

LETTERS TO THE EDITOR

Acute generalized exanthematous pustulosis: a complication of COVID-19 infection or therapy?

Dear Editor,

During the COVID-19 pandemic, several cases of AGEP have been reported in patients with COVID-19 infection.

A 49-year-old woman with hypertension presented with shortness of breath, low-grade fever, and dry cough. She tested positive for COVID-19 and received a 5-day treatment with oral azithromycin 500 mg once daily and hydroxychloroquine (HCQ) 400 mg orally twice daily on the first day, then 400 mg once daily for the next 4 days. Six days after the completion of the treatment, the patient developed a pruritic rash on her face and neck. Over the next 5 days, she developed widespread erythema, scaling, and pustules covering more than half of her body surface area. She had prominent facial and trunk involvement with no mucosal involvement (Figure 1). She had fever (38.1°C), chills, and generalized aches. White blood cell count was 22 700/ μ L with a left shift and no eosinophilia. Blood cultures were negative. ESR was 35 mm/h. She had no personal or family history of skin diseases. Biopsy revealed intraepidermal and subcorneal collections of neutrophils with no parakeratosis, consistent with a diagnosis of AGEP. Eosinophil infiltration was seen within the superficial dermis. Culture from pustules grew no bacteria. Intravenous methylprednisolone, oral

famotidine, and oral hydroxyzine were initiated. Intravenous vancomycin was administered empirically until cultures returned. On the third day, the methylprednisolone was changed to oral prednisone 50 mg daily, and the edema, erythema, and pustules began to resolve. She was discharged on a tapering dose of oral prednisone, and the rash resolved after 4 weeks.

We found 13 articles that reported 24 cases of AGEP in patients with COVID-19 infection, with 14 males (58%). The details of these manuscripts are summarized in Table 1. Twenty-one cases occurred in patients who received HCQ, three on HCQ monotherapy for the treatment of COVID-19 pneumonia, while the rest received additional medications. Therefore, HCQ is the most common medication administered in patients with COVID-19 who later experienced AGEP. One case of AGEP occurred after chloroquine therapy and one case after the treatment with cefepime for the pseudomonas aeruginosa urinary tract infection who also had COVID-19 infection.¹ One case of AGEP was attributed to cefditoren; however, interestingly the patient initially received HCQ for the treatment of COVID-19 pneumonia.² There was one reported case of AGEP possibly related to COVID-19 infection. AGEP developed three months



FIGURE 1 Facial and trunk involvement in a patient with acute generalized exanthematous pustulosis (AGEP) and COVID-19 pneumonia

TABLE 1 Reported cases of acute generalized exanthematous pustulosis (AGEP) in patients with COVID-19

Sample size	Age (years) and Sex	Medication type	Latency after initiation of the treatment (days)	Specific points about patient or the manuscript:	Outcome	References
1	76 Male	HCQ, azithromycin and ceftriaxone	9	COVID-19 pneumonia led acute respiratory distress syndrome	Patient died due to pulmonary embolism	Delaleu et al. ⁴
1	70 Female	HCQ, lopinavir/ritonavir	13	Patient had erythema multiforme-like lesions	Rash resolved	Robustelli et al. ⁷
1	39 Female	HCQ	18	Authors hypothesized pustular eruptions in COVID-19 patients to be more likely of drug-related origin	Patient died of a massive pulmonary embolism	Litaïem et al. ⁵
1	34 Male	HCQ, azithromycin, oseltamivir, ribavirin, lopinavir, prednisolone, ceftriaxone, clindamycin, interferon (IFN) beta, and ceftazidime	22	Authors could not confirm AGEP to be a late and severe complication of COVID-19 infection. However, AGEP could be a rare adverse effect of HCQ therapy	Rash resolved	Alzahrani et al. ⁸
1	31 Female	HCQ	9	AGEP was resistant to methylprednisolone (60 mg daily), and cyclosporine 4 mg/kg/day was started	Rash resolved	Sánchez-Velázquez et al. ⁹
1	47 Male	HCQ	3	AGEP was treated with topical steroid, moisturizing and antihistamine	Rash resolved	Tosun ¹⁰
1	48 Male	Chloroquine, lopinavir/ritonavir	9	The systemic and topical corticosteroids were prescribed	Rash resolved	Punyaratabandhu et al. ¹¹
1	49 Female	HCQ, Cefditoren, interferon beta, HCQ; azithromycin, ceftriaxone, lopinavir-ritonavir; methylprednisolone and tocilizumab	7	Cefditoren was introduced as a cause for AGEP in this case report; however, initially she received HCQ	Rash resolved	Torres-Navarro et al. ²
1	78 Male	Cefepime	7	Patient was admitted due to septic shock secondary to a Pseudomonas aeruginosa urinary tract infection. COVID-19 was diagnosed on the same day that his fever began and his rash appeared	Rash resolved	Haraszti et al. ¹
1	33 Male	azithromycin	90	Patient had a history of COVID-19 three months before the skin lesions. At that time, he was treated with oral azithromycin	Rash resolved	Ayatollahi et al. ³
12	8 male and 4 female, age range: 54–84 years	HCQ, darunavir, ritonavir, heparin, ceftriaxone, and azithromycin	MD	All these 12 cases were diagnosed in two months, between March 2020 and April 2020	Most of the patients were treated with systemic corticosteroids. Rash resolved	Pezzarossa et al. ¹²

(Continues)

TABLE 1 (Continued)

Sample size	Age (years) and Sex	Medication type	Latency after initiation of the treatment (days)	Specific points about patient or the manuscript:	Outcome	References
1	49 Female	HCQ, azithromycin	11	The AGEP was managed by methylprednisolone, famotidine, and hydroxyzine	Rash resolved	Etaee et al. ⁶
1	73 Female	intravenous ceftriaxone, azithromycin, HCQ, darunavir/cobicistat	25	The AGEP was associated with erosive conjunctival and oral involvement. She received intravenous immunoglobulin therapy	Rash resolved	Stingeni et al. ¹³

Abbreviations: AGEP, acute generalized exanthematous pustulosis; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; MD, missing data.

after COVID-19 infection that was treated with azithromycin. It is unclear whether the AGEP was related to COVID-19 infection and/or azithromycin.³ The onset of AGEP following COVID-19 diagnosis/treatment was ranging from 3 days to 3 months. Two out of 24 cases died due to pulmonary thromboembolism^{4,5}; no one died due to COVID-19 pneumonia alone. One of these two patients developed acute respiratory distress syndrome requiring invasive mechanical ventilation.⁴

In reviewing all cases, we found no reports of AGEP in the setting of COVID-19 in patients who were not receiving drug therapy. It appears that AGEP can be a complication of medications utilized in the treatment of COVID-19, not the infection itself. On the contrary, since both drugs and viral infections are known causes of AGEP, and all 24 patients had both risk factors, it is possible that an interaction between the immune system, viral infection, and medications may account for the development of AGEP. The mechanism may be a transient virus-mediated immune modification and the development of a reversible delayed-type hypersensitivity reaction for drugs.⁶ Accordingly, COVID-19 infection in and of itself may not be a cause of AGEP, although it may be a factor. Future studies should examine the interplay between COVID-19, medications and AGEP.

CONFLICT OF INTEREST

Not declared.

ETHICAL APPROVAL

The authors declare that no ethical approval was needed for this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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