American Journal of Medical Case Reports, 2022, Vol. 10, No. 9, 218-223
Available online at http://pubs.sciepub.com/ajmcr/10/9/2
Published by Science and Education Publishing
DOI:10.12691/ajmcr-10-9-2

SARS-CoV 2 Virus Causing Fulminant Myocarditis: A Rare But Serious Complication of COVID-19 Infection

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Received July 26, 2022; Revised September 04, 2022; Accepted September 12, 2022

Abstract The COVID-19 pandemic has been one that has brought widespread suffering and grief throughout the world; and the complications associated-both short and long term have been widespread and autonomous. We present a case of a 68-year-old White Hispanic male who presented to the emergency department with worsening exertional dyspnea and fatigue eight days after testing positive for SARS-CoV-2. On arrival the patient was afebrile, hypotensive, tachycardic, tachypneic and hypoxemic. Initial workup was significant for ~~high~~ elevated inflammatory markers, troponin and β-natriuretic peptide. EKG was unremarkable. Transthoracic echocardiogram revealed severe global hypokinesis of the left ventricle, reduced ejection fraction of 25%-30%, grade II diastolic dysfunction, mild pulmonary hypertension and mild elevated right atrial pressures, and no pericardial effusion. PCR analysis for usual cardiotropic viruses were all negative, Antinuclear antibody (ANA) was negative, therefore the patient was diagnosed with fulminant COVID-19 myocarditis. Patient was treated with heparin drip, oxygen support, pressors, and high dose corticosteroid therapy in the intensive care unit for 5 days. After showing significant signs of improvement, the patient was discharged on hospital stay day 7. Cardio-respiratory complications are the leading cause of morbidity and mortality in terms of patients suffering with COVID-19. In this case we discuss the importance of early diagnosis and prompt management to reduce the high mortality and complications associated with these complications.

Keywords: *Covid-19, myocarditis, SARS-CoV-2, complications, cardiac*

Cite This Article: Abou Dargham Hanadi, Brar Rajvir, Dadashzadeh Shima, Hanna Mena, and Chong Josebelo, "SARS-CoV 2 Virus Causing Fulminant Myocarditis: A Rare But Serious Complication of COVID-19 Infection." *American Journal of Medical Case Reports*, vol. 10, no. 9 (2022): 218-223. doi: 10.12691/ajmcr-10-9-2.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a global pandemic and is one of the leading causes of all-age morbidity and mortality (over 240,000 deaths) in the year 2020, behind only cardiovascular disease and cancers [1]. COVID-19 has a diverse range of manifestations in infected patients, ranging from asymptomatic, to flu-like symptoms, to acute respiratory distress syndrome (ARDS), fulminant multi-organ dysfunction, and death [2]. Predisposing comorbidities such as diabetes, obesity, hypertension, and pre-existing cardiovascular disease were observed in over 15-30% of affected patients [4,5,6]. In recent retrospective studies, 11-20% of hospitalized COVID-19 patients were found to have evidence of cardiac injury with an associated five-fold chance of requiring mechanical ventilation with over a 50% mortality rate [5,7].

Cardiac complications include atrial or ventricular tachyarrhythmias, heart failure, ventricular wall thickening, nonischemic wall motion abnormalities, pulmonary hypertension, and rarely myocarditis (0.1%), pericarditis, acute coronary syndrome, stress cardiomyopathy cardiac tamponade, and cardiogenic shock [2,6,7,8,9,10,12]. Recently, concerns of endothelial dysfunction have been associated with COVID-19, leading to consequential thrombogenesis in adults and multi-system inflammatory syndrome in children, an atypical form of Kawasaki disease [4].

The pathophysiology of COVID-19 is not well described yet. COVID-19 purportedly induced indirect myocardial injury through a systemic inflammatory response mediated by cytokines [5,11]. Corticosteroid therapy is largely the mainstay of treatment for inflammatory COVID-19 myocarditis as it's been used in ARDS with a demonstrated 23% reduction in 28-day mortality rates [1].

Colchicine, an anti-inflammatory medication used most often to treat gout, intravenous immunoglobulin, and other immunotherapies are being investigated. Other proven COVID-19 therapies include convalescent plasma and remdesivir with somewhat equivocal results.

2. Case Description

A 68-year-old White Hispanic male from a correctional facility presented to our emergency department with worsening exertional dyspnea and fatigue eight days after a positive SARS-CoV-2 nucleic acid amplification by polymerase chain reaction (PCR) nasopharyngeal swab. He denied chest pain or abdominal pain. His past medical history was significant for hemodialysis-dependent end stage renal disease, type II diabetes mellitus, essential hypertension, carotid artery stenosis, and coronary artery disease.

On presentation, he was afebrile (37.1°C), hypotensive (86/43 mm hg), tachycardic (110 beats per minutes), tachypneic (24 respirations per minute), and hypoxemic (89% on room air). He appeared fatigued but not in distress. His cardiovascular examination revealed no audible murmurs or jugular venous distention. His lung fields were clear to auscultation. Initial laboratory workup showed high levels of inflammatory and cardiac biomarkers with troponin I of 296.109 ng/ml (0-0.033 ng/ml); β-natriuretic peptide of 4,360 pg/ml (<100 pg/ml), a blood urea nitrogen of 46.4 mg/dL (8.4-25.7 mg/dL); creatinine of 7.0 mg/dL (0.7-1.3 mg/dL), C-reactive protein (CRP) of 20.30 mg/dL (0.01-0.82 mg/dL); erythrocyte sedimentation rate (ESR) of 78 mm/hr (<1.15 mm/hr), hemoglobin of 10.4 gm/dL (13.6-17.0 gm/dL), serum glucose level of 202 mg/dL (70-110 mg/dL); Interleukin (IL) 6 was elevated at 231.82 pg/ml (<5.00 pg/ml) (Table 1).

A twelve-lead electrocardiogram (ECG) showed a normal sinus rhythm, incomplete right bundle branch block and left ventricular hypertrophy. Chest x-ray showed basal predominant ground glass opacification of the lungs with no pleural effusions. Heart size within normal limits (Figure 1). Computed tomography angiogram of the chest with contrast showed patchy ground glass opacities scattered throughout the lungs with small bilateral pleural effusions and extensive mediastinal lymphadenopathy (Figure 2a, 2b). Due to elevated cardiac biomarkers, the patient was started on heparin drip. A transthoracic echocardiogram (TTE) was performed that revealed severe global hypokinesis of the left ventricle, reduced ejection fraction of 25%-30%, grade II diastolic dysfunction, mild pulmonary hypertension and mild elevated right atrial pressures and, no pericardial effusion.

Table 1. Laboratory Studies during Hospitalization

Variable	Initial Presentation	5th day of Hospitalization	Adult Reference Range
White Blood Cell	6.1	12.6	4000-10000 uL
Bicarbonate	26	21	22-29 mmol/L
Anion Gap	23	25	5-14
Troponin I	296.109	86.868	0-0.33 ng/mL
ALT/ AST	63/326	57/56	0-55 u/L / 5-34 u/L
C Reactive Protein	20.3	5.6	0.01-0.82 mg/dL
Interleukin-6	231.82	12.77	<5.00 pg/mL
Blood Urea Nitrogen (BUN)	62	117.4	8.4-25.7 mg/dL
Creatinine	7.5	9	0.7-1.3 mg/dL
Hemoglobin	9.1	9	13.6-17. Gm/dL
Hematocrit	26	26.7	39-49%
Platelet	88	173	150,000-400,000 uL

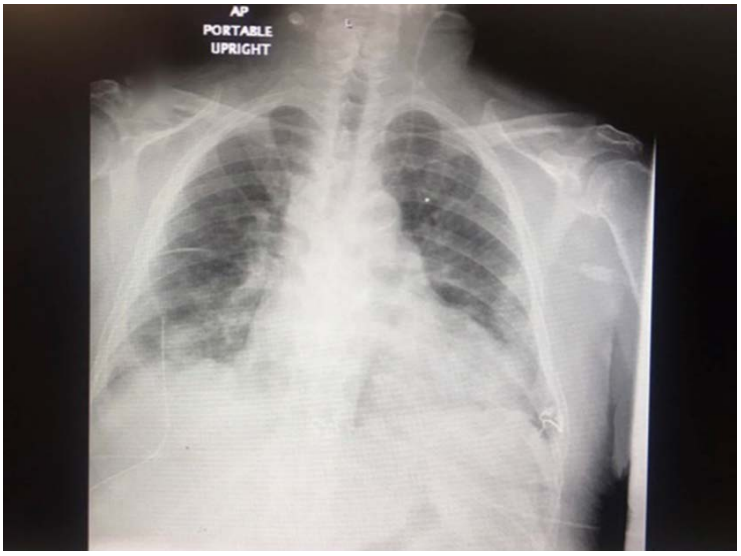

Figure 1. CXR findings on admission showing ground glass opacification of the lungs with no pleural effusions

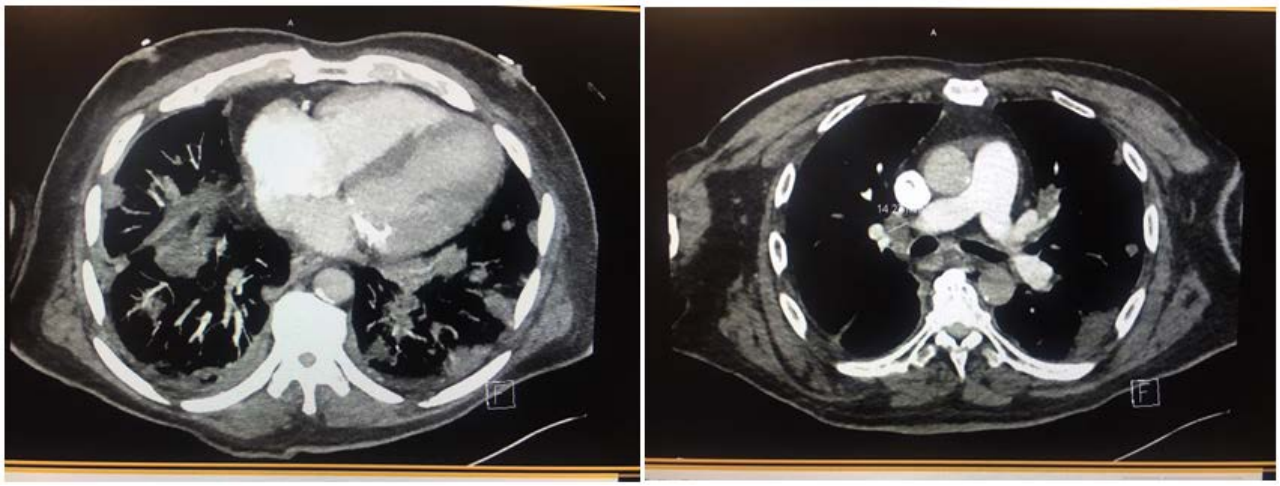

Figure 2a/2b. CT Angiogram of chest shows scattered patchy ground glass opacities throughout the lung parenchyma with small bilateral pleural effusions and extensive mediastinal lymphadenopathy

On hospital day one, the patient underwent left heart catheterization that revealed nonobstructive coronary artery disease with TIMI-3 flow in all vessels, patent stents and elevated left ventricular end diastolic filling pressures. PCR analysis for usual cardiotropic viruses including influenza, coxsackie A & B, CMV, adenovirus, and parvovirus B19 were all negative. Antinuclear antibody (ANA) was negative. Based on the clinical presentation, markedly elevated inflammatory and cardiac biomarkers, normal ECG, normal coronary angiogram, echocardiographic changes, positive SARS-COV-2 PCR, the patient was diagnosed with fulminant COVID-19 myocarditis with stage B cardiogenic shock and acute hypoxic respiratory failure secondary to COVID-19 pneumonia.

Treatment in the intensive care unit consisted of oxygen supplementation (10 L via nasal cannula) without the need for mechanical ventilation; pressor support with norepinephrine infusion titrated to keep a mean arterial pressure greater (MAP) than 65 mm Hg; intravenous heparin drip; pulse therapy with high-dose methylprednisolone (500 mg daily) for three days; empiric antibiotic coverage with ceftriaxone and doxycycline for five days; aspirin (81 mg daily); and atorvastatin (80 mg daily) in addition to hemodialysis for fluid management.

On hospital days four and five, the patient showed signs of significant clinical, hemodynamic and respiratory improvement. His oxygen requirement was reduced to 2 liters/minute via nasal cannula and norepinephrine was discontinued. His troponin I level peaked at 361.425 ng/ml, CRP trended down to 5 mg/dl; interleukin (IL)-6 to 12.7 pg/ml (Table 1). After completing three days of intravenous steroids, he was started on oral prednisone (40 mg daily). After seven days of hospital stay (5 days in the ICU), the patient was discharged back to his correctional facility on 2 liters oxygen via nasal cannula; prednisone (40 mg daily with a plan to complete a four to six week course); heart failure management which included metoprolol (12.5 mg daily), lisinopril (40 mg daily), aspirin (81 mg daily), and atorvastatin (40 mg daily); hemodialysis per his schedule for fluid management.

3. Discussion

COVID-19 has spread rapidly from country to country covering the globe, with more than 74.7 million reported cases by December 2020 [13]. More than 1.65 million people have succumbed to the viral syndrome, and at least 42.1 million people have essentially recovered [13]. COVID-19 has symptoms that can be focal or systemic. The respiratory system is most commonly affected which can range from sneezing, rhinitis, shortness of breath, non productive cough, and pharyngitis. Diarrhea symptoms have also been seen. Systemically, fever and fatigue has been noted.

SARS-CoV-2 is a virus that consists of a single strand of RNA topped by a “sticky” crown of proteins with fast mutation and recombination, and high similarity to other coronaviruses which have appeared in previous years (SARS and MERS) [14]. The shape of the virus lends or gives credence to its name: corona, which is Latin for crown. The spikes attach to the host; whether human or animal, and allow the virus to insert its genetic material into the cell nucleus. Coronaviruses are classified as zoonotic; meaning they can affect both animals and humans [2].

Cardiac injury, indicated by increased hypersensitive troponin I, is a common comorbidity in COVID-19 patients, reported in 12 to 77% of cases[15]. Patients with more cardiovascular comorbidities are more likely to develop cardiac complications. Regardless of previous history of cardiovascular disease; acute cardiac injury and heart failure are more commonly seen in diseased patients [15]. Interstitial mononuclear inflammatory cells have been noted to infiltrate the myocardium of the heart. Cytokines such as interleukin (IL), interferon (IFN), and monocyte chemotactic protein 1 (MCP-1) have been noted to be elevated.

IL-6 has been detected in COVID-19 patients with illness deterioration and associated death [15]. Various types of myocarditis may induce different contents of cytokine storm, which can cause cardiac dysfunction, even death [15]. The cytokine release syndrome or cytokine storm, a hypothesis related to the severity of inflammation in the infection by COVID-19 that generates cardiac

involvement, signifies the importance of utilizing systemic corticosteroids and IVIG to counteract its effects [14].

Greater than 20% of patients with COVID-19 have elevations in cardiac troponin and other manifestations of cardiac injury i.e. impaired left ventricular ejection fraction and an elevation in type-B natriuretic peptide (BNP)[4]. Four mechanisms have been proposed for the underlying etiology of cardiac injury in COVID-19; myocarditis, cytokine storm, coronary artery ischemia in the setting of underlying coronary artery disease and increased vascular thrombosis of small and large coronary arteries that can occur in the absence of coronary artery disease[4]. Increased thrombosis and pro-coagulative changes, plaque rupture, demand ischemia or vasospasm are also associated proposed mechanisms[16].It is known that the presence of cardiovascular disease is a risk factor for a poor prognosis in COVID-19 infection. The cardiac injury could also occur as a result of global ischemia related to multi organ failure, respiratory distress and associated hemodynamic and metabolic abnormalities [4].

Fulminant myocarditis is characterized by sudden and severe diffuse inflammation of the myocardium, which can lead to ventricular arrhythmias, cardiogenic shock and death [16]. While most patients have no previous history of cardiovascular comorbidities, our patient however had type II diabetes mellitus, hypertension and CAD which is known to worsen cardiac complications secondary to COVID-19 [4].

Our patient's c reactive protein (CRP) and Interleukin 6 were elevated at 20.30 mg/L and 231.82 pg/ml, respectively. This was likely due to a cytokine storm secondary to COVID-19 myocarditis. ESR levels are elevated in localized and systemic inflammatory and infectious processes in the body. They can also be elevated in tissue injury/ischemia [4]. Interleukin (IL) 6 is a potent proinflammatory mediator that is vital in immune defense and immune-mediated disease. There are IL-6 inhibitors which are monoclonal antibodies directed against the IL-6 receptor (IL-6R). COVID-19 purportedly induces an indirect myocardial injury through a systemic inflammatory response mediated by cytokines [5,11]. The predominant portal of entry for COVID-19 infection is by angiotensin converting enzyme 2 (ACE2) expression in the upper respiratory epithelium in the lungs, however in a single-center report of 416 patients hospitalized with COVID-19, 19.7% had some evidence of cardiac injury which is suggestive of a possible pathologic role for myocardial ACE2 expression [5]. Expressions of host genetic factors such as the ACE2, TMPRSS2, and DPP4 genes in pericytes, cardiomyocytes, and vascular smooth muscle cells play pivotal roles in determining the severity of COVID-19 infection [5]. COVID-19's surface spike protein also binds to human ACE-2 receptors, replicates within myocardial cells, leading to direct myocardial injury evidenced by elevated serum troponin levels and serum cardiac enzymes [7]. This could be misconstrued as acute coronary syndrome sometimes in positive cases of COVID-19.

Viral myocarditis has been a major cause of dilated cardiomyopathy that can lead to heart failure. Historically adenovirus and coxsackievirus have been commonly linked to myocarditis. Human herpesvirus-6 and parvovirus B19 are common causes of myocarditis in the United States. A viral panel in regards to the etiology of the pericarditis was completed on our patient. Cytomegalovirus (CMV) IgM, adenovirus antibody, coxsackie A & B, parvovirus B19 IgM were all negative in this patient's case. COVID-19 testing was the only viral test that was positive. In our patient and based on his coronary angiogram he was significantly suspected to have fulminant COVID-19 myocarditis.

The definitive diagnosis of myocarditis is with an endomyocardial biopsy (EMB) with evidence of inflammatory cells in the myocardium, abnormal cardiac magnetic resonance (CMR) imaging, or at the molecular level where there is direct evidence of viral infection and replication [4]. Lake Louise Criteria for CMR diagnosis of myocarditis is at least two of the following criteria; myocardial edema with myocardial signal intensity increase in T2-weighted images, hyperemia and capillary leakage with increased signal intensity ratio between myocardium and skeletal muscle in T1-weighted images with late gadolinium enhancement (LGE), and/or LGE defined as at least one focal lesion with non ischemic regional distribution in T1-weighted images [16,18].

Clinical criteria for the diagnosis of myocarditis includes acute chest pain (pericarditis or pseudo-ischemic), palpitations, unexplained arrhythmia, syncope, and/or unexplained cardiogenic shock. Objective criteria include an ECG (i.e. new onset bundle branch block, premature ventricular complexes, QT prolongation), elevation in troponin T or I, or functional or structural abnormalities on cardiac imaging (i.e. echocardiogram, angiogram, CMR [22]. A meta summary and analysis of COVID19-induced myocarditis showed that the median age of infection was 55 with 69% of those patients being male [16]. Common presenting symptoms were fever, cough, shortness of breath, and chest pain. ECG changes included non-specific ST-segment and T-wave changes and ventricular tachycardia [16].

The mortality rate of COVID-19 is estimated to be less than 1% which is mainly due to severe acute respiratory syndrome and multi organ dysfunction [21]. The prevalence of myocarditis among COVID-19 patients is unclear mainly due to early reports that lacked the specific diagnostic modalities to assess myocarditis. Roughly up to 7% of COVID-19 related deaths were attributable to myocarditis [21]. The long-term impact of COVID-19 myocarditis, including the majority of mild cases, remains unknown [21].

Treatment of confirmed myocarditis ranged from systemic corticosteroids i.e. methylprednisolone, hydrocortisone, oral prednisone; hydroxychloroquine, lopinavir/ritonavir, colchicine, tocilizumab, and IVIG. Antivirals, anti-inflammatory agents, immunosuppressives have played a role in the treatment of viral illnesses that are not well known. Guidelines from the European Society of Cardiology Working Group on Myocardial and Pericardial Disease recommend that heart failure and arrhythmias caused by myocarditis should be optimally managed including ACE inhibitors, beta-adrenergic blockade, anti arrhythmics, diuretics, temporary pacing if indicated, and extracorporeal membrane oxygenation (ECMO) [16]. For our patient, he was above the median age for those with severe cardiac complications due to infection with COVID-19.

The American Heart Association (AHA) recommends initial management of fulminant myocarditis with subsequent cardiogenic shock utilizing inotropes and/or vasopressors [21]. If indicated based on patient clinical status, mechanical ventilation or mechanical circulatory support i.e. extracorporeal membrane oxygenation (ECMO), ventricular assist device, or intra aortic balloon pump for long term management. Tocilizumab, sarilumab, and siltuximab are interleukin-6 inhibitors that have potential utility in acute cardiovascular syndrome (ACovCS) secondary to COVID-19 [22]. Acute cardiovascular syndrome (ACovCS) has been proposed as a syndrome secondary to COVID-19 [22]. It includes, however, is not limited to acute myocardial injury, cardiomyopathy, and arrhythmias. Tocilizumab is now being tested in randomized controlled trials that recruits patients with COVID-19 and elevated IL-6 levels. This particular antibody may be beneficial in the management of cytokine storm syndrome resulting from chimeric antigen receptor T cell therapy and help to alleviate myocardial inflammation [22]. In the interim, these agents can be utilized on a case by case basis for compassionate use with a multidisciplinary approach in mind [21]. Given the association between myocarditis and autoantibodies, the use of intravenous immunoglobulin (IVIG) is theorized as a possible treatment modality in viral myocarditis.

A well conducted study showed that IVIG did not improve left ventricular ejection fraction, myocarditis, or event-free survival at a one-year follow up [22]. Due to a lack of supporting evidence, its routine use is discouraged however the treatment did not appear to have any deleterious effects on patient clinical outcome. The use of corticosteroids in active-infection myocarditis according to the European Society of Cardiology (ESC) is likewise discouraged due to ineffectiveness [21]. Managing arrhythmias secondary to fulminant myocarditis is based on type of arrhythmia with bradyarrhythmias requiring temporary cardiac pacing and tachyarrhythmias with antiarrhythmics (i.e. lidocaine and mexiletine) [21].

This case illustrates the importance of prompt diagnosis of COVID-19 fulminant myocarditis based on ECG, cardiac biomarker, echocardiographic changes and endomyocardial biopsy when available and quick initiation of supportive treatment to reduce the high mortality and complications associated with it.

4. Conclusion

While SARS-CoV-2 primarily causes symptomology of a pulmonary infection, presentations such as fulminant myocarditis have been shown, and remain a dangerous complication of COVID-19. Those with cardiovascular disease and heart failure are at higher risk but with early diagnosis and management, we hope that morbidity and mortality from such complications can be minimized. Mechanisms for the cardiac damage caused by the coronavirus have been postulated, including effects of cytokines, especially IL-6 which is commonly elevated in patients with COVID-19 infection. Agents aimed at reducing overall inflammation, including specifically decreasing IL-6 levels, such as Tocilizumab have been found to play a significant role in symptom reduction and management. We hope that by early detection and management many long term sequelae can be prevented and complications can be avoided.

List of Abbreviations

ANA - Anti-neutrophil antibody
ARDS - Acute respiratory distress syndrome
MERS - Middle East Respiratory Syndrome
ACE2 - Angiotensin Converting Enzyme 2
CMV - Cytomegalovirus
EMB - Endomyocardial biopsy
CMRI - Cardiac magnetic resonance imaging
LGE - Late gadolinium enhancement

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