LETTER
DERMATOLOGY

Generalized exanthema due to hydroxychloroquine during COVID-19 prophylaxis

Hydroxychloroquine (HCQ) is a drug that is used for both chemoprophylaxis and treatment of COVID-19. At the moment, HCQ maintains its popularity and tens of thousands of people across the world are still receiving the current drug.1 After the COVID-19 pandemic, several cutaneous side effects of HCQ are reported.2,7 Herein, we reported generalized exanthema after a single dose of using HCQ. A 58-year-old male patient presented with resistant rashes on his upper extremities and neck region. Rashes appeared all over the body along with severe pruritus just a day after receiving a single 200 mg dose of oral hydroxychloroquine for COVID-19 prophylaxis. The patient had started hydroxychloroquine without any recommendation. He was also receiving pramipexole for restless legs syndrome for 3 years. He presented to our dermatology outpatient clinic 10 days after the beginning of the rashes. When he presented to our clinic, the rashes have begun to disappear except on the neck and arms. Also, there was still mild pruritus in his body. There was no other new drug, over-the-counter drug, nutrient, food supplement, past or active infection history to explain the rash. With these clinical findings, a diagnosis of hydroxychloroquine associated generalized exanthema was made. Because of its characteristic features, we did not perform a histopathologic examination. We searched published articles in PubMed about cutaneous side effects of HCQ during the COVID-19 pandemic between January 1, and July 1, 2020. These side effects can be listed as acute generalized exanthematous pustulosis, urticaria, palmoplantar itching, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, and exacerbation of psoriasis (Table 1).2-7

As we know, there is a dilemma for cutaneous reactions in patients with COVID-19. It is difficult to differentiate whether they appear because of the infection itself or because of the drugs used in the treatment. In this regard, we divided articles which were mentioned above into three categories according to the indications in order to analyze HCQ reactions in the COVID-19 pandemic as follows: "HCQ use for COVID-19 infection," "HCQ use for COVID-19 prophylaxis" and "HCQ use for diseases unrelated to the COVID-19." The duration of treatment and doses of HCQ is different according to the indications. These differences may give some clues for the dilemmas of cutaneous manifestations of COVID-19 is not known exactly. In this context, acute generalized exanthematous pustulosis as in cases 7 and 9 approximately appeared at the same time which may suggest that case 9 was more compatible with a drug reaction rather than a manifestation of COVID-19 (Table 1).5,7 The group of “HCQ use for diseases unrelated to the COVID-19" may show that cutaneous reactions such as AGEP, DRESS, and erythema multiforme may appear with long term HCQ use. Moreover, “HCQ use for COVID-19 prophylaxis" group shows that even low and single doses of HCQ may lead to cutaneous side effects such as urticaria and pruritus. In this report, we first describe a generalized exanthema after using a single low-dose of HCQ during the COVID-19 pandemic. Although the patient had no risk factors for COVID-19, he started 200 mg HCQ per week for 3 weeks on his own. This situation shows the possible effects of unnecessary drug use during the COVID-19 pandemic.

Given the anticipated widespread use of HCQ, we believe that reviewing cutaneous side effects of the HCQ during the COVID-19 pandemic is important especially for the consultations of COVID-19 patients.

DISCLOSURE
The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY STATEMENT
The data of this case are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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Table 1: Cutaneous side effects of Hydroxychloroquine during the COVID-19 pandemic

| No/type of drug reaction | Age/ gender | HCQ treatment doses | Indications | Duration of lesions occurrence | Additional drugs/duration of treatment | References |
|--------------------------|-------------|---------------------|-------------|---------------------------------|----------------------------------------|------------|
| 1/Exacerbation of Psoriasis | 71/W | 800 mg on the first day followed by 400 mg daily for the next days | COVID-19 | 4 day | Oseltamivir/4 days | Kutlu et al² |
| 2/Urticaria with maculopapular rash and palmoplantar itching | 26/W | 800 mg on the first day followed by 400mg weekly for the next weeks | COVID-19 prophylaxis | 2 day after starting the loading dose | None | Sardana et al³ |
| 3/Urticaria | 37/W | | | 7 days after starting the loading dose | | |
| 4/Palmoplantar itching | 22/W | | | 7 days after starting the loading dose | | |
| 5/Urticaria | 26/W | | | One week after 3rd weekly dose | | |
| 6/Drug reaction with urticaria with maculopapular rash and palmoplantar itching | 69/W | 400 mg daily | Lichen planopilaris | 20 days | PPI/3 years | Grandolfo et al⁴ |
| 7/Acute generalized exanthematous pustulosis | 76/M | 400 mg daily | Calcium pyrophosphate dihydrate crystal deposition disease | 18 days | None | Munshi et al⁵ |
| 8/Erythema multiforme | 60/W | 400 mg daily | Arthritis | 19 days | N/A | Koumaki et al⁶ |
| 9/Acute generalized exanthematous pustulosis | 39/W | 600 mg daily | COVID-19 | 18 days | Enoxaparin 18 day | Litaiem et al⁷ |
| 10/Generalized exanthema | 58/M | 200 mg single dose | COVID-19 prophylaxis | 1 day | Pramipexole/3 years | Current article |

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; HCQ, hydroxychloroquine; M, man; N/A, not applicable; PPI, proton pump inhibitor; W, woman.

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