Deteriorating Atrioventricular Block in COVID-19 Suspected Patient after Receiving Initial Dose of Azythromycin and Hydroxychloroquine

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ABSTRACT

Coronavirus 2019 (COVID-19) is an infectious disease that is becoming a pandemic. Hydroxychloroquine in combination with azythromycin are among drugs currently in use to eradicate COVID-19. Despite concerns due to its potential cardiac toxicity, hydroxychloroquine is widely accepted in mild and moderate COVID-19 pneumonia. In this case report, we report a case of a young Indonesian adult male with suspected COVID-19 pneumonia who received hydroxychloroquine and azythromycin therapies and during 24 hour experienced deterioration of atrioventricular block.

Keywords: COVID-19; azythromycin; hydroxychloroquine; atrioventricular block

1. 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 pathogen that causes this disease has been identified as Severe Acute Respiratory Corona Virus 2 (SARS-CoV-2).\(^1\) The clinical manifestations of SARS-CoV-2 infection or 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.\(^3\)

Until now there are several potential drugs for the treatment of COVID-19, one of which is chloroquine and, its derivative hydroxychloroquine.\(^4\) Despite concerns due to its potential cardiac toxicity, hydroxychloroquine is widely used to battle COVID-19. In Indonesia,
which also affected by COVID-19, the national guideline recommend the administration of chloroquine or hydroxychloroquine in combination with antibiotics such as azythromycin or levofloxacine in COVID-19 pneumonia cases.\(^5\) In this case report, we report a case of a young Indonesian adult male with suspected COVID-19 pneumonia who received hydroxychloroquine and azythromycin therapy and during 24 hour experienced deterioration of atrioventricular block.

2. CASE PRESENTATION

A 26-year-old male, Indonesian citizen, 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, but did not take the medication until only 2 months. Patients had history of hypertension, with irregular treatment. No history of the beta blocker or digitalis use (antiarrhythmia drugs). The patient had no history of contact with patients confirmed or suspected COVID-19. The patient had a history of traveling to the local COVID-19 transmission area. Hospital score for COVID-19 screening indicated that patient had high probability score.

The physical examination as follows: fully conscious, axillae temperature 36.8°C, blood pressure 130/90 mmHg, pulse 120 beats / min, breathing rate 28 beats / min and peripheral oxygen saturation 98% at 3 liters / min nasal cannula. Physical examination of the lungs found rough crackles in both lung fields. Heart examination found cardiomegaly, no gallop and murmur obtained. Abdominal examination was within normal finding. Examination of the extremities found no edema or clubbing finger.
The laboratory tests showed hemoglobin of 11.2 g / dL, leukocytes 18,900 /mm³, platelets 648,000 /mm³, neutrophils 15,876/mm³, lymphocytes 1,550/ mm³, albumin 2.83 g / dL, glutamic-oxaloacetic transaminase 48 g / dL, glutamic-pyruvic transaminase 42 g / dL, urea nitrogen 15.4 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.

Electrocardiogram examination showed sinus tachycardia, normal axis, first-degree atrioventricular block, left ventricular hypertrophy (figure 1). The calculation of QT corrected was 470-480 ms, calculated on V3 lead on electrocardiogram strip (figure 1), based on Frederica formula. The Tisdale score on admission of this patient was 9 (loop diuretics use: 1, admission QTc ≥450 ms: 2, ≥ 2 QTc-prolonging drugs: 3 and heart failure: 3) and classified as moderate risk category. 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 moderate pneumonia with suspected Covid-19, acute heart failure and hypertension. Patients was performed nasopharyngeal swabs twice in consecutive days. Patient was treated in the ward for Covid-19 patients and given treatment namely intravenous cefriaxon 1 gram/12 hours, intravenous furosemid 20 mg/24 hours, oral candesartan 8 mg q.i.d, oral slow release potassium 1 tablet q.i.d, oral azythromycin 500 mg q.i.d, oral hydroxychloroquine 400 mg b.i.d for day 1 followed by 400 mg q.i.d for the next days, and intravenous vitamin C 400 mg/8 hours.
On day-1, electrocardiogram evaluation after 3 hours second dose of hydroxychloroquine 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 examination obtained blood pressure 170/60 mmHg, pulse 58 time/min, breathing rate 26 times/min, body temperature 36.8 °C. Because there was an alteration in electrocardiogram from first-degree atrioventricular block degenerating into high-degree atrioventricular block and left bundle branch block with prolonged QT interval, the Cardiologist was consulted. The deteriorating atrioventricular block in this patient was considered to be due to the effect of hydroxychloroquine, 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 hydroxychloroquine and the patient was put on heart monitor equipment. No steroids or antiinflammation were added.

On day-2, electrocardiogram evaluation (24 hours after hydroxychloroquine termination) showed sinus tachycardia, second-degree atrioventricular block Mobitz type II, left ventricle hypertrophy (figure 4). The complaints of progressing shortness of breath, chest pain, dizziness or palpitations were not found.

On day-3, electrocardiogram evaluation (48 hours after hydroxychloroquine termination) showed sinus tachycardia, first-degree atrioventricular block, left ventricular hypertrophy (figure 5). The patient felt better and clinical condition improved. The work-up for tuberculosis yielded negative result.
On day-4 until day-6, the patient clinical condition improved and uneventful. The subjective and objective parameters for pneumonia and heart failure were improved. The daily electrocardiogram evaluation showed sinus tachycardia and first-degree atrioventricular block.

On day-7, electrocardiogram evaluation was sinus tachycardia (120 time/min), PR interval 200 ms and left ventricular hyperthrophy (figure 6). The patient was stable and discharge home. The cardiac abnormality would be followed up on outpatient setting after discharge.

3. DISCUSSION

The management strategy of COVID-19 therapy is still a challenge today. A report of studies which stated that hydroxychloroquine alone or in combination with azithromycin would cause a reduction in viral shedding from COVID-19. In cohort of 90 patients with COVID-19, hydroxychloroquine alone or in combination with azithromycin pose increased risk to develop prolongation of corrected QT interval. In patient with underlying cardiac condition infected with COVID-19 or cardiac involvement due to COVID-19, the preponderance of cardiac complication is greater. Here we reported the early cardiac rhythm deterioration in young male patient, whom also had abnormal cardiac condition before beginning the treatment with hydroxychloroquine and azithromycin.

In our patient, the combination of azithromycin 500 mg q.i.d and hydroxychloroquine 400 mg b.i.d per oral was administered on day 0. On admission, the Tisdale score indicated moderate risk to develop QTc prolongation. The American College of Cardiology issued guidelines that the use of azithromycin and/or hydroxychloroquine for COVID-19 need concomitant electrocardiogram monitoring of corrected QT interval and adjusting the dose according to the QT interval. Based on this guidance, after 3 hours from the second dose of
hydroxychloroquine we evaluated electrocardiogram 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 hydroxychloroquine 800 mg oral loading. The QT interval during high-degree atrioventricular block was prolonged. After stopping the hydroxychloroquine, the electrocardiogram returned to baseline. We speculated that hydroxychloroquine worsened the atrioventricular blockade in this patient.

Acute hydroxychloroquine toxicity can manifest as hypoventilation, bradycardia, arrhythmia and seizures.\textsuperscript{10} Hydroxychloroquine is quickly absorbed from gastrointestinal tract and usually within the first 1–3 hour later the onset of symptoms develop.\textsuperscript{10} The duration of its effect is short-lived, usually no more than 24 hour.\textsuperscript{10} 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.\textsuperscript{11} Usually atrioventricular block occurred in chronic usage of chloroquine.\textsuperscript{12} This acute toxicity effect occurs after ingestion of high-dose chloroquine or hydroxychloroquine. However, the underlying cause such as heart failure or previous arrhythmia may precipitate electrocardiogram 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.\textsuperscript{13} 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.\textsuperscript{13} Since SARS-
CoV-2 PCRs were negative, the use of hydroxychloroquine was terminated and other treatment for underlying cause and cardiac monitoring were continued. The improved atrioventricular conduction after stopping hydroxychloroquine 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.

We have reported the early cardiac adverse effect of initial dose of azithromycin and hydroxychloroquine with manifestation of progressing atrioventricular blockade from first-degree into high-degree atrioventricular block, which was reversible after drug discontinuation. This event occurred in patient with underlying cardiac disease with moderate risk Tisdale score.

**Ethical Approval:**

This study has been approved by the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada - Dr. Sardjito General Hospital (ethical protocol code: KE/FK/0510/EC/2020). Informed consent was obtained from the subject.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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FIGURE LEGENDS
Figure 1. A 12-lead electrocardiogram (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).

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

Figure 3. A 12-lead electrocardiogram (upper) and strip (lower) showed sinus tachycardia, high-degree atroventricular block with junctional escape beat and left bundle branch block. QT interval 600 ms.

Figure 4. A 12-lead electrocardiogram (upper) and strip (lower) showed sinus tachycardia, second-degree atrioventricular block Mobitz type II.

Figure 5. A 12-lead electrocardiogram (upper) and strip (lower) showed sinus tachycardia, first-degree atroventricular block, left ventricular hypertrophy.

Figure 6. A 12-lead electrocardiogram just before discharge showed sinus tachycardia (115 time/min), PR interval 200 ms and left ventricular hypertrophy.
Figure 1.
Figure 2.
Figure 3.

Figure 4.
Figure 5.

Figure 6.