DOI: 10.1002/cia2.12020

LETTER TO THE EDITOR

WILEY Journal of Cutaneous Immunology and Allergy

Acute generalized exanthematous pustulosis caused by fexofenadine

Dear Editor,

Acute generalized exanthematous pustulosis (AGEP) is a diffuse pustular disorder characterized by small, nonfollicular, sterile pustules with widespread edema and erythema and by fever and leukocytosis.[1,2] Subcorneal infiltration of neutrophils is the histopathological feature. The majority of the cases are induced by adverse drug reactions.[1] Lymphocyte transformation test (LTT) is usually positive with high levels of stimulation index (SI) toward drugs in AGEP.[3] Drug-specific T cells are present in the blood and secrete interleukin-8 (IL-8)/CXCL8, a neutrophil chemoattractant.[2] However, IL-8 is not only secreted by T cells, but can also be released from epidermal keratinocytes.[2,4] Th17 cell-derived IL-17 and IL-22 may stimulate keratinocytes to produce IL-8.[4] The frequency of circulating Th17 cells and the serum level of IL-22 were increased in patients with AGEP.[5]

Here, we report a case of AGEP caused by fexofenadine. Our finding suggests that the source of IL-8 is not necessarily peripheral blood mononuclear cells (PBMCs), but IL-8 may be elaborated in the skin local milieu.

A previously healthy 31-year-old woman was referred to us for a skin eruption that occurred three days ago. One day before, she was administered with a combination tablet of fexofenadine and pseudoephedrine (Dellegra®) for rhinitis. Six hours after the administration, the patient developed an erythematous eruption on her limbs with general fatigue, vomiting, and fever. On examination, she had diffuse erythema on the four extremities. Notably, small pustules were scattered on the erythematous background (Figure 1A). Blood examination revealed leukocytosis (14 690/μl) with neutrophilia and a high CRP level (2.33 mg/dL; normal, <0.3). A skin biopsy specimen showed epidermal spongiosis and perivascular infiltration of lymphocytes and neutrophils in the upper dermis (Figure 1B) with subepidermal collection of neutrophils (Figure 1C). LTT with fexofenadine was positive with SI of 3.09. The patient's AGEP score was 10, which represented definitive AGEP.[6] The patient was effectively

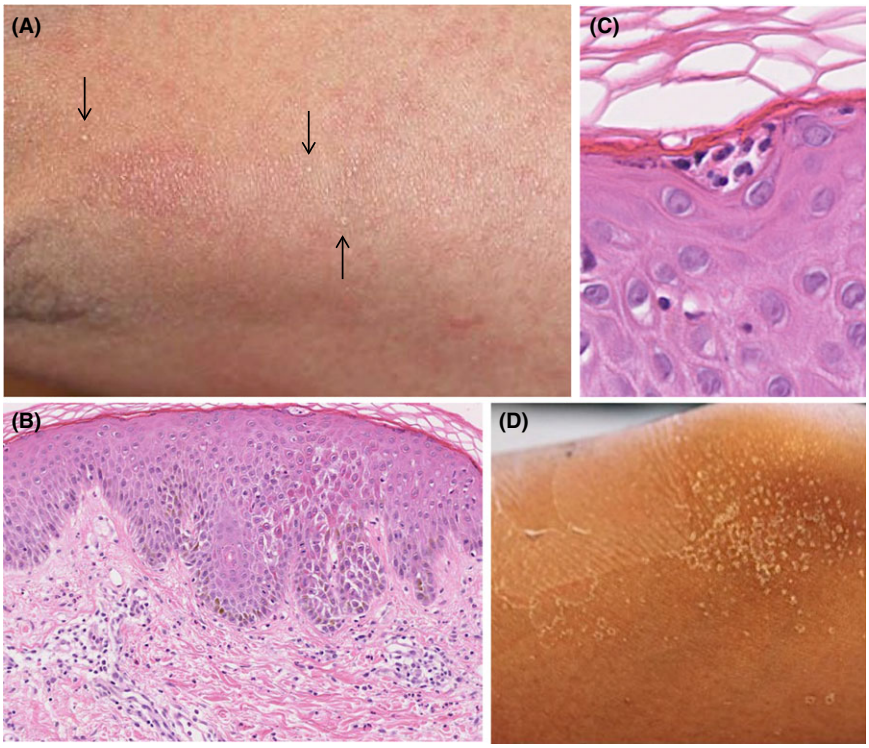

FIGURE 1 Clinical appearance and histopathological findings. A, Multiple tiny pustules with the erythematous background on the upper arm. B, Histopathology showing epidermal spongiosis and perivascular inflammatory cell infiltration (HE, original magnification ×100). C, High power view showing subcorneal collection of neutrophils (HE, original magnification ×200). D, Scaling sequelae upon recovery on the thigh

treated with prednisolone, 30 mg daily (Figure 1D), which was tapered and discontinued.

We investigated the effect of fexofenadine on the production of IL-8 by PBMCs. PBMCs were cultured with fexofenadine at 10^{-4}, 10^{-5}, and 10^{-6} M, and the concentration of IL-8 was measured in the culture supernatants. Fexofenadine did not stimulate the PBMCs to produce IL-8, but rather decreased the IL-8 production by 28.3%, 17.6%, and 1.4%, respectively.

As causative drugs of AGEP, antihistamines have been rarely reported and include cetirizine,[7] clemastine, diphenhydramine, and hydroxyzine.[8] This is the second case of fexofenadine-induced AGEP.[9] Antihistaminic drugs can function as inverse agonists to H1 receptor and suppress the activities of various immunocompetent cells, such as T-cell cytokine production and epithelial cell cytokine/chemokine production.[10] While antihistamines serve as causative drugs for AGEP, they might depress the occurrence of AGEP by virtue of these antiinflammatory activities. Our in vitro study showed that fexofenadine rather decreased the PBMC production of IL-8. This raises a possibility that fexofenadine increases T-cell proliferation, as assessed by LTT, but reduces monocyte IL-8 release. It is suggested that the antigenic moiety of the drug overcomes its immunosuppressive capacity in antihistamine-induced AGEP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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