Dear Editors,

Hydroxychloroquine is an antimalarial drug that is commonly used as an effective treatment for autoimmune conditions. It has been suggested as a potentially effective therapeutic option for COVID-19, and many patients with confirmed or suspected SARS-CoV-2 infection are being treated with it. It is expected that the widespread use of this medication will result in an increased number of drug-related adverse events. We present two cases of refractory acute generalized exanthematous pustulosis (AGEP) due to hydroxychloroquine therapy, which were successfully managed with cyclosporine. Clinicians should be aware of this severe skin reaction, since hydroxychloroquine is prescribed widely in the era of COVID-19, and in any case prompt and accurate diagnosis is crucial for its management.

A 31-year-old woman, otherwise healthy, presented with a five-day history of pruritic maculopapular lesions that began on her face and spread rapidly to her trunk. She had been recently diagnosed with COVID-19, and hydroxychloroquine was administered for five days. She did not take any other medications. The cutaneous eruption appeared nine days after starting hydroxychloroquine treatment. Physical examination revealed widespread erythematous papules that coalesced into plaques studded with multiple non-follicular pustules over the patient’s face, chest, abdomen, back, and extremities (Figure 1). We also noted prominent facial edema. The patient had fever (38.5°C), neutrophilic leukocytosis (WBC count: 20.0 x 10³/μL, neutrophils: 92.6%) and increased C-reactive protein levels (7.17 mg/dL). A workup for signs of infection or autoimmune disease was negative. Skin biopsy revealed the presence of subcorneal pustules, a mixed inflammatory cell infiltrate in the upper dermis and a few eosinophils (Figure 1). Based on these findings, we diagnosed AGEP induced by hydroxychloroquine. Intravenous methylprednisolone (60 mg daily) was initiated with no improvement.

Figure 1 Numerous papules that coalesce into plaques studded with non-follicular pustules over the face, chest (a) and back (b). Note the facial edema. Histopathological analysis revealed a subcorneal pustule, mild spongiosis in the surrounding epidermis and mixed inflammatory cell infiltrate in the upper dermis (hematoxylin-eosin stain, original magnification x 40) (c).
During the following days the patient developed new lesions with targetoid morphology over the upper extremities and dorsum of the hand. Treatment with cyclosporine 4 mg/kg/day was started and the lesions eventually resolved after 40 days.

The second patient, a 43-year-old woman with no significant medical history, presented with a seven-day history of a diffuse pustular eruption twenty days after initiation of hydroxychloroquine for wrist synovitis. She denied taking other medications. Laboratory tests revealed neutrophilic leukocytosis (WBC count: 21.1 × 10^3/μL, neutrophils: 96.4%). The workup for autoimmune disease and infection was negative. Skin examination showed non-follicular pustules within large erythematous and edematous plaques over the trunk, neck, and extremities, with focal desquamation of the outermost layer of the skin. Multiple lesions with a targetoid appearance were noted (Figure 2). Histopathological analysis of the skin biopsy was consistent with AGEP (Figure 3). Hydroxychloroquine was discontinued and intravenous methylprednisolone 60 mg daily was initiated. Skin lesions continued to develop despite the treatment, so that cyclosporine 4.5 mg/kg/day was added, achieving complete resolution after two months.

ADEP is a severe cutaneous adverse reaction characterized by the rapid appearance of sterile non-follicular pustules on a background of edematous erythema, usually localized on the trunk and major flexures [1]. AGEP generally has a rapid onset and resolution. In most cases, the prognosis is excellent after the culprit drug is discontinued. Systemic corticosteroids may be required in cases with more extensive involvement. Sharma et al. conducted a systematic review of the adverse dermatological effects of hydroxychloroquine, and found that drug eruptions were the most common side effect, followed by hyperpigmentation [2]. Hydroxychloroquine has been reported as a rare causative agent of AGEP with distinct features [3]. It appears to have a longer latent period (median onset of 11 days rather than one day after initial drug exposure) and tends to be more severe and resistant to systemic treatment. Facial edema and atypical targets are occasionally observed. Twenty-seven cases of hydroxychloroquine-induced AGEP have been reported in the English-language literature [2]. Only four cases of refractory AGEP that were treated successfully with cyclosporine have been reported [4–7]; these patients had underlying autoimmune conditions,
and it has been speculated that immunological dysregulation may be a predisposing factor for the development of refractory forms [4]. Our findings of refractory AGEP occurred in otherwise healthy patients, supporting the idea that all patients are at risk of developing severe, refractory, and potentially life-threatening AGEP, even with low cumulative doses. This must be taken into account, since hydroxychloroquine is currently prescribed worldwide due to COVID-19. In any case, patients who contract connective tissue diseases during the pandemic should initiate or continue treatment with hydroxychloroquine if necessary [8, 9]. We believe that is important to identify and recognize this adverse reaction since early withdrawal of hydroxychloroquine is mandatory for its management. We also emphasize the potentially beneficial role of cyclosporine for refractory cases of AGEP.

Conflict of interest
None.

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