CASE REPORT OLGU SUNUMU

DOI: 10.5336/dermato.2024-107598

Colchicine Treatment in Hydroxychloroquine-Induced Acute Generalized Exanthematous Pustulosis: Treatment Challenge

Hidroksiklorokin ile İndüklenen Kolşisin ile Tedavi Edilen Akut Generalize Ekzantematöz Püstülozis: Tedavi Zorluğu

Esranur ÜNAL[a], Muhammed Burak YÜCEL[b], Ragıp ERTAŞ[c]

[a]Kayseri City Training and Research Hospital, Clinic of Dermatology, Kayseri, Türkiye
[b]Ergani State Hospital, Clinic of Dermatology, Diyarbakır, Türkiye
[c]University of Health Sciences Faculty of Medicine, Kayseri City Hospital, Department of Dermatology, Kayseri, Türkiye

ABSTRACT Acute generalized exanthematous pustulosis is a cutaneous adverse drug reaction characterized by the abrupt onset of non-follicular, sterile pustules on an edamatous erythema. After drug exposure, the reaction usually starts within 48 hours and resolves spontaneously within 15 days. Acute generalised exanthematous pustulosis is most commonly triggered by antibiotics. Hydroxychloroquine-induced acute generalised exanthematous pustulosis is a rare condition and shows different features from the cases of acute generalised exanthematous pustulosis induced by other drugs in the literature. Hydroxychloroquine-induced acute generalised exanthematous pustulosis differs from the classical acute generalised exanthematous pustulosis by having a prolonged latent periodand a extended recovery phase Colchicine should be should be considered as a potential therapeutic option in cases of acute generalised exanthematous pustulosis resistant to classical treatments.

Keywords: Drug reaction; hydroxychloroquine; colchicine

ÖZET Akut jeneralize ekzantematöz püstülozis, eritemli ödemli zeminde, non-foliküler, steril püstüllerin ani oluşumuyla karakterize, kutanöz advers ilaç reaksiyonudur. İlaç maruziyetinden sonra reaksiyon genellikle 48 saat içinde başlar ve 15 gün içerisinde spontan olarak geriler. Akut jeneralize ekzantematöz püstülozis en sık antibiyotikler tarafından tetiklenir. Hidroksiklorokine bağlı akut jeneralize ekzantematöz püstüloz ise nadir görülen bir durumdur ve literatürdeki diğer ilaçların tetiklediği akut jeneralize ekzantematöz püstüloz vakalarından farklı özellikler göstermektedir. Hidroksiklorokin ile indüklenen akut jeneralize ekzantematöz püstülozis uzun latent periyoda sahip olması, iyileşme süresinin uzun olması ile klasik akut jeneralize ekzantematöz püstülozis vakalarından ayrılır. Klasik tedavilere dirençli akut jeneralize ekzantematöz püstülozis vakalarında kolşisin tedavi seçeneği olarak akılda tutulmalıdır.

Anahtar Kelimeler: İlaç reaksiyonu; hidroksiklorokin; kolşisin

Acute generalized exanthematous pustulosis (AGEP) is a cutaneous adverse drug reaction characterized by the abrupt onset of multiple, non-follicular, sterile pustules on an edematous erythema.[1,2] AGEP is usually triggered by antibiotics. AGEP induced by hydroxychloroquine (HCQ) is a rare entity.[2] It is known that AGEP cases due to HCQ have different clinical features due to their late onset and late response to classical treatments.[1,3] Despite this, information in the literature on how to manage this situation is extremely limited. A single case of AGEP, which was induced by HCQ and started on colchicine because it was resistant to systemic steroid therapy, has been reported in the literatüre.[3] Here, we

TO CITE THIS ARTICLE:
Ünal E, Yücel MB, Ertaş R. Colchicine treatment in hydroxychloroquine-induced acute generalized exanthematous pustulosis: Treatment challenge. Turkiye Klinikleri J Dermatol. 2025;35(2):73-6.

Correspondence: Esranur ÜNAL
Kayseri City Training and Research Hospital, Clinic of Dermatology, Kayseri, Türkiye
E-mail: esranur9419unal@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Dermatology.

Received: 16 Dec 2024 ***Received in revised form:*** 06 May 2025 ***Accepted:*** 23 May 2025 ***Available online:*** 07 Jul 2025

present here two cases of AGEP induced by HCQ, resistant to systemic steroid therapy and responding well to colchicine therapy.

CASE REPORTS

CASE 1

A 62-year-old female patient was started HCQ treatment for rheumatoid arthritis. On the 21st day of the HCQ treatment, she developed a rash initially on the neck and ears, which thenspread to the axilla, trunk and extremities. The patient had no fever when the rash occurred. She had no personal or family history of psoriasis. In the dermatological examination, there were pustules on the erythematous plaque on the neck, and pustules on the periphery of the erythematous annular plaques in the anterior legs and trunk and gluteal region, back (Figure 1a, Figure 1b, Figure 1c). In laboratory examination, neutrophilia (87.1%), leukocytosis (12,520/µL; normal 4,500-10,000/µL), and elevated C-reactive protein (CRP) (14.1 mg/L; normal 0-5 mg/L) were detected. A skin biopsy was performed with a preliminary diagnosis of AGEP, pustular psoriasis, subcorneal pustular dermatosis, and Immunoglobulin A (IgA) pemphigus. In the histopathological examination; mild spongiosis, subcorneal pustules, edema in the superficial areas of the dermis, perivascular neutrophils, lymphocyte infiltration and a few eosinophils were detected. The clinical presentation, along with laboratory findings such as neutrophilia, leukocytosis, and elevated CRP, as well as histopathological features including subcorneal pustules, dermal edema, and perivascular neutrophilic infiltration, strongly support the diagnosis of AGEP. Based on clinical and laboratory findings, the patient was diagnosed with AGEP with a score of 6 (probable AGEP) on the European Severe Cutaneous Adverse Reaction Study (EuroSCAR) validation scale. The patient was started on 40 mg/day oral methylprednisolone (Precort® 16 mg tablet, Koçak Farma) and mometasone furoate (Elocon® %0.1 cream, Schering-Plough/MSD) cream. Colchicine (Colchium-Dispert® 0.5 mg, İbrahim Etem-Menarini) (0.5 mg twice daily) was added to the patient's treatment on the 21st day of steroid treatment, as the lesions were resistant. As methylprednisolone was gradually reduced. The skin lesions resolved completely without recurrence 60 days after the onset of the disease, and no recurrence was observed during 1 year of follow-up.

CASE 2

A 23-year-old male patient was initiated HCQ treatment due to urticarial vasculitis,on the 17th day of the treatment, widespread rashes occurred on the body, during which the body temperature was 37.3 degrees.

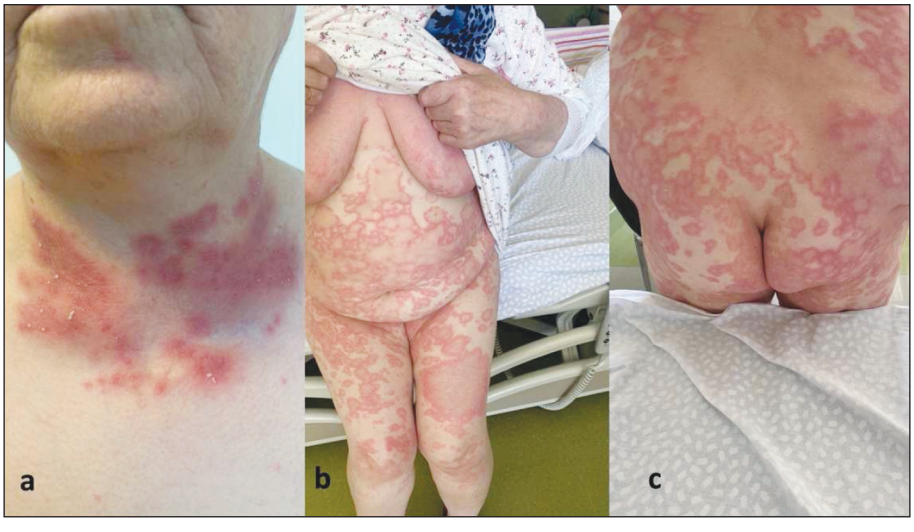

FIGURE 1: a: Pustules in places on the erythematous plaque in the neck, **b:** Anterior of the trunk and legs annular plaques with pustules at the periphery, **c:** Back and gluteal region annular plaques with pustules at the periphery

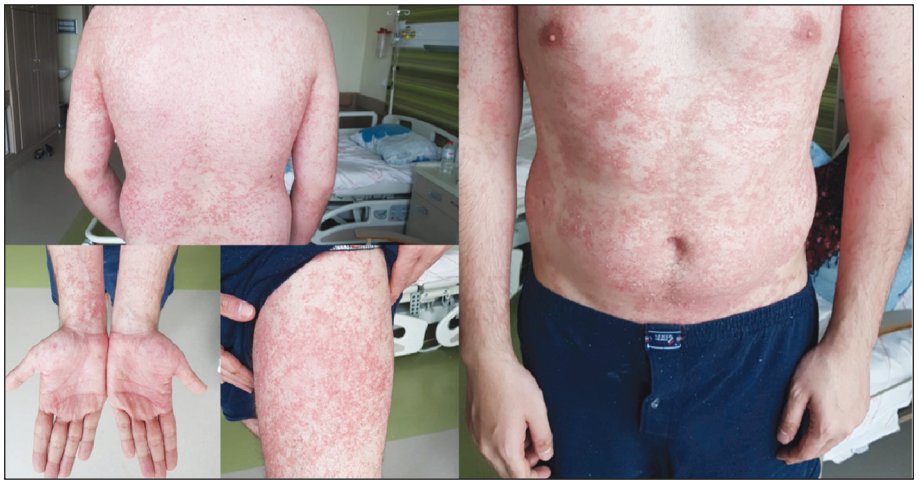

FIGURE 2: Anterior and posterior of the trunk, the gluteal region and the extensor aspect of the right thigh, the hands and forearms annular plaques with pustules at the periphery

He had no personal or family history of psoriasis. Upon dermatological examination, there were pustules on the periphery of erythematous annular plaques on the neck, axilla, front and back of the trunk, extremities and palmar region (Figure 2). In laboratory examination, neutrophilia (82.7%), leukocytosis (20,650/µL; normal 4,500-10,000/µL), elevated CRP (15.8 mg/L; normal 0-5 mg/L), and increased sedimentation rate (41 mm/h; normal 0-15 mm/h) were detected. A skin biopsy was performed with a preliminary diagnosis of AGEP, pustular psoriasis, subcorneal pustular dermatosis, and IgA pemphigus. In the histopathological examination; spongiotic subcorneal pustules, perivascular neutrophils, lymphocytes and eosinophil infiltration were detected. The clinical presentation, along with laboratory findings, strongly suggest AGEP. The histopathological features, including subcorneal pustules with a neutrophilic and eosinophilic infiltrate, further reinforce this diagnosis. Additionally, based on clinical and laboratory findings, a diagnosis of AGEP was made with score of 5 (possible AGEP) on the EuroSCAR validation scale. The patient was started on 60 mg/day oral methylprednisol and clobetasol propionate (Dermovate® %0.05 cream, GlaxoSmithKline) cream. Colchicine (0.5 mg twice a daily) was added to the patient's treatment on the 19th day of steroid treatment, because the existing lesions did not improve and new lesions appeared, and systemic methylprednisolone was gradually reduced. The skin lesions resolved completely without recurrence 40 days after the onset of the disease and no recurrence was observed during 9 months of follow-up. Informed consent was obtained from the patients.

DISCUSSION

Acute generalised exanthematous pustulosis is a rare and serious cutaneous adverse reaction.[1,2] HCQ has been reported as a uncommon cause of AGEP. However, the EuroSCAR study found a higher risk of AGEP in patients treated with HCQ.[1]

In AGEP, the interval between drug exposure and the onset of the reaction is typically 48 hours.[4] AGEP usually resolves spontaneously within 15 days.[1]

Histologic features of AGEP include intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema and neutrophilic and eosinophilic infiltrates. The majority of intraepidermal pustules are located in the upper epidermis, often adjacent to subcorneal pustules. These pustules are typically large and eosinophil-rich. Spongiform changes are observed in both intracorneal and subcorneal pustules, along with spongiosis, neutrophil exocytosis, and necrotic keratinocytes in the epidermis.[4] Our cases also exhibited spongiosis, subcorneal pustules, perivascular neutrophils, and infiltration of lymphocytes and eosinophils in the histopathological examination.

The diagnosis of AGEP relies on clinical and histologic criteria. The AGEP validation score, developed by the EuroSCAR group, is a standardized system based on morphology, clinical course, and histology, classifying suspected cases as definite, probable, possible, or not AGEP.[4]

However, AGEP induced by HCQ exhibits several clinical differences. In HCQ-induced AGEP, the onset time of the reaction typically occurs between 2 and 3 weeks, and the recovery time ranges from 7 to 81 days after discontinuation of HCQ.[2,3] The prolonged duration of symptoms may be attributed to the long half-life of HCQ, which is approximately 40 to 50 days.[3]

The pathogenesis of AGEP remains incompletely understood. The accumulation of cytokines released by T-helper cells and drug-induced antigen-antibody complexes in the skin are responsible for this reaction.[5]

The primary treatment for AGEP involves the cessation of the causative drug. In prolonged cases, topical corticosteroids can be used and in patients with very widespread rash, short-term systemic steroid treatment can be given.[4] In patients resistant to systemic steroid therapy have been reported other treatment option in the form of of case reports. Colchicine is one of these agents. Colchicine is an anti-inflammatory agent used in the treatment of many dermatological diseases with neutrophilic infiltration. It prevents microtubule formation by binding tubulins.[6] A single case of AGEP, which was induced by HCQ and started on colchicine because it was resistant to systemic steroid treatment, has been reported in the literatüre.[3] In our cases, colchicine was added to the treatment regimen to utilise its anti-inflammatory effect on neutrophils, since there was no response to systemic corticosteroid treatment.

HCQ-induced AGEP is a rare condition and has different characteristics from other AGEP's. Compared to classical AGEP, the latent period and recovery period after discontinuation of the drug are longer, creating difficulties for the clinician. Resistance to treatment can also cause confusion. Colchicine should be considered as a treatment option, especially in cases of AGEP resistant to systemic corticosteroid treatment. Further supporting literatüre and more comprehensive studies are needed to better elucidate thepathogenesis and optimize treatment strategies for this condition.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ragıp Ertaş;* ***Design:*** *Esranur Ünal;* ***Control/Supervision:*** *Ragıp Ertaş;* ***Data Collection and/or Processing:*** *Esranur Ünal, Muhammed Burak Yücel;* ***Literature Review:*** *Muhammed Burak Yücel;* ***Writing the Article:*** *Esranur Ünal;* ***Critical Review:*** *Ragıp Ertaş;* ***Materials:*** *Esranur Ünal.*

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