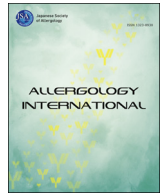




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Letter to the Editor

## Drug eruption to clavulanic acid with sparing of cellulitis-affecting site

Dear Editor

$\beta$ -lactam antibiotics are most frequently used as empiric therapy against *Streptococcus pyogenes* ( $\beta$ -hemolytic streptococcus) and *Staphylococcus aureus*, which are the most common pathogens of cellulitis.<sup>1</sup> Clavulanic acid (CLAV) is a  $\beta$ -lactam antibiotic with a weak antibacterial potential but a strong  $\beta$ -lactamase inhibitory activity, and is employed as a combination form with amoxicillin (AMOX). Here, we report a patient with cellulitis, who was treated with the combination of AMOX and CLAV, and developed a drug eruption to CLAV with characteristic sparing of cellulitis-affecting site.

A 46-year-old Japanese woman presented with acute onset of tender erythema on the dorsum of the left foot. Under the diagnosis of cellulitis, she was treated with oral AMOX/CLAV. The next day, the tender erythema extended to the left lower extremity (Fig. 1a), representing lymphangitis. She also developed erythematous macules and papules mainly on the right aspect of her

abdomen and the right inguinal region, extending to the right thigh (Fig. 1b). A biopsy specimen from her left shin showed a diffuse infiltrate of neutrophils and lymphocytes in the dermis and fat tissue with edema and fat degeneration (Fig. 1c), confirming cellulitis or phlegmone. Meanwhile, a biopsy specimen from her right abdomen exhibited perivascular infiltrates of lymphocytes and eosinophils in the upper dermis with invasion of lymphocytes into the epidermis (Fig. 1d), suggesting a drug eruption. AMOX/CLAV, as the culprit drug, was discontinued, and intravenous cefazolin therapy was administered. The treatment improved both cellulitis and drug eruption.

She regularly received valproic acid for cerebral palsy and ferric pyrophosphate for iron-deficiency anemia. These drugs were not discontinued during her clinical course. To determine the causative drug, we performed skin patch tests, which showed a positive reaction to AMOX/CLAV at 48 h, but not AMOX alone, valproic acid, or ferric pyrophosphate. Results of skin prick tests were all negative. We also performed the oral challenge test with AMOX, which

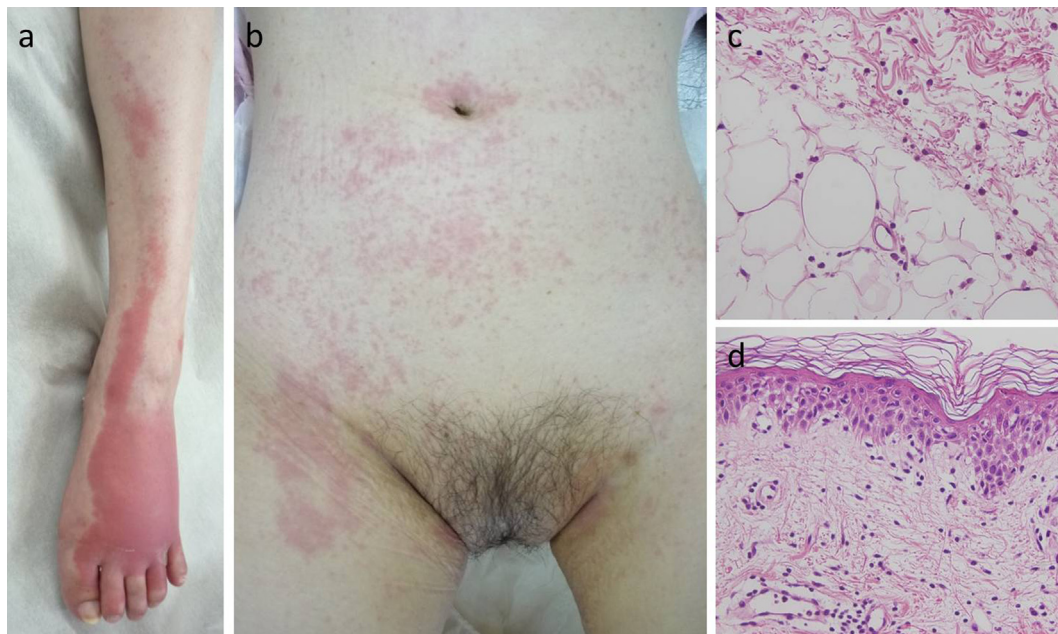


**Fig. 1.** Clinical findings (a, b) and histopathological findings (c, d). (a) Cellulitis and lymphangitis on the left lower extremity. (b) Drug eruption on the right abdomen and the right thigh. (c) Histopathology of the lesion on the left lower limb, showing edema and degeneration in the deep dermis and fat, suggestive of cellulitis (HE,  $\times 200$ ). (d) Histopathology of the lesion on the abdomen, showing infiltration of lymphocytes and eosinophils in the upper dermis, compatible with drug eruption (HE,  $\times 200$ ).

Peer review under responsibility of Japanese Society of Allergy.

<http://dx.doi.org/10.1016/j.alit.2014.12.007>

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showed a negative reaction. Thus, it is considered that the rash was a T-cell-mediated drug eruption to CLAV.

Although initial studies showed that CLAV had a low immunogenic capacity, CLAV may be the component responsible for hypersensitivity reactions in AMOX/CLAV.<sup>2</sup> There are few reports of hypersensitivity to CLAV,<sup>3</sup> presumably because AMOX/CLAV is a material available for skin tests in clinical practice. In our case, the drug eruption occurred during AMOX/CLAV therapy. She developed a maculopapular-type eruption due to CLAV. We observed the drug eruption on the next day to AMOX/CLAV administration. The onset of our case was immediate in consideration of ordinary delayed hypersensitivity reaction. As far as we checked the patient's medical history, she had not received AMOX/CLAV therapy. However, she might have been sensitized with CLAV in the past. Alternatively, it is possible that she was sensitized with another drug possessing cross-reactivity with CLAV.

It was speculated that delayed hypersensitivity reactions were prone to take place in association with cellulitis.<sup>4</sup> In our case, however, the drug eruption was markedly observed on the right abdomen and right lower limb, sparing the left aspects where the cellulitis occurred. The mechanism underlying this phenomenon remains unclear, but the cellulitis-associated stimulation of Th1 cells might depress the drug eruption-exerting Th2 cells and eosinophils in the left abdomen and lower limb. Given Th1 and Th17 cells are activated in cellulitis, these T cell populations might induce the drug eruption.<sup>5</sup> It is also possible that T cells inducing the drug eruption may be deleted in the cellulitis side.

#### Conflict of interest

The authors have no conflict of interest to declare.

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#### References

1. Gunderson CG, Martinello RA. A systematic review of bacteremias in cellulitis and erysipelas. *J Infect* 2012;**64**:148–55.
2. Torres MJ, Ariza A, Mayorga C, Doña I, Blanca-Lopez N, Rondon C, et al. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. *J Allergy Clin Immunol* 2010;**125**:502–5. e2.
3. Sanchez-Morillas L, Perez-Ezquerro PR, Reano-Martos M, Laguna-Martinez JJ, Sanz ML, Martinez LM. Selective allergic reactions to clavulanic acid: a report of 9 cases. *J Allergy Clin Immunol* 2010;**126**:177–9.
4. Baddour LM, Googe PB, Prince TL. Possible role of cellular immunity: a case of cellulitis. *Clin Infect Dis* 2001;**32**:E17–21.
5. Fujiyama T, Kawakami C, Sugita K, Kubo-Kabashima R, Sawada Y, Hino R, et al. Increased frequencies of Th17 cells in drug eruptions. *J Dermatol Sci* 2014;**73**: 85–8.

Received 18 November 2014

Received in revised form 18 December 2014

Accepted 25 December 2014

Available online xxx