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

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

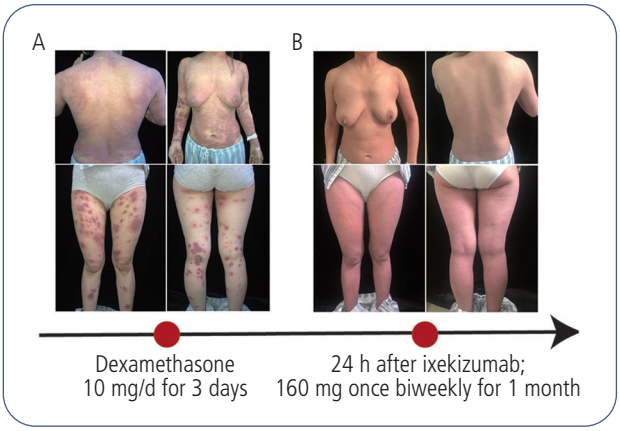

Figure. Skin lesions after corticosteroid treatment (A) and ixekizumab (B).

We report the case of a 30-year-old woman who was diagnosed with systemic lupus erythematosus (SLE) and was treated with hydroxychloroquine 200 mg/d and oral methylprednisolone 10 mg/d for about 1 month. Twenty-eight days later, she developed an itchy red rash and pustules on her neck, trunk, and upper extremities accompanied by fever (38°C) (Supplemental Figure 1, A). Physical examination revealed generalized erythematous plaques with nonfollicular pustules and atypical targetoid lesions on her arms. The patient gave written consent for her data to be published.

The patient had no personal or family history of psoriasis. Upon admission, routine laboratory testing revealed a white blood cell (WBC) count of 19.5 g/L (normal range, 3.5-9.5 g/L), neutrophil count of 17.9 g/L (normal range, 1.8-6.3 g/L) and a serum C-reactive protein (CRP) level of 14 mg/dL (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 Therefore, hydroxychloroquine was withdrawn, and oral corticosteroids were switched to intravenous dexamethasone 10 mg/d (Figure, A). However, 3 days later, the cutaneous eruption progressed, and inflammatory markers increased (WBC, 22.08 g/L; neutrophils, 18.9 g/L; CRP, 62.10 mg/dL). Treatment was escalated to intravenous methylprednisolone 80 mg/d plus intravenous immunoglobulin (IVIG) at 20 g/d for 3 days, resulting in partial improvement of the lesions (Supplemental Figure 1, C). Unfortunately, when methylprednisolone was reduced to oral prednisone 75 mg/d on day 22 after admission, the AGEP lesions recurred immediately (Supplemental Figure 1, D). Considering the resistance to corticosteroids for 3 weeks and the role of inflammatory cytokines in the pathophysiology of AGEP, immunohistochemical staining of IL-17A and TNF-α was performed on the patient's previous biopsy tissue [3]. Comparison with another AGEP patient without targetoid lesions and a healthy control revealed that 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, the rash had improved markedly, and subsequent corticosteroid tapering was successful (Figure, B). The rash resolved after 10 days. In order to prevent recurrence, the patient was treated with 2 additional doses of ixekizumab given 2 weeks apart. No flare-ups were reported during the 20-month follow-up.

We performed a literature review to determine the clinical characteristics of corticosteroid-resistant AGEP and summarized the details of 14 patients (Supplemental Table 1). Most patients were female (11/14, 78.57%), and the most

frequently reported suspect drug was hydroxychloroquine (10/14, 64.28%). Corticosteroid-resistant AGEP tends to occur in populations who are predisposed to autoimmune diseases and may also be related to the need for hydroxychloroquine. The drug has a half-life of 40-50 days, and the literature suggests that AGEP related to hydroxychloroquine typically has a longer latency period, more complicated disease course, and poorer clinical outcomes than other drugs [4]. Interestingly, after excluding the 3 patients for whom data on targetoid lesions were not mentioned in the original studies, 8 of the remaining 11 (72.73%) corticosteroid-resistant patients presented with targetoid lesions. The lesions were induced by hydroxychloroquine in 10 of these patients; therefore, the proportion of AGEP patients with targetoid lesions who developed corticosteroid resistance was 8/10. In another literature review of hydroxychloroquine-induced AGEP (Supplemental Tables 2 and 3), the proportion of corticosteroid-resistant patients without targetoid lesions was 2/10 [4]. Thus, patients with hydroxychloroquine-related corticosteroid-resistant AGEP are more likely to have targetoid lesions (8/10 vs 2/10, *P*=.02) (Supplemental Figure 2, B).

To seek a rational treatment alternative in the present case, we investigated cytokine expression and found increased IL-17A instead of TNF-α involvement in the localized skin lesions (Supplemental Figure 2, A). The T_H17 pathway, which stimulates the inflammatory response of keratinocytes, has been recognized as a core element in the pathogenesis of AGEP [3]. Secretion of IL-17A by $CD4^+$ T_H17 cells could be induced by chloroquine-treated monocyte-derived Langerhans-like cells [5]. Studies have found that proinflammatory human T_H17 cells, which express the drug efflux protein, P-glycoprotein, are insensitive to corticosteroids [6]. Therefore, IL-17A may be a rational treatment target for corticosteroid-resistant AGEP with targetoid lesions. However, the relationship between the T_H17 pathway and targeted damage requires further exploration.

Besides IL-17A inhibitors, reported treatments include cyclosporine alone or in combination with systemic corticosteroids (5 cases), corticosteroids combined with IVIG, dapsone, or etretinate (3 cases), pulse therapy with methylprednisolone (1 case), and biologics (3 cases with infliximab, 1 case with secukinumab, and 1 case with ixekizumab). With respect to these treatments, patients treated with cyclosporine in monotherapy had the longest duration of illness (range, 22-210 days) and required slow tapering over 2 to 3 months. The disease duration for dapsone and etretinate was similar, namely, 35 and 84 days, respectively. Disease duration is shorter for biologics (range, 3-14 days) and corticosteroids plus IVIG (10 days). 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 results for cytokines.

Limited by the rarity of the disease entity and publication bias, the conclusions drawn from the small number of cases reported in this study need to be further validated in the future. Moreover, the lack of standard 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 corticosteroid resistance. While the underlying pathogenesis remains unclear, cytokine profiling of skin lesions can help tailor treatment options. Biologics, especially IL-17A inhibitors, may be a promising option for treatment of corticosteroid-resistant patients owing to their rapid onset of action.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): A review and update. J Am Acad Dermatol. 2015;73(5):843-8.
2. Hadavand MA, Kaffenberger B, Cartron AM, Trinidad JCL. Clinical presentation and management of atypical and recalcitrant acute generalized exanthematous pustulosis. J Am Acad Dermatol. 2020;S0190-9622(20):32609-17.
3. Gualtieri B, Solimani F, Hertl M, Buhl T, Möbs C, Pfützner W. Interleukin 17 as a therapeutic target of acute generalized exanthematous pustulosis (AGEP). J Allergy Clin Immunol Pract. 2020;8(6):2081-4.e2082.
4. Mohaghegh F, Jelvan M, Rajabi P. A case of prolonged generalized exanthematous pustulosis caused by hydroxychloroquine-Literature review. Clin Case Rep. 2018;6(12):2391-5.
5. Said A, Bock S, Lajqi T, Müller G, Weindl G. Chloroquine promotes IL-17 production by CD4+ T cells via p38-dependent IL-23 release by monocyte-derived Langerhans-like cells. J Immunol. 2014;193(12):6135-43.
6. Ramesh R, Kozhaya L, McKevitt K, Djuretic IM, Carlson TJ, Quintero MA, et al. Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. J Exp Med. 2014;211(1):89-104.

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