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DERMATOLOGIC THERAPY WILEY

LETTER

Acute generalized exanthematous pustulosis induced by empiric hydroxychloroquine for presumed COVID-19

Dear Editor,

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction. Rare cases secondary to hydroxychloroquine (HCQ) are documented in the literature.[1-8] We report a case of a woman who developed AGEP after initiating HCQ for a presumed diagnosis of COVID-19. Results of her initial and repeat COVID-19 testing were ultimately negative. We present this case to shed light on the potentially dangerous skin toxicities associated with HCQ.

A 29-year-old woman with a history of Protein S deficiency and Stevens-Johnson syndrome due to cefaclor presented to her physician for subjective fever, cough, and sore throat. Given recent exposure to a COVID-19 positive individual, she was tested for COVID-19, and given a five-day course of oral azithromycin, doxycycline and prednisone, with no improvement. Eight days later, as her COVID-19 results were not yet available, she was started empirically on HCQ 200 mg twice daily. After four days of treatment, she awoke with rash on the neck and abdomen that spread to the face and extremities (Figure 1). She was instructed to stop HCQ and received a six-day oral methylprednisolone taper, which did not improve her rash. Her COVID-19 testing returned negative. The rash spread and pruritus was unrelenting. Twelve days after she began HCQ, she presented at an outside hospital, where she was given intravenous methylprednisolone 125 mg. The rash continued to progress, and she developed facial swelling, so she presented to the University of Texas Southwestern Medical Center Emergency Room for evaluation. She was afebrile with normal vital signs on ambient air. Her skin exam was notable for facial edema, erythematous macules and edematous papules coalescing into plaques on the face, trunk, bilateral arms and thighs. On the lateral neck and abdomen were scattered, non-follicular pustules. Nikolsky's sign was negative. The oral mucosa was hyperemic with no erosions or ulcerations. Laboratory tests were notable for renal and hepatic function within normal limits, an elevated white blood cell count of 16.7 per microliter with neutrophilia and no eosinophilia, and negative COVID-19 testing.

The patient was admitted and treated conservatively with topical triamcinolone 0.1% ointment but experienced significant pruritus and additional pustule formation, necessitating one administration of IV methylprednisolone 500 mg. The following morning her skin was less erythematous and she denied mucosal pain. Laboratory studies remained

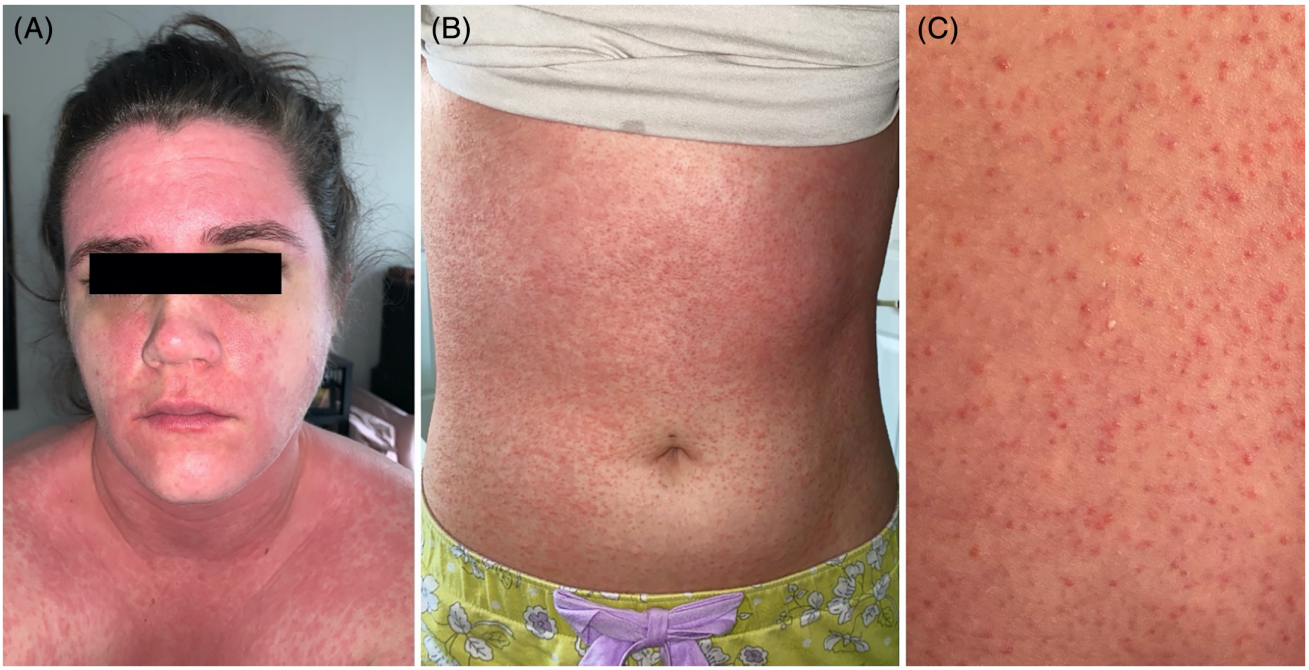

FIGURE 1 Patient's Rash. Red-pink erythematous papules and non-follicular pustules involving, A, face and B, abdomen. C, Close up of pinpoint pustules. Informed consent was obtained from the patient to publish these photos

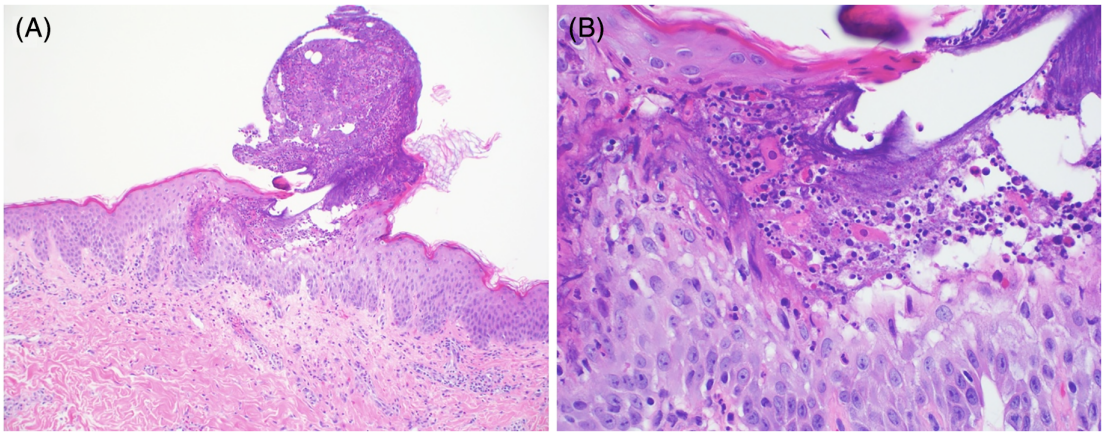

FIGURE 2 Skin biopsy pathology. A, Hematoxylin-eosin stained punch biopsy from the abdomen showing a ruptured subcorneal pustule (100× magnification); B, with neutrophils and eosinophils consistent with acute generalized exanthematous pustulosis (400× magnification)

stable. She was transitioned to an oral prednisone taper to further treat her active but improving rash. A skin biopsy, collected prior to treatment, showed a subcorneal pustule with neutrophils and eosinophils consistent with a diagnosis of acute generalized exanthematous pustulosis (Figure 2). The rash resolved with the prednisone taper after 38 days.

The rapid spread of COVID-19 has left health care providers across the world in search of treatment options to combat the virus. This case highlights a severe cutaneous adverse reaction to HCQ, which is currently being used empirically, despite a lack of evidence to support its use.[9] In classic AGEP, onset occurs within 48 hours of drug initiation, and most cases resolve within 2 weeks after the offending medication is stopped.[1,4,5] In reported cases of HCQ-induced AGEP, there is a longer latency period, ranging from four to 30 days. Additionally, the duration of the eruption may be lengthy, up to 81 days, and prolonged treatment with systemic steroids or cyclosporine may be necessary to treat the reaction.[4-8] It is possible that the protracted course is secondary to HCQ's long half-life.[4,5] Our patient's presentation was likely somewhat attenuated, with fewer pustules, due to the systemic steroids she received prior to presentation. The absence of reliable, rapid COVID-19 testing contributed in this case. While HCQ is generally well-tolerated, dermatologic adverse effects can occur and may be severe.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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REFERENCES

1. Szatkowsk J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol*. 2015;73:843-848.
2. Evans CC, Bergstresser PR. Acute generalized exanthematous pustulosis precipitated by hydroxychloroquine. *J Am Acad Dermatol*. 2004;50:650-651.
3. Sharma AN, Mesinkovska NA, Paravar T. Characterizing the adverse dermatologic effects of hydroxychloroquine: a systematic review. *J Am Acad Dermatol*. 2020;S0190-9622(20)30564-8 [published online ahead of print, 2020 Apr 11]. https://doi.org/10.1016/j.jaad.2020.04.02.
4. Castner NB, Harris JC, Motaparthi K. Cyclosporine for corticosteroid-refractory acute generalized exanthematous pustulosis due to hydroxychloroquine. *Dermatol Ther*. 2018;31(5):e12660.
5. Pearson KC, Morrell DS, Runge SR, Jolly P. Prolonged pustular eruption from hydroxychloroquine: an unusual case of acute generalized exanthematous pustulosis. *Cutis*. 2016;97(3):212-216.
6. Duman H, Topal IO, Kocaturk E, Cure K, Mansuroglu I. Acute generalized exanthematous pustulosis induced by hydroxychloroquine: a case with atypical clinical presentation. *An Bras Dermatol*. 2017;92(3):404-406.
7. Di Lernia V, Grenzi L, Guareschi E, Ricci C. Rapid clearing of acute generalized exanthematous pustulosis after administration of ciclosporin. *Clin Exp Dermatol*. 2009;34(8):e757-e759.
8. Mohaghegh F, Jelvan M, Rajabi P. A case of prolonged generalized exanthematous pustulosis caused by hydroxychloroquine-literature review. *Clin Case Rep*. 2018;6(12):2391-2395.
9. Finh SD, Perencevich E, Bradley SM. Caution needed on the use of chloroquine and hydroxychloroquine for coronavirus disease 2019. *JAMA Netw Open*. 2020;3:e209035.