Recurrent generalized pustular psoriasis possibly triggered by apremilast

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To the Editor: Generalized pustular psoriasis (GPP) is a rare, life-threatening skin disease characterized by recurrent episodes of pustulation. Apremilast, a phosphodiesterase 4 (PDE4) inhibitor, is a relatively new drug for the treatment of moderate to severe plaque psoriasis. Herein, we reported a patient of recurrent GPP possibly triggered by apremilast.

A 33-year-old man with a 10-year history of GPP and psoriasis vulgaris had been receiving infliximab or adalimumab for 2 years, and remained in clinical remission.

After being prescribed apremilast (graduated dosing, 10 mg at Day 1, 10 + 10 mg at Day 2, 10 + 20 mg at Day 3, 20 + 20 mg at Day 4, 20 + 30 mg at Day 5), the patient presented with 2- to 3-mm sized sterile pustules overlying painful, erythematous skin involving the entire body. Physical examination showed erythema with superficial scale involving approximately 70% of his body surface area. The pustules occurred at the edges of expanding erythematous plaques or over erythematous skin [Figure 1A]. Laboratory findings showed leukocytosis (white blood cell count 17.24×10^9/L with 14.36×10^9/L neutrophil granulocytes), hemoglobin 144 g/L, platelet count 244×10^9/L, alanine aminotransferase 24 IU/L, aspartate amino transferase 17 IU/L, high-sensitivity C-reactive protein 74.34 mg/L, erythrocyte sedimentation rate 36 mm/h, interleukin (IL)-6 80.7 pg/mL, tumor necrosis factor (TNF)-α 7.0 pg/mL, urinary protein 0.3 g/L. The severity rating score for GPP was 8 (5 score for dermal symptoms plus 3 score for general symptoms and blood tests).[1] The *IL36RN* gene was examined from the patient. Genetic analysis showed heterozygous mutations of *IL36RN* c.115+6T>C [Figure 1B], but had no mutations in *IL36RN* c.227C>T [Figure 1C]. The patient was treated with 80 mg of adalimumab once and at week 1, and then 40 mg every 2 weeks thereafter. He experienced a complete remission in 8 weeks.

Previous research has reported a phenomenon named paradoxical manifestations during biological therapy, which can be defined as the appearance or exacerbation of a pathological condition that usually responds to this class of drug, for example, to anti-TNF-α agents, ustekinumab, and secukinumab.[2] PDE4 is a member of an enzyme family that catalyzes the breakdown of cyclic adenosine 3′,5′-monophosphate (cAMP) in several types of cells, including inflammatory cells, resulting in decreased intracellular cAMP levels. PDE4 is considered as an important player in the inflammatory cascade. As a PDE4 inhibitor, apremilast is approved for the treatment of psoriatic arthritis (PsA) and psoriasis. Previous studies have showed that the side effects of apremilast include diarrhea, headache, nausea, vomiting, depression, and weight loss. Our patient presented with paradoxical GPP after the treatment of apremilast. The mutations of *IL36RN* were revealed in patients with GPP and the mutations c.115+6T>C was the most common one.[3] Heterozygous mutation of *IL36RN* c.115+6T>C was found in our patient, which may indicate that he has a high risk of developing GPP.

GPP can be triggered by environmental factors and immune disorders, such as pregnancy, infections, drugs, and electrolyte imbalance. However, the mechanism of paradoxical manifestations has not yet been clearly demonstrated. Previous studies found that inhibition of PDE4 can increase the intracellular concentration of cAMP, preferentially block pro-inflammatory cytokines production (such as TNF-α, interferon-γ, and IL-2) and increase anti-inflammatory factors (such as IL-10). Some studies also found that the increased cAMP within the cell can active cAMP-dependent protein kinase A (PKA) and affect the associated second messenger system.[4] All of these effects can activate or inhibit different signal pathways. In a study of peripheral blood mononuclear cells from healthy human donors conducted by Schafer and colleagues, apremilast reduced the production of TNF-α,

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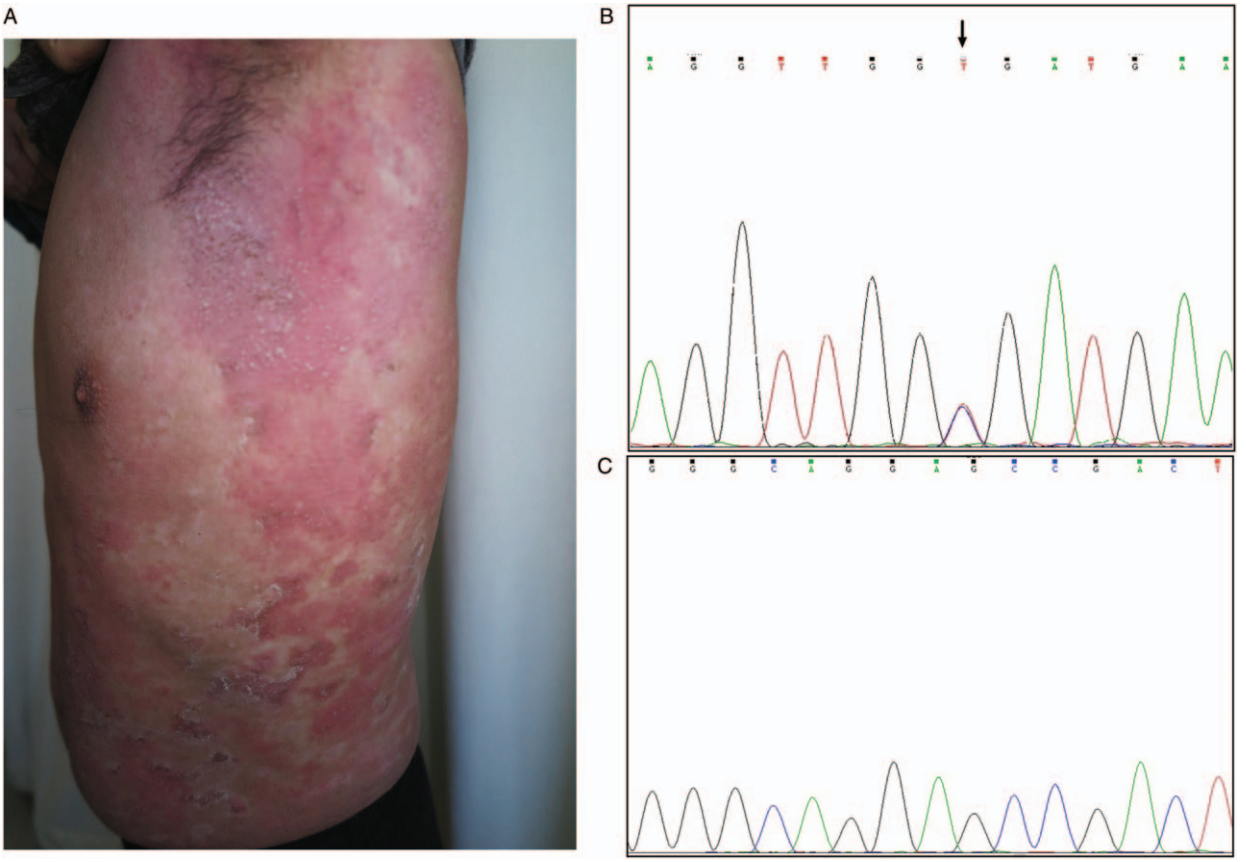

Figure 1: (A) Diffuse erythema with pustules on the left lateral chest. Heterozygous mutation of *IL36RN* c.115+6T>C (B) and no mutation in c.227C>T (C) of this patient.

interferon-γ, and IL-12p70 with 50% inhibitory concentrations of 0.110, 0.013, and 0.120 μmol/L, respectively. In contrast, apremilast enhanced the expression of IL-10 and IL-6 at 1 and 10 μmol/L, respectively.[5] These results indicated there may be a conflict between the concentration of required to block pro-inflammatory cytokines production and to increase anti-inflammatory factors. Collectively, these data suggest the concentration of apremilast used may be important in the recurrent of GPP.

Together, our case highlights that dermatologists should be aware of the possibility of apremilast triggered paradoxical GPP.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the article. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interests

None.

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