Received: 5 December 2018 | Revised: 7 December 2018 | Accepted: 10 December 2018

DOI: 10.1002/cia2.12044

ORIGINAL ARTICLE

WILEY Journal of Cutaneous Immunology and Allergy

Stevens-Johnson syndrome and toxic epidermal necrolysis cases treated at our hospital over the past 10 years

Makoto Nakae[1] | Risa Tamagawa-Mineoka[1] | Koji Masuda[1] | Mayumi Ueta[2] | Chie Sotozono[3] | Norito Katoh[1]

[1]Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

[2]Department of Frontier Medical Science and Technology for Ophthalmology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

[3]Department of Ophthalmology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Correspondence
Risa Tamagawa-Mineoka, Department of Dermatology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kamigyo-ku, Kyoto, Japan.
Email: risat@koto.kpu-m.ac.jp

Funding information
Ministry of Education, Culture, Sports, Science and Technology of the Japanese government (BioBank Japan Project); JSPS Core-to-Core Program, A. Advanced Research Networks

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute inflammatory diseases of the skin and mucous membranes such as the ocular surface. This study aimed to evaluate the backgrounds, clinical symptoms, and disease course of SJS/TEN patients in our hospital. We retrospectively collected the data of the medical history, clinical symptoms, examinations, and treatments in patients with SJS or TEN, which were diagnosed in the Department of Dermatology, Kyoto Prefectural University of Medicine Hospital between April 2007 and March 2017. The subjects were 15 patients with SJS and five with TEN. All five children had cold symptoms and took cold medications. On the other hand, 15 adult patients took various types of drugs, such as antibiotics, cold medications, or anticonvulsants. Interestingly, all pediatric patients did not have large skin lesions but suffered from severe eye symptoms, while the severity of their skin and mucous lesions was various in adult patients. All patients were treated with oral corticosteroid therapy. Furthermore, 18 patients were treated with corticosteroid pulse therapy, six with high-dose immunoglobulin therapy, and one with plasmapheresis. Our findings imply that cold symptoms and cold medicines may be associated with severe ocular involvement in SJS/TEN patients.

KEYWORDS
common cold, drug eruption, ocular involvement, Stevens-Johnson syndrome, toxic epidermal necrolysis

1 | INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute inflammatory diseases of the skin and mucous membranes such as the ocular surface. In some cases, there are severe mucous membrane symptoms in spite of a range of skin lesions. On the other hand, other patients have no or mild mucous lesions although their skin symptoms are serious. Thus, the degree of clinical symptoms varies from case to case. This study aimed to evaluate the backgrounds, symptoms, and disease course of SJS/TEN patients in our hospital and to examine whether the clinical manifestations of skin and mucous lesions tend to be related to certain clinical background factors.

Nakae and Tamagawa-Mineoka contributed equally to this study.

TABLE 1 Demographics and clinical characteristics of the patients treated at our hospital

Patient no.	Sex	Age	Diagnosis	Past medical history	Cold symptoms[a] before the onset of SJS/TEN	Potential cause of SJS/TEN	Skin symptoms severity	Acute ocular symptoms severity		Oral symptoms severity
								Ocular sequelae		
1.	F	6	SJS	None	+	Infection (Mycoplasma pneumonia, chlamydia pneumonia), and various drugs	1	3 None		1
2.	M	8	SJS	None	+	Cefdinir[b], carbocisteine[b], tranexamic acid[b]	1	3 Dry eye, eyelid conjunctival cicatricial change		2
3.	F	9	SJS	None	+	Acetaminophen[b]	1	3 Dry eye, eyelid conjunctival cicatricial change		2
4.	M	17	SJS	None	+	Infection (Group A streptococcus), Garenoxacin, loxoprofen, codeine phosphate	1	3 None		3
5.	F	19	SJS	None	+	Acetaminophen[b], loxoprofen, carbocysteine, tranexamic acid	1	3 Dry eye, eyelid conjunctival cicatricial change		2
6.	M	29	SJS	None	+	Cold remedy[b]	1	3 Corneal perforation		2
7.	F	32	SJS	None	+	Cold remedy[b], carbocysteine	1	2 Dry eye		2
8.	F	40	SJS	Mixed connective tissue disease	+	Levofloxacin[b], diclofenac	1	1 None		2
9.	F	47	SJS	Maculopapular drug eruption due to cefuroxime	−	Pregabalin, neurotropin®	1	2 None		3
10.	M	55	SJS	Chronic subdural hematoma	−	Zonisamide, lansoprazole	1	2 Dry eye, eyelid conjunctival cicatricial change		1
11.	F	59	SJS	Lung cancer, metastatic brain tumor	−	Phenytoin	1	3 None		2
12.	M	64	SJS	None	+	Acetaminophen[b], cold remedy[b]	1	3 Dry eye, eyelid conjunctival cicatricial change		3

(Continues)

TABLE 1 (Continued)

Patient no.	Sex	Age	Diagnosis	Past medical history	Cold symptoms[a] before the onset of SJS/TEN	Potential cause of SJS/TEN	Skin symptoms severity	Acute ocular symptoms severity		Oral symptoms severity
								Ocular sequelae		
13.	F	66	SJS	Sjögren's syndrome	+	Cefcapin, acetaminophen, loxoprofen, and various drugs	1	3	Dry eye	2
14.	F	78	SJS	None	−	Tosufloxacin, excelase®	1	3	Dry eye, eyelid conjunctival cicatricial change, mild corneal opacity	2
15.	M	78	SJS	SJS, cataract surgery	−	Levofloxacin, mefenamic acid, piroxicam, teprenone[b]	1	0	None	2
16.	M	52	TEN	Intramedullary hematoma	−	Vancomycin[b], cefazolin, loxoprofen, and various drugs	2	0	None	2
17.	F	52	TEN	None	+	Cold remedy, cefcapin, ibuprofen, and various drugs	3	3	Eyelid conjunctival cicatricial change	2
18.	F	66	TEN	Renal cell carcinoma	−	Cefotiam, meloxicam, naproxen, and various drugs	3	2	None	Unknown
19.	M	70	TEN	Multiple myeloma, on hemodialysis	+	Cold remedy[b], azithromycin[b]	2	0	None	2
20.	F	91	TEN	Breast cancer	+	Oseltamivir[b]	2	2	None	2

[a]Cold symptoms include nasal discharge, sore throat, or cough.
[b]Drugs with positive responses in drug lymphocyte stimulation tests.

TABLE 2 Comparison of clinical data of children and adults

	Children[a] (n = 5)	Adults[a] (n = 15)
Age, median (range)	9 (6-19)	59 (29-91)
Gender, M/F	2/3	6/9
Diagnosis	SJS: 5, TEN: 0	SJS: 10, TEN: 5
Past medical history	None: 5	Drug eruption: 2, collagen disease: 2, malignant tumor: 4
Cold symptoms[b] before the onset of SJS/TEN	With cold symptoms: 5 Without cold symptoms: 0	With cold symptoms: 8 Without cold symptoms: 7
Drugs with probability of cause	Antibiotics: 3, acetaminophen: 2, NSAIDs: 2	Antibiotics: 9, NSAIDs: 7, cold remedies: 4, anticonvulsants: 2, and other drugs
Skin symptom grade	Grade (3, 2, 1): (0, 0, 5)	Grade (3, 2, 1): (2, 3, 10)
Ocular symptom grade	Grade (3, 2, 1, 0): (5, 0, 0, 0)	Grade (3, 2, 1, 0): (6, 5, 1, 3)
Oral symptom grade	Grade (3, 2, 1, 0): (1, 3, 1, 0)	Grade (3, 2, 1, 0): (2, 11, 1, 0), Unknown: 1
Other symptoms and complications	Hepatic dysfunction: 1, acute kidney injury: 1	Acute kidney injury: 2, bronchiolitis obliterans: 1, sepsis: 2

[a]We defined adults to be 20 y old or older patients and children to be younger than 20 y old.
[b]Cold symptoms include nasal discharge, sore throat, or cough.

2 | METHODS

We retrospectively collected the data of the medical history, clinical symptoms, examinations, and treatments of patients in whom SJS or TEN was diagnosed in the Department of Dermatology, Kyoto Prefectural University of Medicine Hospital between April 2007 and March 2017. Patients were diagnosed as having SJS or TEN based on the 2016 Diagnostic Guidelines of the Japanese Dermatological Association.[1] The symptoms with epidermal detachment (including blisters or erosions) involved over 10% of the body surface area were diagnosed as TEN,[1] which is different from the contents in the international diagnostic criteria. In the international criteria, when the epidermal detachment area accounts for 10%-29% of the body surface area, the disease type is evaluated as overlapping SJS/TEN.[2,3] We defined adults to be older than 19 years old and children to be 19 years or younger patients. The severity of the skin and mucous lesions was defined as shown in Table S1, as previously reported.[1,4]

3 | RESULTS

There were 20 cases fulfilling the criteria (8 men, 12 women), including 15 cases of SJS and five cases of TEN (Table 1). Ages of the patients ranged from 6 to 91, with a median age of 52 for all patients (40 for SJS and 66 for TEN).

Almost all SJS patients presented with atypical target lesions on their skin at their first visits, with an exceptional patient no. 4 who only presented with mucosal lesions in the lips and eyes with no rash on the skin at the first visit. Patients with TEN (patient no. 16-20) had epidermal detachment involving on the body surface area (median: 20%; range: 15%-50%). Their histological findings revealed that full thickness necrotic keratinocytes in the epidermis and subepidermal blisters were found, in addition to superficial perivascular and interface dermatitis.

All pediatric patients suffered from severe eye symptoms, as shown in Table 2. On the other hand, the severity of eye lesions was various in the adult patients. While most patients had moderate to severe erosions in the oral mucosa, erosions in two of the SJS patients (patient no. 1 and 8) were limited to a small area in the mucosal junction of the skin and lips. Liver damage (alanine aminotransferase > 100 IU/L) occurred in one SJS patients (patient no. 3) and acute kidney injury occurred in three SJS patients (patient no. 4, 12, and 14). Two TEN patients had a severe form of hypoalbuminemia, accompanied by pneumonia (patient no. 19) and sepsis (patient no. 20). Three patients (patient no. 6, 18, and 19) had sepsis, and two patients of them (patient no. 6 and 18) died.

All patients were tested for the presence of *Mycoplasma* antibodies using particle agglutination test, as well as for the presence of IgM and IgG against herpes simplex virus, cytomegalovirus, and Epstein-Barr virus. Group A β-hemolytic streptococcal infection was suspected in two pediatric cases of SJS (patient no. 2 and 4). Another pediatric case of SJS had increased levels of antibodies against *Mycoplasma* (patient no. 1).

Drugs that were suspected to have contributed to the onset of SJS and TEN in most patients were antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and cold remedies, with only two cases suspected to have been caused by antiepileptic agents. Drug lymphocyte stimulation tests revealed a positive response to the suspected drugs in nine patients. Of those patients, three patients showed positive responses to multiple drugs. Six patients showed negative responses to all drugs tested. A patch test was performed in seven patients, but all of them showed negative responses.

All patients underwent systemic corticosteroid therapy. In addition, 17 patients were treated with corticosteroid pulse therapy

TABLE 3 Comparison of clinical data of patients with or without cold symptoms[a] before the onset of SJS/TEN

	With cold symptoms (n = 13)	Without cold symptoms (n = 7)
Age	32 (6-91)	59 (47-78)
Gender (M/F)	5/8	3/4
Diagnosis	SJS: 10, TEN: 3	SJS: 5, TEN: 2
Drugs with probability of cause	Antibiotics: 8, cold remedies: 4, acetaminophen: 3, and other drugs.	Antibiotics: 4, NSAIDs: 3, anticonvulsants: 2, and other drugs.
Skin symptom grade	Grade (3, 2, 1): (1, 2, 10)	Grade (3, 2, 1): (1, 1, 5)
Ocular symptom grade	Grade (3, 2, 1, 0): (9, 2, 1, 1)	Grade (3, 2, 1, 0): (2, 3, 0, 2)
Oral symptom grade	Grade (3, 2, 1, 0): (2, 10, 1, 0)	Grade (3, 2, 1, 0): (1, 4, 1, 0), Unknown: 1

[a]Cold symptoms include nasal discharge, sore throat, or cough.

for 3 days at 500-1000 mg/d of methylprednisolone. Three patients did not undergo corticosteroid pulse therapy, because patient no. 10 was no longer in the acute phase of SJS, and patient no. 13 had no severe symptom, and patient no. 19 was septic at the first visit. Three SJS patients and three TEN patients were also treated with high-dose intravenous immunoglobulin (IVIg, 400 mg/kg for 5 days). IVIg was given to most TEN patients, as well as to those who had severe symptoms or whose eruptions did not resolve following pulse therapy. Plasma exchange (PE) was performed in one of the TEN patients (patient no. 19). The patient had a positive treatment outcome with the combined treatment approach with IVIg and PE.

The median TEN-specific severity illness score (SCORTEN)[5] was 3 for TEN patients. Two patients died during the course of treatment at our hospital (patient no. 6 and 18). Also, patient no. 19 died 1 month after discharge because of acute bacterial peritonitis due to hypoalbuminemia and cirrhosis that had been suffering. Patient no. 20 was unable to ingest orally due to erosion in the oral cavity and reduced ability to swallow and was discharged with enteral tube feeding. Some patients have been treated for their ocular complications such as dry eye symptoms and conjunctival cicatricial changes.

4 | DISCUSSION

Our study indicates that all pediatric patients suffered from severe ocular symptoms and did not have large skin lesions, while the severity of their skin and mucous lesions was various in adult patients (Table 2). Moreover, all children had cold symptoms and took medicine for their cold before the onset of SJS, implying that cold symptoms and medications might be related to ocular complications. Thus, we compared the symptoms between the patients with and without cold symptoms (Table 3). Interestingly, the patients with cold symptoms and medications tended to have the severe ocular involvement. Therefore, there may be an association between cold symptoms/medications and ocular symptoms of SJS/TEN patients.

Sotozono et al have reported that patients who take cold remedies or NSAIDs have a tendency to suffer from the severe ocular involvement. In addition, Ueta et al[6] have reported that polymorphisms in the gene of Toll-like receptor 3 (TLR3), which recognizes double-stranded RNA in viral infections, are related to SJS/TEN with ocular surface complications in the Japanese population. Furthermore, we have shown that TLR3 signaling can increase allergic responses in the skin and eyes in mice.[7–9] Taken together, these findings suggest that the innate immune system including TLR3 signaling may be involved in the pathomechanisms of SJS/TEN with severe ocular involvement following cold symptoms and cold medicine use.[10] However, the sample size was too small to perform a detailed statistical analysis for the relationships among the clinical backgrounds and symptoms of SJS/TEN. Therefore, a multicenter study for accumulation and analysis of the clinical data of SJS/TEN cases is necessary in the future.

ACKNOWLEDGEMENTS

This work was partially supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese government (BioBank Japan Project) and by the JSPS Core-to-Core Program, A. Advanced Research Networks.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Risa Tamagawa-Mineoka https://orcid.org/0000-0001-9379-9584

REFERENCES

1. Shiohara T, Kano Y, Mizukawa Y, et al. Severe erythema exudativum multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis clinical practice guideline. Jpn J Dermatol. 2016;126(9):1637–85.
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129(1):92–6.

3. Valeyrie-Allanore L, Roujeau JC. Epidermal necrolysis (Stevens-Johnson Syndrome and toxic epidermal necrolysis). In: Goldsmith LA, Fitzpatrick TB, editors. Fitzpatrick's dermatoloogy in general medicine. 8th ed. New York, NY: McGraw-Hill Professional, 2012; p. 439–48.
4. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. Am J Ophthalmol. 2015;160(2):228–37.
5. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau JC, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol. 2006;126(2):272–6.
6. Ueta M, Sotozono C, Inatomi T, et al. Toll-like receptor 3 gene polymorphisms in Japanese patients with Stevens-Johnson syndrome. Br J Ophthalmol. 2007;91(7):962–5.
7. Nakamura N, Tamagawa-Mineoka R, Ueta M, Kinoshita S, Katoh N. Toll-like receptor 3 increases allergic and irritant contact dermatitis. J Invest Dermatol. 2015;135(2):411–7.
8. Yasuike R, Tamagawa-Mineoka R, Ueta M, Nakamura N, Kinoshita S, Katoh N. The role of toll-like receptor 3 in chronic contact hypersensitivity induced by repeated elicitation. J Dermatol Sci. 2017;88(2):184–91.
9. Ueta M, Uematsu S, Akira S, Kinoshita S. Toll-like receptor 3 enhances late-phase reaction of experimental allergic conjunctivitis. J Allergy Clin Immunol. 2009;123(5):1187–9.
10. Ueta M, Kinoshita S. Ocular surface inflammation is regulated by innate immunity. Prog Retin Eye Res. 2012;31(6):551–75.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Nakae M, Tamagawa-Mineoka R, Masuda K, Ueta M, Sotozono C, Katoh N. Stevens-Johnson syndrome and toxic epidermal necrolysis cases treated at our hospital over the past 10 years. *J Cutan Immunol Allergy.* 2019;2:25–30. https://doi.org/10.1002/cia2.12044