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Letter to the Editor

## A case of zonisamide-induced toxic epidermal necrolysis with acute respiratory failure

Dear Editor,

Toxic epidermal necrolysis (TEN) is a life-threatening cutaneous adverse drug reaction characterized by a high fever and widespread erosions of the skin and mucosa, including the lips, oropharynx and genital region.<sup>1</sup> The visceral organs are frequently affected in TEN, and treatment in the intensive-care unit (ICU) is required, especially in patients with respiratory failure. Many therapeutic options, including systemic steroids, plasmapheresis and intravenous immunoglobulin (IVIG), have been used and are considered effective for the treatment of TEN, although no gold standard has been established.

In Japan, systemic high-dose corticosteroid therapy has been chosen as the first-line treatment according to the Japanese guideline for the management of Stevens-Johnson syndrome (SJS) and TEN, and the addition of steroid pulse therapy, plasmapheresis and/or IVIG is recommended in intractable cases.<sup>2</sup> Transfusion-related acute lung injury (TRALI), which is a rare complication after transfusion of blood or blood products, including fresh-frozen plasma and IVIG, is characterized by the acute onset of respiratory failure due to increased pulmonary vascular permeability.<sup>3,4</sup> TRALI usually occurs within 6 h after the end of transfusion and requires treatments ranging from supplemental oxygen to mechanical ventilation.

We herein report a case of TEN with acute respiratory failure developing after the initiation of IVIG that required differentiation from other respiratory disorders, such as pneumonia and TRALI.

A 43-year-old man complained of a high fever, conjunctival injection, oral mucosal erosions and erythema on the trunk 41 days after taking zonisamide (300 mg/day) to prevent epilepsy. He sometimes took loxoprofen sodium for the treatment of headache on demand. After discontinuing zonisamide and loxoprofen sodium, the erythema on the trunk expanded and became confluent with blisters and erosions. Under a diagnosis of TEN, steroid pulse therapy (methylprednisolone 1 g/day for 3 days) was performed. As his symptoms worsened the next day, he was transferred to our hospital after starting IVIG therapy (27.5 g/day).

At admission, his body temperature, heart rate and SpO<sub>2</sub> were 37.9 °C, 113 bpm and 93% (ambient air), respectively. He presented with hemorrhagic erosions of the lips, oral mucosa and pharynx and ocular complications associated with conjunctivitis and pseudomembrane formation (Fig. 1A). Erythema with blisters and erosions were observed on approximately 50% of the total body surface area, and Nikolsky's sign was positive (Fig. 1B). A biopsy

of the abdomen skin revealed vacuolar changes at the dermoepidermal junction and scattered necrotic keratinocytes in the basal and suprabasal layers (Fig. 1C). The diagnosis of TEN was made clinically and histologically.

A laboratory examination revealed leukocytopenia (2270/μL), elevated serum C-reactive protein levels (17.99 mg/dL) and no *Mycoplasma pneumoniae* antibodies. Thirty minutes after the end of IVIG administration, dyspnea and bronchial hypersecretion were observed, and 5 L/min oxygen through a face mask was required to maintain an SpO<sub>2</sub> of 95%. Chest computed tomography (CT) showed bilateral bronchial and bronchiolar wall thickening and focal consolidation at the periphery of the right upper lobe (Fig. 1D). Intravenous 8 mg betamethasone sodium phosphate administration was started; however, his respiratory condition dramatically deteriorated during the first 24 h. He was transferred to the ICU next day and ultimately required 10 L/min oxygen through a nonrebreather face mask. A chest radiograph showed bilateral ground-glass opacities (Fig. 1E). Further chest CT revealed patchy areas of ground-glass opacities and consolidation along the bilateral bronchovascular bundles without pleural effusion (Fig. 1F). The respiratory symptoms were progressing too rapidly for pulmonary infection, and the findings of chest CT at the onset of respiratory failure did not seem to be typical for TRALI. Thus, under a diagnosis of intractable TEN with pulmonary involvement, IVIG therapy was stopped, and 2 plasmapheresis procedures and empiric antibiotic therapy were performed (Fig. 2).

His skin and respiratory condition gradually recovered, and he left the ICU 8 days later while receiving 3 L/min oxygen through a face mask. Zonisamide had been taken for 41 days before the onset of TEN, and SJS/TEN often develops more than 3 weeks after starting anticonvulsants.<sup>5</sup> A drug lymphocyte stimulation test (DLST) was positive for zonisamide with a stimulation index of 2.7 and negative for loxoprofen sodium. Therefore, we concluded that zonisamide had caused TEN.

Pulmonary complications are frequently seen in TEN/SJS.<sup>1,6</sup> Lebargy classified acute pulmonary complications into early and delayed manifestations.<sup>7</sup> Early manifestations are characterized by dyspnea, bronchial hypersecretion and the acute onset of severe respiratory failure immediately after the onset of mucocutaneous symptoms and are related to bronchial epithelium detachment due to epithelial necrosis. Delayed manifestations include nonspecific pulmonary symptoms, such as atelectasis, pulmonary edema and bacterial pneumonia during the disease course. In our case, respiratory failure occurred after the end of IVIG administration, and differentiating between TEN-induced acute respiratory failure and TRALI by clinical symptoms was very difficult due to the similarity

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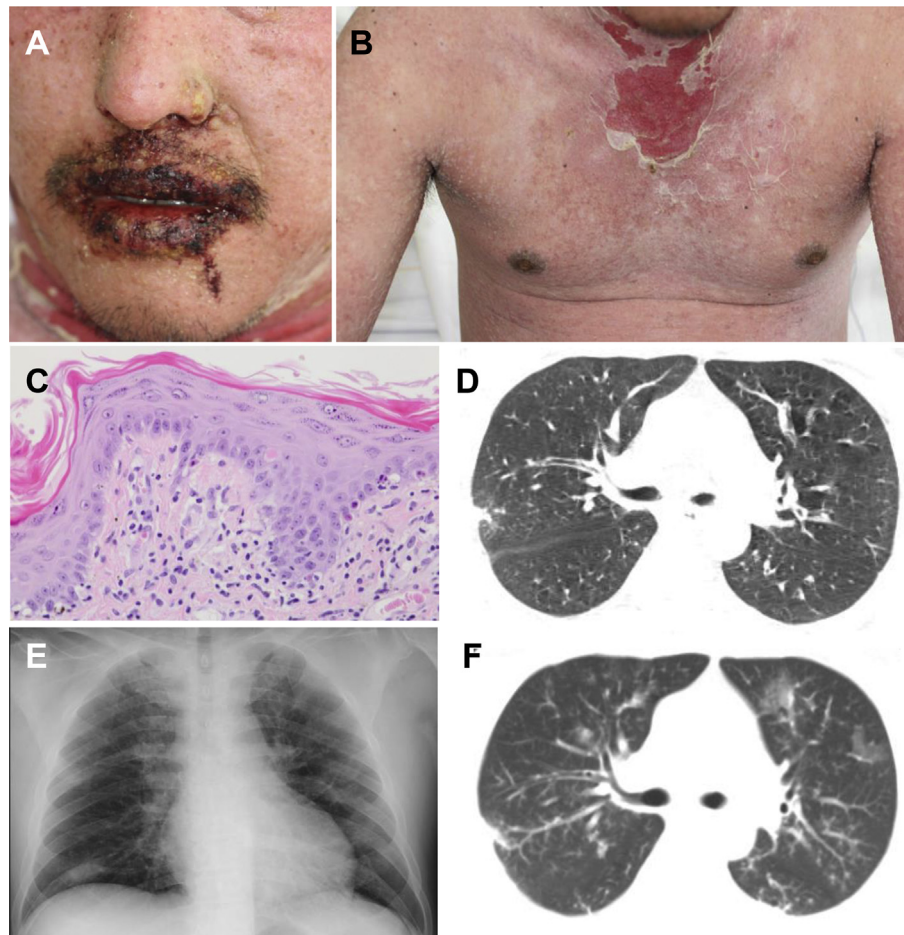


**Fig. 1.** (A) Erosions with hemorrhagic crusts on the lips. (B) Erythema with blisters and erosions on the trunk and upper and lower extremities. (C) Vacuolar changes at the dermoepidermal junction and scattered necrotic keratinocytes in the basal and suprabasal layers. (D) Chest computed tomography at the onset of respiratory failure. Bilateral bronchial and bronchiolar wall thickening and focal consolidation at the periphery of the right lung. (E–F) Chest radiograph (E) and chest CT (F) findings after transferring to the ICU. (E) Bilateral ground-glass opacities. (F) Patchy areas of ground-glass opacities and consolidation along the bilateral bronchovascular bundles without pleural effusion. A permission from the patient has been obtained for the images (A, B).

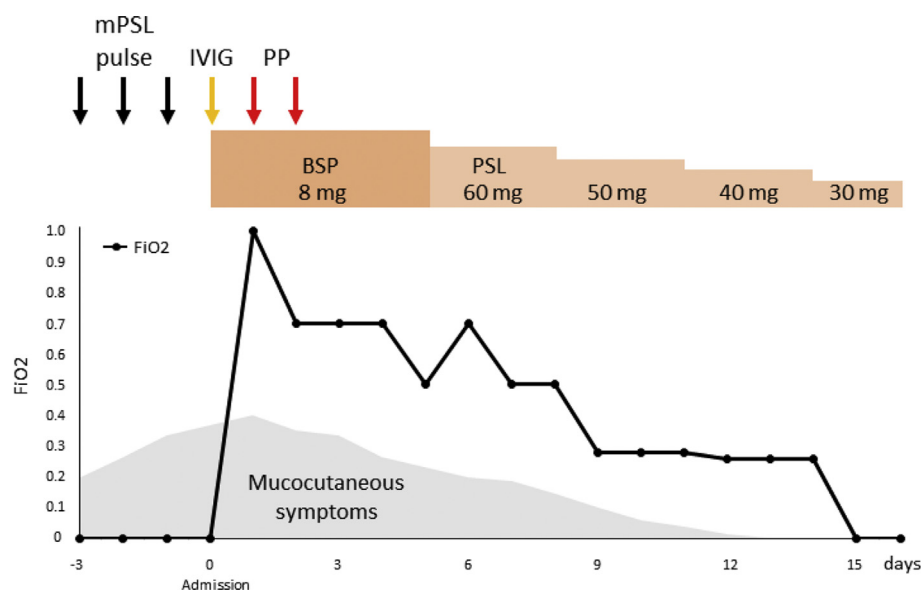


**Fig. 2.** Clinical course. mPSL, methylprednisolone; IVIG, intravenous immunoglobulin; PP, plasmapheresis; FIO2, fractional inspired oxygen concentration; BSP, betamethasone sodium phosphate; PSL, prednisolone.

of their symptoms.<sup>3,4,7</sup> In TRALI, laboratory examinations are not specific, and transient leukocytopenia and thrombocytopenia are sometimes observed; however, our patient showed leukocytopenia before IVIG therapy, which was a complication of TEN. The chest radiographic findings are normal at the onset of respiratory failure and soon reveal interstitial infiltrates in most cases of TEN with acute pulmonary manifestations,<sup>7</sup> whereas interstitial infiltrates are already observed at the onset of respiratory failure in TRALI, and the radiographic findings are worse than the physical examination findings.<sup>8</sup>

Several reports have shown that the findings on chest CT in TRALI were characterized by dense infiltrations and air bronchograms in both lungs with occasional pleural effusion.<sup>8–10</sup> In our case, bronchial wall thickening, which had not been previously reported in cases of TRALI, was the main finding on chest CT at the development of acute pulmonary manifestations, and fewer findings were observed in the bilateral lung fields, which differed from the typical course of TRALI. Thus, bronchial wall thickening might have reflected edema and inflammation of the bronchi due to the diffuse loss of bronchial epithelium, although we didn't perform bronchoscopy.

While there have been no reports describing the chest CT findings at the onset of acute respiratory failure in TEN, chest CT in TEN patients with mucocutaneous symptoms might help predict the possibility of developing severe respiratory failure.

#### Conflict of interest

The authors have no conflict of interest to declare.

Miki Kume <sup>a</sup>, Yukinobu Nakagawa <sup>a,\*</sup>, Eiji Kiyohara <sup>a</sup>, Noriko Arase <sup>a</sup>, Mari Wataya-Kaneda <sup>a</sup>, Moto Yaga <sup>b</sup>, Masahiro Yanagawa <sup>c</sup>, Manabu Fujimoto <sup>a</sup>

<sup>a</sup> Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

<sup>b</sup> Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan

<sup>c</sup> Department of Radiology, Graduate School of Medicine, Osaka University, Osaka, Japan

\* Corresponding author. Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.

E-mail address: nakagawa@derma.med.osaka-u.ac.jp (Y. Nakagawa).

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