Tosufloxacin-induced acute generalized exanthematous pustulosis confirmed by a drug-induced lymphocyte stimulation test

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INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe cutaneous adverse drug reaction characterized by the rapid development of numerous, small, nonfollicular, sterile pustules usually on an edematous, erythematous background.[1] AGEP is caused by drugs—mainly antibiotics such as penicillin—and macrolides, and recently has been found to be caused by quinolones.[2] Tosufloxacin is a fluoroquinolone developed in Japan that is frequently prescribed for bronchitis or community-acquired pneumonia. The drug-induced lymphocyte stimulation test (DLST), also known as the lymphocyte transformation test, is used to detect the causative drug in cases of cutaneous adverse drug reaction.[3]

This report highlights tosufloxacin as a novel causative agent for drug-induced AGEP, as well as the beneficial contribution of DLST in the identification of quinolone-induced allergic reactions, especially in severe drug allergy cases.

Abbreviations used:

AGEP: acute generalized exanthematous pustulosis
DLST: drug-induced lymphocyte stimulation test

CASE REPORT

A 47-year-old Japanese woman presented to the emergency department with acute-onset fever and rapidly spreading systemic, erythematous eruptions. One day before the onset of symptoms, the patient received oral tosufloxacin, carbocisteine, pranlukast hydrate, and Huscode combination tablets (generic name: dihydrocodeine phosphate, *dl*-methylephedrine hydrochloride, and chlorpheniramine maleate) for a common cold. The patient's medical history included panic attacks. Her medications were duloxetine hydrochloride and alprazolam. She received no over-the-counter medications or nutritional supplements and had no history of psoriasis, cutaneous drug reactions, or immunosuppression.

On examination, the patient was febrile (temperature of 38.1°C or 100.58°F) and tachycardic (122/min), although other vital signs were normal. Physical examination revealed an erythematous eruption mainly in the intertriginous areas and a few small, nonfollicular pustules on the neck. The Nikolsky sign was negative. No mucosal lesions, bullae, erosions, or generalized peripheral lymphadenopathy was observed. The initial laboratory evaluation revealed leukocytosis (16,530/mm^3), neutrophilia (91.1%), and increased C-reactive protein level (0.95 mg/dL). Renal or liver involvements were absent on laboratory examination. The patient was referred to our dermatology department the following day after the withdrawal of all medication. Skin examination revealed widespread erythematous rash studded with numerous, small, nonfollicular pustules on the neck (Fig 1). The second blood tests also revealed leukocytosis (21,610/mm^3), neutrophilia (89.5%), and increased C-reactive protein level (9.33 mg/dL). Vital signs were normal except for body temperature (37.9°C or 100.22°F).

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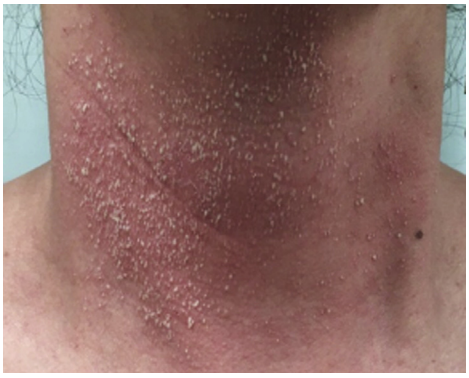

Fig 1. Acute generalized exanthematous pustulosis. Erythematous eruption with hundreds of pinpoint nonfollicular pustules on the neck.

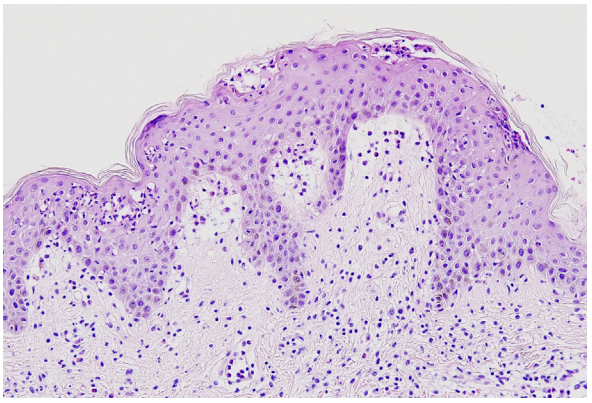

Fig 2. Histologic picture. Spongiform subcorneal pustules, intraepidermal spongiosis, marked edema in papillary dermis, and inflammatory infiltrate of neutrophils with perivascular accentuation. (Hematoxylin-eosin stain; original magnification: ×200.)

A skin biopsy revealed spongiform, subcorneal, neutrophilic pustules with epidermal spongiosis, marked edema at the papillary dermis, and superficial perivascular neutrophilic infiltrate that were all consistent with AGEP (Fig 2). Bacterial culture result from the pustule content was negative. The patient began receiving 25 mg of oral prednisolone once daily with a topical steroid, which was tapered and terminated within 8 days. After the withdrawal of all drugs, the patient's cutaneous lesions and laboratory results resolved within a few days of steroid therapy.

Conventional DLST was performed, following the standard methods.[3] The result for a DLST performed on day 2 with tosufloxacin was positive, with a stimulation index of 400% (cutoff index of DLST >180%) and showed no stimulation with carbocisteine, pranlukast hydrate, or Huscode combination tablets. Results for patch tests conducted 3 weeks later with tosufloxacin and concomitant drugs except for carbocisteine, diluted at 30% in white petrolatum in standard Finn chambers, were negative after 48 hours, 72 hours, and 7 days. Simultaneous DLSTs on healthy volunteers and oral provocation tests were not performed.

DISCUSSION

AGEP is an uncommon severe cutaneous adverse drug reaction and is diagnosed with the validation score developed by the EuroSCAR study group.[4] Our patient's score was the highest, 12 points, representing definitive AGEP (score breakdown: morphology 7, clinical course 2, histology 3). Additionally, a positive DLST outcome was a significant contributor in identifying tosufloxacin as the causative agent.

DLST is a widely used in vitro test for investigating the offending drugs in polymedicated patients with severe cutaneous adverse drug reaction, as well as in vivo patch testing. It is reported to be useful in understanding AGEP pathogenesis involving a T-cell–mediated immunoresponse because the test evaluates antigen-specific reactivity of T cells by measuring their proliferation on drug exposure.[3,5] A study found that DLST results were frequently positive in patients with AGEP and for a variety of quinolones, although results may differ, depending on the drugs and target diseases.[6] Nevertheless, because to our knowledge the diagnostic accuracy of the DLST for tosufloxacin allergy has not been evaluated to date, and the stimulation index of healthy volunteers was unclear in our case, a false-positive DLST result could not be excluded. On the other hand, quinolones can cause drug-specific lymphocyte stimulation instead of nonspecific stimulation in patients with a history of hypersensitivity to quinolones, indicating that DLST for tosufloxacin has less possibility of a false-positive result and can be used for the diagnosis of its allergenic potiential.[7] Additionally, although data regarding the diagnostic role of DLST in AGEP are minimal, reports indicated that DLST has high specificity (98%-99%) and low sensitivity (37%-67%) in patients with severe cutaneous adverse drug reaction.[8] Therefore, DLST positivity for tosufloxacin may have sufficient specificity for diagnosing tosufloxacin allergy, although negativity for other drugs cannot exclude their hypersensitivities. Moreover, the sensitivity of patch testing in patients with AGEP is unsatisfactory, suggesting possible false-negative results.[9] Therefore, additional analysis of the clinical course could be useful for the exclusion of drug allergies.

Generally, the period of onset after initiation of the offending medication is short for AGEP and varies for different drugs. The median latency was 1 day for antibiotics and 11 days for other medications.[2] In our case, AGEP occurred within 1 day of

drug administration, suggesting tosufloxacin-associated AGEP. Theoretically, a previous sensitization to tosufloxacin could be a rational explanation for the reaction. Although former administration of tosufloxacin could not be confirmed, previous sensitization can be assumed. Otherwise, a likely explanation is a cross-reactivity among the different quinolones, which is frequently reported in quinolone hypersensitivity.[7]

The discrepancy of positive DLST and negative patch test results to tosufloxacin can be attributed to various factors, including insufficient penetration of the drug through the epidermis and a drug metabolite as the actual source of the cutaneous reaction.[10]

This case underlines the potential that tosufloxacin is a novel causative agent of AGEP and the valuable contribution of DLST in the confirmation of quinolone-associated drug allergy.

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REFERENCES

1. Speeckaert MM, Speeckaert R, Lambert J, Brochez L. Acute generalized exanthematous pustulosis: an overview of the clinical, immunological and diagnostic concepts. *Eur J Dermatol*. 2010;20:425-433.
2. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Br J Dermatol*. 2007;157:989-996.
3. Hanafusa T, Azukizawa H, Matsumura S, Katayama I. The predominant drug-specific T-cell population may switch from cytotoxic T cells to regulatory T cells during the course of anticonvulsant-induced hypersensitivity. *J Dermatol Sci*. 2012;65:213-219.
4. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. *J Cutan Pathol*. 2001;28:113-119.
5. Girardi M, Duncan KO, Tigelaar RE, Imaeda S, Watsky KL, McNiff JM. Cross-comparison of patch test and lymphocyte proliferation responses in patients with a history of acute generalized exanthematous pustulosis. *Am J Dermatopathol*. 2005;27:343-346.
6. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy*. 2004;59:809-820.
7. Schmid DA, Depta JPH, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. *Clin Exp Allergy*. 2006;36:59-69.
8. Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? *Int J Mol Sci* 2017;18:1737.
9. Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol*. 2013;168:555-562.
10. Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch testing in non-immediate drug eruptions. *Allergy Asthma Clin Immunol*. 2008;4:66-74.