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Deterioration of Heart Rhythm during Short-Term Hydroxychloroquine Therapy for COVID-19: Report of Two Cases

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ABSTRACT

The rapid spread of the coronavirus disease 2019 (COVID-19) has resulted in significant morbidity and mortality globally. Hydroxychloroquine is one of the medications for eradicating COVID-19. Despite concerns due to its potential cardiac toxicity, hydroxychloroquine is widely used in treating mild and moderate COVID-19 pneumonia. In this case report, we report two cases of Indonesian adult patients with suspected COVID-19 pneumonia who received hydroxychloroquine as part of the medications and experienced deterioration of cardiac conduction which required stopping the drug prematurely. This case report highlights the need for risk stratification, electrocardiogram monitor and QTc evaluation before and during hydroxychloroquine therapy.

INTISARI

Penyakit koronavirus atau COVID-19 telah menyebabkan angka kesakitan dan kematian yang bermakna di seluruh dunia. Hidroksiklorokuin merupakan salah satu pengobatan untuk mengeradikasi COVID-19. Meskipun ada kewaspadaan tentang potensi toksisitas pada jantung, hidroksiklorokuin secara luas digunakan untuk mengobati pneumonia COVID-19 ringan dan sedang. Pada kasus ini kami melaporkan dua kasus pasien dewasa dari Indonesia dengan pneumonia curiga COVID-19 yang mendapatkan pengobatan hidroksiklorokuin dan mengalami pemberatan konduksi jantung yang menyebabkan dihentikannya pengobatan lebih awal. Kasus ini menitikberatkan perlunya stratifikasi risiko, monitor elektrokardiogram dan evaluasi QTc sebelum dan selama pemberian terapi hidroksiklorokuin.

Introduction

Coronavirus 2019 (COVID-19) is a new infectious disease that is spreading rapidly around the world and becoming a pandemic disease.[1,2] The clinical manifestations of COVID-19 are symptoms related to the respiratory tract which include fever, cough, sore throat, weakness and other complications related to pneumonia and respiratory distress syndrome.[3] In early studies, hydroxychloroquine (HCQ) has been touted as a promising therapy for COVID-19 for showing increasing viral clearance and clinical improvements.[4] In Indonesia, HCQ, alone or in combination with azithromycin or other antiviral and supportive drugs, has been used to treat suspected and confirmed cases of COVID-19.[5] Since its approval in 1955, there have been post-market reports of corrected QT (QTc) interval prolongation that may lead to lethal arrhythmias like torsades de pointes (TdP).[6-9]

Studies evaluating HCQ in COVID-19 patients reported that 2 out of 189 patients developed ventricular arrhythmia and other 2 patients developed atrioventricular block and left bundle branch block.[10] However, if HCQ is proven to be lifesaving for COVID-19 patients, evaluating the QT interval to mitigate the risk of lethal arrhythmias will be critical. In this case report, we

report a case of adult Indonesian patients suspected COVID-19 pneumonia who received HCQ as one of medications. During course of treatment, the electrocardiogram (ECG) showed deterioration of cardiac conduction, one patient developed a prolonged QTc interval >500 ms and one patient experienced deterioration of atrioventricular block, which required stopping the drug.

Case Report 1

A 26-year-old male was brought to the Emergency Unit of Dr. Sardjito Hospital, Yogyakarta, Indonesia with the main complaints of dry cough, shortness of breath and fever. The complaints were felt for 7 days. The patient had a history of pulmonary tuberculosis treatment and hypertension, with irregular treatments. No history of the beta blocker or digitalis use (antiarrhythmia drugs). On admission, the hospital screening score for COVID-19 indicated that he had high probability score.

The physical examinations were as follows: fully conscious, body temperature 36.8ºC, blood pressure 130/90 mmHg, tachycardia (120 beats/min (bpm)) and tachypnea (28 times/min) and peripheral oxygen saturation 98% at 3 liters/min nasal cannula. Lung physical examination found rough crackles in both lung fields. Heart examination showed a cardiomegaly. Abdominal and extremity examinations were within normal finding. The laboratory tests showed hemoglobin of 11.2 g/dL, leukocytes 18,900 cells/mm^3, platelets cells 648,000 /mm^3, glutamic-oxaloacetic transaminase 48 g/dL, glutamic-pyruvic transaminase 42 g/dL, creatinine 0.7 g/dL, sodium 132 meq/L, potassium 4.9 meq/L, chloride 100 meq/L, hs-CRP 135 mg/L, ferritin 596 mg/dL, procalcitonin 0.48 ng/mL, hs-troponin I 7.3 ng/L and NT-pro BNP 344.7 pg/mL. Blood gas analysis: pH 7.4, pO2 90%, pCO2 31.2%, SO2 98%, HCO3 23, BE -0.6, AaDO2 84.6, PO2 / FiO2 316.2.

The ECG examination showed sinus tachycardia, normal axis, first-degree atrioventricular block, left ventricular hypertrophy (figure 1). The calculation of QTc was 480 ms (Bazett's formula) (figure 1). The Tisdale score on admission of this patient was 12 (loop diuretics use: 1, admission QTc ≥450 ms: 2, ≥ 2 QTc-prolonging drugs: 6 and heart failure: 3) and classified as high risk category (table 1). The chest x-ray examination indicated cardiomegaly and pneumonia in the right lung (figure 2).

The patient was consulted to Internist-Pulmonologist and was assessed as suspected COVID-19 pneumonia with moderate severity and heart failure and hypertension as comorbidities. The patient was performed nasopharyngeal swabs twice in consecutive days. The patient was treated in the COVID-19 dedicated ward and given treatment with intravenous cefriaxon 1 gram b.i.d., intravenous furosemide 20 mg q.i.d., oral candesartan 8 mg q.i.d., oral slow release KCl 1 tablet q.i.d, oral azythromycin 500 mg q.i.d, and intravenous vitamin C 400 mg/8 hours. The oral HCQ was given as 400 mg b.i.d for day 1 followed by 400 mg q.i.d for the next days.

The ECG evaluation after 3 hours second dose of HCQ showed sinus tachycardia, high-degree atrioventricular block with junctional escape beat and left bundle branch block (figure 3). At that time, the patient did not have any additional complaints. The vital signs were as follows: blood pressure 170/60 mmHg, pulse 58 bpm, breathing rate 26 times/min, and body temperature 36.8 ºC. Because there was an alteration in ECG from first-degree atrioventricular block degenerating into high-degree atrioventricular block and left bundle branch block with prolonged QTc interval, the Cardiologist was consulted. The deteriorating atrioventricular block in this patient was considered to be due to the effect of HCQ, especially in combination with azythromycin. Another possibility was the acute viral/bacterial myocarditis. The results of PCR SARS-CoV-2 from nasopharyngeal swabs were twice negative (on day 0 and day +1). Therefore, the Cardiologist decided to discontinue HCQ and the patient was put on continuous heart monitor apparatus. No steroids or antiinflammation were added.

On day+1, the ECG evaluation (24 hours after HCQ termination) showed sinus tachycardia, second-degree atrioventricular block Mobitz type II, left ventricle hypertrophy and QTc 380 ms (Bazett's formula) at heart rate of 110 bpm (figure 4). The complaints of progressing shortness of breath, chest pain, dizziness or palpitations were not found. On day+2, the ECG showed sinus tachycardia, first-degree atrioventricular block, left ventricular hypertrophy, and QTc 352 ms (Bazett's formula) at heart rate of 110 bpm (figure 5). The patient felt better and clinical condition improved. On day+3 until day+5, the patient clinical condition improved and uneventful. The subjective and objective parameters for pneumonia and heart failure were improved. The daily ECG evaluation showed sinus tachycardia and first-degree atrioventricular block. On day+7, the ECG evaluation was sinus tachycardia (120 time/min), PR interval 200 ms and left ventricular hyperthrophy and QTc 380 ms (Bazett's formula) at heart rate of 110 bpm (figure 6). The patient was stable and discharge home. The cardiac abnormality would be followed up on outpatient setting after discharge.

Case Report 2

A 48-year-old woman presented to the emergency room of Dr. Sardjito Hospital, Yogyakarta, Indonesia with a four-day history of fever and multiple episodes of vomiting before admission. The patient specifically denied having a history of flu-like symptoms, dyspnea, and any history of comorbidities. She further denied any diuretic treatments, laxative medication, or ingestion of any other medication. On admission, the hospital screening score for COVID-19 indicated that he had high probability score.

The physical examinations were as follows: fully conscious, body temperature 36.6ºC, blood pressure 80/40 mmHg, tachycardia (109 bpm) and tachypnea (22 times/min) and peripheral oxygen saturation 96% at 3 liters/min nasal cannula. Clinical laboratory findings at the time of admission showed hypokalemia (potassium level 2.7 mmol/L). Other laboratory examinations were as

follows: thrombocyte 46.000/µL, lymphocyte 7.5 %, albumin 2.51 g/dL, glutamic aspartate transaminase 46 U/L, blood urea nitrogen 34.7 mg/L, creatinine 2.58 mg/dL, procalcitonine >200 ng/mL, and C-reactive protein >150 mg/L. Other laboratory tests were normal. Thorax radiology showed bilateral pneumonia and cardiomegaly (Figure 7). Her initial ECG showed sinus rhythm with QTc interval of 423 ms according to Bazett's formula and low voltage in precordial leads (Figure 8).

The patient was assessed to be in septic shock, pneumonia suspected of COVID-19 and hypokalemia. She was given titrating dose of norepinephrine 0.05 µg/kg/min, oral HCQ 200 mg b.i.d, oral oseltamivir 150 mg b.i.d, KCl 25 mEq infusion over 24 hours, meropenem 1 gr per 12 hours per-iv, vitamin C 1000 gr b.i.d, and selenium 400 mcg q.i.d. The Tisdale score was moderate risk (table 1). The ECG monitor and QTc evaluation was performed daily.

On the day+1, her ECG showed sinus rhythm with QTc interval of 460 ms (Bazett's formula) at heart rate of 70 bpm (Figure 9). On the day+2, her ECG showed sinus rhythm with QTc interval of 581 ms (Bazett's formula) at heart rate of 75 bpm (Figure 10). On the day+3, her ECG showed sinus rhythm with QTc interval of 537 ms (Bazett's formula) at heart rate of 64 bpm (Figure 11). Her potassium level on the day+3 was 3.17 mmol/L. At the beginning, the decision was to administer HCQ for five days; however, it was stopped prematurely owing to a prolonged QTc > 500 ms and an interval increased by more than 60 ms compared to baseline.

Her norepinephrine treatment was stopped on the day+7. Other medications were continued based on clinical conditions. The PCR detection of SARS-CoV-2 from two nasopharyngeal swabs showed negative results and she was discharged from the hospital without any remaining complaints after eleven days of hospitalization.

Discussion

The management strategy of COVID-19 therapy is still a challenge today. A report of studies which stated that hydroxycloroquine alone or in combination with azithromycin would cause a reduction in viral shedding from COVID-19.[4,11] In cohort of 90 patients with COVID-19, HCQ alone or in combination with azithromycin pose increased risk to develop prolongation of corrected QT interval.[7] In patient with underlying cardiac condition infected with COVID-19 or cardiac involvement due to COVID-19, the preponderance of cardiac complication is greater.[7]

In the first case, the combination of azithromycin 500 mg q.i.d and HCQ 400 mg b.i.d per oral was administered on day 0. On admission, the Tisdale score indicated high risk to develop QTc prolongation. The American College of Cardiology (ACC) issued guidelines that the use of azithromycin and/or HCQ for COVID-19 need concomitant ECG monitoring of QTc interval and adjusting the dose according to the QTc interval.[12] Based on this guidance, after 3 hours from the second dose of HCQ we evaluated ECG and found the deterioration of first-degree atrioventricular block become high-degree atrioventricular block and left bundle branch block after ingestion of azithromycin 500 mg and HCQ 800 mg oral loading. The QTc interval during high-degree atrioventricular block was prolonged. After stopping the HCQ, the ECG returned to baseline. We speculated that HCQ worsened the atrioventricular blockade in this patient.

Acute HCQ toxicity can manifest as hypoventilation, bradycardia, arrhythmia and seizures.[13] Hydroxychloroquine is quickly absorbed from gastrointestinal tract and usually within the first 1–3 hour later the onset of symptoms develop.[13] The duration of its effect is short-lived, usually no more than 24 hour.[13] Acute chloroquine poisoning effect has been reported to slow the atrioventricular conduction (prolonged PR interval), in addition to its effects on QT interval prolongation, T wave inversion and ST-segment depression.[14] Usually atrioventricular block occurred in chronic usage of chloroquine.[15] This acute toxicity effect occurs after ingestion of high-dose chloroquine or HCQ. However, the underlying cause such as heart failure or previous arrhytmia may precipitate ECG abnormality even in lower dose.

The acute myocarditis may also the reason for deterioration of atrioventricular conduction, this was based on elevated hs-CRP levels, slightly increased hs-troponin I and signs of acute heart failure. The patient had previous history of hypertension and tuberculosis short medication. The incidence of high-degree AV block due to acute myocarditis was 1.1%, and Asian race has preponderance.[16] Acute inflammation permeates into the atrioventricular node and infra-Hisian conduction system make transitory atrioventricular conduction blockade and bundle branch blockade which will resolve during the convalescence course.[16] Since SARS-CoV-2 PCRs were negative, the use of HCQ was terminated and other treatment for underlying cause and cardiac monitoring were continued. The improved atrioventricular conduction after stopping HCQ was observed. However, due to hospital constraint due to COVID-19 pandemic, we could not perform cardiac disease work-up, such echocardiography and cardiac imaging in this patient during current admission. After seven days hospitalization, the patient condition was improved uneventful.

In the second case, the patient received HCQ due to suspected COVID-19. In this case, meropenem was chosen over azithromycin as the antibiotic is often used for empirical treatment of infections in critically ill patients with acute kidney injuries.[17] This patient has an increased creatinine of 2.58 mg/dL on admission, which returned to 0.6 mg/dL on the third day of treatment. It was highly likely that she experienced acute kidney injury upon admission.

In previous experimental studies, HCQ attributed to a deficit in the glycosylation receptors of the virus cell, thus can decrease the affinity of the virus to angiotensin-converting enzyme 2 (ACE2) receptors expressed in the lung, heart, kidney, and intestine.[18] HCQ as an

antiinflammatory therapy can significantly reduce the proinflammatory markers and cytokines in severe SARS-Cov-2 patients that experience cytokine storms (3). HCQ has less toxic metabolites than CQ; however, both of them can cause side effects like nausea, anorexia, skin exanthema, or other more severe forms like retinopathies or cardiac arrhythmias.[19,20] In the second case, even though the patient experienced vomiting and nausea before admission, she denied another vomiting after HCQ administration and she did not have any other complaints.

Hydroxychloroquine can block the inward potassium channel, which further delay the phase 3 repolarization of the cardiac action potential seen in the ECG as prolonged QT interval with subsequent risk of torsade des pointes, ventricular fibrillation, and sudden cardiac death.[20] The QTc interval was proposed because QT interval is influenced by heart rate, whereas a higher heart rate produces a shorter QT interval and vice versa.[21] Bazett's formula has been used most often because of its simplicity to estimate the QT interval.[22] The QTc interval below 440 ms is considered normal, while between 440 to 460 ms and between 440 to 470 are considered borderline in men and women, respectively.[23] Arrhythmias occur more frequently if the value is above 500 ms.[23] A study analyzing patients with long QT syndrome reported that there is 20% risk of syncope or sudden death in patients with QTc interval below 446 ms and 70% risk of syncope or sudden death in patients with QTc interval above 498 ms.[24] In the second case, the QTc interval progressively rose during shortterm HCQ therapy, at which time the patient did not make any complaints and did not experience syncope. However, the HCQ therapy was stopped immediately for safety reasons such that preventing from TdP.

Hydroxychloroquine has a half-life of 40–50 days.[25] Multiple drugs being used for the treatment of COVID-19 are CYP3A4 inhibitors which can significantly increase serum concentration of CQ and HCQ. In particular, the combination of both drugs and lopinavir/ritonavir or umifenovir/ritonavir is contraindicated because they are a major inhibitor of CYP3A4, thus can further prolong the QT interval.[26] In the second case, the patient only received oseltamivir, another antiviral that did not interfere with CYP3A4, so the probability of polypharmacy-induced QT interval can be eliminated.

The national protocol and the ACC guideline propose criteria for dose reduction or drug discontinuation of HCQ if: the QTc after HCQ administration increased to greater than 500 ms when the baseline QTc is less than 500 ms, the difference between the baseline and evaluation QTc is greater than 60 ms.[5,12] Previous reports showed that QTc interval changes of COVID-19 patients treated with HCQ occurred between the third and fourth days.[26] In the second case, the QTc changes started to increase on the Adasdasdas day+1 and progressing into significant increased on the remaining day.

The exact cause of the QTc prolongation is difficult to identify for certain. In the second case, the ECG was normal and the QTc interval prior to HCQ administration was normal even though the potassium level was below 3 mmol/L and the QTc interval was progressively prolonged during HCQ administration eventhough the potassium level was corrected above 3 mmol/L. Thus, a drug-induced QT prolongation was suspected, and since the patient was not given other medications known to be associated with prolonged QT interval, HCQ was suspected as the cause.

Even in normal ECG, HCQ pose risk to develop arrhytmia. Tisdale et al. made a scoring system to stratify risk of QT prolongation in patients receiving drugs with potential QTc prolongation.[12] The incidence of QTc interval prolongation in the low (score <7), moderate (score 7-10), and high (score ≥ 11) is 15%, 37%, and 73% respectively.[12] In the second case, the patient was female; her baseline potassium was lower than 3.5 mEq/L; she was in septic shock and received 1 QTc prolongation drug; her total score was 9 and fell to moderate risk, meaning that she had more risk of QT prolongation. However, considering the risks and benefits, HCQ was still given with daily ECG monitoring. This case highlights the need for risk stratification by Tisdale scoring, ECG monitoring and QTc evaluation based on the risk of QT prolongation during HCQ therapy alone, in combination, or during other QT prolonging antiviral drugs in COVID-19 patients.

We have reported two cases with the early cardiac adverse effect of short-term usage of hydroxychloroquine with manifestation of progressing atrioventricular blockade from first-degree into high-degree atrioventricular block and progressing QTc prolongation, which were reversible after drug discontinuation. These events occurred in patient with baseline moderate to high risk Tisdale scores. The ECG recording and QTc monitoring and scoring system, such as Tisdale score, need to be implemented in patient taking HCQ alone or in combination.

Conflicts Of Interest

The authors declare that they have no conflicts of interest. The patients had signed an informed consent form to publish the case as anonymous case report.

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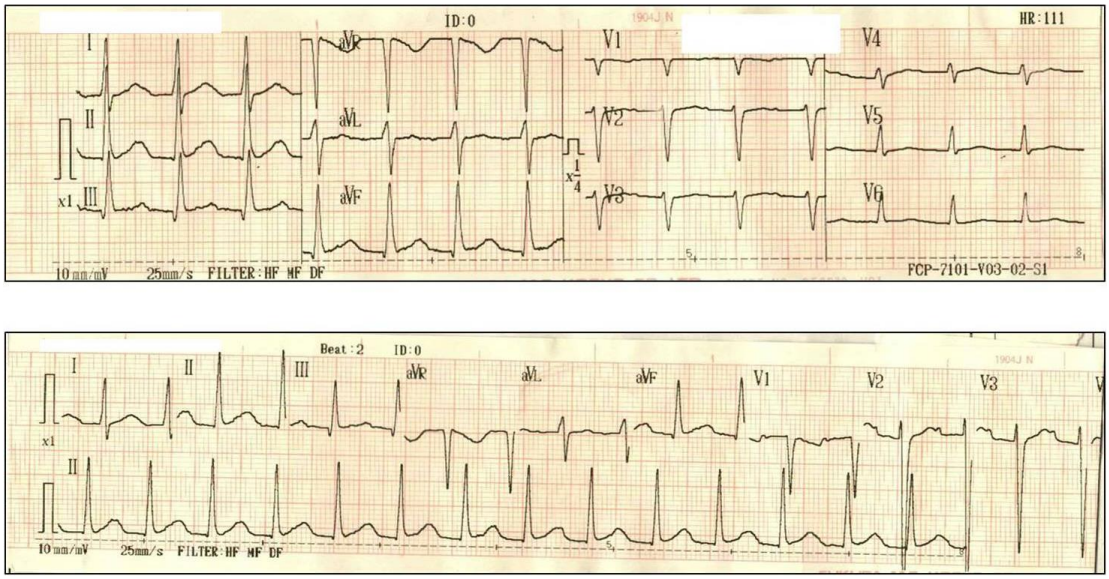

Figure 1.
A 12-lead ECG (upper) and strip (lower) showed sinus tachycardia, normal axis, first-degree atrioventricular block, and left ventricular hypertrophy (poor R wave progression , Sokolow-Lyon voltage criteria) and QTc was 480 ms (Bazett's formula).

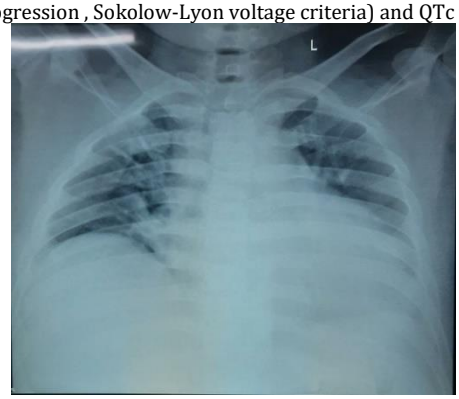

Figure 2.
The chest x-ray examination showed cardiomegaly and pneumonia in the right lung (AP projection).

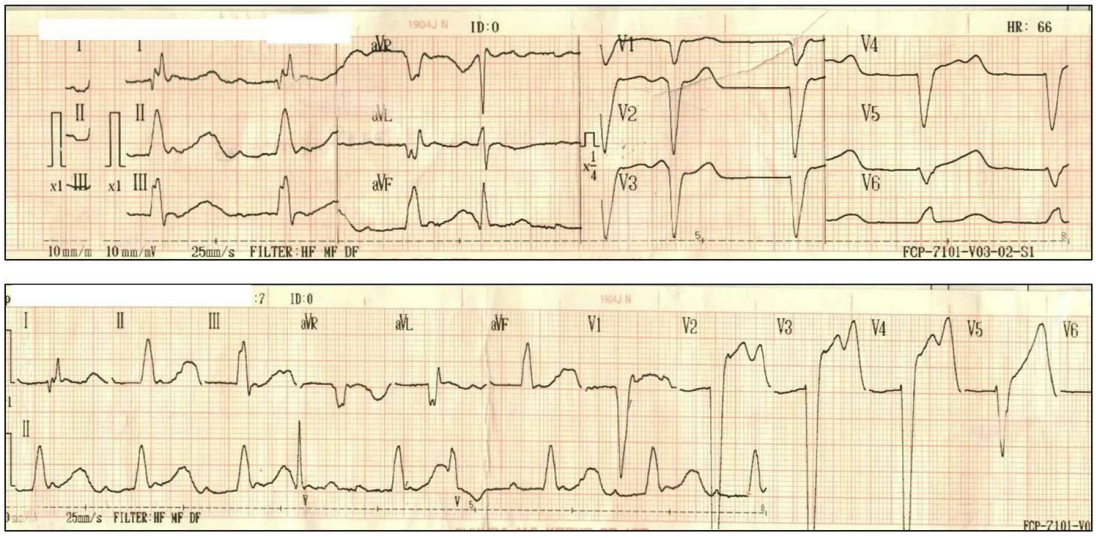

Figure 3.
A 12-lead ECG (upper) and strip (lower) showed sinus tachycardia, high-degree atrioventricular block with junctional escape beat and left bundle branch block and QTc 600 ms (Bazett's formula).

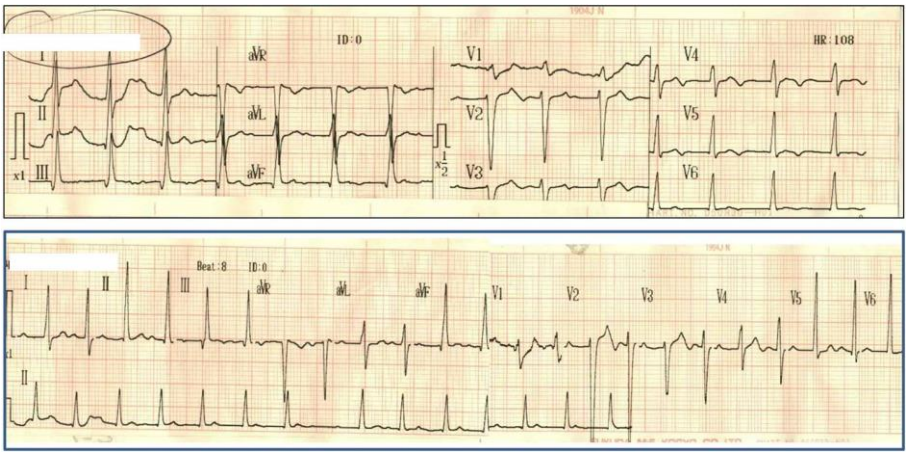

Figure 4.
A 12-lead ECG (upper) and strip (lower) showed sinus tachycardia, second-degree atrioventricular block Mobitz type II and QTc 380 ms (Bazett's formula)

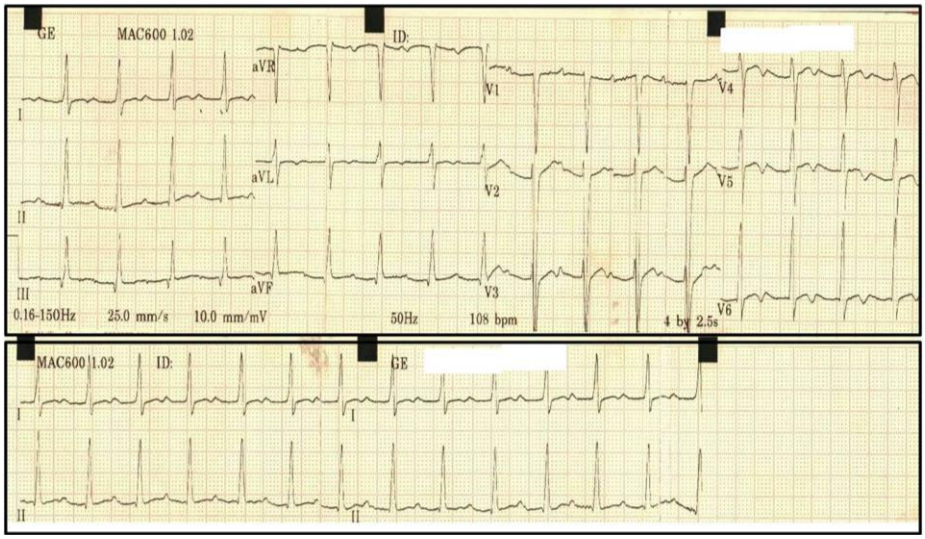

Figure 5.
A 12-lead ECG (upper) and strip (lower) showed showed sinus tachycardia, first-degree atrioventricular block, left ventricular hypertrophy, and QTc 352 ms using Bazett's formula (heart rate of 110 bpm)

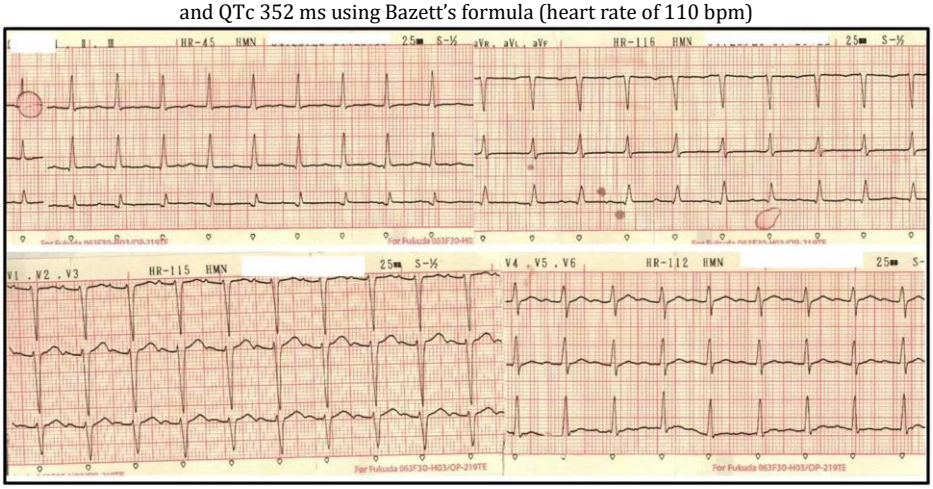

Figure 6.
ECG just before discharge, showing sinus tachycardia, PR interval 200 ms, left ventricular hypertrophy and QTc 380 ms using Bazett's formula (heart rate at 110 bpm).

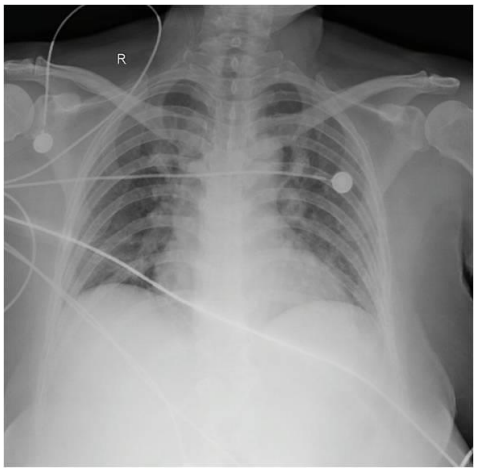

Figure 7.
Chest x-ray of patient on admission showing multiple infiltrates in right and left lung and cardiomegaly.

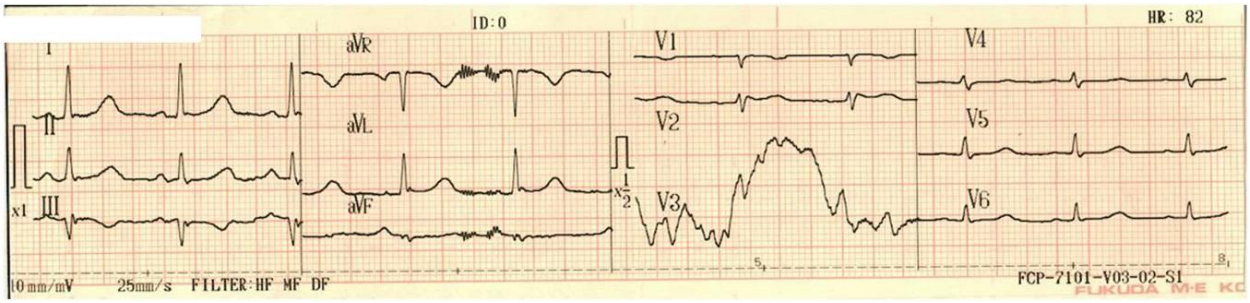

Figure 8.
ECG prior to starting HCQ (day 0) with measured QT of 360 ms, calculated QTc of 423 ms using Bazett's formula (heart rate at 83 bpm).

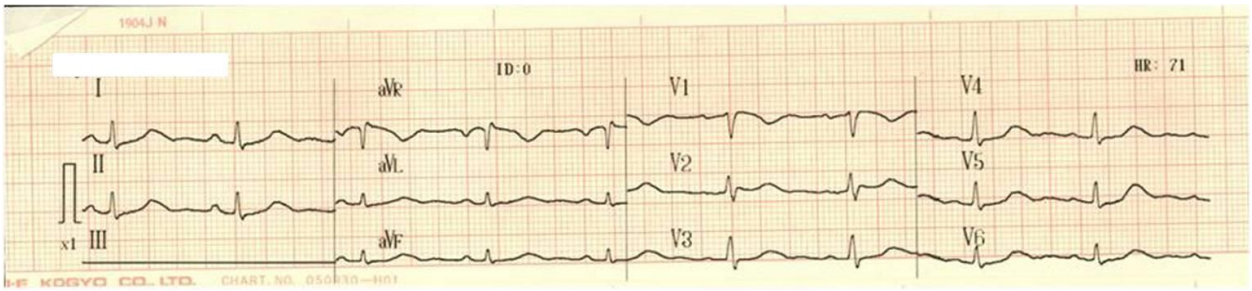

Figure 9.
ECG on day+1, showing measured QT of 426 ms, calculated QTc of 460 ms using Bazett's formula (heart rate 70 bpm).

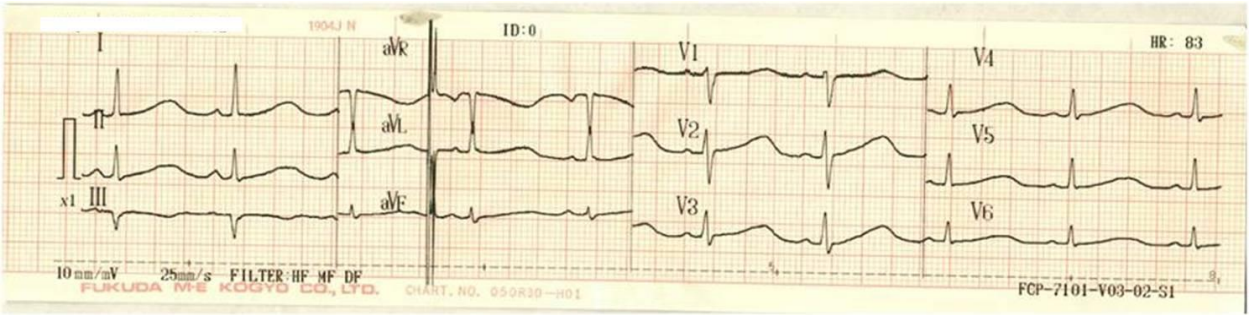

Figure 10.
ECG on day+2, showing measured QT of 520 ms, calculated QTc of 581 ms using Bazett's formula (heart rate 75 bpm).

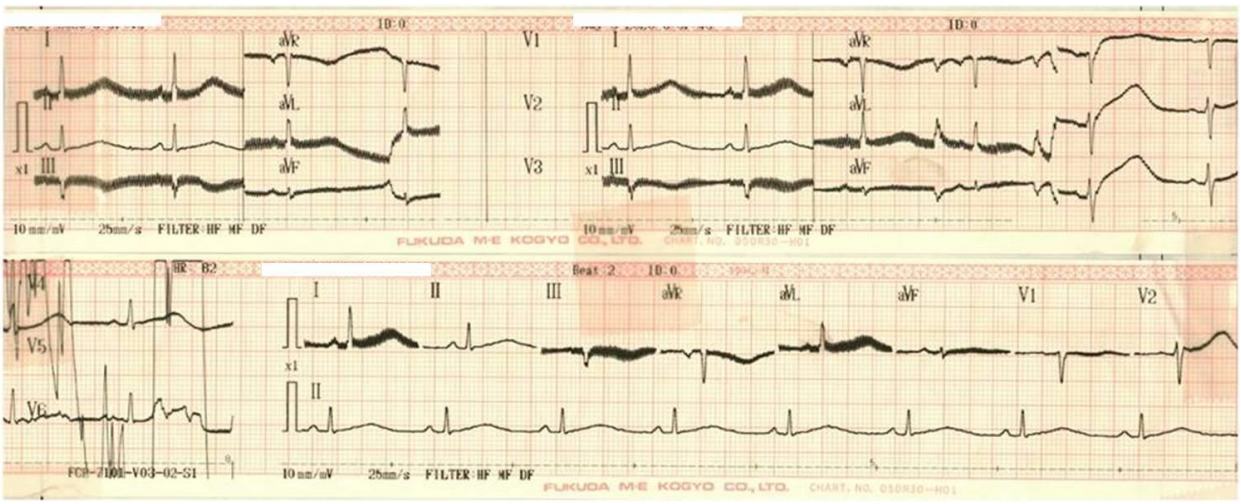

Figure 11.
ECG on day+3, showing measured QT of 520 ms, calculated QTc of 537 ms using Bazett's formula (heart rate 64 bpm).

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