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CASE STUDY

Evaluation of patients with erythema exudativum multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis treated at our department during the previous 9-year period

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Abstract

Erythema exudativum multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are acute inflammatory diseases of the skin and mucous membranes. EM with mucosal eruptions is sometimes difficult to differentiate from SJS or TEN. This study aimed to understand the characteristics of these diseases by evaluating the backgrounds, clinical symptoms, and disease courses of EM/SJS/TEN patients treated at our hospital. It shows that persistent fevers and erosion are common in SJS/TEN. Therefore, we must pay attention to whether they become more severe.

KEYWORDS
drug eruption, erythema exudativum multiforme, mucosal eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis

1 | INTRODUCTION

Erythema exudativum multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which are characterized by erythema and erosion caused by drugs or infections over the entire body. SJS/TEN patients occasionally show rapid progression with potentially fatal outcomes. In addition, these conditions sometimes affect the mucous membranes and inflict permanent damage, such as blindness or internal organ involvement. Therefore, it is desirable to diagnose these conditions and start treatment rapidly. EM with mucosal eruptions is sometimes difficult to differentiate from SJS or TEN. The purpose of this study was to understand the characteristics of these diseases by evaluating the backgrounds, clinical symptoms, and disease course of EM/SJS/TEN patients treated at our hospital. We collected data for patients with EM with mucosal eruptions, SJS, or TEN who were treated at our department during the previous 9-year period.

2 | METHODS

We retrospectively collected data regarding the medical history, clinical symptoms, examination results, and treatment of patients who were diagnosed with EM, SJS, or TEN at the Department of Dermatology, Kyoto Prefectural University of Medicine Hospital, between January 2009 and December 2017. We defined EM as an acute, self-limiting, or episodic syndrome involving symmetrical distinctive round erythematous skin lesions with or without

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mucosal lesions.[1] Patients were diagnosed with SJS or TEN based on the 2016 Diagnostic Guidelines of the Japanese Dermatological Association.[2] Patients that exhibited epidermal detachment (including blisters or erosions) over 10% of their body surface area were diagnosed with TEN,[3] which is different from 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.[4] The severity of the skin and mucous lesions was defined as shown in Table S1, as reported previously.[2,3]

The subjects consisted of 21 EM patients with mucosal lesions in their eyes, oral cavity, or genital area (among 170 patients with EM), 12 patients with SJS, and six patients with TEN who were diagnosed and treated at our department between January 2009 and December 2017. The following items were evaluated: age, sex, medical history, mucosal symptoms, the distribution of eruptions, suspected causes, the presence/absence of fever, the order of the appearance of symptoms (skin eruptions/mucosal eruptions/fever), the results of various hematological examinations, and the treatments employed. In the statistical analyses, the Tukey HSD test was used for comparisons among three groups. This study was performed with the approval of the ethics review board of our university.

3 | RESULTS

As shown in Table 1, there were 10 males and 11 females with EM, five males and seven females with SJS, and three males and three females with TEN. The median ages of the EM, SJS, and TEN patients were 49, 36, and 59, respectively. In the EM group, 4 (19%) patients had a history of malignant tumors, 4 (19%) patients had atopic dermatitis, 3 (14%) patients had collagen vascular disease, and 3 (14%) patients had epilepsy. In the SJS group, one patient (8%) had diabetes mellitus, and 1 (8%) patient had collagen vascular disease. In the TEN group, two patients (33%) had a history of malignant tumors, 1 (17%) patient had diabetes mellitus, and 1 (17%) patient had schizophrenia.

TABLE 1 Summary of patients' backgrounds

	EM	SJS	TEN
Sex			
Male	10 (48%)	5 (42%)	3 (50%)
Female	11 (52%)	7 (58%)	3 (50%)
Median age	49	36	59
Suspected cause			
Drugs	9 (43%)	12 (100%)	6 (100%)
Antiepileptic drugs	3 (14%)	1 (8%)	0
Antibacterial drugs	2 (10%)	5 (42%)	1 (17%)
Antipyretic drugs	0	4 (33%)	3 (50%)
Other drugs	4 (19%)	2 (17%)	2 (33%)
Infection	10 (52%)	0	0
Unknown	2 (10%)	0	0

The trigger of EM was presumed to be an infection in 10 (48%) patients and a drug in 9 (43%) patients, whereas it was unknown in 2 (10%) patients (Table 1). All of the cases of SJS and TEN were suspected to have been triggered by drugs. The suspected causative drug was determined based on the patient's clinical course in each case. Detailed examinations, such as patch tests and drug-induced lymphocyte stimulation tests (DLST), produced positive results in two patients with EM (a patch test with amoxicillin and a DLST with cernitin), four patients with SJS (DLST with a multi-ingredient cold medicine, acetaminophen, levofloxacin, or teprenone), and three patients with TEN (DLST with a multi-ingredient cold medicine, azithromycin, oseltamivir, or vancomycin). The most common types of suspected causative drugs were antiepileptic drugs (14%) and antibacterial drugs (10%) in the EM group; antibacterial drugs (42%), antipyretic analgesics (33%), and antiepileptic drugs (8%) in the SJS group; and antipyretic analgesics (50%) and antibacterial drugs (17%) in the TEN group (these percentages are ratios of each suspected drug to all suspected drugs for each disease).

As shown in Table 2, eruptions were more predominant on the limbs (43%) than on the trunk (10%) in the patients with EM. In the patients with SJS/TEN, eruptions were more predominant on the trunk (SJS: 33%, TEN: 50%). In >50% of the patients with EM, eruption pigmentation and epithelialization occurred, resulting in healing within 10 days. However, in most patients with SJS/TEN, dark red erythema and erosion persisted for more than 10 days. In particular, all of the patients with TEN required >20 days for the epithelialization of erosive lesions and healing. In >50% of the patients with EM/TEN, skin eruptions preceded mucosal eruptions (EM: 53%, TEN: 83%).

We examined ocular symptoms and mucosal symptoms in the oral cavity or the genital area. Of the patients with EM, none showed conjunctival pseudomembrane formation, corneal epithelial defects, or oral erosion accompanied by extensive blood crusts, and only a few showed mucosal symptoms in the oral cavity or the genital area. In contrast, all of the patients with SJS/TEN exhibited lip erosion.

Fever (>38°C) was more common in the patients with SJS/TEN than in those with EM, and persistent fevers were more common in the former group. Abnormal hepatic function was frequently observed in the patients with TEN (EM: 14.3%, SJS: 16.7%, TEN: 66.7%). None of the patients with EM or SJS died. Two TEN patients died because of sepsis and bacterial peritonitis, respectively.

The results of laboratory tests (before steroid administration: EM: $n = 16$, SJS: $n = 10$, and TEN: $n = 3$) are shown in Figure 1. Blood cell counts showed that total leukocytes, lymphocytes, neutrophils, and platelets did not differ significantly among the patients with EM, SJS, and TEN. On the other hand, eosinophils differed significantly

TABLE 2 Summary of patients' symptoms and therapies

	EM	SJS	TEN
Main eruption area			
Limbs	9 (43%)	1 (8%)	0
Trunk	2 (10%)	4 (33%)	3 (50%)
Entire body	9 (43%)	6 (50%)	3 (50%)
Other	1 (5%)	1 (8%)	0
Duration of eruptions			
1–10 days	17 (81%)	1 (8%)	0
11–20 days	3 (14%)	8 (67%)	0
21+ days	1 (5%)	3 (25%)	6 (100%)
Mucosal symptoms			
Conjunctival hyperemia	7 (33%)	11 (91%)	4 (67%)
Pseudomembrane formation	0	3 (25%)	0
Corneal epithelial defects	0	3 (25%)	2 (33%)
Lip erosion	6 (29%)	12 (100%)	6 (100%)
Oral erosion with blood crusts	0	1 (8%)	1 (17%)
Erosion in the genital area	1 (5%)	7 (58%)	4 (67%)
Antecedent symptoms			
Eruptions	11 (52%)	4 (33%)	5 (83%)
Mucosal symptoms	3 (14%)	6 (50%)	1 (17%)
Both	7 (33%)	2 (17%)	0
Fever period (>38°C)			
No fever	4 (19%)	0	0
1–4 days	6 (29%)	3 (25%)	1 (17%)
5–10 days	2 (10%)	2 (17%)	2 (33%)
11+ days	0	1 (8%)	2 (33%)
Unknown period	9 (43%)	6 (50%)	1 (17%)
Abnormal hepatic function	3 (14%)	2 (17%)	4 (67%)
Therapy			
Steroid pulse therapy	0	11 (91%)	5 (83%)
High-dose intravenous immunoglobulins	0	2 (17%)	4 (67%)
Plasma pheresis	0	0	2 (33%)

between the EM and TEN patients and between the SJS and TEN patients. The mean platelet volume (MPV) of the SJS patients was greater than that of the EM patients, and the MPV of the EM patients was greater than that of the TEN patients. To evaluate the degree of inflammation, we examined the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). The NLR differed significantly between the EM and TEN patients and between the SJS and TEN patients. The LMR differed significantly between the SJS and TEN patients. Alanine aminotransferase (ALT) levels and the ratio of AST to ALT did not differ significantly among the EM, SJS, and TEN patients. Therefore, the levels of ALT were not statistically different among the groups although the frequency of liver dysfunction was high in the patients with TEN. The levels of blood urea nitrogen, creatinine, and C-reactive protein (CRP) did not differ significantly among the EM, SJS, and TEN patients.

4 | DISCUSSION

The following results were consistent between this study and a previous nationwide epidemiological survey of SJS and TEN.[3] In patients with SJS/TEN, the most common suspected causative agents were antibiotics and antipyretic analgesics, and hepatic dysfunction was frequently observed (52% of SJS patients and 67% of TEN patients in the previous survey).

In this study, antibacterial drugs (17% of TEN cases, 42% of SJS cases) and antipyretic analgesics (non-steroidal anti-inflammatory drugs [NSAID]: 33% of TEN cases, acetaminophen: 17% of TEN cases and 33% of SJS cases) were the most common causative drugs in cases of SJS/TEN. We previously reported that SJS/TEN patients with cold symptoms and medications tended to have severe ocular involvement.[5] Sotozono et al. reported that patients who take cold remedies or NSAID have a tendency to suffer from severe ocular involvement.[6] These findings suggest that NSAID or cold remedies may be related to SJS/TEN with severe ocular complications.

In addition, in SJS/TEN, eruptions are generally considered to predominantly arise on the trunk,[2] and they were also more predominant on the trunk than on the limbs in this study. In the previous survey,[3] skin eruptions frequently preceded mucosal eruptions in SJS/TEN (in 55% of SJS cases and 63% of TEN cases). In this study, mucosal eruptions preceded skin eruptions in SJS patients slightly more frequently than in the previous survey, and skin eruptions preceded mucosal eruptions in many TEN patients. In EM, fever tended to subside within a week. In SJS/TEN, fever tended to persist. Regarding blood test results, the TEN patients exhibited lower values for blood cell-related parameters, for example, the MPV and platelet count, than the SJS or EM patients. This implies that blood cell production might be inhibited in TEN.

In conclusion, our results indicate that persistent fever and erosion are common in SJS/TEN. Therefore, we must pay attention to whether such patients' conditions become more severe. In addition, in EM or SJS patients with thrombocytopenia, the treatment should be performed while paying careful attention to the potential for the condition to transition to TEN.

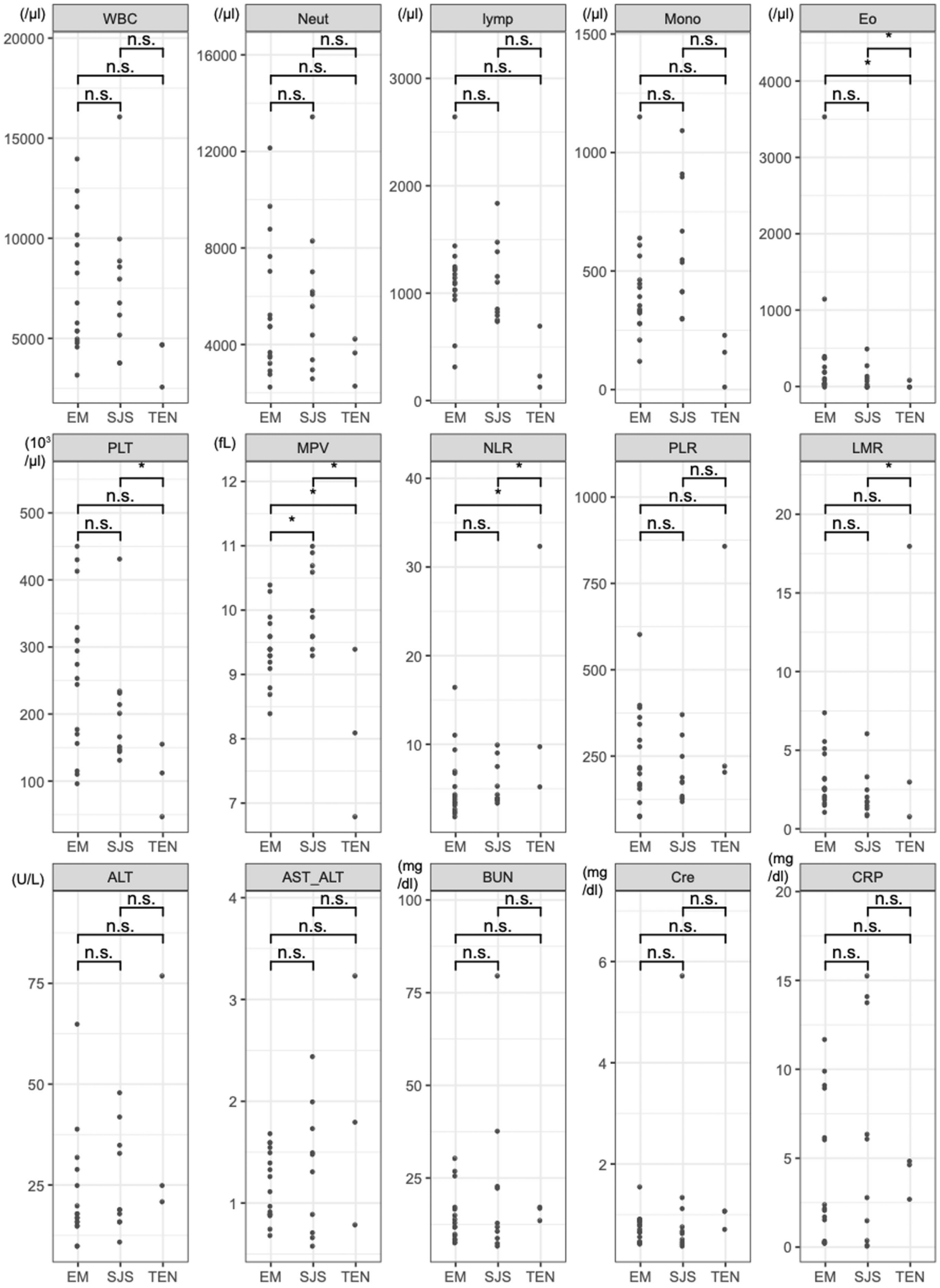

FIGURE 1 Comparison of laboratory test results among EM, SJS, and TEN. The laboratory test results of the EM, SJS, and TEN patients are shown. Each point represents a patient. *p*-Value were calculated using the Tukey HSD test. $^{*}p < .05$

CONFLICT OF INTEREST

Dr. Norito Katoh is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision-making, for this article was undertaken by Editor in Chief.

DECLARATION SECTION

Approval of the research protocol: The study protocol was approved by the ethics committee of Kyoto Prefectural University of Medicine (ERB-C-567). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Since this study was a retrospective study, explanations and consents to patients were made by opting out on the bulletin board of Kyoto Prefectural University of Medicine.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

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

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