junction. Thus, she was diagnosed with Stevens–Johnson syndrome 3 months before admission to our hospital. Her skin detachment was progressing (Fig. 1a,b) and histopathological findings showed massive keratinocyte necrosis and subepidermal bullae, confirming a TEN diagnosis (Fig. 1c). Lymphoma cells were not detected in the specimen. Methylprednisolone pulse therapy (1000 mg/day for 3 days) and four plasma exchanges temporarily improved her skin and mucosal erosions. However, her lesions relapsed following reduction of oral PSL to 10 mg/day.

Upon admission to our hospital, she had a high-grade fever and skin detachment over 30% of her body accompanied by oral mucosal erosion (Fig. 1d,e). Laboratory findings revealed peripheral eosinophilia (16.5% of $3.9 \times 10^9$/L white blood cells), anemia (hemoglobin, 6.4 g/dL), hypoalbumia (albumin, 2.5 g/dL), liver dysfunction (γ-glutamyltransferase, 197 U/L) and systemic inflammation (C-reactive protein, 11.25 mg/dL). Immunoglobulin (Ig) levels were low: IgG, 436 mg/dL; IgM, 62 mg/dL; and IgA, 18 mg/dL. A skin biopsy showed findings similar to previous studies. Vesiculobullous skin diseases such as bullous pemphigoid, pemphigus including paraneoplastic pemphigus and linear IgA dermatosis were ruled out because of the absence of autoantibodies in serum checked by indirect immunofluorescent tests, enzyme-linked immunosorbent assay and immunoblotting test. It was also difficult to deny thymoma-associated multi-organ autoimmunity. But the mass in mediastinum was diagnosed with lymphoma by biopsy. Thus, she was diagnosed as having TEN.

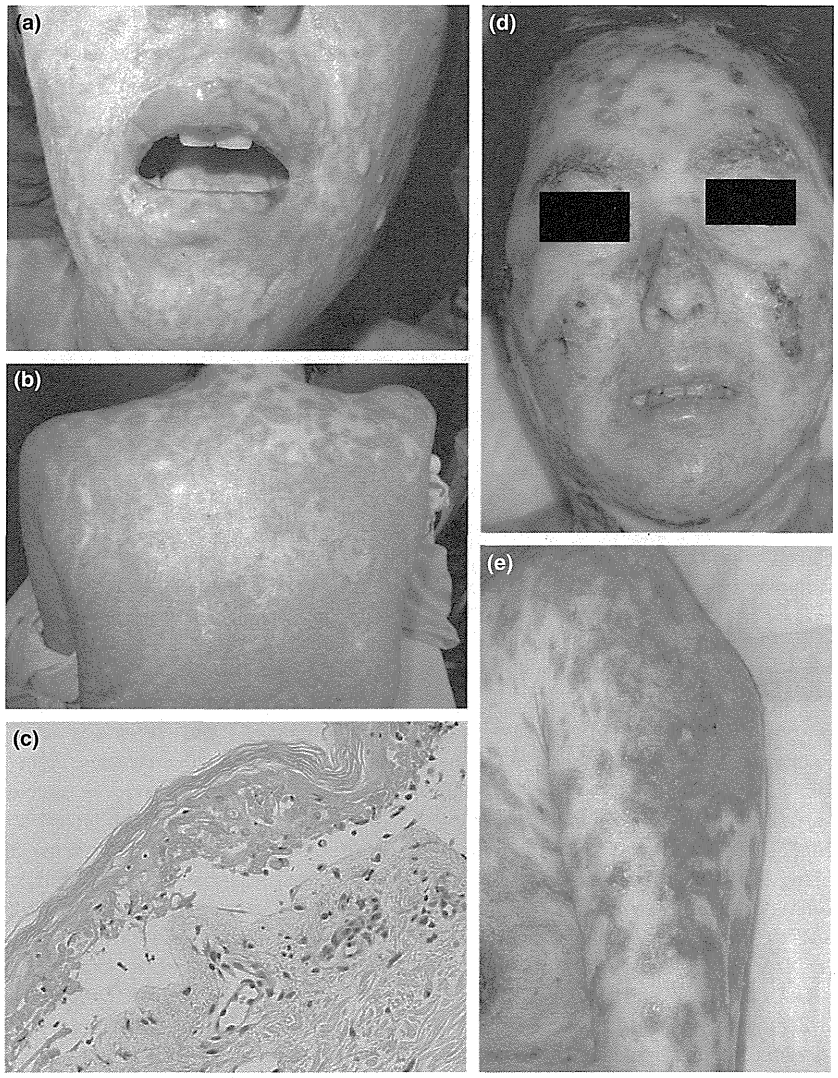


**Figure 1.** Clinical findings and histopathology. (a) At the onset, widespread epidermal loss was observed on the face of the patient. (b) The trunk and limbs displayed widespread atypical target lesions and blistering. Nikolsky's signs were positive on the patient's back. (c) Histopathological analysis by hematoxylin–eosin staining showed prominent keratinocyte death and liquefaction at the epidermal–dermal junction (original magnification × 200). (d,e) On admission to our department, painful erythema with erosion was observed widely. The epidermal detachment area was approximately 30% of the body surface area.

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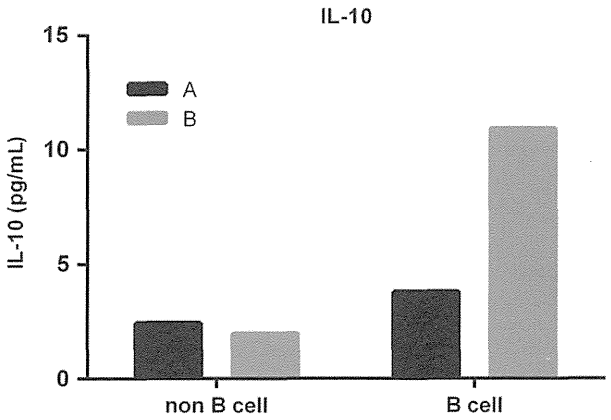


**Figure 2.** Interleukin (IL)-10 production by toxic epidermal necrolysis peripheral blood mononuclear cells (PBMC) in patients A and B. B cells were purified from PBMC by magnetic-activated cell sorting from a patient having B-cell lymphoma and treated with B-cell depletion therapy (patient A), and a patient without B-cell lymphoma (patient B). B-cell subsets were stimulated with lipopolysaccharide and non-B-cell PBMC were stimulated with anti-CD3/CD28 antibodies. Patient B cells without B-cell lymphoma produced remarkably high levels of IL-10 (light gray). Supernatant IL-10 was analyzed by luminometric bead arrays.

Methylprednisolone pulse therapy besides oral PSL (50 mg/day) improved her skin erosions to some extent. However, erosions were not completely epithelized. Although lymphoma cells were not detected in skin biopsies during hospitalization, lymphoma was detected in pleural effusions at 4 months after admission. Finally, she was transferred for treatment of lymphoma.

We hypothesized the reason severe skin lesions were intractable was related to B-cell dysfunction, because she received intensive B-cell depletion therapy with anti-CD20 antibodies. The low Ig levels indicated impaired humoral immunity, in which B cells play a central role. To clarify if the prolonged symptoms were due to B-cell dysfunction, we investigated cytokine and chemokine production using peripheral blood mononuclear cells (PBMC). PBMC were obtained at the time of admission. To analyze the immunological mechanism of intractable TEN in the patient (patient A), control PBMC were obtained at the peak of disease from a 74-year-old man who developed severe TEN with 90% of skin detachment while being treated for sepsis. He had had diabetes mellitus, chronic renal failure and bacterial endocarditis but recovered in 4 weeks with steroid and plasma exchange (patient B). B-cell subsets were isolated from PBMC using magnetic beads, and stimulated with lipopolysaccharide. The remaining PBMC regarded as non-B-cell subsets, including T cells, natural killer (NK) cells, NK T cells, dendritic cells, granulocytes and monocytes were stimulated with anti-CD3/CD28 antibodies. B cells ($5 \times 10^4$ cells/well) and non-B cells ($6 \times 10^4$ cells/well) were cultured in 96-well plates for 48 h. Supernatant cytokines and chemokines from both B cells and non-B cells were analyzed by luminometric bead arrays.

First, we compared IL-10 production. Although IL-10 production from the non-B-cell subset was similar in both patients, IL-10 levels from B-cell subsets were remarkably decreased in patient A (3.8 pg/mL), compared with patient B (10.92 pg/mL) (Fig. 2). In healthy controls, the IL-10 levels were as low as that in patient A (3.33 and 3.18 pg/mL, respectively). We next examined production of inflammatory cytokines and chemokines. In contrast to what we observed for IL-10, the levels of the following cytokines and chemokines from the non-B-cell subset were much higher in patient A than in patient B; namely, IL-2, IL-6, IL-8 (CXCL8), IL-9, IL-12, IL-17, γ-interferon, tumor necrosis factor-α, monocyte chemotactic protein-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, regulated on activation of normal T-cell expressed and secreted and γ-interferon inducible protein-10 (CXCL10) (Fig. 3). There was no marked difference in these cytokines and chemokines from the B-cell subset between the patients (data not shown).

## DISCUSSION

CD20 is a B-cell-specific differentiating antigen, selectively expressed by mature, healthy and malignant B cells. Anti-CD20 antibodies are widely used for the treatment of hematopoietic cancer and autoimmune diseases. Conversely, several reports suggest that B-cell depletion therapy may induce autoimmune diseases such as ulcerative colitis[9] and psoriasis.[10] In our patients, decreased Ig levels suggested impaired B-cell humoral immunity.

Interleukin-10 is regarded as important in severe cADR pathogenesis by preventing disease onset and reducing symptoms. Besides Treg, some B-cell subsets have also been identified as a source of IL-10. We investigated IL-10 production from B and non-B cells in the current case and compared it with what was observed in a recovered TEN patient who did not exhibit B-cell dysfunction. The results indicate that B-cell IL-10 was suppressed in the current patient although IL-10 production from the non-B-cell subset was similar in both patients. We also found that inflammatory cytokines and chemokines produced by T cells and monocytes were much higher in the TEN patient with B-cell dysfunction. Therefore, decreased B-cell IL-10 production and hyperproduction of non-B-cell inflammatory cytokines and chemokines may at least partially explain the prolonged symptoms.

Certain B-cell subpopulations have regulatory functions and are called regulatory B cells (Breg). Breg suppress antigen presentation, co-stimulatory molecule expression and secrete pro-inflammatory cytokines thought to be mediated by IL-10.[11] Breg not only suppress effector T-helper (Th)1 and Th2 cells but also alter dendritic cell (DC) activity to become tolerogenic DC that expand Treg subsets[12] and suppress Th17 responses.[13] A recent report indicated suppressive Breg functions include suppression of monocyte activation besides suppressing Th differentiation and Treg induction.[14] Taken together, the increase of multiple cytokines and chemokines from non-B cells in the current patient suggested involvement in suppressing Breg function, which may adversely impact Th


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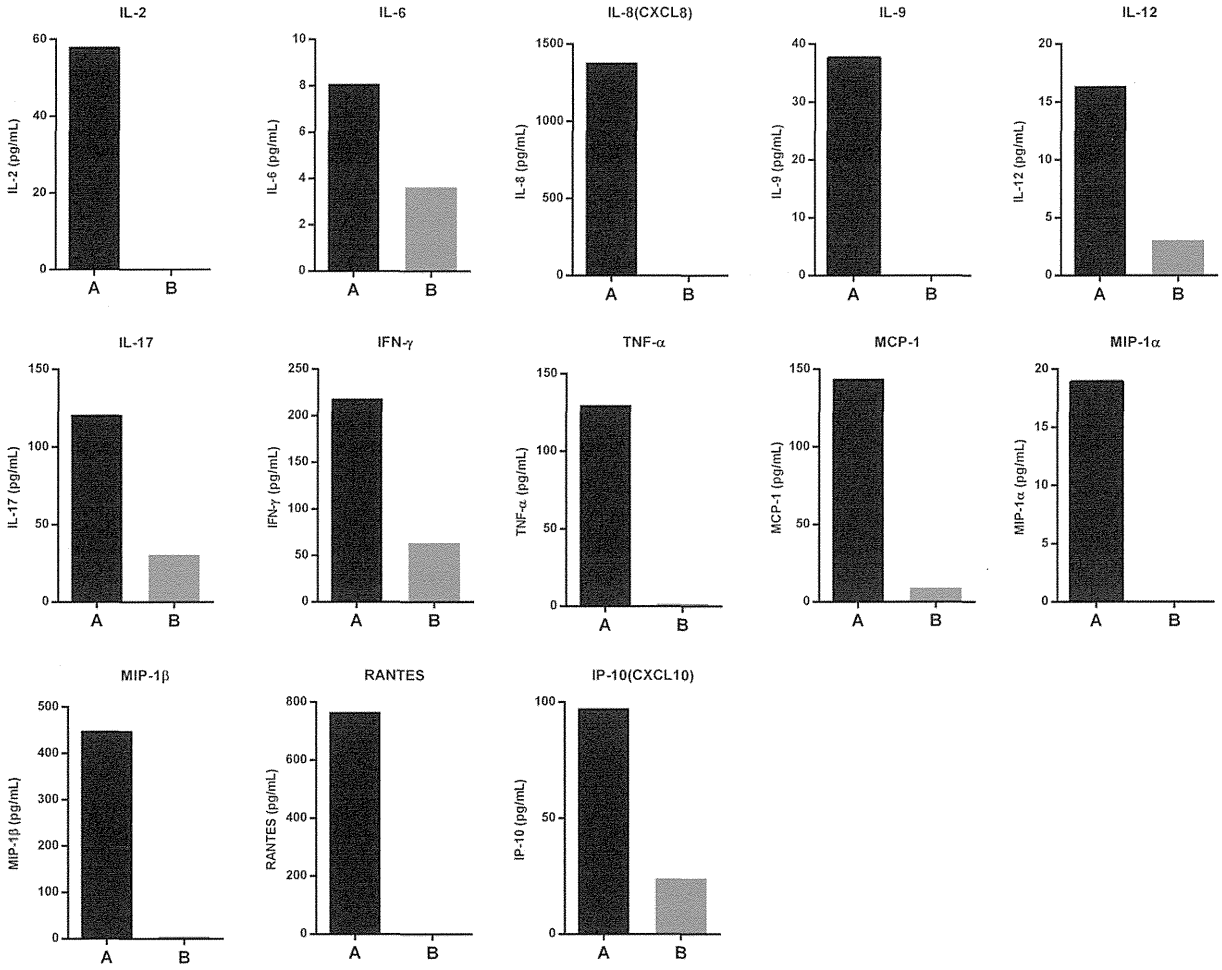


**Figure 3.** Peripheral non-B-cell cytokine and chemokine production in toxic epidermal necrolysis patients A and B. (A) Non-B cells from patient A with B-cell lymphoma and treated with B-cell depletion therapy (B) produced elevated cytokine and chemokine levels compared with the patient without B-cell lymphoma. Supernatant cytokine and chemokine levels from non-B cells were analyzed by luminometric bead arrays. IFN, interferon; IL, interleukin; IP, γ-interferon inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; RANTES, regulated and normal T-cell expressed and secreted; TNF, tumor necrosis factor.

and monocyte suppression. In TEN, the balance between T-effector (Teff) and Treg cells is thought to be important for the onset and/or exacerbation of symptoms.[8] The patient presumably had dysfunctional Breg, which may contribute to TEN progression by shifting the T-cell balance predominantly toward Teff, resulting in disease intractability.

In conclusion, Breg-mediated suppressive responses involving IL-10 production may be important for controlling TEN. Further researches will be required to clarify the pathophysiological mechanisms of TEN mediated by B cells.

**ACKNOWLEDGMENTS:** We thank Professor Takashi Hashimoto of Kurume University Institute of Cutaneous Cell Biology, Kurume, for their help in analyzing indirect immunofluorescent test, ELISA and immunoblotting test. This work was partially supported by JSPS KAKENHI (grant no. 24790534) and by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan (H26-nanchi(nan)-ippan-081).

**CONFLICT OF INTEREST:** None declared.

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THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13073
*Journal of Dermatology* 2015; **42**: 1–4

CONCISE COMMUNICATION

# Toxic epidermal necrolysis caused by acetaminophen featuring almost 100% skin detachment: Acetaminophen is associated with a risk of severe cutaneous adverse reactions

**Hideaki WATANABE,[1] Taisuke KAMIYAMA,[1] Shun SASAKI,[1] Kae KOBAYASHI,[1] Kenichiro FUKUDA,[2] Yasufumi MIYAKE,[2] Tohru ARUGA,[2] Hirohiko SUEKI[1]**

[1]*Department of Dermatology, Showa University School of Medicine,* [2]*Department of Emergency and Critical Care Medicine, Showa University, Tokyo, Japan*

## ABSTRACT

**Toxic epidermal necrolysis (TEN) is an adverse reaction that can be induced by various drugs; the associated mortality rate is 20–25%. A previous report showed a weak association between TEN and acetaminophen. Recently, the US Food and Drug Administration declared that acetaminophen is associated with a risk of serious skin reactions, including TEN. Here, we describe the case of a 43-year-old Japanese woman with TEN caused by acetaminophen. She had poorly controlled ulcerative colitis and was treated with high doses of prednisolone, infliximab, acetaminophen and lansoprazole. Nine days after administrating acetaminophen, targetoid erythematous and bullous lesions appeared on the patient's trunk, palms and the soles of her feet. The skin lesions expanded rapidly; within 3 weeks, skin detachment was detected across nearly 100% of the patient's body. However, no mucosal involvement of the eyes, oral cavity or genitalia was found. We performed lymphocyte transformation tests using various drugs; however, a high stimulation index was obtained only with acetaminophen. The patient recovered following treatment with plasmapheresis, i.v. immunoglobulin therapy, topical medication and supportive therapy. Acetaminophen is included in many prescription and over-the-counter products; thus, clinicians should monitor their patients for severe drug reactions, including TEN.**

**Key words:** acetaminophen, lymphocyte transformation test, severe cutaneous adverse reaction, toxic epidermal necrolysis.

## INTRODUCTION

Toxic epidermal necrolysis (TEN) is a serious, life-threatening, cutaneous adverse drug reaction with a high mortality rate (20–25%).[1–3] The disorder is characterized by a rapidly developing blistering exanthema of purpuric macules and targetoid lesions accompanied by mucosal involvement and variable skin detachment.[4] TEN is defined as skin detachment exceeding 30%.[4] Strong associations have been reported between TEN and a number of drugs, including anticonvulsants, allopurinol, anti-infective sulfonamides and nevirapine.[2] A multivariate analysis showed a weak association with acetaminophen.[2] However, the US Food and Drug Administration recently informed the public that acetaminophen is associated with a risk of serious skin reactions, including TEN.[5] We herein describe a severe case of TEN due to acetaminophen that exhibited no mucosal involvement of the eyes, oral cavity or genitalia.

## CASE REPORT

A 43-year-old Japanese woman with ulcerative colitis (UC) that was controlled with systemic prednisolone (PSL; 10 mg/day) reported an increase in symptoms. The patient's treatment regimen was changed to high doses of PSL (50 mg/day), infliximab (5 mg/kg), acetaminophen and lansoprazole, and her symptoms of UC improved. However, on 10 July 2013 (9 days after her first dose of acetaminophen), the patient noticed an erythematous eruption on her palms. Two days later, the patient visited her local hospital. Edematous erythema was detected on the patient's palms (Fig. 1a) and soles. Scattered, flat, atypical, targetoid, erythematous lesions were noted on the patient's trunk (Fig. 1b). Moreover, slight erosions and white crusts were evident on the lower lip. The initial diagnosis was hand–foot–mouth disease. Because the clinical findings of hand–foot–mouth disease sometimes mimic those of severe cutaneous adverse reactions,[6] drug eruption was raised as a differential

Correspondence: Hideaki Watanabe, M.D., Department of Dermatology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan. Email: hwatanabe@med.showa-u.ac.jp
Received 3 June 2015; accepted 10 July 2015.

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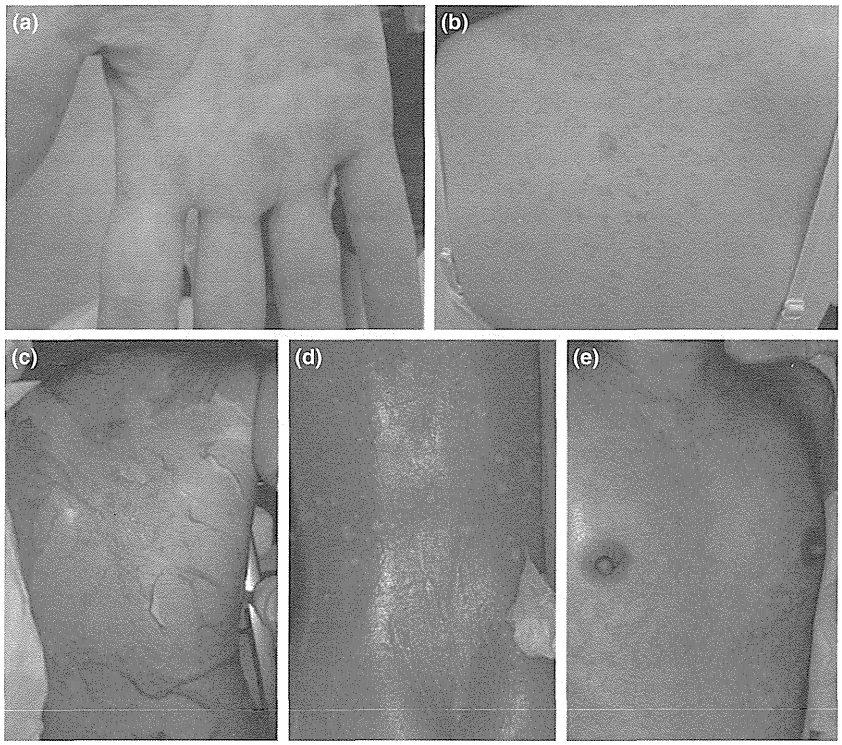


**Figure 1.** Clinical findings 2 days after toxic epidermal necrolysis (TEN) onset. (a) Edematous, erythematous lesions were seen on the patient's palms. (b) Papules and atypical targetoid erythematous lesions were also observed on her back. (c) Epidermal detachment was noted 12 days after the onset of TEN. (d) Skin detachment was noted across nearly 100% of the patient's body 20 days after the onset of TEN (on admission to our hospital). (e) One month after the onset of TEN, the patient's skin lesions had improved.

diagnosis. All drugs except PSL were discontinued. However, the patient's skin lesions expanded rapidly. Twelve days after the onset of TEN, epidermal detachment was detected on the patient's trunk (Fig. 1c). At that point, skin detachment was noted across 60% of the patient's body. The patient was treated with systemic PSL (50 mg/day) for TEN. She was also given i.v. immunoglobulins (3 g/day for 3 days and 10 g/day for 5 days).[7] In addition, plasmapheresis was performed twice, 12 and 14 days after the onset of TEN, respectively.[8,9] Despite these treatments, the patient's skin lesions did not improve, and methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in her blood. The patient was transferred to our hospital 20 days after the onset of TEN (1 August 2013) (Fig. 2).

On admission to our hospital, epidermal detachment was noted across nearly 100% of the patient's body (Fig. 1d). However, no mucosal involvement of the eyes, oral cavity or genitalia was found.

Laboratory investigations on admission revealed the following: white blood cell count, 7.7 $\times$ $10^9$/L (normal, 3.5–9); aspartate aminotransferase, 16 IU/L (10–30); alanine aminotransferase, 7 IU/L (5–25); serum creatinine, 0.38 mg/dL (0.5–0.9); total protein, 4.2 g/dL (6.7–8.4); albumen, 1.7 g/dL (4.0–5.1); and C-reactive protein, 5.20 mg/dL (<0.2). A lymphocyte transformation test (LTT) was performed with acetaminophen and lansoprazole; a positive result was obtained for

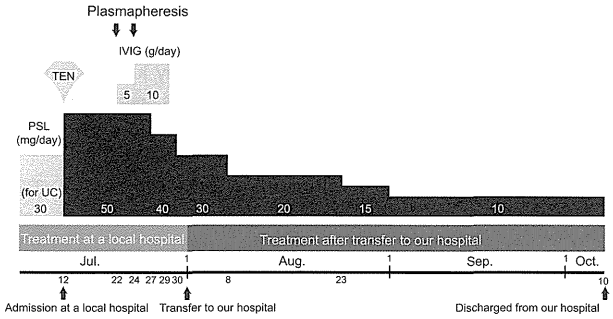


**Figure 2.** Treatment. A physician at the patient's local hospital treated her with systemic prednisolone (PSL) (30 mg/day) for ulcerative colitis (UC). The patient was also given intravenous immunoglobulin (IVIG) therapy (3 g/day for 3 days and 10 g/day for 5 days).[7] Moreover, plasmapheresis was performed twice.[8,9] Despite these treatments, the patient's skin lesions did not show adequate improvement. The systemic steroid dose was tapered in line with improvements in the patient's clinical symptoms. The patient was discharged without sequelae 75 days after the onset of TEN.

acetaminophen (stimulation index [SI] = 10.5; cut-off for the LTT, SI = 1.8), whereas a negative result was obtained for lansoprazole (SI = 1.1). Because the patient had severe UC, she


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was given systemic PSL (30 mg/day: the same dose as on admission), which proved effective for the skin lesions. The patient was also treated with antibiotics for MRSA and methicillin-resistant coagulase-negative staphylococci sepsis. The dose of systemic PSL was tapered in line with the degree of improvement in the patient's clinical symptoms. Twelve days after being transferred to our hospital, the patient exhibited re-epithelialization across most of her skin (Fig. 1e). Given the patient's septic state, we changed the antibiotic regimen according to the results of blood cultures; antibiotic therapy was stopped when the sepsis was resolved. The PSL dose was tapered gradually; ultimately, 10 mg/day was found to effectively control the patient's UC. The patient was discharged 71 days after being transferred to our hospital. The UC relapsed 1 year after discharge and the patient was prescribed infliximab (5 mg/kg) once again. The UC is presently well-controlled with mesalazine, azathioprine and infliximab (5 mg/kg).

## DISCUSSION

Here, we described a case of TEN caused by acetaminophen. Previous multivariate analyses conducted in Europe showed a weak or doubtful association of TEN with acetaminophen.[2] Recently, the US Food and Drug Administration reported that acetaminophen is associated with a risk of serious skin reactions, including TEN;[5] they also stated that Stevens–Johnson syndrome (SJS)/TEN can occur with first-time use of acetaminophen or at any time while it is being taken. Moreover, they reported that it can be difficult to determine how frequently serious skin reactions occur with acetaminophen due to the widespread use of the drug, differences in use among individuals (e.g. occasional vs long-term use) and the long period of time that the drug has been on the market.[5] Therefore, health-care professionals should be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with suspected drug-induced skin reactions.[5] In fact, a suspected case of SJS due to acetaminophen was confirmed by a challenge test.[10]

Regional differences in acetaminophen-induced SJS/TEN were reported by Mockenhaupt *et al.*[2] Additionally, Ueta *et al.*[11] reported that cold medicine (including acetaminophen)-related SJS/TEN was associated with human leukocyte antigen (HLA)-A*02:06 and HLA-B*44:03 in Japanese patients. Furthermore, they found that HLA-B*44:03 was significantly associated with cold medicine-induced SJS/TEN with severe ocular surface involvement in Indian and Brazilian populations, but not in a Korean population, and that HLA-A*02:06 may be weakly associated with the conditions in Korean, but not Indian or Brazilian, populations.[12] Taken together, these data suggest an association between HLA genotypes and acetaminophen in patients with SJS/TEN.

Our patient had been treated with systemic steroid therapy for UC. Notably, a large case–control study conducted by an international group of experts in 1995 demonstrated a significant association between systemic corticosteroids and SJS/TEN.[1] A multinational case–control study conducted in Europe showed that a large proportion of patients taking systemic steroids developed SJS and TEN.[2] Moreover, Lee *et al.*[13] recently showed that prior use of corticosteroids prolonged the period of disease progression without influencing disease severity or mortality. In addition, when SJS/TEN is preceded by the use of a single high-risk drug, the period of latency between the time of commencement of drug intake and SJS/TEN onset may also increase. Such findings suggest that corticosteroids mildly impact the course of SJS/TEN. Our patient had been taking systemic steroids for UC; therefore, we cannot exclude the effect of systemic steroids on SJS and TEN. However, it has not been determined whether corticosteroids are a direct cause of SJS/TEN, a risk factor (by modifying the immune response) or a confounder.[2]

Cutaneous reactions are relatively common in patients treated with tumor necrosis factor (TNF)-α inhibitors. However, SJS/TEN caused by such inhibitors is quite rare. There are only two case reports of SJS attributable to adalimumab. In our patient, infliximab was excluded as the causative drug, because this had been prescribed to treat UC after resolution of TEN, and no skin rash relapse had been noted. However, several recent reports have shown that the TNF-α antagonist etanercept can be used to effectively treat TEN.[14,15] Thus, TNF-α antagonists should be prescribed with caution because of the risk of severe drug reactions. These antagonists modify the immune response in the same manner as corticosteroids. Further work is needed to clarify the roles played by TNF-α antagonists in SJS/TEN treatment.

In conclusion, we presented a case of TEN due to acetaminophen that showed almost 100% skin detachment. Although previous publications reported a weak association between acetaminophen and SJS/TEN,[2] we found that severe drug eruptions may be caused by acetaminophen. Acetaminophen is included in many prescription and over-the-counter products; thus, clinicians should monitor patients for severe drug reactions, including TEN.

**ACKNOWLEDGMENTS:** This work was partially supported by the Practical Research Project for Rare/Intractable Diseases of the Japan Agency for Medical Research and Development (AMED) (grant no. 15ek0109011) and by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan (H26–nanchi [nan]–ippan–081).

**CONFLICT OF INTEREST:** None declared.

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昭和学士会誌　第75巻　第4号〔385-393頁，2015〕

特　　集　医薬品による重篤副作用への対処法と救済制度

# 重症薬疹

昭和大学医学部皮膚科学講座
末木　博彦

## はじめに

薬疹は薬剤による副作用としては最も頻度の高い事象のひとつである．原因薬の中止により後遺症なく，速やかに軽快する薬疹は問題にはならないが，患者の生命を脅かしたり，失明や慢性呼吸障害などの後遺症により患者のQOLを障害する薬疹は大きな問題である．後者の薬疹は重症薬疹として区別され，添付文書にも重大な副作用の項目に記載されている．添付文書の副作用名としては皮膚粘膜眼症候群もしくはStevens-Johnson症候群，中毒性表皮壊死症もしくはLyell症候群，（薬剤性）過敏症症候群，紅皮症，急性汎発性発疹性膿疱症などがある．

これらの重症薬疹は早期に発見し，被疑薬を中止し，適切な治療を行なう必要があることから，患者やその家族，薬剤師や看護師など全ての医療従事者が個々の重症薬疹に関する知識と対処法を知っておく必要がある．このために作られたのが重篤副作用疾患別対応マニュアルである[1]．本マニュアルは厚生労働省の委託により日本皮膚科学会においてマニュアル作成委員会が組織され，日本病院薬剤師会とともに議論を重ねて作成された案を重篤副作用総合対策委員会で検討され取りまとめられたものである．患者用の記載部分と医療関係者向けの記載部分に分けられている．本マニュアルは厚生労働省もしくは医薬品医療機器総合機構（PMDA）のホームページから誰でもダウンロードできる[1]．本稿では本マニュアルに沿って，各薬疹の概要，早期発見と早期対応のポイント，診断法ならびに鑑別診断法，治療方法について解説を加えたい．

## スティーヴンス・ジョンソン症候群（皮膚粘膜眼症候群）

### 1．概要

Stevens-Johnson syndrome（SJS）は1922年にニューヨークの小児科医であるStevensとJohnsonが口内炎と眼病変を伴う新しい熱性発疹症として2例の小児例を報告したのが最初である[2]．皮膚粘膜眼症候群の述語は歴史的にSJSと同義語として使われたため，現在でも添付文書や本マニュアルに併記される．SJSと粘膜症状を伴う多形紅斑を総称する症候名として用いられることがあるが，SJSと多形紅斑は予後が異なる別疾患であり，混乱を招くためこの術語は使用すべきではない．

SJSの発症頻度はわが国の全国調査によれば年間に人口100万人あたり1年間に3.1人である[3]．男女差はなく，30歳代に小ピークが，60歳代に最大のピークがある．死亡率は3%である[3]．

医薬品ときに感染症により生じた免疫アレルギー反応により発症すると考えられている．表皮細胞の壊死を生ずる機序として主にCD8陽性T細胞より産生されるgranulysin[4]や末梢血単球由来の可溶性Fas-ligandと表皮細胞Fasとの結合によるapoptosis，患者血清中のannexin Aと患者の表皮細胞に発現するformyl peptide receptor-1との結合によるnecroptosisが想定されている[5]．制御性T細胞の機能低下が本症の発症や進展に関与するとされ[6]，膠原病などの自己免疫疾患でステロイド薬を含む免疫抑制療法中の患者やCD4陽性細胞が減少するHIV感染患者，制御性T細胞の減少が長期間持続するマイコプラズマ感染症罹患後の患者などは本症のリスクが高い．

38℃以上の発熱を伴う口唇，眼粘膜，外陰部など皮膚粘膜移行部における重症の粘膜疹および皮膚の

紅斑で，しばしば水疱，びらんなど表皮の壊死性障害を認める．およそ2/3の症例では医薬品が原因と考えられるが，残り1/3ではウイルスやマイコプラズマ感染に伴い発症することがある．小児では医薬品よりマイコプラズマ感染症に伴うことが多い[7]．

2．早期発見と早期対応のポイント

原因薬としては抗菌薬，鎮痛解熱薬（総合感冒薬を含む），抗けいれん薬が上位を占める．原因薬の投与開始2週間以内に発症することが多いが数日から1か月以上のこともある[3]．解熱鎮痛薬では7日以内に70%，抗菌薬では7日以内に60%が発症するのに対し，アロプリノールと抗けいれん薬は14日以内に発症する症例は30%弱に過ぎず，14～42日の間に発症する症例が半数を占める[3]．

発症早期に認められる症状は①38℃の発熱，②粘膜症状（結膜充血・眼脂，口唇のびらん・出血，咽頭痛，陰部びらん，排尿排便時痛），③多発する類円形紅斑（進行すると水疱・びらんを伴う）の3主徴である．医療従事者はこれらの症状がみられ，その持続や悪化をみた場合は当日中に入院設備があり，皮膚科，眼科の専門医が常駐する基幹病院に紹介する必要がある（図1～3）．

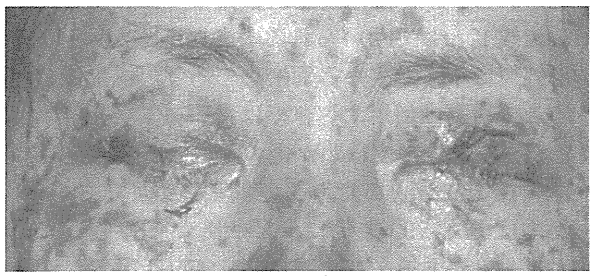

図1　スティーヴンス・ジョンソン症候群（SJS）の眼症状
偽膜性結膜炎のため自力での開眼が困難．

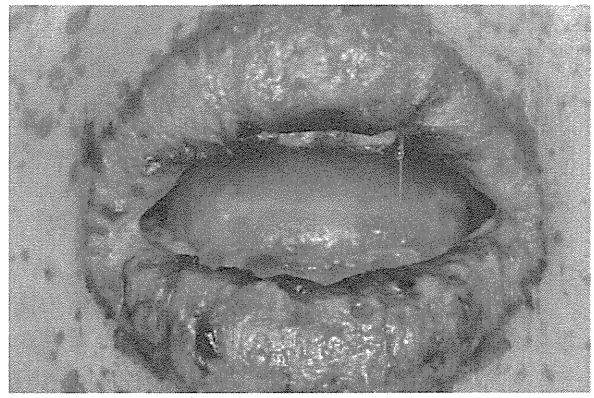

図2　SJSの粘膜症状．口唇の広範囲なびらん・血痂．

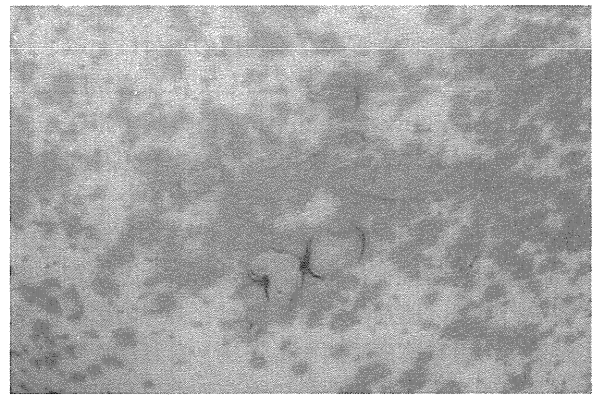

図3　SJSの皮膚症状
紅斑に一部に表皮壊死によるびらんを伴う．

表1　スティーヴンス・ジョンソン症候群（SJS）の診断基準（2005）[8]

概　念
発熱を伴う口唇，眼結膜，外陰部などの皮膚粘膜移行部における重症の粘膜疹および皮膚の紅斑で，しばしば水疱，表皮剝離などの表皮の壊死性障害を認める．原因の多くは薬剤である．

主要所見（必須）
1．皮膚粘膜移行部の重篤な粘膜病変（出血性あるいは充血性）がみられること．
2．しばしば認められるびらんもしくは水疱は，体表面積の10%未満であること．
3．発熱．

副所見
4．皮疹は非典型的なターゲット状多型紅斑．
5．角膜上皮障害と偽膜形成のどちらか，あるいは両方を伴う両眼性の非特異的結膜炎．
6．病理組織学的に，表皮の壊死性変化を認める．

・ただしTENへの移行があり得るため，初期に評価を行った場合には，極期に再評価を行う．
・主要項目の3項目をすべて満たす場合，SJSと診断する．

表 2　中毒性表皮壊死症（TEN）の診断基準（2005）[8]

概　念
広範囲な紅斑と，全身の10%以上の水疱，表皮剝離・びらんなどの顕著な表皮の壊死性障害を認め，高熱と粘膜疹を伴う．原因の大部分は医薬品である．

主要所見（必須）
1. 体表面積の10%を超える水疱，表皮剝離，びらん．
2. ブドウ球菌性熱傷様皮膚症候群（SSSS）を除外できる．
3. 発熱がある．

副 所 見
4. 皮疹は広範囲のびまん性紅斑および斑状紅斑である．
5. 粘膜疹を伴う．服表面上皮（角膜と結膜）では，びらんと偽膜のどちらかあるいは両方を伴う．
6. 病理組織学的に，顕著な表皮の壊死を認める．

主要3項目のすべてを満たすものをTENとする．

●サブタイプの分類
1型：SJS進展型（TEN with spots）*1
2型：びまん性紅斑進展型（TEN without spots）*2
3型：特殊型
*1：SJS進展型TEN（TEN with spotsあるいはTEN with macules）顔面のむくみ，発熱，結膜充血，口唇びらん，咽頭痛を伴う多形紅斑様皮疹
*2：びまん性紅斑型TEN（TEN without spotsあるいはTEN on large erythema）：発熱を伴って急激に発症する広汎な潮紅とびらん

●参考所見
治療等の修飾により，主要所見1の体表面積10%に達しなかったものを不全型とする．

3. 診断と鑑別診断

厚生労働科学研究班による診断基準を表1に示す[8]．紅斑は四肢より躯幹優位に分布する．紅斑は類円形もしくは不整形で隆起せず，境界は不鮮明，中心部は暗紅色～暗褐色調でときに水疱・びらんを伴い，flat atypical targets（扁平，非典型的標的病変）と称される[9]．隆起する小型の浮腫性紅斑上に小水疱を伴う皮疹が少数散在する症例では水痘との鑑別を要する．

皮膚生検による病理組織検査が鑑別診断に有用である．ホルマリン固定，パラフィン切片を作成すると数日を要するため，手術中迅速切片と同様の手順で凍結切片を作成し，HE染色を行なえば，数時間で結果を得ることができる[10]．組織学的には表皮下層を中心に，進行すると表皮全層に及ぶ壊死性変化を特徴とする．リンパ球を中心とする浸潤細胞は比較的少数である．ウイルス感染細胞がみられる水痘や麻疹との鑑別は容易である．多形紅斑は組織学的に真皮の浮腫と血管周囲性の炎症性細胞浸潤を特徴とする．表皮ケラチノサイトの個細胞壊死を伴うことがあるが，SJS/TENにみられるような全層性の壊死や基底層の連続性の壊死による水疱形成はみられない．

4. 治療

被疑薬の中止が第一である．厳重な眼科的管理，皮疹部，口唇・外陰部粘膜の局所処置，補液・栄養管理，感染防止など所謂supportive therapyに加え，以下の薬物療法を行なう[11]．

1）ステロイド全身療法

発症後7日前後までの発症早期に開始する．プレドニン換算で中等症は0.5～1 mg/kg/日，重症は1～2 mg/kg/日で開始する．重症例や急激に進展する症例ではメチルプレドニゾロン500～1000 mg/日，3日間のパルス療法も考慮する．パルス療法直後のステロイド投与量は1～2 mg/kg/日を投与し漸減する．減量速度は個々の症例の回復の程度により調整する．

2）高用量ヒト免疫グロブリン静注（IVIG）療法

ステロイド全身療法で効果不十分な場合に考慮される．400 mg/kg/日を5日間連続で点滴静注する．

3）血漿交換療法

ステロイド全身療法で症状の進行が食い止められ

ない重症例に併用療法として，もしくは重症感染症などステロイド薬の使用が困難な場合に考慮される．単純血漿交換（PE）と二重膜濾過血漿交換法（DFPP）がある．

4. 眼科的局所療法

急性期の眼病変に対しては眼表面の炎症，眼球癒着を抑えて眼表面上皮を温存し，眼表面の二次感染を防止する．ベタメタゾンあるいはデキサメサゾンの頻回の点眼，炎症が高度の場合はベタメタゾン眼軟膏を外用する．感染予防のための抗菌薬点眼も合わせて行なう．偽膜除去の効果については一定の見解はない．瞼球癒着癒着がある場合は点眼局麻下に硝子棒を用いて剥離する．

## 中毒性表皮壊死症

1. 概要

中毒性表皮壊死症（toxic epidermal necrolysis：TEN）は英国の皮膚科医 Lyell[12]により発熱を伴って急激に発症し，重症熱傷様の水疱とびらんを呈し，組織学的に表皮の壊死融解を特徴とする疾患として報告された．Lyell の症例はびまん性紅斑から広範囲に水疱・びらんを生ずるびまん性紅斑型であるが，90％以上の症例は SJS 進展型である．TEN と SJS は基本的には同一の病態と考えられ，わが国では表皮剥離面積が 10％以上を TEN，10％未満を SJS と区別している[8]．

わが国における TEN の発症頻度は人口 100 万人あたり 1 年間に 1.3 人である．30 歳代に小ピークが，60 歳代に最大のピークがある[3]．死亡率は 19％である．TEN では 94％の症例で医薬品が原因と考えられる．死亡例を解析すると発症時年齢が高い，被疑薬は抗菌薬の割合が高い，皮疹より発熱が先行する症例が多い，重症度スコアが高い，感染症合併，肝機能障害，末梢血異常，腎機能障害，呼吸器障害，循環器障害など他臓器障害が多い，などの特徴がみられる[3]．

2. 早期発見と早期対応のポイント

原因薬としては SJS と同様，抗菌薬，解熱鎮痛薬（総合感冒薬を含む），抗けいれん薬が上位を占めるが，どんな薬剤でも発症しうると考えるべきである．原因薬の投与開始 2 週間以内に発症することが多いが，数日から 1 か月以上のこともある．表皮壊死の発症機序は SJS と共通し，患者側のリスク因子も SJS と同様である．

発症早期に認められる症状は SJS と同様に①38℃の発熱，②粘膜症状（結膜充血，口唇のびらん・出血，咽頭痛など），③多発する類円形紅斑もしくはびまん性紅斑（進行すると水疱・びらんを伴う）の 3 主徴であり重症感がある．TEN ではまれに粘膜症状が明らかではない症例もある．①～③の症状がみられ，その持続や悪化をみた場合は当日中に入院設備があり，皮膚科，眼科の専門医が常駐する基幹病院に紹介する必要がある．

3. 診断と鑑別診断

厚生労働科学研究班による診断基準を表 2 に示す[8]．顔面・頸部・体幹を中心に広範囲にびまん性紅斑もしくは斑状紅斑を生ずる．斑状紅斑の標的病変の性状は SJS と同様である．発症早期は SJS と同様，麻疹や水痘などのウイルス感染症や多形紅斑型薬疹との鑑別を要する症例があり，SJS と同様の鑑別診断法を行なう必要がある．病像が完成すると紅斑は融合し体表面積の 10％を越える広範囲の水疱・びらんを呈するため臨床的にも鑑別診断は比較的容易である（図 4）．

ブドウ球菌性熱傷様皮膚症候群は「ブ菌 TEN」とも呼ばれるように臨床症状が類似することから鑑別を要する．生検病理組織で角層下に表皮内水疱を生じていることから鑑別は容易である[13]．

トキシックショック症候群でも全身性のびまん性紅斑と一部に水疱形成がみられ TEN に類似する．トキシックショック症候群では血圧低下，ショック症状を伴う点，生検組織で表皮の壊死性変化なく，表皮下水疱を呈する点から鑑別される[14]．

4. 治療

TEN の基本的な治療方針は SJS と共通である[11]．TEN では表皮剥離面積が大きいため，補液・栄養管理，感染防止など所謂 supportive therapy も重要である．びらん面よりの細菌感染は容易に敗血症に進展するため，重症熱傷と同様，連日の入浴洗浄が必要である．洗浄処置時には鎮痛・鎮静を要することがある．耐性菌の感染を防ぐための感染対策を十分に行う必要がある．

## 薬剤性過敏症症候群

1. 概要

薬剤性過敏症症候群（drug-induced hypersensitivity

表 3　薬剤性過敏症症候群（DIHS）の診断基準（2005）[8]

概　念

高熱と臓器障害を伴う薬疹で，薬剤中止後も遷延化する．多くの場合，発症後2～3週間後にHHV-6の再活性化を生じる．

主要所見

1. 限られた薬剤投与後に遅発性に生じ，急速に拡大する紅斑．しばしば紅皮症に移行する．
2. 原因薬剤中止後も2週間以上遷延する．
3. 38℃以上の発熱
4. 肝機能障害
5. 血液学的異常：a，b，cのうち一つ以上
   a. 白血球増多（11,000/mm$^3$以上）
   b. 異型リンパ球の出現（5%以上）
   c. 好酸球増多（1,500/mm$^3$以上）
6. リンパ節1腫脹
7. 目HHV-6の再活性化

典型DIHS：1～7すべて

非典型DIHS：1～5すべて，ただし4に関しては，その他の重篤な臓器障害をもって代えることができる．

参考所見

1. 原因薬剤は，抗痙攣薬，ジアフェニルスルフォン，サラゾスルファピリジン，アロプリノール，ミノサイクリン，メキシレチンであることが多く，発症までの内服期間は2～6週間が多い．
2. 皮疹は，初期には紅斑丘疹型，多形紅斑型で，後に紅皮症に移行することがある．顔面の浮腫，口唇の紅色丘疹，膿疱，小水疱，鱗屑は特徴的である．粘膜には発赤，点状紫斑，軽度のびらんが見られることがある．
3. 臨床症状の再燃がしばしば見られる．
4. HHV-6の再活性化は，①ペア血清でHHV-6 IgG抗体価が4倍（2管）以上の上昇，②血清（血漿）中のHHV-6 DNAの検出，③末梢血単核球あるいは全血中の明らかなHHV-6 DNAの増加のいずれかにより判断する．ペア血清は発症後14日以内と28日以降（21日以降で可能な場合も多い）の2点にすると確実である．
5. HHV-6以外に，サイトメガロウイルス，HHV-7，EBウイルスの再活性化も認められる．
6. 多臓器障害として，腎障害，糖尿病，脳炎，肺炎，甲状腺炎，心筋炎も生じうる．

syndrome：DIHS）は発熱と臓器障害を伴う薬疹であること，比較的限られた医薬品が原因となること，通常の薬疹と異なり，特定の原因医薬品を2週間から6週間と長期間投与後に発症すること，原因医薬品を中止しても臨床症状は軽快せず，2週間以上症状が遷延化すること，経過中に高率にヘルペス属ウイルスの活性化を生じ，臓器炎により生命予後を脅かすことを特徴とする重症薬疹の1型である．従来より抗けいれん薬による同様の薬疹が知られ，anticonvulsant hypersensitivity syndromeの病名が用いられてきた[15]．1989年に杏林大学と愛媛大学のグループが本症の経過中にEBウイルス，HHV-6，サイトメガロウイルスなどのヘルペス属ウイルスの再活性化を生じ，重篤な臓器障害の原因になることを明らかにしたことで病態の解明が進んだ[16,17]．これを契機にわが国では薬剤性過敏症症候群（DIHS）に病名が統一された．欧州ではdrug reaction with eosinophilia and systemic symptoms（DRSS）の病名が使用されており[18]，国際的にはDIHS/DRESSと併記されている．

すなわち原因薬の内服中に制御性T細胞（Treg）が増加し，末梢血中のB細胞の減少，免疫グロブリンの減少，好酸球増多，thymus and activation-regulated chemokine（TARC）の高値（＞10,000 pg/ml）などの検査異常を示す．原因薬の中止によりTregは減少し，免疫抑制状態から免疫再構築がなされ，再活性化されたウイルスに対するT細胞免疫が賦活化され，皮膚症状の遷延化や臓器障害を来すものと考えられる[19]．ウイルスの再活性化の詳細な機序は未解明な部分が大きい．本症による死亡率については正確なデータがないが，軽快後の続発症によるものも含め10%弱と推測されている．

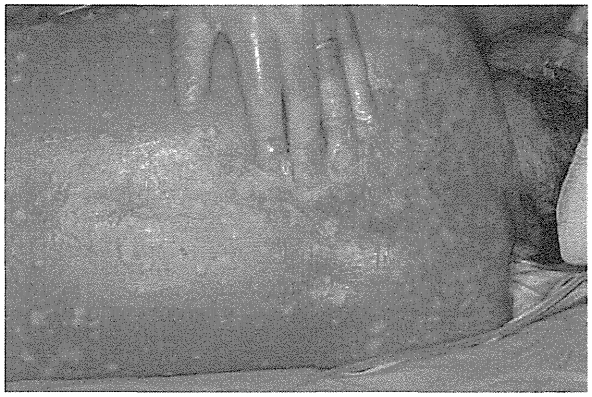

図 4　中毒性表皮壊死症（TEN）の広範なびらん．
白色調の部分は再上皮化．

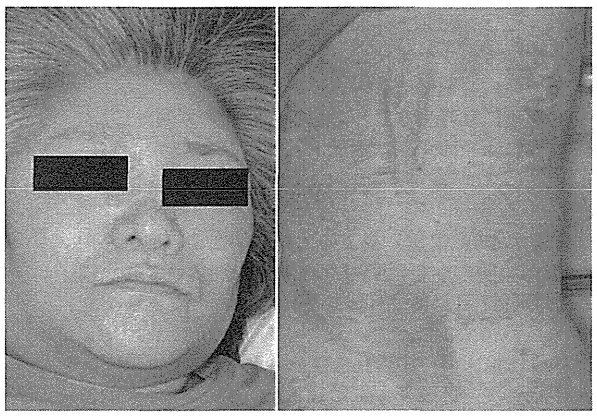

図 5　薬剤性過敏症症候群（DIHS）の皮膚症状．
顔面は浮腫状に腫脹し，鼻囲や口囲に丘疹の集族・痂皮が顕著．体幹では紅斑が融合．

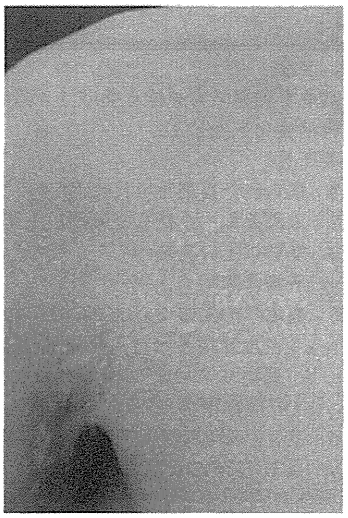

図 6　急性汎発性発疹性膿疱症（AGEP）の皮膚症状．
紅斑上に小膿疱が播種状に多発．間擦部に症状が高度．（末木博彦：これだけは知っておきたい皮膚の副作用．調剤と情報．18:669-675 より転載）

2．早期発見と早期対応のポイント

原因薬は比較的限られており，報告が多いのはカルバマゼピン，アロプリノール，塩酸メキシレチン，ラモトリギン，フェノバルビタール，フェニトイン，サラゾスルファピリジン，ゾニサミド，ジアフェニルスルフォン，ミノマイシンなどである．これらの薬剤を 2 ～ 6 週間内服後に 38℃以上の発熱，全身倦怠感，食欲不振，リンパ節腫脹などの全身症状を伴って全身の広範囲に皮疹を生ずることから本症を疑う．

皮疹は播種状紅斑丘疹型，ときに多形紅斑型に始まり，全身に皮疹が拡大融合し，次第に落屑を伴って紅皮症を呈する．顔面では浮腫がみられ，鼻や口囲に紅斑，丘疹，鱗屑，痂皮などが顕著であり，この特徴から本症を疑うことができる（図 5）．

3．診断と鑑別診断

厚生労働科学研究班による診断基準を表 3 に示す[8]．前述の臨床経過に加え，血液検査では白血球増多（極く初期には白血球減少），好酸球増多，異型リンパ球の出現，肝機能障害が高率に認められる．ときに腎機能障害もみられる．前述の TARC 値は保険適用外であるが 10,000 pg/ml 以上の高値を示すことが多く，多形紅斑型や播種状紅斑丘疹型薬疹との早期鑑別診断に有用である[20]．これらの症状が原因薬中止後も 2 週間以上遷延することが主要所見であり，発症初期には DIHS の診断は確定できず，全経過で判断する必要がある．発症後 14 日以内と 28 日以降にペア血清で HHV-6 IgG 抗体価の 4 倍以上の上昇，もしくは血清中の HHV-6 DNA の検出により再活性化の判断を行なう．再活性化の有無は重症度と関連し，再活性化群では TARC，TNF-α，LDH，CRP の高値が認められる[21, 22]．

鑑別診断を要する疾患として麻疹や伝染性単核球症などのウイルス感染症がある．麻疹とは薬剤歴，二相性発熱，カタル症状から鑑別されることが多い．咽頭粘液からの麻疹ウイルス DNA の検出が早期鑑別診断に有用である．伝染性単核球症とは類似点が

表 4　急性汎発性発疹性膿疱症（AGEP）の診断基準[1]

(1) 概念
薬剤使用後，高熱とともに急速に出現する多数の無菌性小膿疱を有する汎発性の紅斑で，末梢血の好中球増多を伴う．

(2) 主要所見
①急速に出現，拡大する紅斑
②紅斑上に多発する無菌性の非毛孔性小膿疱
③末梢血の白血球中の好中球増多（7,000/$mm^3$ 以上）
④発熱（38℃以上）

(3) 副所見
①皮膚病理組織学的に角層下膿疱あるいは表皮内膿疱
②除外疾患：膿疱性乾癬，角層下膿疱症，中毒性表皮壊死症，汗疹，敗血疹

主要所見のすべてをみたすものを急性汎発性発疹性膿疱症とする．

(4) 参考所見
・皮疹は間擦部や圧迫部に出現しやすい
・膿疱は 5 mm 大以下のことが多い
・多くで粘膜疹は認めない
・ウイルスや細菌感染が先行あるいは増悪因子となることがある
・基礎疾患（乾癬，関節リウマチ，骨髄性白血病，潰瘍性大腸炎，掌蹠膿疱症，糖尿病など）が存在していることが多い

あるが，薬剤歴，咽頭・扁桃炎の有無，最終的にはウイルス学的所見により鑑別する．

4. 治療[23]

入院治療を原則とする．多剤感作を生じやすいため，被疑薬のほか発症時に服用していた薬剤は可能な限り中止することが望ましい．発疹および全身症状に対し効果を期待できる治療法は副腎皮質ステロイド薬の全身投与である．初期量はプレドニゾロン換算で 0.5 ～ 1 mg/kg/日で開始する．初期量は原則として 7 ～ 14 日間投与する．臨床症状の軽快に伴い，1 ～ 2 週間毎に 5 ～ 10 mg/日ずつ漸減する．HHV-6 やサイトメガロウイルスの再活性化による再燃をみた場合は原則としてステロイド量の増減は行なわない．サイトメガロウイルス感染症ではガンシクロビル等の抗ウイルス薬投与，免疫グロブリン製剤の併用を考慮する．

## 急性汎発性発疹性膿疱症

1. 概要

急性汎発性発疹性膿疱症（acute generalized exanthematous pustulosis：AGEP）は乾癬の既往なく，高熱とともに急速に全身に浮腫性紅斑やびまん性紅斑上に小膿疱が多発し，急性の経過をとる発疹症にたいし膿疱性乾癬とは別症としてフランス語の論文に発表されたのが最初である[24, 25]．通常粘膜疹はない．血液検査で好中球優位の白血球増多と炎症反応上昇が特徴である．原因薬としては抗菌薬・抗真菌薬が大半を占め，内服開始数時間～数日以内に発症する例と 1 ～ 2 週後に発症する例がある．原因薬の中止により 2 週間以内に軽快し再発はないが，極くまれに TEN と症状のオーバーラップがみられる症例がある[26]．発症機序としてはリンパ球刺激試験[27]やパッチテストの陽性率が高く[28]，アレルギー機序が考えられている．最初に薬剤特異的 T 細胞が表皮に集まり，ケラチノサイトを障害し，T 細胞，ケラチノサイトから産生される GM-CSF や IL-8 により好中球が角層下に集積される一方，表皮の壊死を免れるのではないかと推測されている[29]．

2. 早期発見と早期対応のポイント

原因薬服用後 38℃以上の発熱とともに急速に出現するびまん性紅斑もしくは浮腫性紅斑上に毛孔に一致しない無数の小膿疱をみた場合は本症を疑い，

早急に皮膚科入院施設のある基幹病院に紹介する（図6）.

3. 診断と鑑別診断

重篤副作用疾患別対応マニュアルの診断基準を表4に示す[1]. 臨床症状に末梢血好中球増多（7,000/mm$^3$以上）を含む主要所見の4項目全てを満たすものをAGEPと診断する. 生検病理組織では角層下膿疱あるいは表皮内膿疱が認められる.

皮疹は膿疱性乾癬と類似するが, 膿疱性乾癬では乾癬の既往や局面が先行する点, 発熱の持続期間が長い点, 組織学的に表皮肥厚や錯角化がみられる点, 膿疱が2週間以上にわたって軽快しない点, 薬剤内服歴などから鑑別される. 角層下膿疱症では発熱など全身症状は通常なく, 間擦部位を中心に紅斑・膿疱が数日から数週のサイクルで出現する. しばしば環状・蛇行状を呈する[30]. 急性汎発性膿疱性細菌疹は通常上気道感染症に引き続いて全身に紅暈を伴う膿疱, 小紫斑が散在する. 膿疱はAGEPより大型である. 組織学的に免疫複合体による血管炎を認めることがある[31].

4. 治療

被疑薬を中止し, 必要に応じて他系統の薬剤に変更する. プレドニン換算0.5～0.7 mg/kg/日より投与を開始し, 症状に応じて減量する.

## おわりに

医薬品副作用被害救済制度では本稿で解説した4疾患以外の病型でも, 入院治療を必要とする程度の薬疹（一般的には中等量以上のステロイド薬治療を要するもの）に対しては入院期間が短期間であっても救済給付の対象になる. 巻頭言でも述べたように本制度は患者もしくは家族が申請するものであり, 患者に本制度の存在を説明する必要がある.

謝辞　本論文は厚生労働省科学研究費補助金（難治性疾患等政策研究事業（難治性疾患政策研究事業）（H26-難治等（難）-一般-081）の援助を受けた.

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JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13073
*Journal of Dermatology* 2015; **42**: 1–4

CONCISE COMMUNICATION

# Toxic epidermal necrolysis caused by acetaminophen featuring almost 100% skin detachment: Acetaminophen is associated with a risk of severe cutaneous adverse reactions

**Hideaki WATANABE,[1] Taisuke KAMIYAMA,[1] Shun SASAKI,[1] Kae KOBAYASHI,[1] Kenichiro FUKUDA,[2] Yasufumi MIYAKE,[2] Tohru ARUGA,[2] Hirohiko SUEKI[1]**

[1]*Department of Dermatology, Showa University School of Medicine,* [2]*Department of Emergency and Critical Care Medicine, Showa University, Tokyo, Japan*

## ABSTRACT

**Toxic epidermal necrolysis (TEN) is an adverse reaction that can be induced by various drugs; the associated mortality rate is 20–25%. A previous report showed a weak association between TEN and acetaminophen. Recently, the US Food and Drug Administration declared that acetaminophen is associated with a risk of serious skin reactions, including TEN. Here, we describe the case of a 43-year-old Japanese woman with TEN caused by acetaminophen. She had poorly controlled ulcerative colitis and was treated with high doses of prednisolone, infliximab, acetaminophen and lansoprazole. Nine days after administrating acetaminophen, targetoid erythematous and bullous lesions appeared on the patient's trunk, palms and the soles of her feet. The skin lesions expanded rapidly; within 3 weeks, skin detachment was detected across nearly 100% of the patient's body. However, no mucosal involvement of the eyes, oral cavity or genitalia was found. We performed lymphocyte transformation tests using various drugs; however, a high stimulation index was obtained only with acetaminophen. The patient recovered following treatment with plasmapheresis, i.v. immunoglobulin therapy, topical medication and supportive therapy. Acetaminophen is included in many prescription and over-the-counter products; thus, clinicians should monitor their patients for severe drug reactions, including TEN.**

**Key words:** acetaminophen, lymphocyte transformation test, severe cutaneous adverse reaction, toxic epidermal necrolysis.

## INTRODUCTION

Toxic epidermal necrolysis (TEN) is a serious, life-threatening, cutaneous adverse drug reaction with a high mortality rate (20–25%).[1–3] The disorder is characterized by a rapidly developing blistering exanthema of purpuric macules and targetoid lesions accompanied by mucosal involvement and variable skin detachment.[4] TEN is defined as skin detachment exceeding 30%.[4] Strong associations have been reported between TEN and a number of drugs, including anticonvulsants, allopurinol, anti-infective sulfonamides and nevirapine.[2] A multivariate analysis showed a weak association with acetaminophen.[2] However, the US Food and Drug Administration recently informed the public that acetaminophen is associated with a risk of serious skin reactions, including TEN.[5] We herein describe a severe case of TEN due to acetaminophen that exhibited no mucosal involvement of the eyes, oral cavity or genitalia.

## CASE REPORT

A 43-year-old Japanese woman with ulcerative colitis (UC) that was controlled with systemic prednisolone (PSL; 10 mg/day) reported an increase in symptoms. The patient's treatment regimen was changed to high doses of PSL (50 mg/day), infliximab (5 mg/kg), acetaminophen and lansoprazole, and her symptoms of UC improved. However, on 10 July 2013 (9 days after her first dose of acetaminophen), the patient noticed an erythematous eruption on her palms. Two days later, the patient visited her local hospital. Edematous erythema was detected on the patient's palms (Fig. 1a) and soles. Scattered, flat, atypical, targetoid, erythematous lesions were noted on the patient's trunk (Fig. 1b). Moreover, slight erosions and white crusts were evident on the lower lip. The initial diagnosis was hand–foot–mouth disease. Because the clinical findings of hand–foot–mouth disease sometimes mimic those of severe cutaneous adverse reactions,[6] drug eruption was raised as a differential

Correspondence: Hideaki Watanabe, M.D., Department of Dermatology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan. Email: hwatanabe@med.showa-u.ac.jp
Received 3 June 2015; accepted 10 July 2015.

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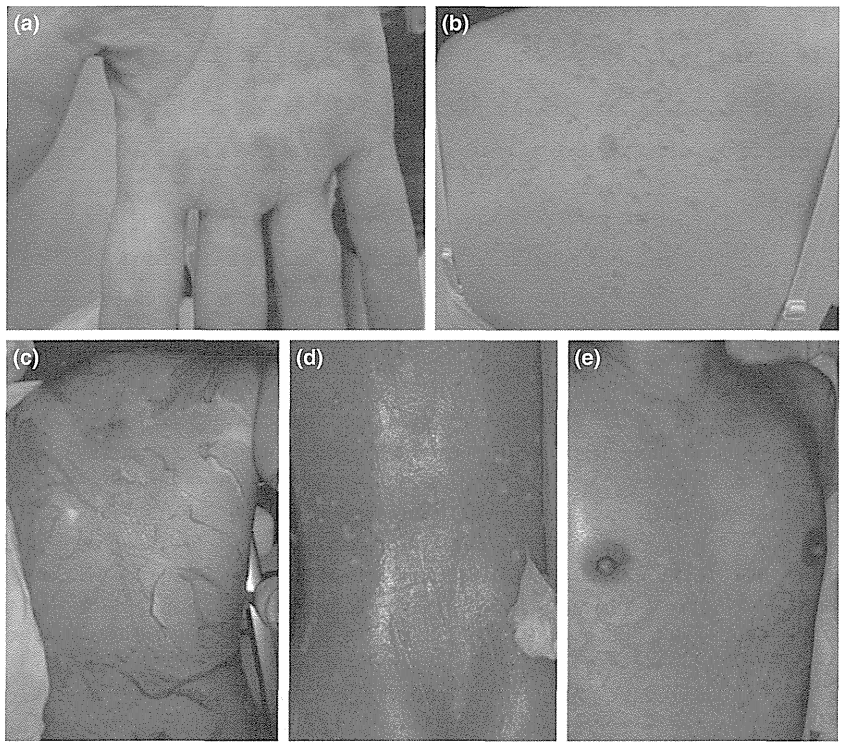


**Figure 1.** Clinical findings 2 days after toxic epidermal necrolysis (TEN) onset. (a) Edematous, erythematous lesions were seen on the patient's palms. (b) Papules and atypical targetoid erythematous lesions were also observed on her back. (c) Epidermal detachment was noted 12 days after the onset of TEN. (d) Skin detachment was noted across nearly 100% of the patient's body 20 days after the onset of TEN (on admission to our hospital). (e) One month after the onset of TEN, the patient's skin lesions had improved.

diagnosis. All drugs except PSL were discontinued. However, the patient's skin lesions expanded rapidly. Twelve days after the onset of TEN, epidermal detachment was detected on the patient's trunk (Fig. 1c). At that point, skin detachment was noted across 60% of the patient's body. The patient was treated with systemic PSL (50 mg/day) for TEN. She was also given i.v. immunoglobulins (3 g/day for 3 days and 10 g/day for 5 days).[7] In addition, plasmapheresis was performed twice, 12 and 14 days after the onset of TEN, respectively.[8,9] Despite these treatments, the patient's skin lesions did not improve, and methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in her blood. The patient was transferred to our hospital 20 days after the onset of TEN (1 August 2013) (Fig. 2).

On admission to our hospital, epidermal detachment was noted across nearly 100% of the patient's body (Fig. 1d). However, no mucosal involvement of the eyes, oral cavity or genitalia was found.

Laboratory investigations on admission revealed the following: white blood cell count, 7.7 $\times$ $10^9$/L (normal, 3.5–9); aspartate aminotransferase, 16 IU/L (10–30); alanine aminotransferase, 7 IU/L (5–25); serum creatinine, 0.38 mg/dL (0.5–0.9); total protein, 4.2 g/dL (6.7–8.4); albumen, 1.7 g/dL (4.0–5.1); and C-reactive protein, 5.20 mg/dL (<0.2). A lymphocyte transformation test (LTT) was performed with acetaminophen and lansoprazole; a positive result was obtained for

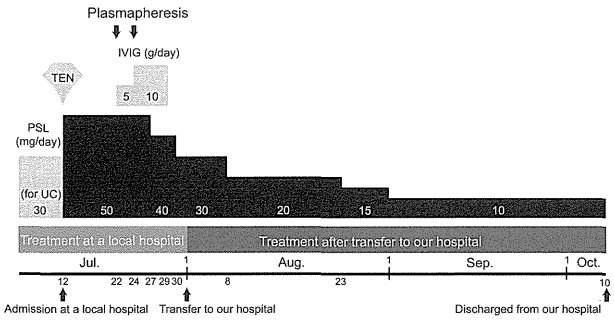


**Figure 2.** Treatment. A physician at the patient's local hospital treated her with systemic prednisolone (PSL) (30 mg/day) for ulcerative colitis (UC). The patient was also given intravenous immunoglobulin (IVIG) therapy (3 g/day for 3 days and 10 g/day for 5 days).[7] Moreover, plasmapheresis was performed twice.[8,9] Despite these treatments, the patient's skin lesions did not show adequate improvement. The systemic steroid dose was tapered in line with improvements in the patient's clinical symptoms. The patient was discharged without sequelae 75 days after the onset of TEN.

acetaminophen (stimulation index [SI] = 10.5; cut-off for the LTT, SI = 1.8), whereas a negative result was obtained for lansoprazole (SI = 1.1). Because the patient had severe UC, she


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was given systemic PSL (30 mg/day: the same dose as on admission), which proved effective for the skin lesions. The patient was also treated with antibiotics for MRSA and methicillin-resistant coagulase-negative staphylococci sepsis. The dose of systemic PSL was tapered in line with the degree of improvement in the patient's clinical symptoms. Twelve days after being transferred to our hospital, the patient exhibited re-epithelialization across most of her skin (Fig. 1e). Given the patient's septic state, we changed the antibiotic regimen according to the results of blood cultures; antibiotic therapy was stopped when the sepsis was resolved. The PSL dose was tapered gradually; ultimately, 10 mg/day was found to effectively control the patient's UC. The patient was discharged 71 days after being transferred to our hospital. The UC relapsed 1 year after discharge and the patient was prescribed infliximab (5 mg/kg) once again. The UC is presently well-controlled with mesalazine, azathioprine and infliximab (5 mg/kg).

## DISCUSSION

Here, we described a case of TEN caused by acetaminophen. Previous multivariate analyses conducted in Europe showed a weak or doubtful association of TEN with acetaminophen.[2] Recently, the US Food and Drug Administration reported that acetaminophen is associated with a risk of serious skin reactions, including TEN;[5] they also stated that Stevens–Johnson syndrome (SJS)/TEN can occur with first-time use of acetaminophen or at any time while it is being taken. Moreover, they reported that it can be difficult to determine how frequently serious skin reactions occur with acetaminophen due to the widespread use of the drug, differences in use among individuals (e.g. occasional vs long-term use) and the long period of time that the drug has been on the market.[5] Therefore, health-care professionals should be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with suspected drug-induced skin reactions.[5] In fact, a suspected case of SJS due to acetaminophen was confirmed by a challenge test.[10]

Regional differences in acetaminophen-induced SJS/TEN were reported by Mockenhaupt *et al.*[2] Additionally, Ueta *et al.*[11] reported that cold medicine (including acetaminophen)-related SJS/TEN was associated with human leukocyte antigen (HLA)-A*02:06 and HLA-B*44:03 in Japanese patients. Furthermore, they found that HLA-B*44:03 was significantly associated with cold medicine-induced SJS/TEN with severe ocular surface involvement in Indian and Brazilian populations, but not in a Korean population, and that HLA-A*02:06 may be weakly associated with the conditions in Korean, but not Indian or Brazilian, populations.[12] Taken together, these data suggest an association between HLA genotypes and acetaminophen in patients with SJS/TEN.

Our patient had been treated with systemic steroid therapy for UC. Notably, a large case–control study conducted by an international group of experts in 1995 demonstrated a significant association between systemic corticosteroids and SJS/TEN.[1] A multinational case–control study conducted in Europe showed that a large proportion of patients taking systemic steroids developed SJS and TEN.[2] Moreover, Lee *et al.*[13] recently showed that prior use of corticosteroids prolonged the period of disease progression without influencing disease severity or mortality. In addition, when SJS/TEN is preceded by the use of a single high-risk drug, the period of latency between the time of commencement of drug intake and SJS/TEN onset may also increase. Such findings suggest that corticosteroids mildly impact the course of SJS/TEN. Our patient had been taking systemic steroids for UC; therefore, we cannot exclude the effect of systemic steroids on SJS and TEN. However, it has not been determined whether corticosteroids are a direct cause of SJS/TEN, a risk factor (by modifying the immune response) or a confounder.[2]

Cutaneous reactions are relatively common in patients treated with tumor necrosis factor (TNF)-α inhibitors. However, SJS/TEN caused by such inhibitors is quite rare. There are only two case reports of SJS attributable to adalimumab. In our patient, infliximab was excluded as the causative drug, because this had been prescribed to treat UC after resolution of TEN, and no skin rash relapse had been noted. However, several recent reports have shown that the TNF-α antagonist etanercept can be used to effectively treat TEN.[14,15] Thus, TNF-α antagonists should be prescribed with caution because of the risk of severe drug reactions. These antagonists modify the immune response in the same manner as corticosteroids. Further work is needed to clarify the roles played by TNF-α antagonists in SJS/TEN treatment.

In conclusion, we presented a case of TEN due to acetaminophen that showed almost 100% skin detachment. Although previous publications reported a weak association between acetaminophen and SJS/TEN,[2] we found that severe drug eruptions may be caused by acetaminophen. Acetaminophen is included in many prescription and over-the-counter products; thus, clinicians should monitor patients for severe drug reactions, including TEN.

**ACKNOWLEDGMENTS:** This work was partially supported by the Practical Research Project for Rare/Intractable Diseases of the Japan Agency for Medical Research and Development (AMED) (grant no. 15ek0109011) and by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan (H26–nanchi [nan]–ippan–081).

**CONFLICT OF INTEREST:** None declared.

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