

# Ixekizumab for treatment of refractory acute generalized exanthematous pustulosis caused by hydroxychloroquine



Mohammad Munshi, MD, Alexandra Junge, Karolina Gadaldi, MD, Nikhil Yawalkar, MD, and Kristine Heidemeyer, MD  
Bern, Switzerland

**Key words:** acute generalized exanthematous pustulosis; hydroxychloroquine; ixekizumab.

## INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is usually a drug-related severe reaction characterized by an acute rash with pinhead-sized sterile pustules on erythematous ground, often starting in the main folds.<sup>1</sup> Systemic involvement can occur in approximately 20% of cases of AGEP and the mortality rate is less than 5%. Although symptoms resolve within 15 days in most cases, prolonged courses have been reported.<sup>2</sup>

Drug-induced AGEP is considered a T-cell-mediated reaction with concomitant activation of neutrophils.<sup>3</sup> Increasing evidence indicates that interleukin (IL) 17 is an important factor in the pathogenesis of AGEP in concert with other proinflammatory mediators. Increased IL-17 levels have also been found in patients with AGEP.<sup>4</sup> Here, we report a case of recalcitrant AGEP elicited by hydroxychloroquine, with rapid clinical improvement after a single treatment with the anti-IL-17 monoclonal antibody ixekizumab.

## CASE REPORT

A 76-year-old man presented to our outpatient clinic with an acute rash that started 18 days after intake of hydroxychloroquine (400 mg/d) for the treatment of calcium pyrophosphate dihydrate crystal deposition disease. Intake of other concomitant medication or symptoms of infection were denied. Neither the patient nor members of his family had a history of psoriasis.

### Abbreviations used:

AGEP: acute generalized exanthematous  
pustulosis  
IL: interleukin

The patient's clinical examination revealed a generalized erythematous rash with widespread nonfollicular, pinpoint pustules, mainly on the trunk and in the axillary folds (Fig 1, A and B). There was no mucosal involvement. Bacteriologic examination result for a pustule was negative. Laboratory tests showed elevated levels of C-reactive protein (44 mg/L; normal <3 mg/L) and leukocytosis (12 G/L; normal range 3.0-10.5 G/L), as well as neutrophilia (10.46 G/L; normal range 1.6-7.4 G/L). His serum creatinine level was elevated (122  $\mu$ mol/L; normal range 59-104  $\mu$ mol/L) and creatinine clearance was low (52 mL/min; normal 59 mL/min) because of preexisting chronic kidney disease. Liver enzyme levels were normal.

Histopathologic examination showed diffuse spongiosis of the epidermis and formation of subcorneal pustules. Mild lichenoid inflammation was observed at the dermoepidermal junction and a perivascular infiltrate with lymphocytes and histiocytes, along with conspicuous neutrophils and eosinophils, was present in the superficial dermis (Fig 2, A). Immunohistologic staining for IL-17A was performed as described previously<sup>5</sup> and showed increased IL-17A expression in the inflammatory infiltrate and the pustule (Fig 2, B). The AGEP

From the Department of Dermatology, Inselspital, Bern University Hospital, University of Bern.

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Correspondence to: Kristine Heidemeyer, MD, University Hospital, Department of Dermatology, Bern, Inselspital, Freiburgstrasse, 3010 Bern, Switzerland. E-mail: [Kristine.heidemeyer@insel.ch](mailto:Kristine.heidemeyer@insel.ch).

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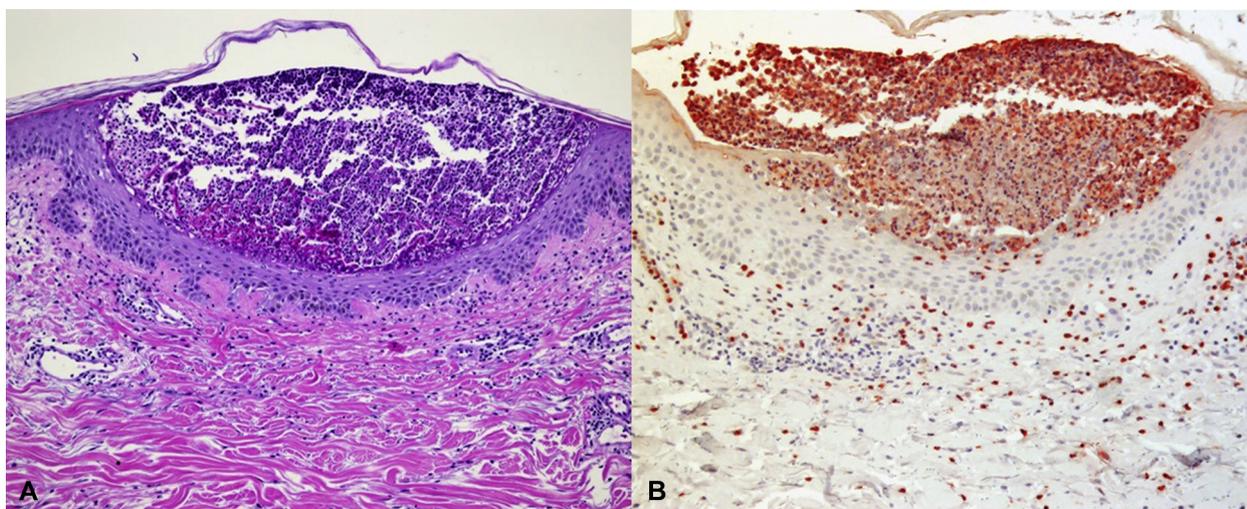
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**Fig 1.** Clinical presentation before (**A** and **B**) and after (**C**) a single treatment with ixekizumab 160 mg subcutaneously.



**Fig 2.** **A**, Staining of a pustule. **B**, Immunoreactivity for interleukin 17A in the inflammatory infiltrate and the pustule. (**A** and **B**, Hematoxylin-eosin stain; original magnification  $\times 10$ .)

validation score of the European Severe Cutaneous Adverse Reactions study group<sup>6</sup> was 10, indicating AGEP.

Despite the discontinuation of hydroxychloroquine and treatment with topical steroids (clobetasol propionate 0.05% ointment and mometasone furoate 0.1% cream) and systemic steroids (50-80 mg/d), the rash worsened and levels of inflammatory parameters in the peripheral blood increased (leukocytosis 22.7 G/L; C-reactive protein 74 mg/L). Because of the recalcitrant course of the disease for 4 weeks, therapy with ixekizumab 160 mg subcutaneously (single dose) was initiated. Within 5 days, a marked improvement of the skin and decreased inflammatory parameters (leukocytosis 7.92 G/L, neutrophils 6.4 G/L, and C-reactive protein 33 mg/L) were noted, and after 11 days, only slight erythema was visible. In the follow-up visits after 1, 2, 6, 12, and 21 months, no new flare-up was observed (Fig 1, C).

## DISCUSSION

AGEP is a rare but potentially life-threatening reaction, mainly caused by drugs. The agents commonly implicated in the development of AGEP include aminopenicillins, quinolones, macrolides, sulfonamides, terbinafine, diltiazem, and, as in our case, antimalarials. Although the symptoms of AGEP typically resolve within 15 days after the discontinuation of the causative drug, a prolonged disease course with several flares, particularly after hydroxychloroquine use, has been reported.<sup>2</sup> A prolonged disease course extending beyond 15 days could be due to the long half-life of hydroxychloroquine, which is approximately 45 days. Because hydroxychloroquine is mainly excreted by the kidneys, renal impairment with a subsequently lower clearance of the drug may also have contributed to the continual symptoms in our patient. Rarely, antimalarial drugs have been reported to induce or exacerbate pustular

psoriasis, and differentiating this disease from AGEP can be challenging.<sup>7</sup> Together with the high AGEP validation score of the European Severe Cutaneous Adverse Reactions study group, the absence of a personal or family history of psoriasis and psoriasis arthritis, the lack of recurrence of pustular lesions at follow-up, and some histologic findings such as the presence of eosinophils and slight lichenoid inflammation support our diagnosis of AGEP.

To date, the pathophysiology of AGEP and the mechanism of neutrophilic skin inflammation are not fully elucidated. Initially, CD4<sup>+</sup> and CD8<sup>+</sup> T cells as well as cytotoxic mediators including granzyme B/perforin and Fas ligand were thought to play major roles in eliciting neutrophilic skin inflammation.<sup>1,3</sup> After keratinocyte activation, partly with apoptosis and vesicle formation, increased amounts of proinflammatory cytokines (eg, tumor necrosis factor- $\alpha$ , IL-36) and chemokines (in particular CXCL-8) are released, leading to chemotaxis and neutrophil activation with subsequent pustule formation. Furthermore, T-helper type 17 effector cytokines, namely, IL-17 and IL-22, may synergistically participate in stimulating keratinocytes to produce IL-8.<sup>5</sup> It has also been suggested that besides T-helper 17 cells, innate immune cells such as neutrophils, mast cells, and macrophages are a source of IL-17A in AGEP.<sup>5</sup> This is in accordance with the findings of our immunohistochemical analyses, which showed increased IL-17 expression in the inflammatory infiltrate and the pustule (Fig 2, B).

Ixekizumab is a high-affinity, humanized, anti-IL-17A, monoclonal antibody that has been approved for treating severe plaque psoriasis and psoriasis arthritis.<sup>8</sup> It has also been approved for treating pustular and erythrodermic psoriasis in Japan.<sup>9</sup> Ixekizumab acts faster and is more efficacious compared with other biologics such as etanercept and ustekinumab.<sup>8</sup> The rationale for treating our patient with ixekizumab was as follows: First, the patient had a severe and prolonged disease course and was unresponsive to topical and systemic corticosteroids. Second, IL-17 could potentially have been involved in the pathogenesis of AGEP together with IL-17 upregulation in the skin lesion of our patient. Third, there is evidence for the positive therapeutic

effect of ixekizumab on generalized pustular psoriasis, which is also related to neutrophilic skin inflammation. Fourth, severe AGEP has been successfully treated previously in 2 patients with secukinumab, another anti-IL-17 antagonist.<sup>10,11</sup>

In conclusion, physicians should be aware that hydroxychloroquine may induce an atypical and prolonged course of AGEP, and IL-17 inhibitors such as ixekizumab can help treat prolonged, recalcitrant AGEP.

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