

COVID-19-related Myocarditis: Current Issue in Pandemic Situation

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a worldwide medical issue since it is easily transmitted from human to human. The human angiotensin-converting enzyme-2 (hACE2) expression gives access to SARS-CoV-2 through its affinity with the spike protein of SARS-CoV-2. Right after the patient has been infected with SARS-CoV-2; subsequently, it may lead to COVID-19-related myocarditis. However, no practical guidelines still that significantly affects the morbidity and mortality status of COVID-19 patients. In this case report, we are showing challenges in diagnosing and treating COVID-19-related myocarditis.

Case presentation: A-45 years old man was referred to our hospital from Emergency Hospital for COVID-19 Kemayoran Athletes Village with typical chest pain. He felt a crushing sensation in his chest, and it was intensifying every minute. The ECG examination showed ST-segment elevation in all precordial lead and inferior lead. His laboratory works revealed a significant increase of inflammation and cardiac troponin markers. His angiography examination came up with non-significant lesion. Unfortunately, biopsy could not be done due to pandemic limitations. We were diagnosing the patient with COVID-19-related myocarditis, and he was discharged from the hospital one week after treatment. Currently, there are no diagnostic and treatment guidelines for COVID-19-related myocarditis.

Conclusions: COVID-19 has become a novel glitch in medical practice situations. Not only lungs, but it involves many other organs, and the heart is one of the most common organs involved. One of the cardiac complications of COVID-19 infection is COVID-19-related myocarditis. Currently, there is no guideline in diagnosing and treating COVID-19-related myocarditis, and we are encouraging the international society to put an eye on it.

Keywords: myocarditis - COVID-19 – pandemic - ACE2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-single stranded RNA virus that has phylogenetic correspondence but is not a direct descendent, severe acute respiratory syndrome coronavirus

(SARS).¹ It has become a worldwide medical issue because it is easily transmitted from human to human (anthroponoses). However, the first reservoir origin, mechanism of infection between animals, and zoonotic mechanism are enigmatic.² COVID-19 gives a wide range of clinical features such as myalgia,

diarrhea, chest tightness, dyspnea, acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulopathy because its receptor, human angiotensin-converting enzyme-2 (hACE2), are found in several organs.^{1,3} As a result, hypertension and other cardiovascular comorbidities give higher mortality events in COVID-19 patients.⁴

Angiotensin-converting enzyme (ACE), part of the renin-angiotensin system (RAS), converts angiotensin I (AngI) to angiotensin II (Ang II) which serves as a systemic vasoconstrictor agent and stimulant agent for releasing aldosterone. Meanwhile, ACE2 decreases the level of angiotensin, both Ang I and Ang II, and promotes vascular vasodilation with additional anti-fibrotic, anti-proliferative, and anti-inflammatory effects.^{1,5} The hACE2 expression gives access to SARS-CoV-2 through its affinity with the spike protein of SARS-CoV-2. Moreover, the hACE2 gene is linked to the X chromosome, making males more prone to COVID-19 than females.⁵ Right after the patient has been infected with SARS-CoV-2, paradoxically, ACE2 will downregulate. Subsequently, there will be over-accumulation of AngII and it may lead to acute respiratory distress syndrome (ARDS) and fulminant myocarditis.^{3,5}

Myocarditis defines as an inflammation disease, microscopically marked with infiltration of mononuclear cells to the myocardium or muscle cell of the heart. Unfortunately, there is no

landmark in clinical presentation for myocarditis. Sometimes myocarditis could be asymptomatic therefore making it underdiagnosed.⁶ In fact, even endomyocardial biopsy (EMB) remains as the gold standard for diagnosing myocarditis, practically during the COVID-19 pandemic, it is barely done. Several early studies used specific signs and symptoms with laboratory investigations like elevated troponin serum to diagnose myocarditis.⁷ There is no guideline for diagnosing and treating COVID-19-related myocarditis.

One study found that from 112 patients with COVID-19-related acute myocarditis, only 32% of the patients had undergone an endomyocardial biopsy, and the rest underwent non-invasive diagnostic procedures. Almost 40% of patients with COVID-19-related myocarditis required inotropic support, which significantly affects the morbidity and mortality status of COVID-19 patients.⁸ Myocarditis is 15.7 times higher in hospitalized patients with COVID-19.⁹ Current evidence suggests SARS-CoV-2 causes viral myocarditis via a combination of direct viral injury and immune-mediated cell death.¹⁰ Since COVID-19-related myocarditis has been devastating the clinical outcome, early diagnosis and proper treatment are crucial despite no rigid guidelines for this situation.

In this article, we present a case report of a COVID-19 patient who comes with symptoms of severe chest pain and ST-elevation in all ECG

lead. During laboratory examination, we found a significant increase in the cardiac enzyme. We had preceded the investigation into cardiac vascular examination via catheterization laboratory since any other imaging modality did not have a protocol for COVID-19 patients. We found no significant lesion. Unfortunately, we could not conduct an endomyocardial biopsy due to facility limitations. Based on the evidence, we diagnosed the patient with COVID-19 - related myocarditis. We treated the patient with a beta-blocker alongside with COVID-19 drug and thankfully the patient recovered soon.

CASE – ILLUSTRATION

A 45-year-old man was referred to our hospital from Emergency Hospital for COVID-19 Kemayoran Athletes Village with typical chest pain. He felt a crushing sensation in his chest and it was intensifying every minute. The sore was penetrating through his back and spreading to his left arm. It was not deteriorating with either activities or position. Around half an hour later, it became sporadic. He denied any previous medical condition before, but he routinely smoked one to two cigarettes daily.

Before he was admitted to our hospital, he had been hospitalized for 4-days at Emergency Hospital for COVID-19 Kemayoran Athletes Village with several symptoms; fever, dry cough, and fatigue for the last 7-days. Three days before, he was undertaking Reverse-Transcriptase Polymerase Chain Reaction (RT-

PCR) SARS-CoV-2 and the result was positive (RdRp- Gene 21.95 and N-Gene 22.81).

Physical examinations revealed no remarkable findings, no alteration of mental status, and normal vital signs. His laboratory results showed; hemoglobin 13.2 g/dL, hematocrit 37.1%, Leucocytes 21.610/ μ l (remarkably increase), and platelet 607.000/ μ l. The absolute lymphocyte count was slightly reduced (1210/ μ l) and the Neutrophil/Lymphocyte Ratio (NLR) was high (15.93). His kidney function and chemistry panel examinations remained stable (blood urea 49 mg/dL, creatinine 1.41 mg/dL, blood glucose 101 mg/dL, sodium 140 mmol/L, potassium 4.2 mmol/L, chloride 105 mmol/L, aspartate transaminase/AST 33 U/L, alanine aminotransferase /ALT 75 U/L, and non-reactive for HbsAg). Coagulation test; activated partial thromboplastin time/aPTT: 37.3 (control:34.8), prothrombin time/PT: 12.4 (control 14.4), fibrinogen 413 mg/dL, and D-dimer 0.20 μ g/mL. However, the cardiac enzyme of both CK-MB and Troponin-I were dramatically increased (71 U/L and 20073, respectively).

His electrocardiogram revealed ST-segment elevation in all precordial lead and inferior lead (II, III, AvF). (Fig. 1) His chest X-ray showed infiltrate in both lungs (Fig. 2)

During his treatment at Emergency Hospital, the patient was receiving Ceftriaxone 2x1 gram

Intravenously (IV), Favipiravir 1x1600 mg (first day) and 2x600 mg for the second to the fifth day, Ibuprofen 3x600 mg, Colchicine 2x0.5 mg,

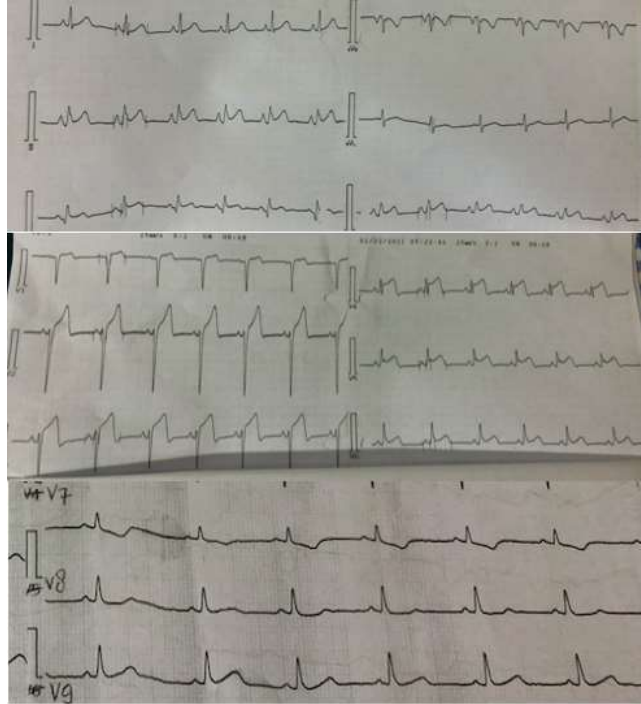


Fig 1. ECG Examination: ST-elevation almost in all lead

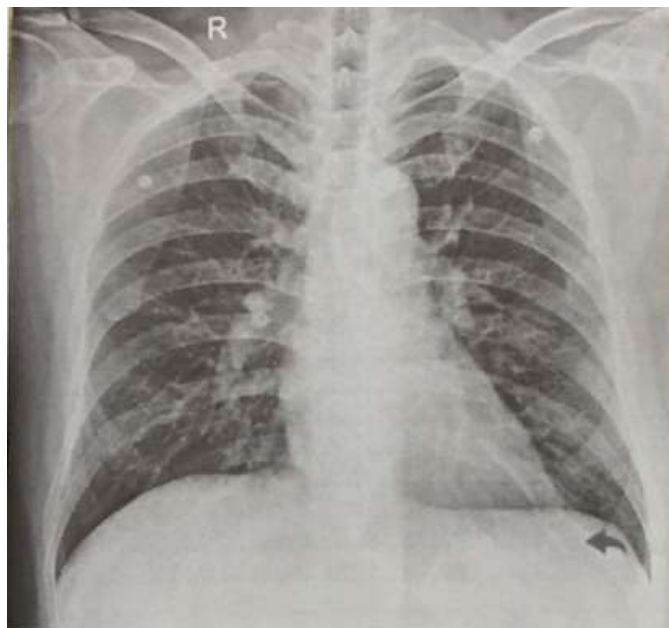


Fig 2. Chest Rontgen: Infiltrate in both lungs

Diazepam 1x2 mg, and multivitamins once daily (Vitamin C, Vitamin D3, and zinc). He also received Acetylsalicylic acid 320 mg, Clopidogrel 1x300 mg, Isosorbide dinitrate 5 mg, and Atorvastatin 40 mg during his acute reaction at the emergency hospital. Right after his admission to our hospital, he was delivered to our catheterization laboratory (cathlab), and the procedure was done from the right radialis using sheath 6F, heparin 5000-unit, nitroglycerin 300 unit, and Cath TIG 5Fr. His angiography showed left dominant system circulation, with ectasia vessels, residual thrombus, and TIMI 2 flow to the distal segment at the left anterior descendent/LAD. (Fig. 3). However, we could not continue our examination to endomyocardial biopsy due to facility limitations and the pandemic situation

(lowering time of exposure). He was diagnosed with COVID-19-related myocarditis after we proved no significant stenosis lesion.

Based on the angiography result, we decided to discontinue acetylsalicylic acid, clopidogrel, and isosorbide dinitrate. We gave the patient 2.5 mg beta-blocker to reduce oxygen consumption, and treatment of COVID-19 continued by our pulmonologist. We continued our treatment in the isolation ward and his condition was getting better every day. One week later, the patient received a negative result for the PCR test and sinus rhythm for the ECG examination with chest pain-free. He was permitted to leave the hospital and we advised him to take the drug until further evaluation at the outpatient clinic.

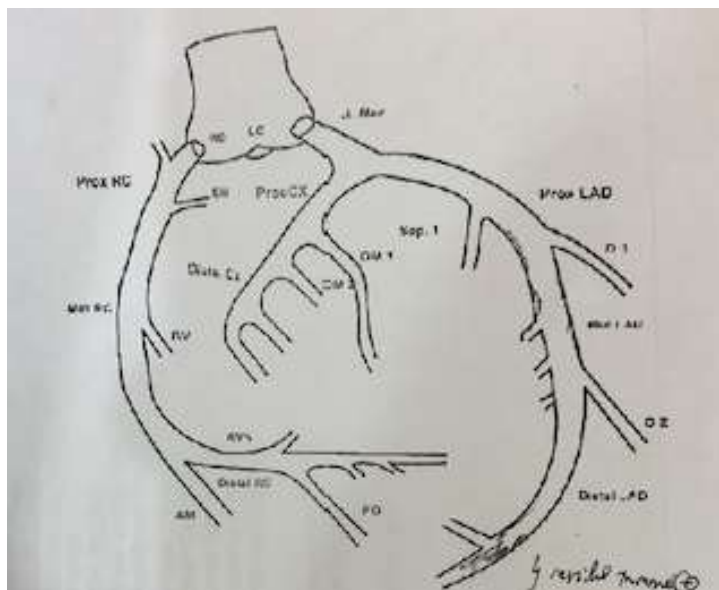


Fig 3. Schematic Representation of Angiography Result

DISCUSSION

Viral myocarditis is the most common myocarditis, and it can be divided into three phases; acute phase (virus replicate in the highest intensity), subacute phase (activation of antibody), and chronic phase (inflammation of the heart is resolved and cardiac remodeling).¹¹ Besides direct infiltration, heart damage could be caused by cross-reactivity between antibodies or T cells.¹² Current evidence shows that SARS-CoV-2 also causes myocarditis through cross-reactivity.¹³ This condition might worsen with cytokine storm with interleukin-6 (IL-6) as the central mediator.¹⁴ Pro-inflammatory cells and cytokines in COVID-19 patients could initiate or deteriorate arrhythmia in patients with pre-existing heart rhythm problems.¹⁵

Post-mortem cardiac tissue real-time reverse transcription polymerase chain reaction (RT-PCR) found SARS-CoV-2 in a child's heart tissue with COVID-19 and proved that SARS-CoV-2 has cardiac tropism.¹⁶ SARS-CoV-2 attaches to angiotensin-converting enzyme-2 (ACE2) via spike protein which cleaves as the S1/S2 and it is mediated by a serine protein (TMPRSS2).¹⁷ Interaction between SARS-CoV-2 and renin-angiotensin system (RAS) via hACE2 triggers a fulminant immune response and coagulation abnormality that leads to COVID-19-related myocarditis.¹⁸ The RAS has an important role in microvascular which lead to multiorgan injuries, especially in COVID-19-related myocarditis.¹⁹ The liver organ simultaneously releases

angiotensinogen that circulates in the systemic circulation. Renin, which is produced by the kidney, breaks it into angiotensin I (AngI). The AngI is cleaved by ACE, which is located on the vascular, into angiotensin II (Ang).^{1,20} Ang II is the most active product in the "classical pathway" of the RAS and causes vasoconstriction, fibrosis, oxidative stress, proinflammatory, and aldosterone release. Meanwhile, angiotensin II (AngII) and angiotensin receptor II will provide a protective mechanism.¹⁶ On the other hand, ACE2 converts AngI and AngII which later on attach to MAS receptors which also serve as a protective mechanism.²¹

Diagnosing COVID-19-related myocarditis is challenging in a pandemic situation. It has a broad spectrum of symptoms.²² In severe conditions, the patient could present with chest pain several days after virus exposure.²³ Blood examination test in myocarditis shows elevated inflammation markers such as increasing leucocytes, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and other inflammation markers.¹⁵ Cardiac enzymes such as troponin (Cardiac troponin I and Cardiac troponin T) and creatine kinase are increasing in COVID-19-related myocarditis due to myocardial injury.²⁴ The N-terminal-Pro-B-type natriuretic peptide (NT-proBNP) could elevate due to indirect myocardial stress in COVID-19-related myocarditis.²⁵ One of the simplest tools for screening myocarditis is an

electrocardiogram which presents with ST-segment changes, including ST-segment elevation and PR depression.²⁶ Even though the EMB is still the gold standard for diagnosing myocarditis, both American Heart Association (AHA) and European Society of Cardiology (ESC) realized in pandemic situations that EBM procedure is unfavor.^{23,26} The American Heart Association (AHA) recommends cardiovascular magnetic resonance (CMR) for diagnostic assessment in COVID-19-related myocarditis. However, not all hospitals have a COVID-19 protocol for magnetic resonance imaging examination.²³

In our case, the patient was presented with chest escalating chest pain, ST-elevation, increasing cardiac enzyme value, and inflammation marker. Previous COVID-19-related myocarditis, both in younger and older patients, showed elevation of cardiac enzyme due to cardiac injury and elevation of inflammation marker due to immune response.^{27,28} However, the ECG examination presented inconsistent results in COVID-19-related myocarditis.²⁹ Since not all hospital has a protocol for CMR and EBM to diagnose COVID-19-related myocarditis, the European Society of Cardiology (ESC) encourages to rule out coronary artery disease (CAD) in a patient suspected with COVID-19-related myocarditis and it is reasonable for us to exclude CAD condition using coronary angiography.³⁰ In our case, we diagnosed COVID-19-related

myocarditis after combining symptoms, laboratory work, and ruling out CAD through coronary angiography examination. There is no rigid rule for treating COVID-19-related myocarditis. The previous report encouraged the use of corticosteroids for COVID-19-related myocarditis.³¹ In our situation, as the inflammation markers remarkably increased, we persisted in not using immunosuppression in active inflammation conditions.³⁰

CONCLUSIONS

COVID-19 has become a novel glitch in medical practice situations. Not only lungs, but it involves many other organs, and the heart is one of the most common organs involved. Cardiac manifestation varies from coronary rhythm to inflammation problems. Myocarditis is one of the challenging heart diseases, especially during a pandemic. Cardiac biopsy is the gold standard assessment for diagnosing myocarditis, but international societies even realize how hard it is in a pandemic situation. Even though it is tricky, diagnosing COVID-19-related myocarditis depends on available local resources. Moreover, since there is no guideline for treating COVID-19-related myocarditis, clinical judgment is needed to treat COVID-19-related myocarditis according to the patient's condition. We are also suggesting international cardiology society to conduct management guidelines for COVID-19-related myocarditis.

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