Hydroxychloroquine-Induced Stevens-Johnson Syndrome in COVID-19: A rare Case Report

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Case Report

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Abstract

Background: The international outbreak of respiratory illness termed coronavirus disease 2019 (COVID-19) began in December 2019 that has affected more than 0.8 million individuals. To date, there are no specific therapeutic agents for coronavirus infections. One of the drugs that have an effective role in improving the condition of patients with COVID-19 is hydroxychloroquine (HCQ). This drug is not a definitive treatment for this disease and has a supportive role. Like all medications, HCQ has side effects and may occur in COVID-19 patients. Stevens-Johnson syndrome caused by HCQ is very rare.

Case presentation: A 42-year-old woman, presented with fever and dry cough in the past two days to her family physician. Lab tests revealed elevated lactate dehydrogenase (LDH, 648 units/liter (U/L)), C-reactive protein level (CRP, 52 milligrams/Liter (mg/L), normal: <10 mg/L), aspartate aminotransferase (AST, 59 U/L, normal: 10-40 U/L), thrombocytopenia, and leukopenia. Mild bilateral patchy ground-glass opacity was seen in lung CT-Scan. Due to COVID-19 pandemic and clinical findings, the nasopharyngeal swab test was done and SARS-CoV-2 nucleic acid was detected by RT-PCR. HCQ 200 mg twice daily was started. After two days, the patient presented with a pruritic erythematous maculopapular rash and flat atypical targets that started from the distal of upper extremities and rapidly, involved the entire body, and torn blisters which were only be seen as ulcers on orolabial area. The Nikolsky sign was positive. Due to the likelihood of a drug reaction, HCQ was discontinued, and COVID-19 treatment was changed to lopinavir/ritonavir (LPV/RTV) 400 mg twice daily. Finally, she was discharged after five days with nonpruritic scalded skin on the distal of upper extremities.

Conclusions: It is worth noting that although HCQ appears to be safe and has mild side effects, however, the boundary between therapeutic and toxic doses is narrow and severe disorders of their use can life-threatening. One of the side effects of HCQ is SJS caused by the drug, and given the worldwide pandemic of COVID-19 and the increasing need for this drug, we need to be careful about its use in order to control and manage the side effects of this drug.

Background

The international outbreak of respiratory illness termed coronavirus disease 2019 (COVID-19) began in December 2019 and has affected more than 0.8 million individuals and has been leaded to 40598 deaths until 1st April 2020 (1). The disease is highly contagious, with the pandemic reported in the 51st WHO Status Report on 11 March 2020 (2). Self-limiting respiratory tract involvement, severe pneumonia, multiorgan failure, and death are the spectrum of COVID-19. To date, there are no specific therapeutic agents for coronavirus infections. One such medication that has an effective role in improving the condition of patients with COVID-19 includes the antimalarial hydroxychloroquine (HCQ), which recently reported as a supportive drug (not known as a definitive treatment for the disease) for shortening the duration of COVID-19 symptoms, reducing inflammatory reactions to infection, impairing exacerbation of pneumonia, and boosting lung imaging findings (3). Like all medications, HCQ has side effects and may occur in COVID-19 patients. Despite its positive effect, its side effects should be taken into consideration

and replaced with other effective medications if possible. We decided to report a case of the HCQ side effects and the appropriate management to it.

Case presentation

A 42-year-old woman, presented with fever and dry cough in the past two days to her family physician. She had a history of contacting someone with similar symptoms and no underlying problems. No abnormality was found in the physical examination, her temperature was 38 ºC and other vital signs were normal. Oxygen saturation was 98%. Imaging and laboratory tests were requested. Lab tests revealed elevated lactate dehydrogenase (LDH, 648 units/liter (U/L), normal: 140-280 U/L), C-reactive protein level (CRP, 52 milligrams/Liter (mg/L), normal: <10 mg/L), aspartate aminotransferase (AST, 59 U/L, normal: 10-40 U/L), thrombocytopenia, and leukopenia (white blood cells=2600/microliter, 31% lymphocyte cells). Serology for rheumatoid factor, antinuclear factor, anti-DNA, anti-smooth muscle, and antimitochondrial antibodies were negative as well as HBsAg and anti-HCV antibodies. Mild bilateral patchy ground-glass opacification/opacity was seen in lung CT-Scan (Figure 1). Due to COVID-19 pandemic and clinical findings, the nasopharyngeal swab test was done and SARS-CoV-2 nucleic acid was detected by RT-PCR. HCQ 200 mg twice daily was started and 500 mg of acetaminophen every 6 hours. After two days, the patient presented with a pruritic erythematous maculopapular rash and flat atypical targets that started from the distal of upper extremities (Figure 2) and rapidly, involved the entire body, and torn blisters which were only be seen as ulcers on orolabial area (Figure 3). She had genital mucosal involvement but did not allow us to take pictures. The Nikolsky sign was positive (figure 4). Finally, a diagnosis of Stevens-Johnson syndrome due to HCQ was made.

Due to the likelihood of a drug reaction, HCQ was discontinued, and COVID-19 treatment was changed to lopinavir/ritonavir (LPV/RTV) 400 mg twice daily in the hospital. Loratadine 10 mg twice daily and Diphenhydramine 50 mg three times daily. She was discharged after five days with nonpruritic scalded skin on the distal of upper extremities (Figure 4).

Discussion And Conclusions

COVID-19 is an emerging disease that currently has no specific treatment and the treatments are purely supportive. CQ and its derivatives, such as HCQ, have a long history of being used as prophylactic drugs in malaria areas. In some studies, HCQ has been used to improve the symptoms of patients with COVID-19. This drug is used to support patients with COVID-19 and is not known as a definitive treatment for the disease (3, 4). The mechanism of action of CQ and its derivatives is to affect intracellular components such as endosomes, lysosomes and Golgi vesicles and to increase their pH, which interferes with the steps of virus replication including fusion and uncoating (5). HCQ has few side effects. The most common HCQ usage complications are headache, dizziness, gastrointestinal complications such as vomiting and diarrhea. Some studies of COVID-19 patients have reported complications such as gastrointestinal distress, headache, blurred vision, insomnia, and prolonged QT interval (3, 6) which were different from our study. In our case, erythema multiforme with maculopapular rash and flat atypical

targets were seen in the distal part of the limb. The skin complications caused by HCQ use are infrequent. These include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and rashes. HCQ is a very rare cause of drug-induced Steven-Johnson syndrome. This condition begins as itchy papular erythematous eruptions in the trunk and then affects the face, organs, and mucous membranes of the mouth. It also had purulent rashes on the trunk, limbs, and face (7). In a study by Volpe et al., A patient with rheumatoid arthritis after taking hydroxychloroquine developed diffuse, erythematous-exfoliative rash involving trunk and limbs which diagnosed as a drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (8). In a study by Leckie et al., After taking HCQ, the patient developed skin symptoms of SJS such as a pruritic rash over her abdomen, which described as 'targets' with a persisting exfoliating rash and eczematous patches (9).

Numerous studies have shown that the use of HCQ in some people with COVID-19 causes gastrointestinal symptoms and heart problems, (3, 6) but so far there have been no reports that taking HCQ leads to the symptoms of Steven-Johnson syndrome, which develops skin rashes in different parts of the body, especially in the oropharynx. Skin manifestations of COVID-19 disease included erythematous rash, urticaria, and chickenpox-like vesicles. The trunk of the body was the main area of skin involvement. The itching was mild or absent (10). However, our patient did not show any of the skin symptoms associated with COVID-19 at the time of the examination, and two days after receiving HCQ, she showed symptoms of SJS caused by HCQ. Also, Nikolsky sign and flat atypical targets, which are important symptoms in the diagnosis and differentiation of SJS, were seen in our patient (figure 2 & 4), which differ from skin problems caused by COVID-19.

Given that it has been shown to be effective in treating COVID-19 patients, (3, 6) we should be concerned about these complications and obtain comprehensive information on patient management. The pharmacokinetic properties of HCQ is complex. The side effects of taking this drug occur when it is not sufficiently dispersed through the relatively small central portion. Therefore, the amount of drug entering the central part is an important factor in causing skin reactions (5).

It is worth noting that although HCQ appears to be safe and has mild side effects, however, the boundary between therapeutic and toxic doses is narrow and severe disorders of their use can life-threatening. One of the side effects of HCQ is SJS caused by the drug, and given the worldwide pandemic of COVID-19 and the increasing need for this drug, we need to be careful about its use in order to control and manage the side effects of this drug.

Abbreviations

HCQ: hydroxychlroquine; WHO: World Health Organization; COVID-19: Coronavirus disease 2019; LDH: lactate dehydrogenase; CRP: C- reactive protein; AST: aspartate aminotransferase; U/L: units/liter; mg/L: milligrams/liter; HBsAg: Hepatitis B surface antigen; HCV: hepatitis C virus; RT-PCR: Real Time - Polymerase Chain Reaction; LPV/RTV: lopinavir/ritonavir; SARS-Cov-2: severe acute respiratory syndrome

coronavirus 2; DRESS: drug rash with eosinophilia and systemic symptoms syndrome; CQ: chlroquine; AGEP: acute generalized exanthematous pustulosis; SJS: Stevens-Johnson syndrome;

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for the publication of this case report as well as accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for publication

Informed written consent for publication was obtained from the patient prior to collecting information. The patient gave written consent for their personal or clinical details along with any identifying images to be published in this study.

Availability of data and materials

The datasets generated and/or analyzed during the current study may be made available from the corresponding author on a reasonable request.

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Competing interests

The authors declare that they have no competing interests.

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Author's contributions

AR, HJ and AK analyzed the data and was a major contributor in writing the manuscript. ES and ZA performed the diagnostic tests. HJ and LD collected the clinical data. AR designed the case report and was responsible for communicating the work. All authors read and approved the final manuscript.

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Figures

Figure 1

Chest CT showed Mild bilateral patchy GGO

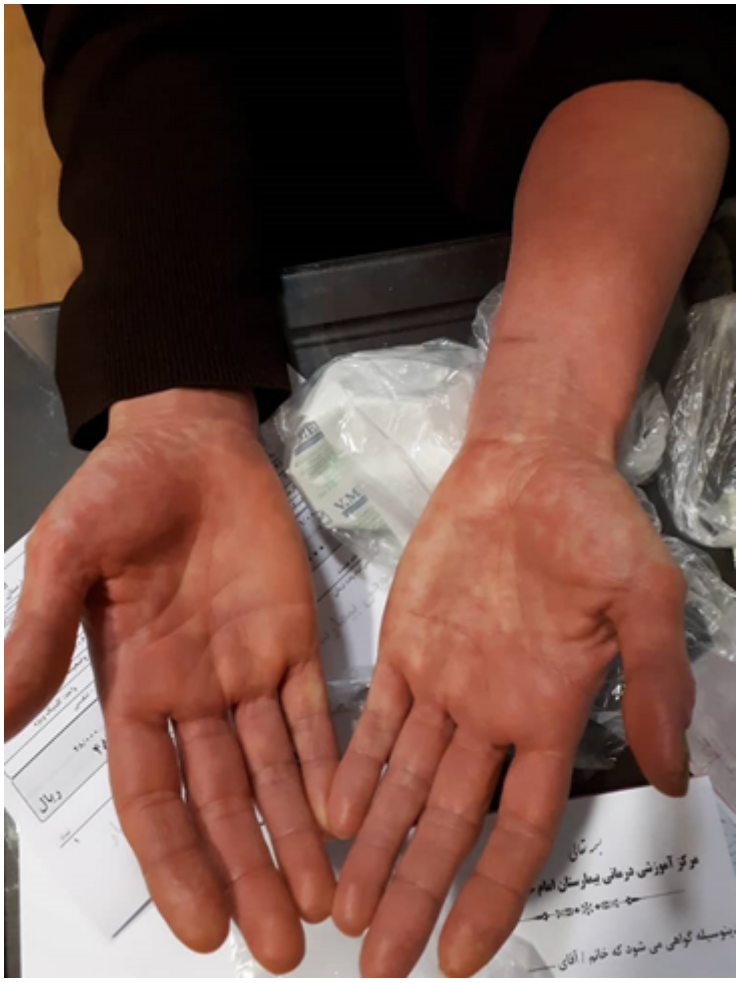

Figure 2

Pruritic erythematous maculopapular rash on the distal extremities due to CQ consumption

Figure 3

Small blisters on orolabial area

Figure 4

Nonpruritic scalded skin