

BRIEF ARTICLE

Hydroxychloroquine and Acute Generalized Exanthematous Pustulosis

Justine Galambus, BS¹, Atefah Vafa, MD²

¹ Morsani College of Medicine, University of South Florida, Tampa, FL

² Department of Rheumatology, University of South Florida, Tampa, FL

ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a rare, potentially lethal, cutaneous reaction most commonly precipitated by drugs. Removal of the offending drug or treatment of the underlying infection usually results in recovery, though corticosteroids are often used to bolster treatment. We report a case of hydroxychloroquine-induced AGEP in an adult female. Though removal of hydroxychloroquine (HCQ) did largely resolve her rash, she continued to require corticosteroids over 200 days after she first began taking HCQ.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare, potentially lethal, cutaneous reaction precipitated by drugs in more than 90% of cases,¹ with the most common triggers being pristinamycin, aminopenicillins, quinolones, (hydroxy)chloroquine, sulfonamides, terbinafine, and diltiazem.¹ AGEP typically presents within one day of treatment after antibiotic exposure versus eleven days after other drugs, including hydroxychloroquine (HCQ, Plaquenil).¹ AGEP presents with innumerable pinhead-sized pustules arising on a diffuse erythematous background and are reported to localize in intertriginous zones, the trunk, and upper extremities.² Diagnostic criteria outside of a pustular eruption include a fever, neutrophilia with or without mild eosinophilia, subcorneal or intraepidermal pustules on skin biopsy, and spontaneous resolution in less than 15 days.¹ Sidoroff et al developed a validation

scale founded in these criteria to aid clinicians in the diagnosis of AGEP.

The first step in drug-induced AGEP treatment is withdrawal of the culprit drug.³ Though spontaneous resolution without intervention is reported,⁴ first-line therapy is steroids, recurrent or refractory cases can be treated with cyclosporin,⁵ etretinate,⁶ or dapsone⁷. Though the reaction can be very disconcerting and uncomfortable for the patient, the general prognosis is good with the overall mortality rate of up to 5%;² those with the highest risk have comorbidities.⁸

HCQ is an antimalarial medication that is frequently used as an immunosuppressive. HCQ-precipitated AGEP is predominantly reported in the context of HCQ's immunosuppressive action, most commonly when used to treat Rheumatoid Arthritis,⁹ Sjogren's Syndrome,⁵ and Systemic Lupus Erythematous.⁶ However, with the increased use of HCQ as an antiviral for treatment of COVID-19, several cases of AGEP have been reported.¹⁰ AGEP tends to affect women, and HCQ-precipitated AGEP

certainly follows that pattern as evidenced by this literature review. However, this can, at least in part, be attributed to the common indications for HCQ predominantly affecting women. The overall incidence rate of AGEP is between 1 to 5 cases per million per year based on the EuroSCAR study, however, this is reported with the caveat that reliable data is missing.¹ The prevalence of HCQ-precipitated AGEP has not been studied. HCQ-precipitated AGEP is associated with a delayed onset as well as recalcitrant course, leading to the proposal of a new classification, generalized pustular figurate erythema (GPFE).⁷ GPFE presents as a sudden eruption of pruritic, erythematous papules on the face, with concurrent fever and neutrophilic leukocytosis. There have only been two reports of death following HCQ-precipitated AGEP; however, both were COVID-19 patients who died following COVID-19-attributed pulmonary emboli.

CASE REPORT

A 38-year old African America female with a prior history of eczema presented with a diffuse desquamating rash with a prior medical history of recently diagnosed systemic lupus erythematosus (SLE), arthritis, intermittent parotid swelling and dry mouth, and previous pustular palmar rashes. The patient was originally prescribed hydroxychloroquine 200 mg BID for treatment of her SLE. An antibody panel revealed elevated Anti-Nuclear Antibodies, anti-SSA and anti-SSB antibodies. Rheumatoid factor, anti-dsDNA antibodies, anti-Smith antibodies, and anti-SCL-70 antibodies were negative. Biopsy showed a spongiotic epidermis with hyperkeratosis, variable loss of the granular layer, and scattered corneal pustules. The dermis has a mild inflammatory neutrophilic infiltrate with scattered eosinophils. Gram

staining, GMS (Gomori methenamine silver, used to detect fungi) and PAS (Periodic Acid-Schiff, also can be used to detect fungi) stains were negative. Immunofluorescence for IgG, IgA, IgM, C3, fibrin, and albumin were also negative. The biopsy findings were consistent with AGEP and ruled out SJS/TEN.

Approximately two weeks after beginning HCQ, the patient noted a diffuse rash covering her body; she did not note where the rash began. Upon admission, she was found to be afebrile with a rash on the trunk and bilaterally on the upper and lower extremities, sparing mucosal sites. HCQ was stopped owing to suspected drug reaction, and after four days, the patient was discharged with prednisone. Prior to discharge, the patient developed urticarial lesions around her eyes that were determined not to be related to AGEP.

Following discharge and HCQ discontinuation, she had worsening periorbital urticaria and swelling, as well as worsening pruritic, painful desquamating rash with rash on her upper extremities. She eventually began experiencing some relief with continued prednisone. Approximately six months after initial admission, the patient rash was noted to have new pustular rashes over the wrists, abdomen, and face. Her subsequent disease course and treatment is summarized in Figure 1.

DISCUSSION

Hydroxychloroquine is associated with a distinct form of AGEP, prompting consideration of a distinct classification. Typical AGEP diagnostic criteria include of a pustular eruption, fever, neutrophilia with or without mild eosinophilia, subcorneal or intraepidermal pustules on skin biopsy, and spontaneous resolution in less than 15

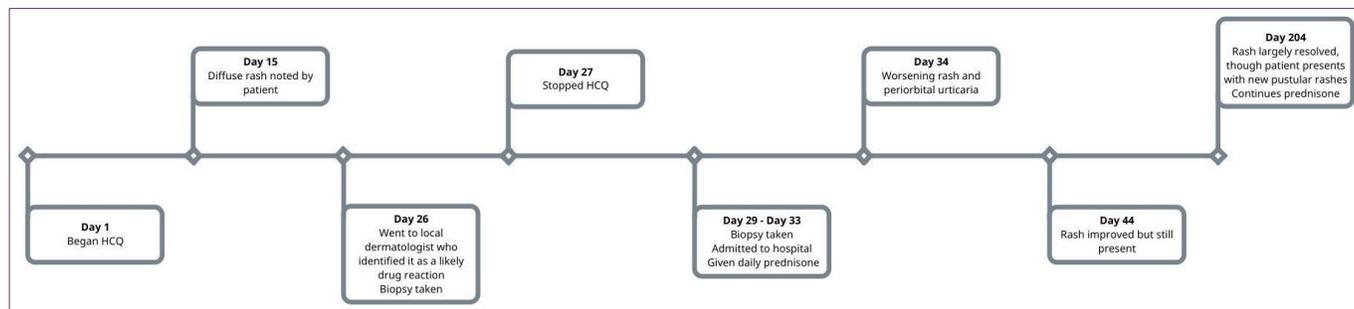


Figure 1. Timeline showing the disease course of the patient's hydroxychloroquine-induced AGEP

days.¹ The patient here presented with a pustular eruption with neutrophilia, mild eosinophilia, and intraepidermal pustules on biopsy. However, the patient was notably afebrile, and resolution was not achieved by day 30. It is unclear when the patient experienced initial full resolution of her rash. Hydroxychloroquine is notable for a long half-life, approximately 40-50 days.¹¹ It takes approximately 5-6 half-lives to significantly eliminate a drug, meaning that it could take upwards of 200 days in order to clear HCQ. This could explain why AGEP is notably recalcitrant and can last longer than the typical 15-day resolution when secondary to HCQ use. Though HCQ-induced AGEP can have spontaneous resolution, prednisolone or prednisone is often used to ease symptoms as with this patient. Prednisone was noted to have the dual benefit of aiding with the patient's arthritis as well.

CONCLUSION

While this was not the case for this patient, of note is the use of HCQ in treatment of COVID-19. Though no longer recommended,¹² some physicians and patients may be inclined to pursue HCQ as treatment for COVID-19. Though the deaths following HCQ-induced AGEP were attributed to pulmonary emboli, it is important for patients to understand AGEP as a potentially severe side effect. In particular, the longer course and pain

associated with the rash may significantly impact patient well-being long after potential COVID-19 resolution. Therefore, this should be discussed as part of an informed consent with patients who desire treatment with HCQ.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:

Justine Galambus, BS
Morsani College of Medicine
University of South Florida
560 Channelside Dr
Tampa, FL 33602, USA
Email: galambus@usf.edu

References:

1. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Case Control Study. Br J Dermatol.* Nov 2007;157(5):989-96. doi:10.1111/j.1365-2133.2007.08156.x
2. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Review. Toxicology.* Apr 15 2005;209(2):123-9. doi:10.1016/j.tox.2004.12.022
3. Hoetzenecker W, Nageli M, Mehra ET, et al. Adverse cutaneous drug eruptions: current understanding. *Review. Semin Immunopathol.* Jan 2016;38(1):75-86. doi:10.1007/s00281-015-0540-2
4. Evans CC, Bergstresser PR. Acute generalized exanthematous pustulosis precipitated by hydroxychloroquine. *Case Report. J Am Acad Dermatol.* Apr 2004;50(4):650-1. doi:10.1016/s0190-9622(03)02733-6

5. Castner NB, Harris JC, Motaparthy K. Cyclosporine for corticosteroid-refractory acute generalized exanthematous pustulosis due to hydroxychloroquine. Case Report. *Dermatol Ther*. Sep 2018;31(5):e12660. doi:10.1111/dth.12660
6. Matsuda-Hirose H, Sho Y, Yamate T, et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine successfully treated with etretinate. Case Report. *J Dermatol*. Feb 2020;47(2):e53-e54. doi:10.1111/1346-8138.15185
7. Schwartz RA, Janniger CK. Generalized pustular figurate erythema: A newly delineated severe cutaneous drug reaction linked with hydroxychloroquine. Article. *Dermatol Ther*. May 2020;33(3):e13380. doi:10.1111/dth.13380
8. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): A review and update. Review. *J Am Acad Dermatol*. Nov 2015;73(5):843-8. doi:10.1016/j.jaad.2015.07.017
9. Pearson KC, Morrell DS, Runge SR, Jolly P. Prolonged pustular eruption from hydroxychloroquine: an unusual case of acute generalized exanthematous pustulosis. Case Report. *Cutis*. Mar 2016;97(3):212-6.
10. Delaleu J, Deniau B, Battistella M, et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. Case Report. *J Allergy Clin Immunol Pract*. Jun 7 2020;doi:10.1016/j.jaip.2020.05.046
11. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. Mar 2020;16(3):155-166. doi:10.1038/s41584-020-0372-x
12. Elavarasi A, Prasad M, Seth T, et al. Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis. *J Gen Intern Med*. Nov 2020;35(11):3308-3314. doi:10.1007/s11606-020-06146-w