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Letters to the Editor

Acute generalized exanthematous pustulosis triggered by acetaminophen in an *IL36RN* variant heterozygote

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Dear Editor,

A Japanese woman in her fifties was hospitalized for dental periodontitis treatment. She had no history of psoriasis vulgaris. Intravenous acetaminophen and clindamycin were administrated during exodontia of a wisdom tooth. The next day, erythema developed on the trunk and the arms. She continued the oral acetaminophen every day after the exodontia for pain relief. Four days after the exodontia, she had a fever over 38.0 ℃ and the erythematous lesions had spread over her entire body (Figure 1a). Non-follicular, pinhead-sized pustules emerged on the trunk and lower extremities (Figure 1b, 1c). Mucosal involvement was not seen. Laboratory examinations revealed a white blood cell count of 12400/ μ l with 85.0 % neutrophils, serum aspartate aminotransferase of 11 U/L, alanine aminotransferase of 8 U/L, creatinine of 2.07 mg/dL, C-reactive protein of 3.68 mg/dL, and albumin of 2.9 g/dL. We performed a skin biopsy from a pustular lesion on the left lower leg. Haematoxylin and eosin (HE) staining showed subcorneal pustules and edema in the papillary dermis(Figure 1d, 1e).

The histopathological findings were consistent with acute generalized exanthematous pustulosis (AGEP). Therefore, from the clinical features and histopathological findings, we diagnosed her with AGEP.

The patient improved with oral prednisolone and topical corticosteroid treatment. We suspected that intravenous acetaminophen was the causative drug andstopped the oral acetaminophen five days after the exodontia. The skin symptoms had completely disappeared at 14 days after that cessation. Lymphocyte transformation test (LTT)[1] findings were positive for acetaminophen (stimulation index: 6.26) but negative for clindamycin (stimulation index: 0.66). She has had no recurrence of similar eruptions for almost two years.

Ethical approval was obtained and all research was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient. Sanger sequencing revealed a heterozygous *IL36RN* nonsynonymous variant, c.140A>G (p.Asn47Ser), in the patient. This varianthad been reported as a predisposing factor for generalized pustular psoriasis (GPP) in a Chinese female.[2] Only weak immunohistopathological staining for interleukin-36 receptor antagonist (IL-36Ra) was detected (Figure 1f, g).

IL36RN encodes IL-36Ra, an anti-inflammatory cytokine. The present nonsynonymous variant of *IL36RN* is thought to be a loss-of-function variant and isexpected to cause reduced function of IL-36Ra.[2] Deficiency of interleukin-36 receptor antagonist (DITRA) is an autoinflammatory disease whose cutaneous symptoms are mainly pustular lesions. We speculate that, in GPP and AGEP patients with *IL36RN* variants, the deficient IL-36Ra function leads to up-regulated IL-36 signaling and the accelerated secretion of inflammatory cytokines, resulting in GPP and AGEP. Disorders included in autoinflammatory keratinization diseases (AiKDs) comprise pustular psoriasis and related disorders with *IL36RN* or *CARD14* variants, pityriasis rubra pilaris (PRP) type V and keratosis lichenoides chronica (KLC).[3] Some AGEP cases have a genetic background, such as loss-of-function mutations in *IL36RN*. Several cases of AGEP with *IL36RN* mutations have been reported,[4,5] although the number of the cases is still limited. The further accumulation of patients is required. AGEPpatients with *IL36RN* variants could be classified as having AiKDs.

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Conflicts of Interest: None declared

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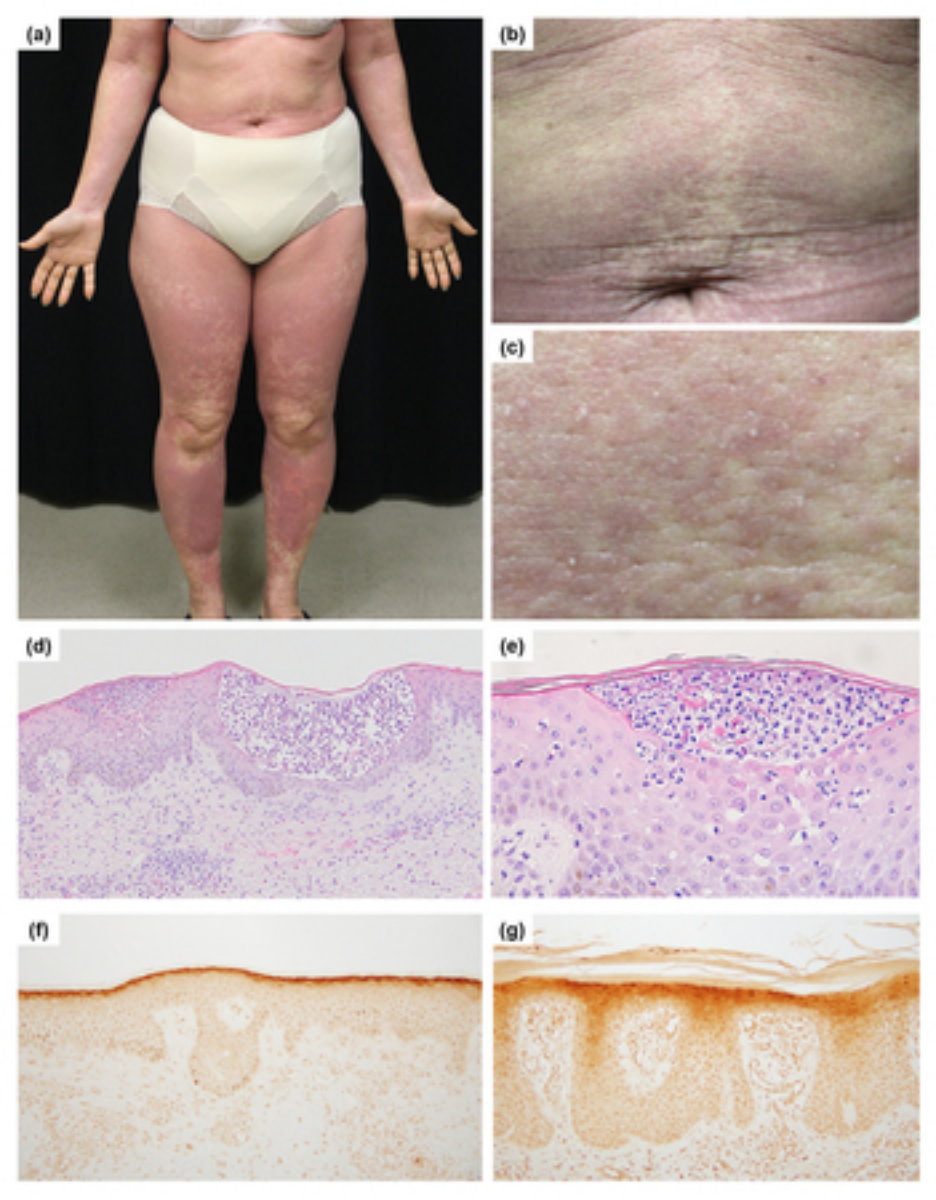
Figure Legends

Figure 1. Clinical features and histopathological findings

(a) Widespread erythematous lesions on edematous skin on the trunk and the extremities. (b, c) Numerous pinhead-sized pustules on erythematous lesions ofthe trunk. (d, e) Hematoxylin-eosin (HE) staining shows subcorneal pustules (d, e) and perivascular infiltrates with eosinophils and neutrophils (d). (original magnification: [d] ×100, [e] ×400). (f, g) Immunohistopathological staining for interleukin-36 receptor antagonist (IL-36Ra). Weak immunostaining is seen in a skin lesion from the patient (f), compared with strong staining in a positive control specimen taken from a typical psoriatic plaque on a patient with psoriasis vulgaris (original magnification: ×200).


(a)
(b)
(c)
(d)
(e)
(f)
(g)