

## LETTER

# Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine

Dear Editor,

Hydroxychloroquine (HCQ) was recently suggested for both chemoprophylaxis and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.<sup>1</sup> However, data on the safety profile of HCQ in coronavirus disease-19 (COVID-19) treatment is still scarce, especially if millions of patients would be exposed to HCQ. As of April 29, 2020, the total number of confirmed COVID-19 cases exceeded 3 million.<sup>2</sup> If HCQ treatment is prescribed massively for COVID-19 chemoprophylaxis and treatment, rare and severe side effects related to treatment would become more prevalent. Adverse effects of HCQ include exanthema, stomatitis, itching, and hyperpigmentation.<sup>3</sup> Severe side effects encompass Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP).<sup>3,4</sup> The latter is the most frequently reported serious side effect related to HCQ.<sup>3</sup>

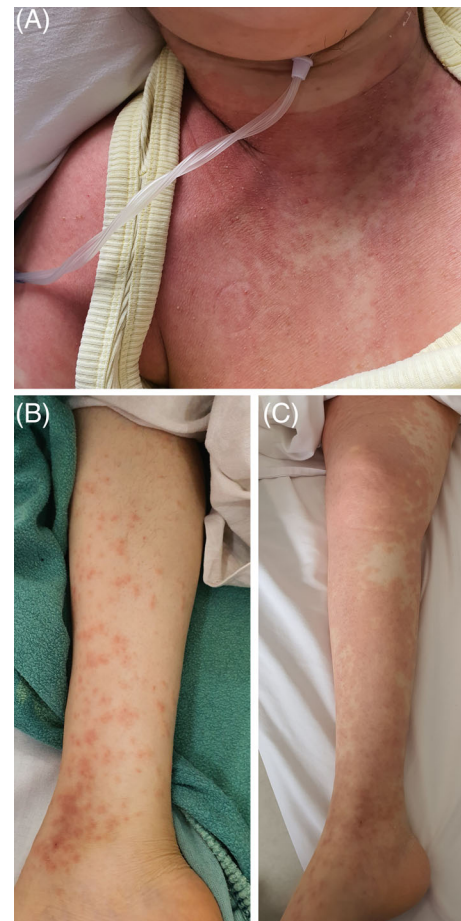
We would like to share our experience from Tunisia. As of April 26, 2020, there are 967 accumulated COVID-19 cases.<sup>5</sup> A total of 211 cases were diagnosed in Tunis. Among these cases, there was an interesting case of a 39-year-old female patient who developed AGEP after COVID-19 treatment with HCQ. She was hospitalized on March 31 for COVID-19 management. The diagnosis was confirmed after nasopharyngeal swab PCR examination. She was treated with HCQ (600 mg daily), enoxaparin, and supplemental oxygen with a slight improvement of clinical signs (dry cough, dyspnea, and fever) and arterial blood gas analysis. Eighteen days after HCQ initiation, she developed a pruritic eruption. Physical examination revealed a cephalocaudal spread of erythematous and pustular plaques (Figure 1). Laboratory tests showed leukocytosis (WBC: 13 590/mm<sup>3</sup>), eosinophilia (700/mm<sup>3</sup>), and neutrophilia (10 355/mm<sup>3</sup>). The diagnosis of AGEP was made based on clinical and histopathological examinations. Withdrawal of HCQ was indicated with significant improvement of skin lesions. Unfortunately, the patient died of a massive pulmonary embolism. COVID-19 is, indeed, associated with an increased risk of venous thromboembolism, which is responsible for significant disease-related mortality.<sup>6</sup>

AGEP is commonly attributed to antibiotics and usually occurs within 48 hours of treatment initiation.<sup>7</sup> AGEP arising after HCQ treatment is distinguishable by longer incubation period (up to 2-3 weeks), cephalocaudal spread, and atypical clinical presentation including urticarial plaques, targetoid lesions, and blisters.<sup>7</sup>

A dilemma to which a dermatologist would be confronted is whether such cutaneous lesions are related to COVID-19 or its treatment. Reported cutaneous manifestations in COVID-19 are varied

and include exanthems, purpura, urticaria, and varicella-like vesicles.<sup>6</sup> Late-onset lesions are related to vasculitis or thrombotic vasculopathy.<sup>6</sup> The mechanisms by which such lesions are related to SARS-CoV-2 infection remain poorly understood. We hypothesize that pustular eruptions occurring in COVID-19 patients are more likely to support drug-related origin.

Given the anticipated widespread endorsement of HCQ by many governments and institutions worldwide,<sup>8</sup> specific recognition of this serious side effect is vital.




**FIGURE 1** Clinical presentation characterized by initial cephalocaudal spread, A,B. Marked erythema and edema of the trunk associated with multiple small sterile pustules, A. Tiny petechiae of lower legs, B, rapidly extending into large erythematous plaques within 4 days, C

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Khaoula Hajlaoui, Maroua Slouma, and Faten Zeglaoui contributed to the literature search, analysis, and interpretation of the data. Nouredine Litaïem and Manel Karray contributed to the first draft of the manuscript. Faten Zeglaoui critically revised the manuscript and gave final approval. All authors read and approved the final manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work.

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