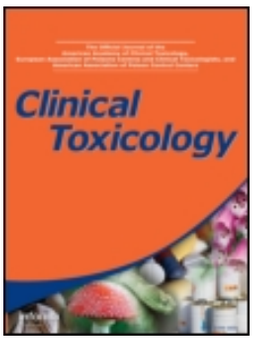

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CASE REPORT

Chronic Hydroxychloroquine Use Associated with QT Prolongation and Refractory Ventricular Arrhythmia

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Background. **Hydroxychloroquine (HCQ) is used for treatment of lupus erythematosus. The cardiac toxicity of HCQ has focused primarily on acute intoxication. We report a case of chronic use of HCQ associated with torsade de pointes.** ***Case report.*** **A 67-year-old female presented with acquired long QT interval syndrome with a refractory ventricular arrhythmia. She was receiving chronic therapeutic doses of HCQ for the treatment of lupus erythematosus. Torsades de pointes was diagnosed in the Emergency Department (ED). After excluding other causes of long QT syndrome, the HCQ was suspected as the cause of her ventricular tachycardia. After discontinuing the HCQ, the QT interval was shorter and the patient recovered after treatment with lidocaine and isoproterenol.** ***Conclusion.*** **The chronic use of HCQ for rheumatic diseases, or as an anti-malarial drug, should be balanced against the risk of developing potentially lethal cardiac arrhythmias.**

CASE REPORT

A 67-year-old female suffered from systemic lupus erythematosus and asthma for which she was receiving prednisolone (15 mg daily), long-acting theophylline (200 mg daily) and HCQ (200 mg daily) for one year. She also had a history of cirrhosis and HBV-related hepatoma with portal vein thrombosis. Cardiac history included an old myocardial infarction with a small muscular type ventricular septal defect. The ECG before this admission was normal sinus rhythm with normal QT interval (Fig. 1a). Generally, her condition was stable There was no chronic renal failure or deterioration in liver function noted before this admission when compared to the previous medical record.

While sitting at home, she experienced a sudden episode of unconsciousness and generalized rigidity. She regained consciousness within minutes with no specific complaints of chest pain, palpitation, limb weakness, incontinence, or a confused mental state. The pattern recurred multiple times thereafter, with the time between episodes ranging from several minutes to 1 h. The increasing frequency of episodes prompted her visit to our ED. Upon admission to the ED, her initial vital signs were 36.6°C, 97 beats per minute (bpm), respiration 22 breaths/minute, and blood pressure 106/56 mmHg. The initial physical and neurological examinations revealed a clear conscious level, a pupil size of 2.5 mm with normal light reflexes. Cardiac examination revealed a regular heart beat with a grade 4/6 holosystolic murmur over the left lower parasternal region.

About 30 min after her admission, the ECG strip showed multiple ventricular premature contractions (VPCs) (Fig. 1b), and the patient experienced another syncopal episode. No palpable carotid pulse was noted, and torsade de pointes (polymorphic ventricular tarchycardia (PMVT), Fig. 1c) was evident. Following three attempts at defibrillation (200, 300, 360 joules) and the administration of lidocaine (100 mg), her cardiac rhythm changed to normal sinus rhythm with a prolong QT interval (QT interval 0.6 sec, QRS interval 0.05 sec). Her carotid pulse was palpable.

Initial blood examinations revealed WBC 8900/μL, hemoglobin 10.9 g/dL, platelets 194,000/μL, Na 130 mEq/L, K 4.3 mEq/L, Ca 7.6 mg/dL, Mg 2.0 mEq/L, digoxin <0.2 ng/ml, theophylline 5.3 μg/ml, AST 106 U/L, total bilirubin 1.4 mg/dL, CK-MB 19 U/L, and Troponin-I <0.4 ng/mL. Other lab results were within normal limits.

After admission, lidocaine treatment continued at 2 mg/min for the control of ventricular arrhythmia. Another ECG revealed a sinus rhythm with a prolonged QT interval and frequent ventricular ectopy couplets. In addition, short bursts of VT were noted. A cardiac 2D-echo revealed an ejection fraction (EF) of 76% and the presence of an apical aneurysm with anteroseptal infarction and small muscular type VSD. Comparison of these findings with those of a previous cardiac 2D-echo done two years ago showed comparable findings. Follow-u CPK isoenzymes and troponin-I values revealed no evidence of acute myocardial infarction.

Since the HCQ was suspected as the cause of VT, it was stopped after this admission. Due to the increased frequency of VT coincident with the use of lidocaine and the absence of

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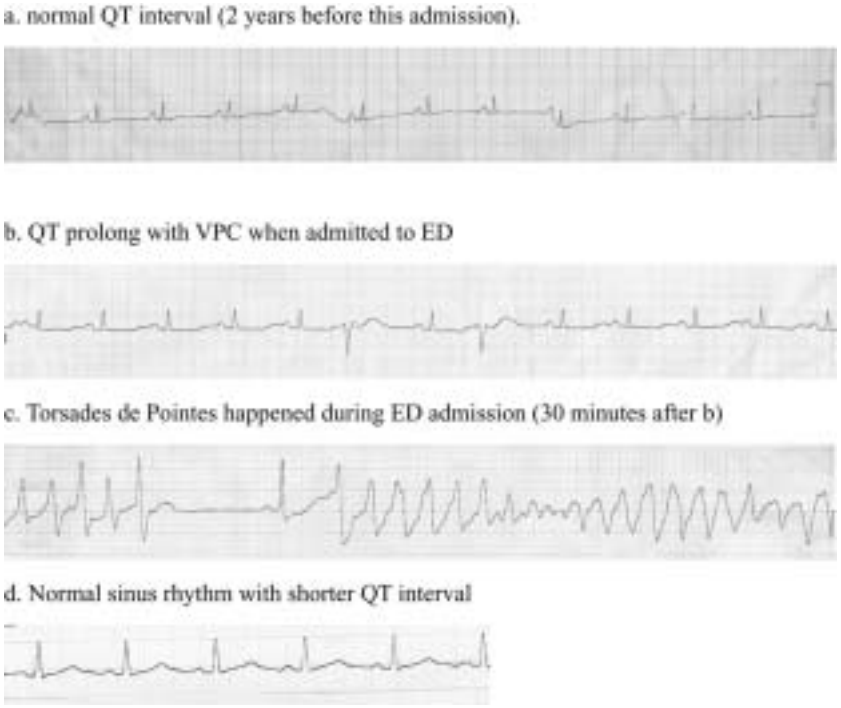

FIG. 1. The serial ECG changes of the patient.

cardiac ischemic change, intravenous $MgSO_4$ (1 g) was administered and followed by isoproterenol (2 ug/min) and titrated to increase the heart rate for refractory VT. After 4 days of this thereapy, the ventricular arrhythmia subsided. However, the ECG showed shorter but still prolonged QT interval (0.5–0.53 s; Fig. 1d). Three weeks after admission, the ventricular dysrhythmias had abated and the patient was discharged on no anti-arrhythmic drugs.

DISCUSSION

Cardiac toxicities caused by hydroxychloroquine (HCQ) include QRS widening, QT interval prolongation, Torsades de pointes, ventricular arrhythmia, hypokalemia and hypotension (1–5).

In the present case, the refractory ventricular tarchycardia was due to QT interval prolongation with frequent ventricular ectopies. We considered the possibility of acquired long QT interval syndrome and attempted to detect the possible causes (1). During admission, no evidence of myocardial ischemic change was found, as evidenced by the normal CPK isoenzyme level, troponin level, and unchanged cardiac 2D-echo findings. Serum electrolytes (K^+, Ca^{2+}, Mg^{2+}) were also within the normal limits. The previous normal QT interval before this admission excluded the congenital QT syndrome. Thus, given the history of HCQ use, a drug-induced acquired long QT interval syndrome was suspected.

In previous case reports, QRS widening, QT interval prolongation, ventricular arrhythmia, cardiac arrest, or hypokalemia have been described in patients ingesting large doses of HCQ. Because of rapid absorption and good bioavailability, cardiac toxicity appeared within a few hours of the acute overdose. However, in our case, the dose had been given for more than one year and was a therapeutic effort to alleviate the malar rash and systematic lupus erythematosus. QT interval prolongation had been noted in this patient for some time prior to this admission, and since the patient was not taking other medications known associated with acquired long QT interval syndrome, and in the absence of cardiac structural problems, HCQ is strongly implicated as the cause.

The steady-state of HCQ requires 3–4 months to be attained, and the terminal half-life is about 6 to 14 days (4). About half the administered HCQ is excreted in urine in an unaltered form, while approximately 1/3 the dose is metabolized in the liver (6,7). Therefore, the QT prolongation noted in the serial ECG evaluation after six months of HCQ therapy was understandable. Other contributing factors were the patient's liver cirrhosis and hepatoma with portal vein thrombosis, which could interfere with HCQ metabolism and increase the plasma drug level to possible toxic levels. Unfortunately, our laboratory did not have the ability to measure HQC concentrations. Lack of the HCQ concentration in this case limits the ability to establish cause and effect. However, the HCQ plasma concentrations in fatal cases range from 2.05 to 29.40 mcmol/L (0.64 to 9.87 mg/L)[3], suggesting that HCQ plasma concentrations may not be useful in assessing toxicity. In our case, the serial ECG changes and the lack of other causes of the long QT

syndrome suggests that the chronic use of HCQ was the cause of our patient's VT.

Hypokalemia is a major finding in acute HCQ poisonings. The absence of hypokalemia in our patient may be a difference between acute and chronic HCQ poisoning.

The treatment of HCQ related VT was suggested as following as by the ACLS guidelines. Torsades de pointes can be treated according to the patient's hemodynamic status. If the patient is hemodynamically unstable, defibrillation is the only choice. If the patient is hemodynamically stable then $MgSO_4$, isoproterenol, phenytoin, lidocaine and overdrive pacing can be used (8).

In chronic HCQ use, potentially lethal cardiac toxicities such as ventricular arrhythmias and QT interval prolongation may be associated with drug accumulation secondary to impaired drug clearance. Although HCQ is safer than its parent compound, chloroquine, and is often used for rheumatic diseases or as an anti-malarial treatment, clinicians should be aware that HCQ presents a risk, not just in an acute overdose, but also with chronic use, especially in patients with underlying hepatic or renal diseases.

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