (11.8%, Fig. 2E, F). The inter-group analysis showed a markedly higher rate of nail changes among the overlap-TEN group than the SJS group (28.6% vs. 7.4%, $p=0.007$). One patient was diagnosed as having bullous pemphigoid with the presentation of many itching erythematous vesicles on her trunk and limbs without mucosal involvement 6 years after SJS. A skin biopsy examination showed subepidermal blister with eosinophil and

lymphocyte infiltration. The patient responded well to topical clobetasol propionate 0.05% ointment and achieved complete remission without relapse.

Ocular sequelae

Late ophthalmic complications developed in 45 patients (44.1%). Common presentations included dry eye syndrome with tearing, foreign body sensation, or hyperaemia (32.4%), chronic conjunctivitis (21.6%), trichiasis (5.9%), corneal erosions (4.9%) and symblepharon/synechia (3.9%). We found the incidences of symblepharon/synechia and trichiasis to be significantly higher among the overlap-TEN group patients, particularly in those patients with severe eye involvement in the acute stage. Most patients with eye sequelae were followed up by ophthalmologists and received treatment for symptom relief. Four patients with large areas of epithelial defect and symblepharon had been treated with amniotic membrane transplantation during the acute or chronic stage.

Other sequalae (case reports)

Connective tissue diseases. One 46-year-old woman, a healthy hepatitis B carrier, was admitted for SJS. Laboratory data investigation showed liver involvement presenting as a cholestatic pattern. Because her high reactive hepatitis B surface antigen (HBsAg) level (> 250 IU/ml) and a hepatitis B virus (HBV) viral load of 1.2 E+04 IU/ml, the patient was treated with cyclosporine for her SJS and entecavir for acute flare of chronic hepatitis B. In the screening examination for acute hepatitis, a positive anti-nuclear antibody (ANA) at a titre of 1:640, homogenous pattern, was detected 10 days after admission. Serial work-up showed no evidence of SLE and negative for serological markers of autoimmune hepatitis (anti-smooth muscle antibodies, anti-mitochondria antibodies, and anti-liver-kidney microsomal-1 antibodies). One year later, she presented with general malaise, persistent fever, arthralgia on multiple peripheral joints, oral ulcers, and central facial rash. Laboratory studies showing an ANA titre of 1:2,560, homogenous pattern, and a positive anti-double-stranded DNA antibody (542 IU/ml, normal range < 100 IU/ml) confirmed the diagnosis of SLE. Meanwhile, the patient was diagnosed as having coexisting Hashimoto thyroiditis based on an elevated anti-thyroglobulin antibody level of 44.89 IU/ml (normal range < 14.3 IU/ml) and an elevated anti-thyroid peroxidase antibody level of 96.27 IU/ml (normal range < 5.5 IU/ml) with euthyroid status. The patient was treated with systemic corticosteroids, azathioprine and hydroxychloroquine, which resulted in satisfactory disease control.

Five patients were diagnosed as having Sjögren's syndrome or Sjögren-like syndrome based on clinical symptoms and objective measures. All 5 patients had persistent symptoms of xerostomia and keratoconjunctivitis sicca before they were identified with positive anti-Sjögren's-syndrome-related antigen A (anti-SSA) or SSB antibodies or abnormal Tc-99m sialoscintigraphy. One of these 5 patients was classified as having secondary Sjögren's syndrome according to the revised American–European Consensus Group (AECG) classification criteria because of underlying rheumatoid arthritis (11). Two patients met the revised AECG classification criteria for primary Sjögren's syndrome. Two patients were diagnosed as having Sjögren-like syndrome due to their significant clinical symptoms and abnormal Tc-99m sialoscintigraphy results, but inadequate objective evidence for diagnosis.

Visceral organ involvement. One patient developed exertional dyspnoea and dry cough one month after the onset of allopurinol-induced SJS. Mycoplasma infection was excluded by serological test. A chest computed tomography examination showed a reticular pattern in the dependent portion of both lung fields. Pulmonary function tests showed moderate impairment of diffusion capacity (diffusing capacity of the lungs for carbon monoxide (DLCO): 56.74% predicted). An autoimmune profile was positive for ANA at a titre of 1:2,560 (centromere) and low C4 level (15.5 mg/dl, range: 27.45 ± 10.72 mg/dl). Following a

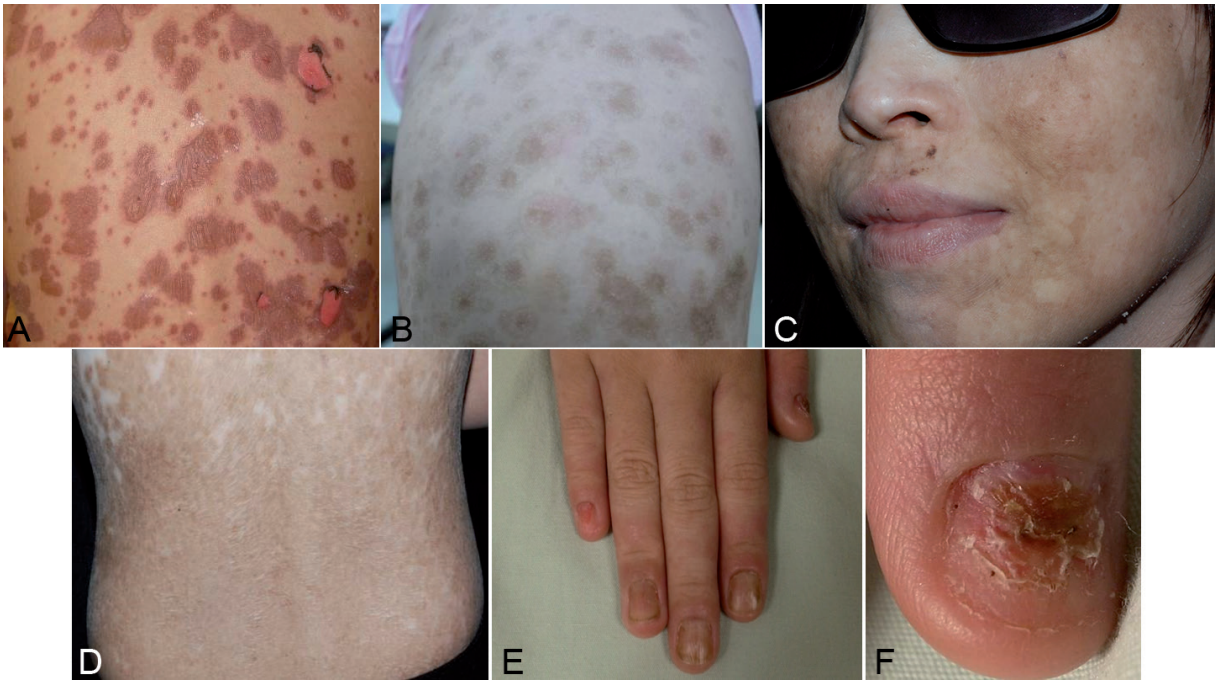

Fig. 2. Epidermal detachment in acute stage (A) and post-inflammatory hyperpigmentation after 3 months (B). Post-inflammatory hypopigmentation on the face (C) and trunk (D). Nail deformities may be found in several fingers (E), and lead to nail dystrophy (F).

diagnosis of ILD, she was treated with 30 mg prednisolone with tapering for 3 months, which subsequently resulted in gradual remission. There was no classifiable connective tissue disease during long-term follow-up.

Two patients developed significant deterioration of pre-existing chronic kidney disease after SJS. Both patients had diabetes mellitus, hypertension, and chronic kidney disease (CKD). One of them was a 63-year-old woman with stage 4 CKD who experienced a worsening of renal function during hospitalization. Although she experienced subsequent recovery, along with an improvement in the SJS, progressive deterioration of her renal function occurred in the following months. She began peritoneal dialysis 3.7 years later. The other patient, a 47-year-old man, had stage 3 CKD and presented with acute chronic kidney failure at the time of the SJS episode. There was no recovery afterwards. The patient progressed to stage 5 CKD and is still regularly followed up at a nephrology clinic.

DISCUSSION

SJS and TEN are rare, but potentially life-threatening, disorders. According to a survival analysis conducted by the RegiSCAR study group, the mortality rates at 6 weeks for SJS, SJS/TEN overlap, and TEN were 12%, 29% and 46%, respectively (6). Our results were comparable to those of this earlier report, with in-hospital mortality rates of 8.9% in the SJS group and 30.3% in the overlap-TEN group. The effect of disease severity on mortality was not so significant after discharge. Among those who died after being discharged, the deaths were not closely related to the sequelae of SJS/TEN (Table SIII[1]).

Cutaneous sequelae were identified as one of the most common chronic complication of SJS/TEN in our cohort. Chronic eczema was a frequent diagnosis among patients who visited dermatology clinics, accompanied by xerosis and pruritus to varying degrees. Both nail changes and post-inflammatory dyspigmentation were observed among the patients in our study, with both problems potentially lasting for years or even becoming permanent. The incidences of nail changes and skin depigmentation in patients with TEN were previously reported to range from 36% to 46% and from 69% to 100%, respectively (7, 8). The lower incidences of all kinds of sequelae found in this study might have been due to more SJS patients being included, the larger sample size, and the longer follow-up period.

Ocular complications are frequently found after SJS/TEN, with the incidence ranging from 20% to 77% (2, 8, 12). In this study, dry eye syndrome and chronic conjunctivitis occurred in 32.4% and 21.6% of patients, respectively. Most of them reported a need for artificial tear drops or gels. In our cohort, 3 patients without eye involvement during the acute stage experienced chronic sequelae after recovery from SJS/TEN. The manifestations of chronic sequelae included concomitant chronic conjunctivitis and nasolacrimal duct obstruction in one patient, chronic conjunctivitis in another, and dry eye syndrome in the third. One previous study on ocular complications of SJS/TEN reported that 5 out of 31 patients with late ocular complications had no eye involvement during the acute stage (13). Taken together, these findings indicate that SJS/TEN patients should be carefully followed up even without eye involvement in the acute stage.

No previous report has mentioned autoimmune disease as a late complication of SJS/TEN. In this study, however, we observed one patient who had SLE with coexisting Hashimoto thyroiditis one year after SJS. Two patients developed primary Sjögren's syndrome and one patient developed secondary Sjögren's syndrome 2–12 years after SJS/TEN. The prevalence of primary Sjögren's syndrome in our study population was slightly higher than that observed in other studies using the same diagnostic criteria (0.09–0.72%) (14). It has previously been reported that Sjögren-like syndrome was not uncommon after TEN (15). Only one previous case report described a patient who developed SJS complicated with definite Sjögren syndrome (16). We observed 2 patients with Sjögren's syndrome presenting several years after being diagnosed with SJS/TEN. The results indicate the necessity of examining serological autoantibodies and salivary gland function in any symptomatic patients after the SJS/TEN episode.

Respiratory complications are sometimes seen after SJS/TEN, especially in patients with early pulmonary symptoms. The most frequently reported presentations are chronic bronchitis/bronchiolitis with obstructive change (5). In our study, ILD was observed in one case of SJS with a high-titre ANA at the recovery stage. There is one previous case report of ILD as a chronic complication in a 2-year-old female with SJS (17). The role of a high-titre ANA in our patient is of particular interest. A new disease entity termed "lung-dominant connective tissue disease (LDCTD)" was proposed in 2010 to describe idiopathic interstitial pneumonia and the presence of specific autoantibodies without classifiable connective tissue disease (CTD) (18). Our patient met the criteria for LDCTD, which subsequently ran a benign course.

The relationship between SJS/TEN and autoimmune sequelae has not yet been clearly established. An autoimmune state triggered by burn injury has been proposed in a lupus-prone mouse model (19). In one study, functional impairment of regulatory T cells (Treg) in patients with TEN during the acute stage was reported, while restoration of Treg function was observed upon recovery (20). Patients in the resolution stage were described as having a lower frequency of interferon-γ producing Treg (21). Until now there is, however, no direct evidence that SJS/TEN plays a role in the pathogenesis of autoimmune disease.

During the acute stage, patients with SJS/TEN and renal involvement commonly presented with prerenal azotemia or acute tubular necrosis, caused by hypovolaemia (22). Glomerulonephritis has been reported as a rare manifestation (23). In previous reports, acute renal failure in SJS/TEN was reported to be associated with risk factors of CKD and use of allopurinol (24) or mul-

tiple antibiotics (25). We observed the same factors in 2 patients with chronic renal sequelae who also presented with acute renal failure in the acute stage. Chronic renal insufficiency is not uncommon in patients with SJS/TEN, but it is still uncertain if the chronic decline of renal function is caused by a SJS/TEN-specific mechanism. Due to a lack of biopsy-proven drug-induced acute interstitial nephritis, we regarded the adverse drug reaction as a worsening rather than causative factor for the irreversible deterioration of renal function.

The main limitations in our study consisted of the retrospective study design and possible recall bias among patients during the long follow-up period. Nonetheless, the study showed the pattern of chronic sequelae in SJS/TEN. Cutaneous and ocular sequelae are common and troublesome. The severe adverse drug reaction may be a worsening factor for pre-existing kidney function impairment. CTD might occur as late complications and so patients should be carefully monitored for CTD during long-term follow-up. This study suggests the importance of both clinicians' alertness and appropriate referrals to different specialists in long-term care for patients with SJS/TEN.

ACKNOWLEDGEMENTS

This work was supported by the National Taiwan University Hospital Hsin-Chu Branch (HCH103-025 and HCH104-050).

The authors declare no conflicts of interest.

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