To the Editor,

Although there have been inconsistent publications on the activity and safety of hydroxychloroquine (HQ), it is recommended by several treatment guidelines to be used in all patients with symptomatic COVID-19 disease. There were several concerns regarding the treatment-related side effects. The most important side effects include QT prolongation and visual-field defects.

A 65-year-old male with chronic obstructive pulmonary disease was admitted to the hospital with the complaints of cough, chest and back pain. Physical examination was unremarkable. Computerized tomography and angiography of chest revealed bilateral emphysematous changes. There was not any finding suggesting venous thromboembolism. Laboratory finding were as follows: hemoglobin (Hb), 14.4 g/dl; mean corpuscular volume (MCV), 96.4 fL; lymphocyte count (lymph), 3070/µL; platelet count (PLT), 150,000/µL; prothrombin time 14 sec, and INR 1.0. Patient had no fever or shortness of breath. There was no previous history of travel abroad and close-contact with anyone who was SARS-CoV-2 positive. Nasal swap was obtained for SARS-CoV-2 polymerase chain reaction (PCR). In outpatient setting, HQ was started without waiting for the test results.

He was reevaluated on the third day of the treatment. There was no improvement in his complaints. SARS-CoV-2 PCR test result was negative. Laboratory results at his second admission were as

Hydroxychloroquine-associated Thrombotic Thrombocytopenic Purpura

Fatma Arıkan¹, Yasin Yıldız², Tarık Ercan¹, Ozen Oruc¹, Seçkin Akçay³, Fergun Yılmaz¹, Tayfur Toptaş¹, Tülin Tuğlular¹

¹Marmara University Faculty of Medicine, Department of Hematology, İstanbul, Turkey
²Marmara University Hospital Clinic of Internal Medicine, İstanbul, Turkey
³Ümraniye Training and Research Hospital, Clinic of Endocrinology, İstanbul, Turkey

Fatma Arıkan, Marmara University Faculty of Medicine, Department of Hematology, İstanbul, Turkey
+90 505 920 2417
fatma-gecgel@hotmail.com

June 10, 2020
July 23, 2020

To the Editor,

Although there have been inconsistent publications on the activity and safety of hydroxychloroquine (HQ), it is recommended by several treatment guidelines to be used in all patients with symptomatic COVID-19 disease. There were several concerns regarding the treatment-related side effects. The most important side effects include QT prolongation and visual-field defects.

A 65-year-old male with chronic obstructive pulmonary disease was admitted to the hospital with the complaints of cough, chest and back pain. Physical examination was unremarkable. Computerized tomography and angiography of chest revealed bilateral emphysematous changes. There was not any finding suggesting venous thromboembolism. Laboratory finding were as follows: hemoglobin (Hb), 14.4 g/dl; mean corpuscular volume (MCV), 96.4 fL; lymphocyte count (lymph), 3070/µL; platelet count (PLT), 150,000/µL; prothrombin time 14 sec, and INR 1.0. Patient had no fever or shortness of breath. There was no previous history of travel abroad and close-contact with anyone who was SARS-CoV-2 positive. Nasal swap was obtained for SARS-CoV-2 polymerase chain reaction (PCR). In outpatient setting, HQ was started without waiting for the test results.

He was reevaluated on the third day of the treatment. There was no improvement in his complaints. SARS-CoV-2 PCR test result was negative. Laboratory results at his second admission were as
follows: Hgb, 10.8 g/dL; PLT, 31,000/µL; lactate dehydrogenase (LDH), 1281 U/L (upper limit of normal: <248 U/L); and creatinine 1.7 g/dL (upper limit of normal: <1.2 mg/dL). The patient had aphasia. Cranial computerized tomography was consistent with the infarction of medial cerebral artery. He was hospitalized with the suspicion of thrombotic thrombocytopenic purpura (TTP). Direct coombs was negative. There was 10% schistocytes in peripheral blood smear. Disseminated intravascular coagulation has been ruled out. PLASMIC score was 6, which was indicating high probability of TTP [1].

After blood sample was taken for ADAMTS13 analyses, HQ was ceased and exchange plasmapheresis with 1.5 volumes was started. Methylprednisolone 1 mg/kg/day and folic acid supplementation was commenced. ADAMTS13 level, ADAMTS13 activity and ADAMTS13 inhibitor levels were <0.012 (0.19-0.81) IU/ml, <0.2 (40-100%), 90 (12) U/mL, respectively. On the fourth day of his admission, thrombocytopenia was improved and LDH level returned to normal ranges. On day 7, plasmapheresis was discontinued.

Acute immune reactions or dose-dependent toxicity play important role in drug-related TTP etiology. The most common drug, which is known to be related with TTP, is quinine [2]. Quinine-dependent antibodies have been shown to induce TTP through immune-mediated mechanisms by interacting with platelets and other cells. HQ belongs to the 4-aminoquinoline class and is an amine acidotropic form of quinine. There are two case reports of possible HQ-related TTP in the literature. A 64-year-old-female with rheumatoid arthritis developed TTP after 3 doses of HQ [3] and a 34-year-old woman with a diagnosis of systemic lupus erythematosus (SLE) had TTP under HQ [4]. However, in the latter, HQ and TTP relation was suspicious. Our case is the third case of possible HQ-related TTP in the literature. Adverse drug reaction probability score was calculated as 4 and the adverse drug reaction is assigned to “possible” category [5] (Table 1). It may be taken into consideration that TTP may be among the rare side effects in the treatment of HQ.

Keywords: Hydroxychloroquine; Thrombotic thrombocytopenic purpura; Severe acute respiratory syndrome-related coronavirus

Anahtar Sözcükler: Hidroksiklorokin; Trombotik trombositopenik purpura; Ağır akut solunum sendromu ilişkili koronavirüs

Conflict of Interest: We confirm that there are no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the patient

Authorship Contributions: Data Collection or Processing: FA, YY, SA, OO, TE; Literature Search: FA, FY, TT, TT; Writing: FA, FY, TT

Conflict of Interest: We confirm that there are no conflicts of interest to declare.

References

<table>
<thead>
<tr>
<th>Table 1. Adverse Drug Reaction Probability Scale (Naranjo Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
</tr>
<tr>
<td>Are there previous conclusive reports of this reaction?</td>
</tr>
<tr>
<td>Did the adverse event appear after the drug was given?</td>
</tr>
<tr>
<td>Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?</td>
</tr>
<tr>
<td>Did the adverse reaction reappear upon re-administering the drug?</td>
</tr>
<tr>
<td>Were there other possible causes for the reaction?</td>
</tr>
<tr>
<td>Did the adverse reaction reappear upon administration of placebo?</td>
</tr>
<tr>
<td>Was the drug detected in the blood or other fluids in toxic concentrations?</td>
</tr>
<tr>
<td>Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the drug or a related agent in the past?</td>
</tr>
<tr>
<td>Was the adverse event confirmed by any other objective evidence?</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Drug probability category according to Naranjo scores: definite, >8; probable, 5 to 8; possible, 1 to 4; doubtful, <1.