Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous eruption that often is a reaction to medications, most commonly antibiotics. Clinically, AGEP closely mimics pustular psoriasis and also is similar to subcorneal pustular dermatosis and IgA pemphigus. For clinicians, it is important to differentiate AGEP from pustular psoriasis. Acute generalized exanthematous pustulosis will have an acute drug association. Few cases have been known to be caused by hydroxychloroquine (HCQ). Proper therapeutic management of AGEP includes withdrawal of the offending agent, and resolution typically occurs within 15 days. We report a case of AGEP after HCQ administration that did not follow the usual course of resolution after medication cessation. The patient continued to experience cutaneous eruptions that waxed and waned for 81 days. Hydroxychloroquine has a particularly long half-life and is a known cause of AGEP; therefore, it is possible that HCQ-induced AGEP may not follow the typical rapid recovery time. Cutis. 2016;97:212-216.
Prolonged Pustular Eruption From Hydroxychloroquine

dermatosis, which typically starts on the face, axilla, and groin and then progresses to most of the body. Approximately 90% of AGEP cases are due to drug hypersensitivity to a newly initiated medication, while the other 10% are thought to be viral in origin. Discontinuation of the offending agent may allow for complete resolution within 15 days. Agents commonly implicated in causing AGEP are antibiotics such as aminopenicillins, macrolides, and cephalosporins. Hydroxychloroquine (HCQ) also has been reported to cause AGEP, with resolution shortly after discontinuation of the drug close to the characteristic 15 days of AGEP due to alternate medications. We report an unusual case of HCQ-induced AGEP that lasted far beyond the typical 15 days. We also review other cases of HCQ-induced AGEP and possible mechanisms to explain our patient’s symptoms.

Case Report

A 50-year-old woman who was previously diagnosed with rheumatoid factor seronegative, nonerosive rheumatoid arthritis, which was only moderately controlled with low-dose prednisone (5 mg once daily) after 2 months of treatment, was started on oral HCQ 200 mg twice daily by her rheumatologist. Two weeks after starting HCQ treatment, she developed a pustular exanthem that gradually spread on the back over the next 24 to 48 hours. She described the eruption initially as pruritic, but she then developed painful stinging sensations as the eruption spread. She visited her primary care physician the next day and stopped the HCQ after 14 days following a discussion with the physician. Her prednisone dosage was increased to 50 mg daily for 5 days, but by the fifth day the lesions had spread to the face, full back, shoulders, and upper chest (Figure 1). Morphologically, she presented to the dermatology clinic with innumerable 1- to 2-mm pustules with confluent erythema on the back, extending to the forearms (Figure 2). She also had scattered erythematous macules and papules on the buttocks, legs, and planar surfaces of the feet. A biopsy taken from the right forearm demonstrated subcorneal pustular dermatosis consistent with AGEP. Prednisone 50 mg once daily was continued. She was scheduled for a follow-up in 3 days but instead went to the emergency department 1 day later due to worsening of the eruption, fever, and malaise. On examination there were multiple discrete and confluent erythematous plaques on the face that extended to the lower extremities. Pustules and scales were noted on the back. New pustules had developed on the hands and feet with intense pruritus.

On admission, her vitals were stable with mild tachycardia. Aggressive intravenous hydration was administered. Her white blood cell count was elevated at 28.3×10⁹/L (reference range, 4.5–10×10⁹/L). She was started on intravenous methylprednisolone 100 mg once daily; topical steroid wet wraps with triamcinolone 0.1% were applied to the trunk, arms, legs, and abdomen twice daily; and hydrocortisone cream 2.5% was applied to the face and intertriginous areas 3 times daily. Over the next
2 days, eruptions continued to persist and the patient reported worsening of pain despite treatment. On day 3, intravenous methylprednisolone 100 mg was switched to oral prednisone 80 mg once daily.

Over the ensuing 5 days, recurrent episodes of erythema on the back had spread to the extremities. After 1 week in the hospital, the diffuse erythema had improved and she had widespread desquamation. She was discharged and prescribed oral prednisone 80 mg once daily and topical therapy twice daily. The patient followed up in the dermatology clinic 4 days after discharge with a mildly pruritic eruption on the trunk and proximal lower extremities but otherwise was doing well. She was instructed to taper the prednisone by 10 mg every 4 days.

At a follow-up 3 weeks later, she had persistent stinging and tingling sensations, widespread xerosis, and diffuse patchy erythema primarily on the back and proximal extremities, which flared over the last week. The patient reported waxing and waning of the erythema and pruritus since being discharged from the hospital. Despite the recent flare, which was her fourth flare of cutaneous eruption, she showed marked improvement since her initial examination and 40 days after discontinuation of HCQ. She was taking prednisone 40 mg once daily and was advised to continue tapering the dose by 2 mg every 6 to 8 days as tolerated. At 81 days after AGEP onset, the eruption had resolved and the patient was back to her baseline prednisone dosage of 5 mg once daily.

**Comment**

Acute generalized exanthematous pustulosis is characterized by the sudden appearance of erythema and hundreds of sterile nonfollicular pustules, fever, and leukocytosis. Histologically, AGEP is composed of subcorneal and intraepidermal pustules, edema of the papillary dermis, and perivascular infiltrates of neutrophils and possible eosinophils. The pathogenesis of AGEP is thought to be due to the release of increased amounts of IL-8 by T cells, which attract and activate polymorphonuclear neutrophils. Psoriasiform changes are uncommon. Clinically, AGEP is similar to pustular psoriasis but has shown to be its own distinct entity. Unlike patients with pustular psoriasis, patients with AGEP lack a personal or family history of psoriasis or arthritis, have a shorter duration of pustules and fever, and have a history of new medication administration. Other conditions to consider in the differential diagnosis include pustular psoriasis, subcorneal pustulosis, IgA pemphigus, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, and acute febrile neutrophilic dermatosis.

In AGEP, the average duration of medication exposure prior to onset varies depending on the causative agent. Antibiotics consistently have been shown to trigger symptoms after 1 day, whereas other medications, including HCQ, averaged closer to 11 days. Hydroxychloroquine is widely used to treat rheumatic and dermatologic diseases and has previously been reported to be a less common cause of AGEP; however, a EuroSCAR study found that patients treated with HCQ were at a greater risk for AGEP. Acute generalized exanthematous pustulosis usually follows a benign self-limiting course. Within days the eruption gradually evolves into superficial desquamation. Characteristically, removal of the offending agent typically leads to spontaneous resolution in less than 15 days. Resolution is generally without complications and, therefore, treatment is not always necessary. Death has been reported in up to 2% of cases. There are no known therapies that prevent the spread of lesions or further decline of the patient's condition. Systemic corticosteroids often are used to treat AGEP with variable results.

Unique to our patient were recurring exacerbations of the cutaneous lesions beyond the typical 15 days for complete resolution. Even up to 40 days after discontinuation of medication, our patient continued to experience cutaneous symptoms. Other reported cases have not described patients with symptoms flaring or continuing for this extended period of time. A review of 7 external AGEP cases caused by HCQ (identified through a PubMed search...
# Review of HCQ-Related Cases of AGEP

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, y/Gender</th>
<th>Disease</th>
<th>HCQ Dosage</th>
<th>Time to Onset</th>
<th>WBC(^a)</th>
<th>Treatment</th>
<th>Time to Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martins et al(^b) (2006)</td>
<td>51/F</td>
<td>RA</td>
<td>400 mg/d</td>
<td>2 wk</td>
<td>NA</td>
<td>Systemic corticosteroids</td>
<td>3 wk</td>
</tr>
<tr>
<td>Paradisi et al(^b) (2008)</td>
<td>36/F</td>
<td>RA, Sjögren syndrome</td>
<td>100 mg bid</td>
<td>21 d</td>
<td>21.7×10^9/L</td>
<td>Prednisolone 40 mg/d, reduced by 10 mg every 4 d</td>
<td>8 d</td>
</tr>
<tr>
<td></td>
<td>70/M</td>
<td>RA</td>
<td>100 mg bid, D/C in 8 d</td>
<td>20 d</td>
<td>13.9×10^9/L</td>
<td>Prednisolone 40 mg/d</td>
<td>12 d</td>
</tr>
<tr>
<td></td>
<td>79/F</td>
<td>Polymyalgia rheumatica</td>
<td>100 mg bid, D/C in 2 d</td>
<td>20 d</td>
<td>16.7×10^9/L</td>
<td>Prednisolone 40 mg/d</td>
<td>15 d</td>
</tr>
<tr>
<td>Lateef et al(^a) (2009)</td>
<td>67/F</td>
<td>SLE</td>
<td>Not reported</td>
<td>3 wk</td>
<td>NA</td>
<td>Supportive for AGEP, corticosteroids and IVIG for TEN</td>
<td>Hospitalized 2 wk</td>
</tr>
<tr>
<td>Di Lernia et al(^b) (2009)</td>
<td>63/F</td>
<td>RA</td>
<td>100 mg bid, D/C 7 d into rash</td>
<td>30 d</td>
<td>21×10^9/L</td>
<td>Cyclosporine</td>
<td>Exacerbation at 18 d, tapered corticosteroid</td>
</tr>
<tr>
<td>Park et al(^a) (2010)</td>
<td>38/F</td>
<td>Dermatomyositis and polyarthritis</td>
<td>200 mg, D/C 7 d into eruption</td>
<td>3 wk</td>
<td>16.7×10^9/L</td>
<td>Methylprednisolone 125 mg</td>
<td>Complete recovery, time not reported</td>
</tr>
<tr>
<td>Current case</td>
<td>50/F</td>
<td>RA</td>
<td>200 mg bid</td>
<td>2 wk</td>
<td>28.3×10^9/L</td>
<td>Methylprednisolone 100 mg/d, triamcinolone ointment, hydrocortisone cream</td>
<td>Exacerbation at 1 wk and 3 wk</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCQ, hydroxychloroquine; AGEP, acute generalized exanthematous pustulosis; WBC, white blood cell count; F, female; RA, rheumatoid arthritis; NA, not available; bid, twice daily; M, male; D/C, discharge; SLE, systemic lupus erythematosus; IVIG, intravenous immunoglobulin; TEN, toxic epidermal necrolysis.

\(^a\)Reference range, 4.5–10×10^9/L.
of articles indexed for MEDLINE using the search terms acute generalized exanthematous pustulosis or eruption with hydroxychloroquine or plaquenil) showed resolution within 8 days to 3 weeks (Table).\textsuperscript{3-6,8} One case report documented disease exacerbation on day 18 after tapering the methylprednisolone dose. This patient was then treated with cyclosporine and had a prompt recovery.\textsuperscript{5} One case of AGEP due to terbinafine reported continual symptoms for approximately 4 weeks after terbinafine discontinuation.\textsuperscript{9} Our patient’s continual symptoms beyond the typical 15 days may be due to the long half-life of HCQ, which is approximately 40 to 50 days. Systemic corticosteroids often are used to control severe eruptions in AGEP and were administered to our patient; however, their utility in shortening the duration or reducing the severity of the eruption has not been proven.

**Conclusion**

Hydroxychloroquine is a commonly used agent for dermatologic and rheumatologic conditions. The rare but severe acute adverse event of AGEP warrants caution in HCQ use. Correct diagnosis of AGEP with HCQ cessation generally is effective as therapy. Our patient demonstrated that not all cases of AGEP show rapid resolution of cutaneous symptoms after cessation of the drug. Hydroxychloroquine’s extended half-life of 40 to 50 days surpasses that of other medications known to cause AGEP and may explain our patient’s symptoms beyond the usual course.

**REFERENCES**