Ref: Ro J Rheumatol. 2022;31(4)
DOI: 10.37897/RJR.2022.4.1

Prolongation of the QT interval under treatment with hydroxychloroquine in a patient with systemic lupus erythematosus: A case report

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ABSTRACT

Hydroxychloroquine (HCQ) is an antimalarial used in the treatment of patients with systemic lupus erythematosus (SLE). HCQ has a good safety profile and favorable results in terms of controlling clinical manifestations in SLE. In addition to known side effects such as retinal toxicity and neuromusculopathy, prolongation of the QT interval is mentioned in multiple studies. The QT interval can be prolonged due to comorbidities, medication or dyselectrolytemia. QT corrected interval (QTc) durations greater than 470ms for women and greater than 450 ms for men are prolonged according to the European Medicines Agency (EMA). QTc interval duration greater than 500 ms predisposes to Torsades des Pointes (TdP), a cause of sudden death. The aim of the present work was to present a case of a SLE patient who was treated with HCQ for over 20 years and who showed a prolongation of the QT interval on the electrocardiogram (ECG).

Keywords: hydroxychloroquine, lupus, SLE, QT interval

INTRODUCTION

Hydroxychloroquine (HCQ), an antimalarial, is a disease-modifying anti-rheumatic drug (DMARD) that is currently one of the most commonly used drugs used in systemic lupus erythematosus (SLE), demonstrating a good safety profile [1]. In addition to the modulatory effect on the immune system, HCQ has shown positive effects on hyperlipidemia and hyperglycemia, and has antithrombotic properties, reducing cardiovascular risk [1-6].

Along with retinal toxicity and neuromyopathy, cases of cardiotoxicity are also documented under HCQ [2]. The first such case was reported in 1971. Manifestations include bundle branch block, atrioventricular block, QT prolongation. The mechanism by which HCQ may prolong the QT interval is by blocking KCNH2-encoded human ether-a-go-go related gene (hERG) hERG/Kv11.1 potassium channel [3]. Multiple studies have shown that one of the causes of QT prolongation can be HCQ treatment [1,7-9].

The QT interval is measured on the in electrocardiography (ECG) in milliseconds (ms) from the beginning of the QRS complex to the end of the T wave. Because the QT-interval can vary depending on heart rate, there are different formulas (Bazett, Fridericia, Framingham, Hodges, Rautaharju) by which the corrected QT is calculated. QTc interval durations greater than 470ms for women and greater than 450ms for men are considered to be prolonged according to the European Medicines Agency (EMA). QTc interval duration greater than 500ms predisposes to Torsades de Pointes (TdP), which can be a cause of sudden death [6]. TdP is a form of ventricular tachycardia that involves characteristic twisting around the isoelectric baseline every 5–20 beats and a heart rate greater than 100 beats per minute [5]. There are other classes of drugs that can prolong the QT-interval: antiarrhythmics (Class Ia, Class III), antidepressants (fluoxetine, amitriptyline, desipramine), antipsychotics (haloperidol, ziprasidone), antibiotics (quinolone, macrolides), diuretics [7]. Vandael et al. compiled a list of risk factors that predispose patients to prolongation of the QT-interval. The most important risk

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Article History:
Received: 26 December 2022
Accepted: 30 December 2022

factors are age, female gender, smoking, hypertension, other cardiac arrhythmias, thyroid disorders, as well as hypokalemia [6].

The aim of the present work was to present the case of a female SLE patient with QT prolongation under HCQ treatment.

CASE REPORT

We report the case of a 41-year-old female patient diagnosed with SLE 25 years ago. The disease began with clinical manifestations (symmetrical arthritis in the small joints of the hands, malar rash, significant weight loss), immunological changes such as positive anti-dsDNA (double stranded DNA) and ANA (antinuclear antibodies), neurological manifestations, and hematological involvement (bicytopenia). The patient's personal history also revealed pulmonary tuberculosis (23 years ago, for which she received treatment), pulmonary fibrosis, severe secondary pulmonary arterial hypertension, chronic venous insufficiency of the lower limbs (Class 4 CEAP), and a history of pulmonary thromboembolism.

During the evolution of the disease, the patient underwent several forms of treatment for SLE (glucocorticoids, azathioprine, cyclophosphamide, HCQ). She started HCQ treatment 25 years ago (daily, either 200 mg or 400 mg HCQ). Nine years ago, she was included in a phase 3 study with Epratuzumab for a year, without any notable adverse effects. She was started on Belimumab 10 mg/kg every 4 weeks (ongoing treatment for the last 3 years), in association with HCQ 400 mg/day and Methylprednisolone 4 mg every 2 days.

During one of the evaluations in the Rheumatology department, the patient complained of heart palpitations. She was directed to the Internal Medicine service, where she was evaluated.

The clinical examination revealed rhythmic heart sounds, tachycardia (101/min), absence of heart murmurs, excess weight (body mass index = 28 kg/m^2). The renal, hepatic and thyroid function were within normal limits. Also, the patient presented a normal level of blood ions (sodium, potassium). The immunological analysis showed the presence of anti-dsDNA antibodies, anti-Ro antibodies, and anti-chromatin antibodies.

Echocardiographically, the patient presented a right ventricle-right atrium gradient of 65 mmHg, a systolic pulmonary arterial pressure of 70 mmHg, Ejection Fraction=57%, Mitral regurgitation grade I, Tricuspid regurgitation grade III.

The patient's ECG showed sinus rhythm, heart rate of 80/min, intermediate QRS axis and an QTc interval = 508 ms, calculated using the Bazett formula (Figure 1).

Anticoagulant treatment (Acenocoumarol depending on the values of INR - international normalized ratio), Diosmin 1000 mg per day and Ivabradine 5 mg twice a day was recommended to the patient, with the maintenance of the therapeutic recommendations made by the treating rheumatologist. It was also recommended that the patient return to the Internal Medicine service in 3 months for investigations.

Three months later, the patient returned to the Internal Medicine service. The physical, biological and echocardiographic examination revealed a station-

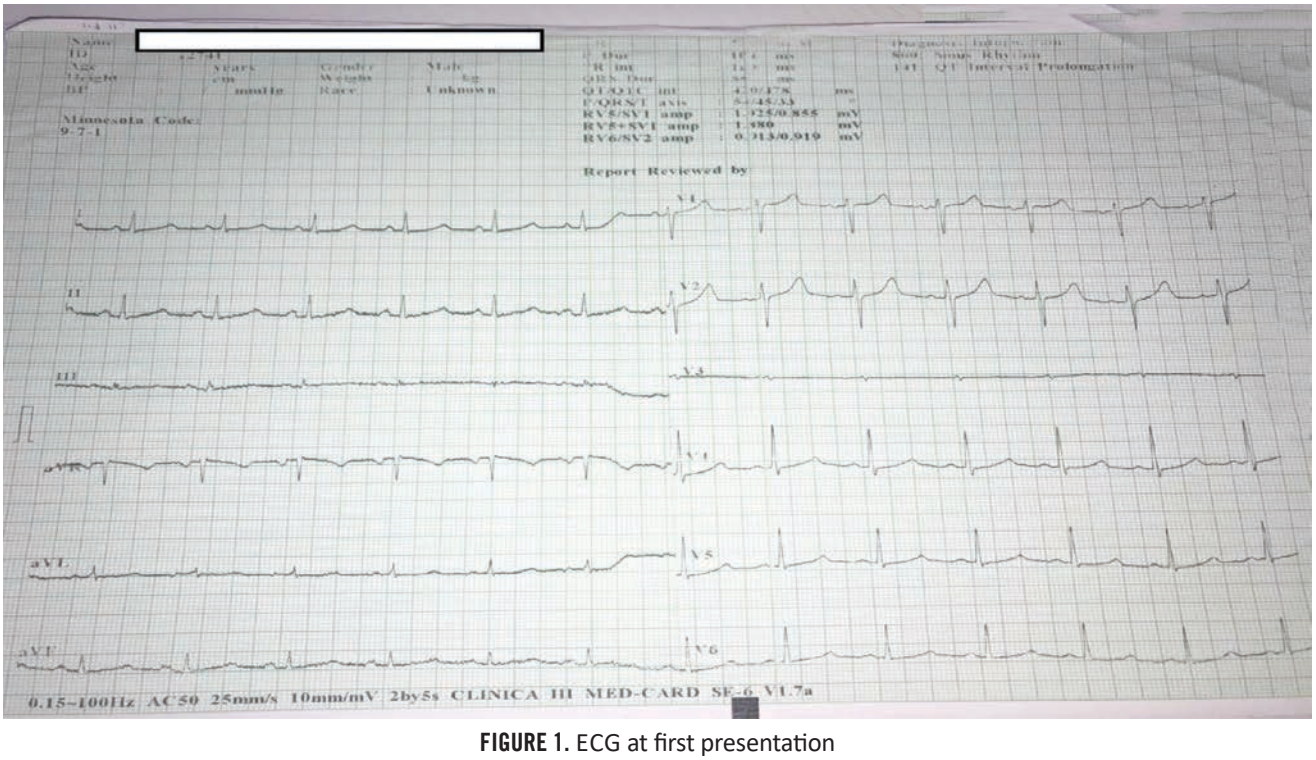

FIGURE 1. ECG at first presentation

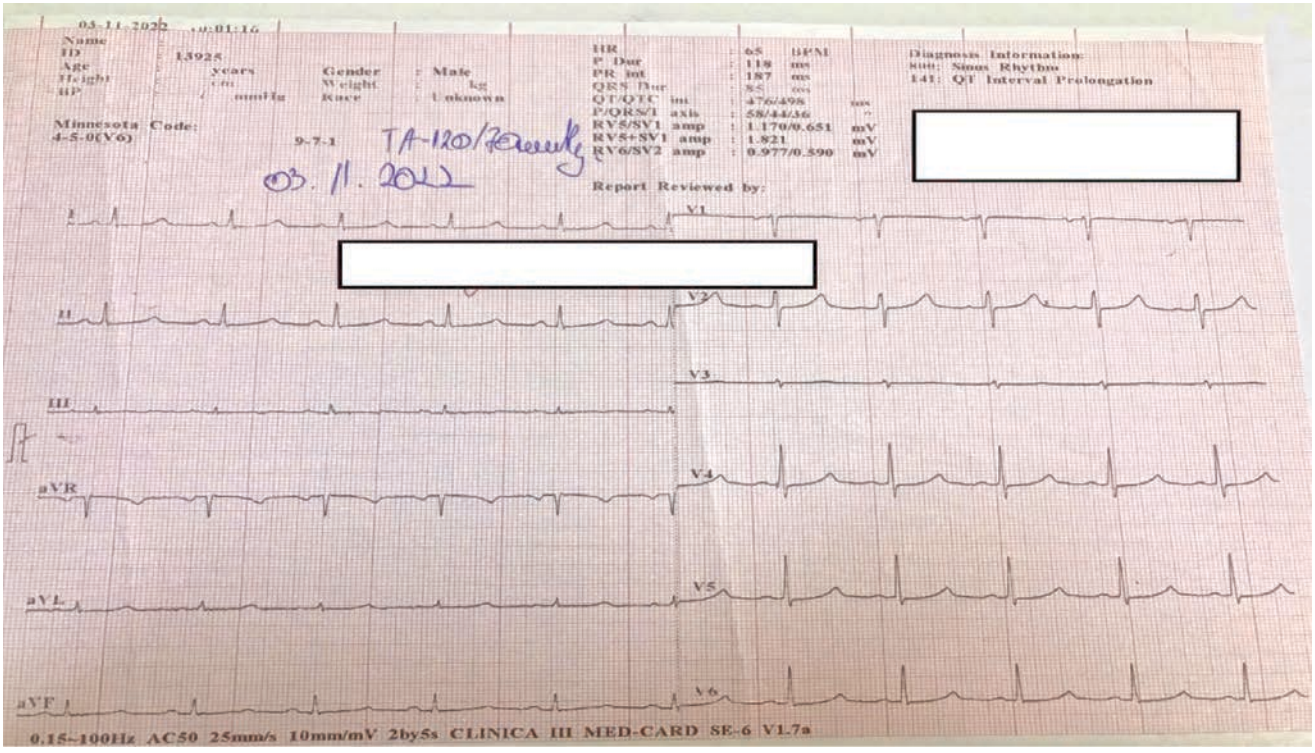

FIGURE 2. ECG at the second presentation

ary aspect compared to the previous evaluation (including normal potassium levels). The ECG showed a prolongation of the QTc-interval to 520 ms (Figure 2). At that moment, after consulting with the treating rheumatologist, it was decided to stop the treatment with HCQ and re-evaluate in 3 months.

After another 3 months, the patient returned to the Internal Medicine service. Again, the clinical, biological (including kalemia), and echocardiographic examinations were stationary compared to the previous evaluations. The patient's ECG showed a prolongation of the QTc interval of 480 ms (Figure 3).

We mention that during the period in which HCQ administration was stopped, the patient did not register any disease flare and was not started on new medication. The recommendation was that HCQ should not be reintroduced, and the patient should return for evaluation in another 3 months.

DISCUSSION

The prolongation of the QT interval has been associated with various risk factors: certain drugs, comorbidities, hydroelectrolytic imbalances, obesity,

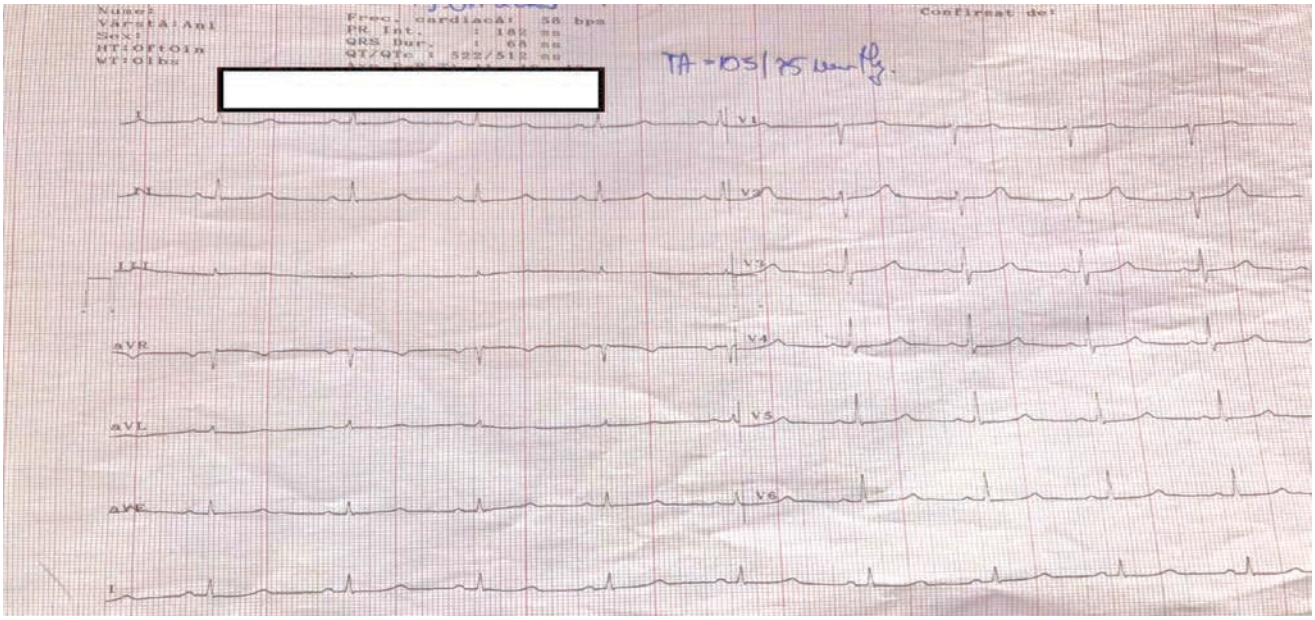

FIGURE 3. ECG at third presentation

female gender, and older age. Our patient is female and overweight, but she is younger than 65 years old. If for the female gender it has been clearly stated that it is a risk factor for QT interval prolongation, for obesity the evidence is moderate [6]. The patient had no comorbidities that could favor the prolongation of the QT interval. However, HCQ treatment was a risk factor for QT prolongation in our patient. What supports this statement is the fact that the QT interval is prolonged more often in patients who are diagnosed with SLE and are treated with HCQ than in those without SLE [8].

HCQ is rarely mentioned as a medication that can prolong the QT interval [9]. In our patient, the QTc interval decreased after stopping HCQ treatment for 3 months (520ms versus 480ms]. In the literature, there are studies that confirm the influence of HCQ on the QT interval. Notably, apart from HCQ, the patient had no other medication that could have prolonged the QT interval, and she did not present with hyperkalemia. Until now, there have been no reported cases of prolongation of the QT interval in patients treated with Belimumab. Regarding treatment with glucocorticoids, the effect is urinary excretion of potassium, which will lead to hypokalemia. Therefore, glucocorticoid medication does not predispose the patient to hyperkalemia [10].

Among the adverse effects reported for treatment with Epratuzumab, QT interval prolongation and other imbalances that could cause QT interval prolongation were not reported [11]. Our patient did not exhibit significant adverse effects (including QT prolongation) under Epratuzumab or other past medications.

McGhie et al., in a study that included 453 patients, demonstrated that 16% of SLE patients treated with HCQ showed conduction disturbances on the ECG. This could not be clearly attributed to HCQ treatment in their study. However, the authors concluded that a cumulative dose over 1207g can induce conduction disorders. At the same time, cumulative doses below this threshold seemed to be protective against conduction disorders [2]. Our patient had been treated with HCQ daily for over 20 years, thus surpassing the cumulative dose threshold of 1,207g.

In the same study conducted by McGhie et al., it was concluded that the cumulative dose of corticosteroids in the previous 3 years could be associated with conduction disorders. Nevertheless, the study did not mention the types of conduction disturbances that were found in their patients [2].

Hooks et al. conducted a study that included 819 patients treated with HCQ for rheumatological diseases (786 with SLE) in which ECGs were analyzed retrospectively between the years 2000-2020. An increase in the QT interval was observed in 8.5% of patients. Compared to those in whom the QT interval was normal, these patients were older and had more frequent comorbidities favoring cardiac conduction disorders such as chronic kidney disease (CKD), history of atrial fibrillation, and history of heart failure [1].

A mechanism by which high concentrations of HCQ can accumulate in the blood is through renal or hepatic dysfunction. Therefore, attention should be paid to patients with chronic kidney disease (CKD) and liver pathology who can present prolonged QT even with low doses of HCQ [1]. Our patient had no such comorbidities or disease-related complications (hepatic comorbidities, kidney involvement).

Another study was conducted on a group of 126 SLE patients who were followed using ECG between 2015-2020. Among the 42 patients treated with HCQ, 26 showed a prolongation of the QT interval, but no significant differences were found compared to the baseline QT interval or significant differences of the QT interval between the first and last ECG. As in other studies, those in whom the QT was prolonged also had other risk factors [4].

A retrospective study conducted by Godeau et al. which included 112 SLE patients treated with HCQ highlighted the presence of cardiac conduction disorders in 18% of these patients [12]. Conduction disorders were reported in 87% of patients receiving long-term HCQ treatment involved in a systematic review [13]. In the literature, there are also case reports of patients who experienced prolongation of the QT interval under HCQ treatment [14,15].

On the other hand, a recent study by Lo CH et al. did not report an increased risk of ventricular arrhythmias in SLE patients treated with HCQ [16]. Likewise, two other studies could not confirm the involvement of HCQ in prolonging the QT interval [17,18].

A particular aspect of the case is the fact that the patient presents anti-Ro antibodies during the immunological evaluation. This type of antibodies can cause repolarization disorders through the action it exerts on L-type and T-type calcium and potassium channels [19]. Although the opinions are not unanimous, there are still studies that support the influence of anti-Ro antibodies on the QT interval [20].

The prolongation of the QT interval over 500ms can have fatal consequences for the patient through the occurrence of TdP which can lead to sudden death. Therefore, an ECG evaluation of patients with SLE is necessary before starting HCQ as well as during treatment, especially if the patient presents with other risk factors. Several ECG screening guidelines have been formulated and proposed for these patients [21]. At this moment, there is no quantitative multivariate risk index that can be used in risk estimation.

CONCLUSION

HCQ is a medication with a good safety profile and favorable results in terms of controlling clinical manifestations in SLE. Other than QT prolongation, our patient exhibited no other adverse events under HCQ. Cardiotoxicity can be one of the adverse effects to be taken into account in case of prolonged HCQ treatment in SLE patients. Due to the potentially severe consequences that QT prolongation may have, it must be taken into consideration in SLE patients treated with HCQ. Importantly, a periodic cardiological evaluation must be done even in young SLE patients without other comorbidities, but who are under HCQ treatment.

Conflict of interest: none declared
Financial support: none declared

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