Case Report
Olgu Sunumu

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Drug eruption: A mimicker of Coronavirus disease-2019 rash

İlaç erüpsiyonu: Koronavirüs hastalığı-2019 döküntüsünün bir taklitçisi

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Abstract

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infections can be associated with several cutaneous lesions, among which maculopapular rash is the most common. A maculopapular rash can also be induced by medications used for Coronavirus disease-2019 (COVID-19) treatment. The distinction between viral rash and drug eruption may be difficult especially in case of several medication use for COVID-19. Thus, this study aimed to describe cutaneous manifestations in six patients with COVID-19 and highlight clues for distinguishing SARS-CoV-2-related rash and drug eruption. Between March and June 2020, 1,492 patients were hospitalized for COVID-19 and treated with hydroxychloroquine in Marmara University Hospital. Among them, six cases were consulted for possible COVID-19-related rash or drug reaction. Hydroxychloroquine was given as monotherapy in one patient. All six patients developed an erythematous, symmetrical, and maculopapular eruption that mainly affected the trunk, axilla, and genitocrural region, 5-21 days after the onset of COVID-19 symptoms. Five patients developed rash in 4-11 days after treatment completion. Pruritus was severe. All were treated with topical corticosteroids and oral antihistamines, which provided partial relief. The resolution of the eruption was typically slow, which took a few weeks. A long period between the COVID-19 symptoms and the eruption, as well as slow recovery, is in favor of drug eruption. The effects of co-existent viral infection, a well-known promoting drug eruption factor, in facilitating adverse drug reaction in patients with COVID-19 needs further observations and research.

Keywords: Anti-malarial, COVID-19, cutaneous adverse drug reaction, hydroxychloroquine

Öz

Şiddetli akut solunum yolu sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonu çeşitli kutanöz lezyonlara sebep olabilir. Bunlar içerisinde en sık görüleni makülopapüler döküntüdür. Makülopapüler döküntü, Koronavirüs hastalığı-2019 (COVİD-19) hastalığının tedavisi için kullanılan ilaçlarla da indüklenebilir. COVİD-19 hastalığı için çeşitli ilaçların kullanıldığı durumlarda, viral döküntü ile ilaç erüpsiyonu arasında ayırım yapmak zor olabilir. Bu çalışmanın amacı, COVİD-19 olan altı hastada kutanöz bulguları tanımlamak ve SARS-CoV-2 ile ilişkili döküntü ile ilaç erüpsiyonunu ayırt etmek için ipuçlarını vurgulamaktır. Mart ve Haziran 2020 arasında, Marmara Üniversitesi Hastanesi'ne yatırılarak hidroksiklorokin ile tedavi edilen 1.492 COVİD-19 olgusu içinde, olası COVİD-19 döküntüsü veya ilaç reaksiyonu olan altı tanesi konsülte edildi. Bir hastada hidroksiklorokin monoterapi olarak verilmişti. Altı hastanın tümünde, COVİD-19 semptomlarının başlangıcından 5 ile 21 gün sonra, başlıca gövdeyi, aksillayı ve genitokrural bölgeyi etkileyen, eritematöz, simetrik, makülopapüler bir erüpsiyon gelişmişti. Beş hastada, tedavinin tamamlanmasından 4 ile 11 gün sonra döküntü ortaya çıkmıştı. Kaşıntı şiddetliydi. Hastaların tümü, topikal kortikosteroidler ve oral antihistaminiklerle kısmi düzelme gösterdi. Erüpsiyonun düzelmesi tipik olarak yavaş olup birkaç hafta sürdü. COVİD-19 semptomları ile erüpsiyonun ortaya çıkışı arasındaki zamanın uzun olması ve yavaş düzelme, ilaç erüpsiyonu lehinedir. Eşlik eden viral enfeksiyonun ilaç erüpsiyonu ortaya çıkışını kolaylaştırıcı bir faktör olduğu iyi bilinmektedir. COVİD-19 hastalarında da viral enfeksiyon varlığında ilaç reaksiyonu ortaya çıkışının kolaylaşabileceği konusu, ileri gözlemler ve araştırmalarla gösterilmelidir.

Anahtar Kelimeler: Antimalaryal, COVİD-19, kutanöz ilaç reaksiyonu, hidroksiklorokin

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Introduction

First reported in December 2019 and caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), Coronavirus disease-2019 (COVID-19) has rapidly spread globally and has been declared as a pandemic by the World Health Organization[1]. As of May 2021, over 169,000,000 cases and 3,530,000 fatalities have been reported[2]. There is currently no evidence for any specific anti-COVID-19 treatment. The United States Food and Drug Administration initially granted the emergency use authorization for hydroxychloroquine sulfate (HCQ) and chloroquine phosphate, but this authorization was later revoked, as available scientific data review concluded that known and potential benefits of chloroquine and HCQ no longer outweighed the known and potential risks for the authorized use[3]. HCQ remained for a long time in the Turkish guidelines for the treatment of adult patients with COVID-19 and prophylaxis after exposure; however, its use gradually declined and the final revision of guidelines on May 7, 2021, no longer recommend hydroxychloroquine. Current practice is to start favipiravir monotherapy as soon as COVID-19 diagnosis is confirmed[4].

Patients with COVID-19 frequently receive multiple treatments, especially when they are hospitalized. Drugs can cause a variety of different skin reactions. Of which, the most frequently seen are maculopapular reactions[5] that are triggered by a wide array of medications, including the ones used for COVID-19 treatment. HCQ is an antimalarial drug that is widely used in dermatology, which causes various cutaneous side effects, but these are rare and mostly mild leading to drug discontinuation only in 3% of patients[6]. A recent systematic review revealed that rash, defined as maculopapular, erythematous, and urticarial lesions, was the most common adverse effect[7].

Between March and June 2020, during which HCQ was routinely commenced as a first-line treatment modality, 1,492 patients were hospitalized for COVID-19 and were treated with HCQ in Marmara University Hospital. Among them, six cases were consulted for possible COVID-19-related rash or drug reaction. Both COVID-19 and medications may cause maculopapular rash[8], thus this case presentation aimed to highlight the clues for distinguishing these two entities.

Case Reports

Case 1

A 64-year-old male patient, with hypertension and heart failure, was diagnosed on April 20, 2020, with COVID-19 pneumonia with characteristic clinical and radiological findings and a positive polymerase chain reaction (PCR) test. Following a 5-day course of HCQ and azithromycin, his findings deteriorated, thus admitted to the intensive care unit (ICU). He had a further course of HCQ, which was discontinued on May 6. On May 10, he developed a symmetrical maculopapular rash mainly on the trunk, axilla, and genitocrural fold (Figure 1). Concurrently, blood eosinophils gradually increased from 1.9% to 16.8% and had a sharp decline when the rash started to fade away. Parenteral antihistamine and topical corticosteroid were administered. The rash gradually resolved within 11 days and the patient was finally discharged from the hospital.

Case 2

A 55-year-old male patient, with type 2 diabetes and hypertension, was diagnosed with COVID-19 based on clinical, radiologic, and PCR findings on April 18, 2020, and treated with HCQ, azithromycin, favipiravir, and later with, tocilizumab and convalescent plasma in the ICU. While on supportive care without any new medication, he developed a maculopapular rash on May 5. It was characterized by bright erythematous maculopapular lesions that symmetrically affected the trunk and back with augmentation in the axilla and genitocrural folds, as well as the proximal extremities and face (Figure 2). His peripheral blood eosinophil levels remained within the normal range. Lesions gradually resolved within a week with oral antihistamine therapy. He recovered from COVID-19 and has been externalized.

Case 3

A 62-year-old male patient was diagnosed with COVID 19 pneumonia through clinical, radiologic, and PCR findings on April 16, 2020, and treated with HCQ, azithromycin, and favipiravir for 10 days, followed by tocilizumab and convalescent plasma. He developed a morbilliform symmetrical rash that affected the trunk and flexural regions on May

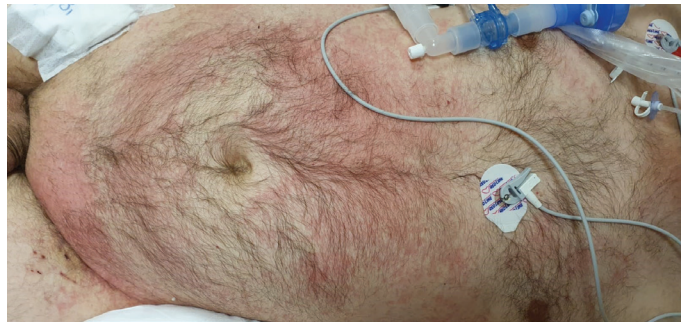

Figure 1. Patient 1. The erythematous rash is composed of macules and papules that mainly affected the trunk

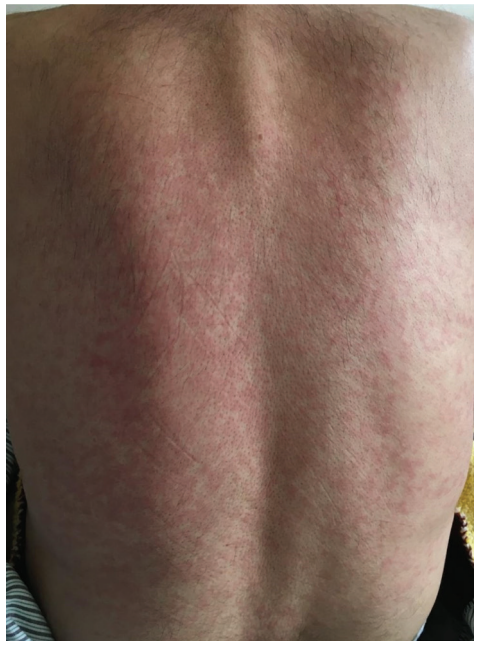

Figure 2. Patient 2. The erythematous rash is composed of macules and papules that mainly affected the trunk

5, 9 days after discontinuing all his medications in the ICU. His blood eosinophils increased up to 12.7% and sharply declined when the rash started to fade. The rash was asymptomatic and gradually resolved in 10 days. He recovered from COVID-19 and has been externalized.

Case 4

A 49-year-old female patient was diagnosed with COVID-19 pneumonia and received HCQ and zinc between April 21 and 28, 2020. She developed an extremely pruritic maculopapular and urticarial rash that affected the legs, arms, and torso on the fifth day of treatment. HCQ was continued for 2 more days. HCQ, clobetasol, and oral antihistamine were discontinued; however, her lesions increasingly worsened within the next 5 days and then gradually resolved within a week with remaining pruritus.

Case 5

A 30-year-old female patient with localized plaque psoriasis was diagnosed with COVID-19 on April 18, 2020. She did not receive antipsoriatic treatment for the last 2 years. HCQ and oseltamivir were prescribed for 5 days. She developed a pruritic maculopapular eruption that mainly affected the trunk and proximal extremities, 11 days after treatment discontinuation. She was treated with oral antihistamine and topical corticosteroid with complete rash resolution after a week. No psoriasis flare was observed.

Case 6

A 61-year-old female patient, with confirmed COVID-19, received HCQ between April 10 and 15, 2020, and enoxaparin between April 18 and 24, 2020. Rash appeared on April 24 and became generalized in 4 days, necessitating a dermatology consultation. Physical examination revealed a bright red symmetrically maculopapular rash that affected the torso and proximal extremities (Figure 3). Antihistamine and topical corticosteroid were commenced and she fully recovered.

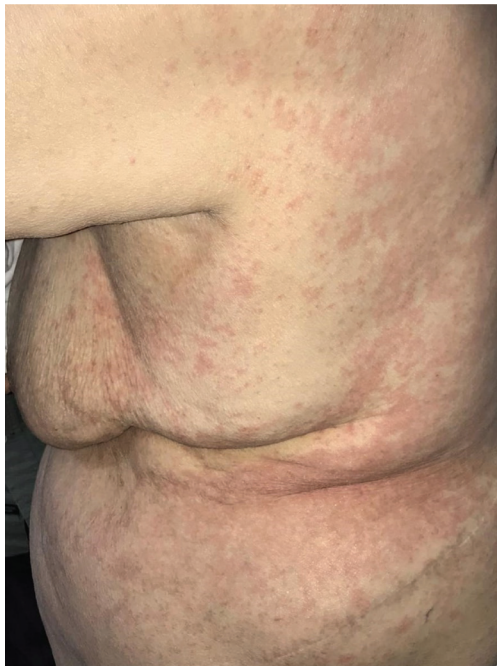

Figure 3. Patient 8. The erythematous rash is composed of macules and papules that mainly affected the trunk

Since it is a retrospective study, patient consent is not obliged. So it was not obtained.

Discussion

Herein, six cases with a maculopapular eruption in the setting of HCQ treatment for COVID-19 are reported. HCQ was given as monotherapy in one of them. The time gap between commencement of HCQ and rash appearance ranged between 5 and 21 days. Furthermore, five patients developed rash in 4-11 days after treatment completion. The eruption was characterized by erythematous, symmetrical, and maculopapular lesions that mainly affected the trunk, axilla, and genitocrural region. Urticarial lesions were also seen. Pruritus was severe. All were treated with topical corticosteroids and/or antihistamines, which provided partial relief. Eruption resolution was typically slow, taking a few weeks.

SARS-CoV-2 infection can be associated with several cutaneous lesions, of which maculopapular rash is the most common. A recent survey of 375 patients from Spain revealed that maculopapular lesions accounted for 47% of all skin manifestations. Maculopapular rash mostly appears at prodrome or simultaneously with COVID-19 symptoms and has a mean duration of 8.6 days. The authors deemed maculopapular lesions as not very useful for COVID-19 diagnosis due to their possible relation to other causes, including drug reactions[8]. Two other large series reported the frequency of rash composed of macules and papules as 9% and 44.3%, respectively[9,10]. The long time gap between COVID-19 symptoms and emergence of eruption, as well as the slow recovery in our patients, help differentiation from viral rash.

Maculopapular drug eruptions mostly appear in 5-7 days after the first drug exposure[11]. Our cases revealed this period as 5-21 days (Table 1). This long latency may be due to the pharmacokinetic properties of medications, possibly HCQ in our cases. After oral administration, HCQ is rapidly absorbed, which generally requires 5-6 weeks for maximum blood concentration, although the loading dose shortens this period[12,13]. HCQ has a very long half-life, approximately 40-60 days, and complete elimination requires >8 months, which may explain slow and gradual rash improvement after drug withdrawal. The long interval between HCQ use and the appearance of the eruption was also underlined in a systematic review on treatment-related mucocutaneous reactions in patients with COVID-19[14]. The most common HCQ-related adverse effects include skin eruptions[15]. A recent systematic review reported maculopapular or urticarial rash in 358 of 689 cases, which appeared within the first 4 weeks and slowly disappeared over weeks[7].

Except for case 4, all patients were under multiple treatments. We were unable to ascertain the causative drug with testing. In addition to in-vitro tests, intradermal, patch, or prick tests can be used to confirm cutaneous adverse drug reaction (CADR)[16,17]. The oral challenge is considered the gold standard but carries the risk of a severe reaction. The data on skin testing reliability is inconclusive in antimalarials. In the largest published series, Soria et al.[18] performed patch and prick tests in 14 of their 20 cases that developed CADR to antimalarials. All of their patients scored over 5 in the Naranjo probability score, indicating a probable link between antimalarial and CADR. Unexpectedly, skin tests remained negative in all of their cases[18].

Table 1. Demographic features of patients and time relationship between COVID-19 diagnosis, medications, and rash

Patient	Age, sex	Co-existing disorders	Medications	Rash beginning-end	Time between COVID-19 symptoms and onset of rash	Time between HCQ discontinuation and onset of rash
1	64, M	HT, CHF, obesity	HCQ (April 20-25, May 1-6) AZIT (April 20-25) FAV (May 1-4) TOCI (May 5-6) PLASMA (May 8)	May 10-21	21 days	4 days
2	55, M	HT, DM, obesity	HCQ (April 20-May 1) AZIT (April 22-27) TOCI (April 26-27) PLASMA (May 2, 4)	May 5-11	16 days	4 days
3	62, M	HT, obesity	HCQ (April 16-25) AZIT (April 16-21) FAV (April 16-21) TOCI (April 20-21) PLASMA (May 2, 4)	May 5-15	20 days	10 days
4	49, F	-	HCQ (April 21-28)	April 25-May 5	5 days	-
5	30, F	Psoriasis	HCQ (April 19-23) OSEL (April 19-23)	May 4-11	16 days	11 days
6	61, F	-	HCQ (April 10-14) ENOX (April 18-28)	April 24-May 1	15 days	10 days

HT: Hypertension, CHF: Congestive heart failure, DM: Diabetes mellitus, HCQ: Hydroxychloroquine, AZIT: Azithromycin, FAV: Favipiravir, TOCI: Tocilizumab, OSEL: Oseltamivir, ENOX: Enoxaparin, COVID-19: Coronavirus disease-2019

Differentiating between viral exanthem and maculopapular drug reactions is challenging. Laboratory tests and histopathology provide little help. Furthermore, an infection may be one of the co-factors that trigger CADR. Concomitant viral infections by human herpes viruses, such as cytomegalovirus, Epstein-Barr virus, human herpesvirus-6, and human immunodeficiency virus, may promote drug sensitization[19]. SARS-CoV-2 as a promoter remains controversial. Cytokine storm characteristic of COVID-19 may facilitate the drug reaction, which is known as a delayed-type hypersensitivity reaction that is mainly mediated through tumor necrosis factor-α and interleukin-12[20,21]. Rash that appeared concomitant with infection-related symptoms and resolution within a short time may be used as clinical clues that favor COVID-19-associated eruption. Among the various clinical patterns of rashes that have been reported in association with COVID-19 to date, acral ischemic and chilblain lesions may be more closely related to the viral infection itself. Additionally, morbilliform, urticarial, erythema multiforme-like and pityriasis rosea-like rashes can be seen in many etiologic factors; therefore, caution before directly linking these symptoms to COVID-19 is essential. Nobari et al.[14] included 25 patients with COVID-19 having drug-related mucocutaneous reactions in their systematic review. Morbilliform and urticarial reactions were the most commonly reported, but others, such as vasculitis, petechiae, targetoid lesions, and pustules, were also seen, the latter was reported to be especially associated with HCQ[14]. The history that is complicated with a viral infection and multiple drugs make the search for the exact cause very difficult and impractical in the clinical setting. This is even more problematic in patients with COVID-19, as we are only recently getting familiar with the disease manifestations, including the skin rashes. Moreover, even with a strong suspicion on the association of the rash with drugs, deciding on drug withdrawal in a patient with COVID-19 is difficult, as many are still unknown, including the benefit-risk ratio of some treatments for these patients.

The major limitation of the current study is the insufficient confirmation of the culprit drug. A maculopapular rash is often nonspecific, thus other diagnoses should be excluded.

Unfortunately, we could not patch/prick test our patients, either due to their prolonged stay in the ICU, constraints because of COVID-19-related travel restrictions, or reluctance of patients to visit the hospital for testing. Additionally, we have a small number of patients. However, we present the reflection of real life in dermatology clinical practice, and our case series draws attention to the possibility of CADR, especially due to HCQ in patients with COVID-19 having a rash. It also provides information on clinical clues, which might help differentiate maculopapular lesions due to SARS-CoV-2 infection or drugs, thereby contributing to the current knowledge.

Ethics

Informed Consent: Since it is a retrospective study, patient consent is not obliged. So it was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.E., İ.E., S.S., E.T.T., Concept: T.E., Design: T.E., Data Collection or Processing: T.E., İ.E., S.S., D.S., E.C.Ö., M.A., Analysis or Interpretation: T.E., D.S., Literature Search: T.E., Writing: T.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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