Rapid Clearance of Corticosteroid-resistant Targetoid Acute Generalized Exanthematous Pustulosis Using IL-17A Inhibitor: A Case Report

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Acute generalized exanthematous pustulosis (AGEP) is a rare and severe cutaneous adverse reaction, which characterized by sudden presence of non-follicular intradermal pustules on an erythematous edematous background [1]. While most cases resolve spontaneously within 15 days after discontinuation of the causative agent, some cases exhibit resistance to first-line treatment (supportive treatment and systemic corticosteroid), resulting in poor clinical outcomes and prolonged disease duration [2]. Thus, identification and appropriate management for corticosteroid-resistant AGEP are critical in improving prognosis.

We here reported a 30-year-old female patient who was diagnosed with systemic lupus erythematosus (SLE) and had been treated with 200 mg/day hydroxychloroquine (HCQ) and 10 mg/day oral methylprednisolone for about one month. Twenty-eight days later, she developed itchy red rash and pustules on her neck, trunk, and upper extremities accompanied by fever (38°C) (Supplemental Figure 1, A). Physical

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examination revealed generalized erythematous plaques with nonfollicularly-based pustules and atypical targetoid lesions on her arms.

The patient had no personal or family history of psoriasis. Upon admission, routine laboratory testing revealed white blood cell (WBC) count of 19.5 G/L (normal range, 3.5-9.5 G/L), neutrophil (NEU) count of 17.9 G/L (normal range, 1.8-6.3 G/L) and serum level of C-reactive protein (CRP) of 14 mg/L (normal range, 0-5 mg/dl). Histopathologic examination revealed spongiosis with apoptotic keratinocytes, intraepidermal neutrophils with subcorneal pustules, and perivascular lymphocytic infiltrates with numerous lymphocytes, neutrophils and eosinophils (Supplemental Figure 2, A). According to the EuroSCAR study, the patient's diagnostic score was 10, meeting the diagnostic criteria of definitive AGEP [2]. Therefore, HCQ was withdrawn and oral steroid were switched to intravenous dexamethasone 10 mg/day (Figure, A). However, 3 days later, cutaneous eruption progressed, and inflammatory markers increased (WBC 22.08 G/L, NEU 18.9 G/L, CRP 62.10 mg/L). Thus, treatment was escalated to intravenous methylprednisolone 80 mg/day plus intravenous immunoglobulin (IVIG) at 20 g/d for 3 days, resulting in partial improvement of the lesions (Supplemental Figure 1, C). Unfortunately, when the methylprednisolone was reduced to oral prednisone 75 mg/day on day 22 after admission, AGEP lesions relapsed immediately (Supplemental Figure 1, D). Considering steroid-resistance for 3 weeks and the role of inflammatory cytokines in the pathophysiology of AGEP, immunohistochemical staining of IL-17A and TNF-α were performed on the patient's

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previous biopsy tissue [3]. Comparing with another AGEP patient without targetoid lesions and a healthy control, IL-17A expression was higher in keratinocytes and perivascular lymphocytes in this case (Supplemental Figure 2, A). Hence, 160 mg (single dose) of ixekizumab was administered subcutaneously. Within 24 hours, marked improvement of rash was noted and subsequent corticosteroid tapering was successful (Figure, B). After 10 days, rash generally resolved. In order to prevent the recurrence, she was treated with two additional doses of ixekizumab, given two weeks apart. During the follow-up of 20 months, no flare-up was reported.

To summarized the clinical characteristics of corticosteroid-resistant AGEP patients, we conclude a literature review and the details of 14 patients were summarized in the Supplemental Table 1. The majority (11/14, 78.57%) of the patients were female and the most frequently reported suspect drug was HCQ (10/14, 64.28%). Corticosteroid-resistant AGEP patients tend to occur in populations who predisposed to autoimmune diseases, and may also be related to the need for HCQ treatment. HCQ has a half-life of 40-50 days, and literature suggests that AGEP patients related to HCQ typically have longer latency period, more complicated disease courses and poorer clinical outcomes compared with other drugs [4]. Interestingly, after excluding the 3 patients for whom the data on targetoid lesions was not mentioned in the original studies, 72.73% (8/11) corticosteroid-resistant patients presented with targetoid lesions. Among them, 10 patients were induced by HCQ and therefore the proportion of AGEP patients with targetoid lesions who developed corticosteroid resistance was 8/10. In another

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literature review of HCQ-induced AGEP cases (Supplemental Table 2 and 3), the proportion of steroid-resistant patients without targetoid lesions was 2/10 [4]. Thus, patients with HCQ-related corticosteroid-resistant AGEP are more likely to have targetoid lesions (8/10 vs 2/10, P = 0.02) (Supplemental Figure 2, B).

To seek a rational treatment alternative, we investigated cytokines expression in our patient and found increased IL-17A instead of TNF-α involvement in the localized skin lesions (Supplemental Figure 2, A). Th17 pathway, which stimulating the inflammatory response of keratinocytes, has been recognized as one of the core pathogeneses of AGEP pathogenesis [3]. IL-17A secretion by $CD4^+$ Th17 cells could be induced by chloroquine-treated monocyte-derived Langerhans-like cells [5]. Studies have found that pro-inflammatory human Th17 cells, which express the drug efflux P-glycoprotein, are insensitive to glucocorticoids [6]. Therefore, IL-17A may be a rational treatment target for corticosteroid-resistant AGEP with targetoid lesions. However, the relationship between the Th17 pathway and targeted damage requires further exploration.

Besides IL-17A inhibitor, reported treatments includes cyclosporine alone or in combination with systemic corticosteroids (5 cases), glucocorticoids combined with intravenous immunoglobulin (IVIG), Dapsone or Etretinate (3 cases), pulse therapy with methylprednisolone (1 cases) and biologics (3 cases with infliximab, 1 case with secukinumab and 1 case with ixekizumab). Among these treatments, patients treated with cyclosporine as monotherapy have the longest duration of illness (range: 22-210

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days) and required slow tapering over 2 to 3 months. The efficacy times for other drugs such as dapsone and etretinate were similar, at 35 and 84 days, respectively. Biologics (range, 3-14 days) and glucocorticoids plus IVIG (10 days) have shorter disease duration. In summary, conventional drugs have a slower onset of action and require slow tapering. Biologics have the advantage of rapid onset and fast recovery and can be used for corticosteroid-resistant patients based on cytokines examination results.

Limited by the rarity of disease entity and publication bias, the conclusions drawn from the small number of reported cases in this study need to be further validated in the future. Moreover, the lack of standardization endpoints among published cases of AGEP makes it difficult to compare disease duration across different treatment modalities.

In conclusion, AGEP patients with targetoid lesions are at a higher risk of developing glucocorticoid resistance. While the underlying pathogenesis remains unclear, cytokine profiling of skin lesions can help tailor individualized treatment options. Biologics, especially IL-17A inhibitors, may be a promising therapy option for corticosteroid-resistant patients due to their rapid onset of action.

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Conflicts of Interest

None declared.

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Figure. Photographs taken after corticosteroid treatment (A) and ixekizumab (B).