QUIZ SECTION

MJS PUBLISHING



# Two Cases of Widespread Erythema with Mucosal Lesions: A Quiz

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Case 1: An 84-year-old man was diagnosed with cutaneous lupus erythematosus based on chilblain erythema on his hands and feet; blood tests were positive for anti-nuclear antibody (2,560 times) 10 years ago, but had not been followed up because he had few symptoms. He noticed chills, a fever over 38 degrees, and erythema on the whole body 7 days prior to his visit. Erosions of the lips and glans penis had appeared, and expanded to the buccal mucosa (Fig. 1A, B). At the same time, erythema and fissures were observed on his fingers and palms (Fig. 1C), with flushing on the whole body (Fig. 1D), while there were no obvious symptoms in the eyes. There was no obvious drug history. The laboratory findings showed mild anaemia (Hb 12.7 g/dL), while cytopenia was not detected. Anti-nuclear antibody was positive (1,280 times in speckled pattern); however, anti-double stranded deoxyribonucleic acid antibody was negative and the serum levels of complements were normal. Anti-Sjögren syndrome A (1200 U/mL) and anti-Sjögren syndrome B antibodies (1,000 U/mL) were both upregulated. Histopathological findings from erythema of the abdomen showed a small number of dyskeratotic cells within the epidermis and remarkable liquefaction degeneration of the basal layer. Focal mild lymphocytic infiltration was observed in the upper dermis and around hair follicles (Fig. 1E, F).

Case 2: A 77-year-old female had erythema all over her body and fever of 38.5°C. PSL 25 mg/day was administered with a diagnosis of toxicoderma; however, the fever and skin rash were not completely improved. Therefore, the patient was referred to our hospital. Erythema was seen on the face with inflamed conjunctiva in both eyes, along with erosions with crusts on her lips (Fig. 1G, H). Erythema was observed on the palms and fingers (Fig. 1I). Flat target dark-red erythema was also present on the trunk and extremities (Fig. 1J). Blood tests were positive for anti-nuclear antibodies (320 times in centromere pattern) and showed decreased complement C4 (8.2 mg/dL), while cytopenia was not detected. The histopathological finding from erythema of the forearm showed dyskeratotic cells in the epidermis and interface change, and a dense cell infiltration mainly composed of lymphocytes in the upper dermis and around the sweat glands (Fig. 1K, L).

We performed immunostaining to investigate this difference using an apoptosis marker (cleaved caspase-3:

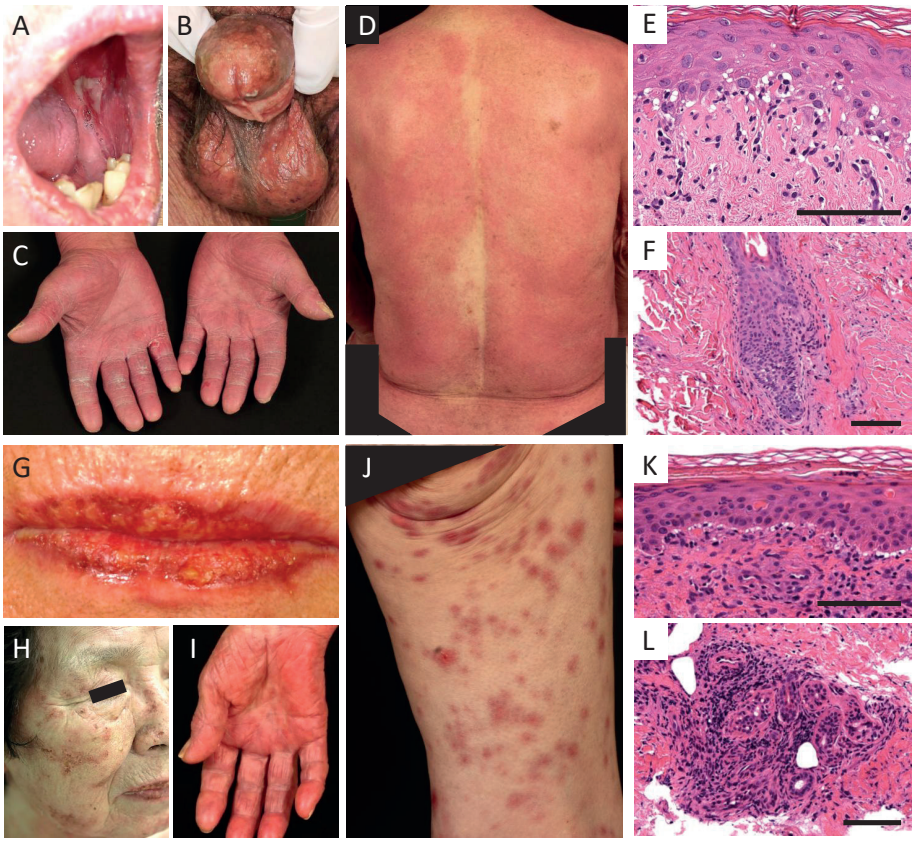


**Fig. 1. Clinical and histopathological findings of case 1 and case 2.** Clinical findings (A–D) and the haematoxylin and eosin (H&E) staining (E, F) of a biopsy specimen from the abdomen of case 1. (A, B) Erosions were observed on the lips, buccal mucosa, glans penis, and scrotum. (C, D) Diffuse erythema was present on the palms and trunk. (E) Dyskeratosis was detected in the epidermis and liquefaction degeneration was identified at the dermal–epidermal junction with a few infiltrating cells. (F) Lymphocytes infiltrated the hair follicle. Clinical findings (G–J) and the H&E staining (K, L) of a biopsy specimen from the forearm of case 2. (G) Erosions were observed on the lips. (H–J) Multiple erythematous lesions were observed in the face, hand, and leg. (K) Dyskeratosis was detected in the epidermis with liquefaction degeneration. (L) Numerous lymphocytes infiltrated the sweat glands. Scale bars = 100 μm.

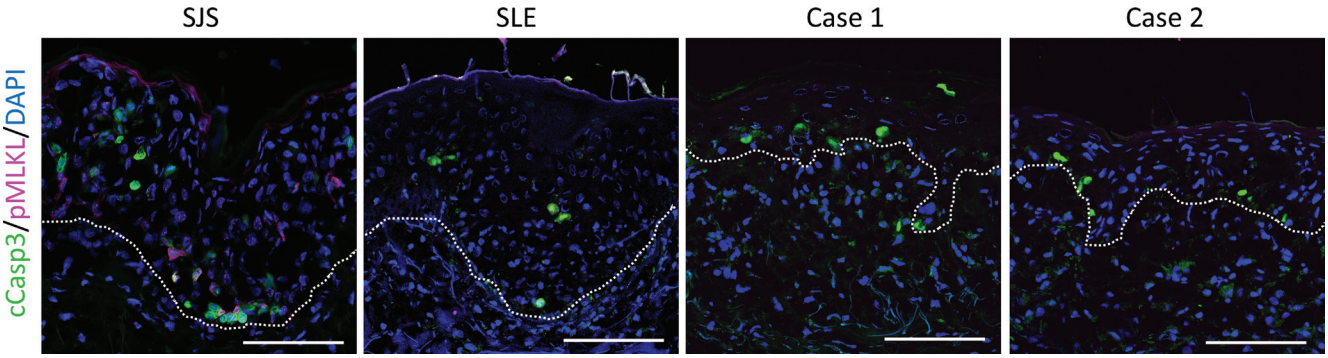


**Fig. 2. Immunofluorescence staining to identify the type of keratinocyte death.** Skin tissues were stained with an apoptosis marker, cleaved caspase-3 (cCasp3; green); a necroptosis marker, phosphorylated-mixed lineage kinase domain-like (pMLKL; magenta), and a nuclear marker, 4′,6-diamidino-2-phenylindole (DAPI; blue). In Stevens–Johnson syndrome (SJS), both apoptotic cells and necroptotic cells were observed in the epidermis. In toxic epidermal necrolysis-like lupus erythematosus cases, including case 1 and case 2, and systemic lupus erythematosus (SLE) only apoptotic cells were detected. Scale bars = 100 μm. Primary antibodies used were rabbit Monoclonal anti-cCasp3 (diluted 1:100; Cell Signaling Technology, Danvers, MA, USA) and mouse Monoclonal anti-pMLKL (diluted 1:100; Signalway Antibody LLC, Greenbelt, MD, USA).

cCasp3) and a necroptosis marker (phosphorylated-mixed lineage kinase domain-like: pMLKL) (Fig. 2). The skin lesion of SJS shows both cCasp3-positive cells and pMLKL-positive cells in the epidermis. On the other hand, only cCasp3-positive cells were observed in the skin lesion of SLE, which is consistent with the notion that keratinocyte death in LE occurs through apoptosis. In our 2 cases, cCasp3-positive cells were detected; however, pMLKL-positive cells were not identified.

*What is your diagnosis?*

1: Stevens–Johnson syndrome
2: Linear IgA bullous dermatosis
3: Toxic epidermal necrolysis-like lupus erythematosus
4: Erythema multiforme major

See next page for answer.

## ANSWERS TO QUIZ

### Two Cases of Widespread Erythema with Mucosal Lesions: A Commentary

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***Diagnosis*: Toxic epidermal necrolysis-like lupus erythematosus (TEN-like LE)**

Toxic epidermal necrolysis-like lupus erythematosus (TEN-like LE) is a rare disease that generally occurs in patients with systemic lupus erythematosus (SLE) and patients with TEN-like LE exhibit similar eruptions to Stevens–Johnson syndrome (SJS)/TEN (1, 2). To the best of our knowledge, 75 cases including our cases have been reported in peer-reviewed English papers and the average age of diagnosis is 45 years (1, 3). Some 46% (35 cases/75 cases) had a confirmed diagnosis of SLE or acute cutaneous lupus erythematosus (ACLE)/subacute cutaneous lupus erythematosus (SCLE) before the onset of TEN-like LE, and others were diagnosed after onset (1, 3).

TEN-like LE shows extensive epidermal exfoliation and blistering like SJS/TEN, and it is often difficult to distinguish from SJS/TEN, whereas TEN-like LE is characterized by lack of a suspect drug, absence or localization of mucosal lesions, and a subacute course (1). In our cases, there were no obvious suspect agents in either of the 2 cases, while the mucosal lesions involved the lips, buccal mucosa, and glans penis. Clinical findings alone do not confirm the diagnosis, and skin biopsy and blood tests are also important for diagnosis. Because SLE is the basis of the disease, blood tests are often positive for anti-nuclear antibodies and they were positive in more than 90% (71 cases/75 cases) (4, 5) in previously reported cases. On the one hand, there were also some cases in which anti-Sjögren syndrome A and anti-Sjögren syndrome B antibodies were positive. All of our cases were positive for anti-nuclear antibodies, but only case 1 was positive for anti-Sjögren syndrome A and anti-Sjögren syndrome B antibodies. Histopathological findings show varying degrees of epidermal necrosis, and often shows findings of LE. In our cases, a small number of dyskeratotic cells in the epidermis, liquefaction degeneration at the dermal–epidermal interface, and lymphocyte infiltration around sweat glands and hair follicles were observed. These LE findings suggest the possibility of TEN-like LE rather than SJS/TEN. Although dyskeratosis could be observed in both SJS/TEN and LE, it has been reported that both apoptosis and necroptosis, a form of programmed cell death that exhibits morphological necrosis, are involved in SJS/TEN (6, 7). The keratinocyte death in LE is considered to be apoptosis (8), and when it is extensive it can lead to TEN-like LE. Therefore, we hypothesized that the form of keratinocyte death differs between SJS/TEN and TEN-like LE. From the results of immunostaining, both apoptosis and necroptosis were involved in the epidermis of SJS lesions, whereas only apoptosis was involved in the epidermis of TEN-like LE lesions. These findings support that our cases are consistent with TEN-like LE, and this difference in the form of keratinocyte death could serve as a diagnostic clue for distinguishing TEN-like LE from SJS/TEN.

We experienced 2 cases of TEN-like LE that required differentiation from SJS. Although distinguishing between them is often challenging, a comprehensive assessment combining clinical findings, blood tests, and histopathology can facilitate an accurate diagnosis. In this report, we highlighted the potential importance of differences in the form of keratinocyte death, such as apoptosis and necroptosis, as a key diagnostic feature.

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