# A MACULOPAPULAR AND PUSTULAR RASH FOLLOWED BY ERYTHEMA MULTIFORME IN A PATIENT TREATED WITH HYDROXYCHLOROQUINE

**Hatice Duman[1], İlteris Oğuz Topal[1], Kübra Cüre[1], Emek Kocatürk[1], Çağlar Çakır[2]**
[1]Okmeydanı Training and Research Hospital, Department of Dermatology, Istanbul
[2]Okmeydanı Training and Research Hospital, Department of Pathology, Istanbul

## ABSTRACT

*Hydroxychloroquine (HCQ) is a synthetic antimalarial drug that has been used widely in the treatment of dermatologic and rheumatologic diseases. Anti-malarials cause many adverse reactions, with ocular, neurological, and cutaneous side effects being the most frequently described. The most common cutaneous adverse reaction is skin pigmentation. Two different clinical patterns in the same patient and erythema multiforme (EM) due to HCQ have rarely been reported. Here, we report a 51-year-old man with rheumatoid arthritis who developed maculopapular and pustular lesions, followed by EM after HCQ treatment.*

***Keywords:*** *Hydroxychloroquine, erythema multiforme, side effect, maculopapular drug eruption.* ***Nobel Med 2016; 12(2): 80-82***

## HİDROKSİKLOROKİN İLE TEDAVİ EDİLEN BİR HASTADA MAKÜLOPAPÜLER VE PÜSTÜLER DÖKÜNTÜ SONRASI ERİTEME MULTİFORME GELİŞİMİ

## ÖZET

Hidroksiklorokin dermatolojik ve romatolojik hastalıkların tedavisinde yaygın olarak kullanılan sentetik antimalaryal bir ilaçtır. Antimalaryaller birçok yan etkiye neden olmaktadırlar; oküler, nörolojik ve kutanöz yan etkiler en sık tanımlanan problemlerdir. En sık görülen kutanöz yan etki ise deri pigmentasyonudur. Aynı hastada hidroksiklorokine bağlı iki farklı klinik patern ve eritema multiforme nadir olarak bildirilmiştir. Burada, hidroksiklorokin tedavisi sonrası makülopapüler, püstüler ve daha sonra da eritema multiforme lezyonları gelişen 51 yaşında romatoid artritli bir hasta sunulmaktadır.

**Anahtar kelimeler:** Hidroksiklorin, eritema multiforme, yan etki, makülopapüler ilaç erüpsiyonu. **Nobel Med 2016; 12(2): 80-82**

## INTRODUCTION

Hydroxychloroquine (HCQ) is a synthetic antimalarial that has been used widely in the treatment of dermatologic and rheumatologic diseases since 1950s due to its immunosuppressive and anti-inflammatory properties.[1] The risks of HCQ treatment are low. Retinal damage and neuromyotoxicity are the most common adverse effects.[2] HCQ-induced cutaneous adverse events have also been reported.[1,3,4] However, HCQ-induced erythema multiforme (EM) combined with two different clinical patterns seen together in the same patient has rarely been reported. We report a patient who developed HCQ-induced maculopapular and pustular lesions and then EM.

## CASE

A 51-year-old man was diagnosed with rheumatoid arthritis one month earlier and was treated with 200 mg/day HCQ and 4 mg/day prednisolone. Twenty-three days after starting the new treatment, he developed a red itchy rash that started on his left foot and then spread to the entire body. The patient had no personal or family history of psoriasis.

On the second day of his rash, he presented with macules, papules, and plaques with erythema accompanied by rare pustules on all extremities and the trunk (Figure 1). Three days after his first symptoms, his maculopapular and pustular lesions evolved into atypical target-like lesions on the trunk and extremities, which spread to the dorsal surface of the hands and palms (Figure 2); there was no mucosal involvement.

The patient had no fever (36.8°C). The hemogram (white blood cell count 9.03x10$^3$/µL, neutrophils 68.9%, eosinophils 4.1%), urine examination, and kidney and liver functions were normal. Anti-cyclic citrullinated peptide was increased and rheumatoid factor, antinuclear antibody, anti-SSA, anti-SSB, and anti-dsDNA were negative. Viral serology for cytomegalovirus, Epstein–Barr virus, rubella, and toxoplasmosis were unremarkable. Bacterial and viral infections were ruled out. A punch biopsy from a pustule revealed orthokeratosis, subcorneal macro- and micro-pustule formation in the epidermis, acanthosis, basal vacuolar degeneration, spongiosis, edema of the papillary dermis, and inflammatory infiltrate on the papillary dermis (Figure 3). The HCQ and oral prednisolone were stopped after the initial presentation of the lesions. The patient was started on intramuscular methylprednisolone 40 mg/day. The next day, the dose was increased to 80 mg/day and administered intravenously; this dose was tapered to 0 mg/day over 2 months. The lesions had resolved completely by the 13$^{th}$ day of treatment, and no new lesions developed during the 7-month follow-up. A patch test with HCQ could not be performed.

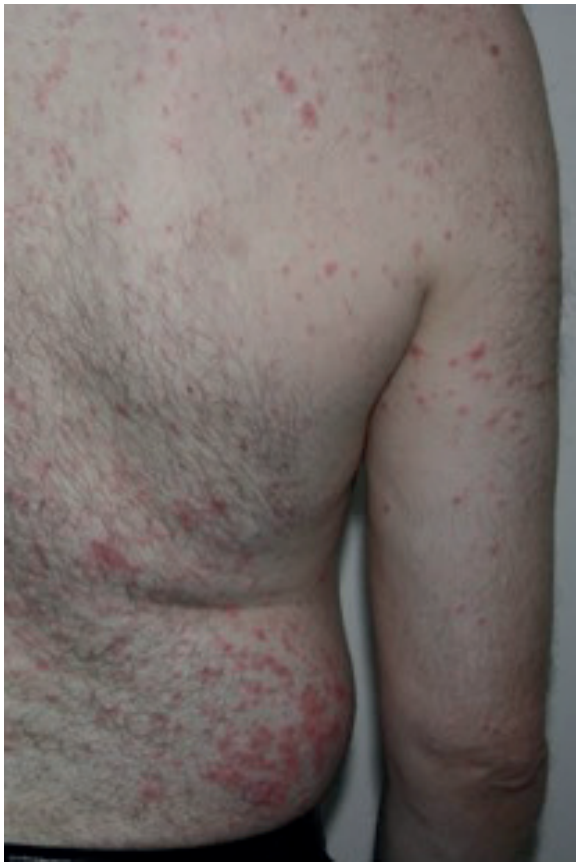

**Figure 1.** Erythematous papules, plaques, macules and pustules on the trunk.

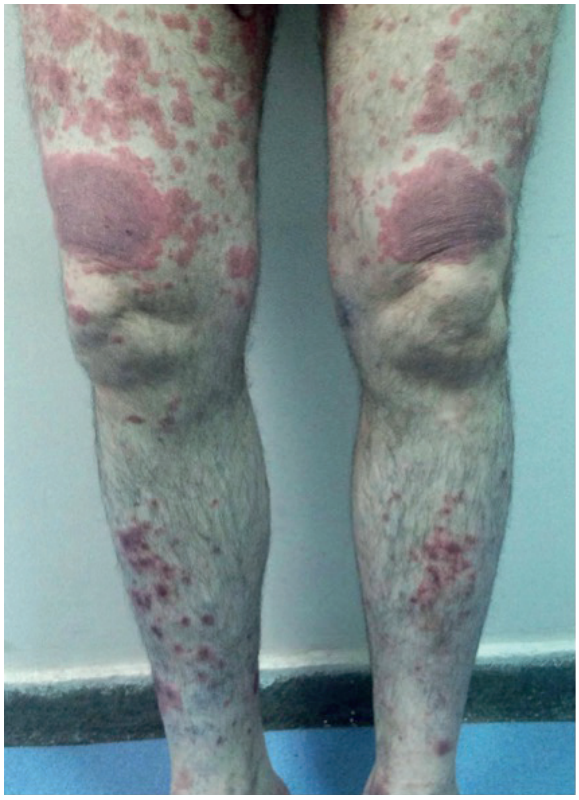

**Figure 2.** Atypical target-like lesions on lower extremities.

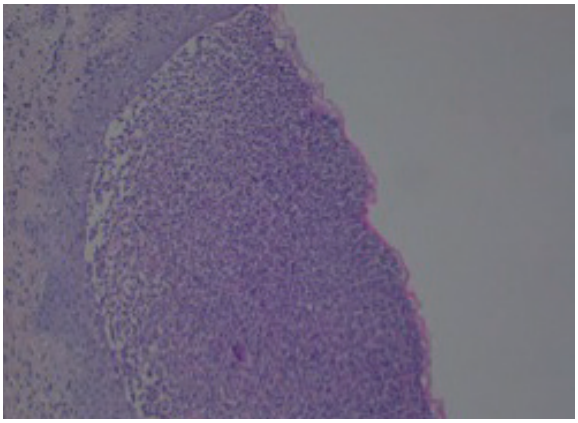

**Figure 3.** Subcorneal pustule formation on the epidermis, basal vacuolar degeneration, spongiosis, edema of the papillary dermis, and superficial perivascular inflammatory infiltrate (haematoxylin & eosin stain x 100).

## DISCUSSION

Cutaneous adverse reactions have been reported with HCQ treatment, such as generalized morbilliform eruptions, erythroderma, drug rash with eosinophilia and systemic symptoms syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).[1,3,4] HCQ-induced EM has rarely been reported. Different types of cutaneous adverse reactions induced by HCQ seen together in the same patient have also been observed. Lateef *et al.* reported a patient who presented with features of AGEP and later developed EM-like lesions and was diagnosed with AGEP-TEN overlap as an adverse reaction to HCQ treatment.[5] Pérez-Ezquerra *et al.* reported a case of two different types of cutaneous eruption induced by HCQ. This patient first presented with EM and subsequently developed a generalized pruriginous erythematous papular exanthema. This was the first case of EM in response to HCQ reported.[6] Leckie and Rees reported four cases of EM associated with HCQ according to the Medicines Control Agency.[7] Our patient had two different clinical eruptions: first maculopapular and pustular lesions, followed by atypical target-like lesions. However, our case had predominantly EM-like lesions. His initial clinical presentation was not typical for AGEP. His pustular lesions were few in number and resolved completely within 3 days. Erythema multiforme is an uncommon, immune-mediated disorder that presents with cutaneous or mucosal lesions or both. It can be triggered by drugs, malignancy, autoimmune disease, radiation, immunization, menstruation, or infections, especially that by herpes simplex virus. Fewer than 10% of cases are reported to be drug-related EM, with nonsteroidal anti-inflammatory drugs, sulfonamides, anti-epileptics, and antibiotics most commonly reported in its etiology.[8]

The skin is one of the most common targets of adverse drug reactions. Immune-mediated or allergic drug reactions comprise 15% of all adverse drug reactions. Type IV reactions can be subclassified into four subtypes based on the clinical, immunohistochemical, and functional heterogeneity of certain drug allergies. Type IVc reactions are related to $CD8^+$ T cells and seem to be predominant in bullous skin reactions, such as SJS and TEN. Clinically, type IVc reactions present as contact dermatitis, maculopapular, pustular and bullous exanthema, and different type IV reactions may occur together.[9] Drug-related EM also involves $CD8^+$ T-cell attack and the expression of tumor necrosis factor alpha, which induces skin infiltration by neutrophils in preference to lymphocytes.[10] These mechanisms may help explain how different clinical presentations appear in the same patient.

## CONCLUSION

Clinicians should keep in mind that HCQ can cause maculopapular, pustular, and EM-like lesions.

*The authors declare that there are no conflicts of interest.

C **CORRESPONDING AUTHOR:** Hatice Duman Okmeydanı Eğitim ve Araştırma Hastanesi, Deri ve Zührevi Hastalıklar Kliniği, Darülaceze Caddesi, Şişli, İstanbul, Türkiye hatice-ergun15@hotmail.com

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