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REVIEW

COVID-19 myocarditis

Reinaldo B. Bestetti, Rosemary Furlan-Daniel, Luciano P. Pereira

Faculty of Medicine, University of Ribeirão Preto, San Paolo, Brazil

Abstract

Background: Myocarditis can be observed in patients with COVID-19. Myocarditis can also be seen in patients vaccinated against SARS-CoV-2 infection, the etiological agent of this disease. Epidemiological, morphological, pathophysiological, clinical aspects, clinical course, and potential therapeutics for patients with COVID-19 myocarditis are not entirely clear.
Methods: We perform a search in PubMed linking the terms "COVID-19 and myocarditis", "SARS-CoV-2 and myocarditis", and "vaccine and myocarditis and COVID-19". A hand-search of references from retrieved papers has also been done. We selected papers dealing with the epidemiological, morphological, clinical aspects, and therapeutic regarding COVID-19 myocarditis.
Results: Myocarditis can be clinically diagnosed in about 2% of patients with COVID-19 illness, but its prevalence is higher (up to 33%) in autopsied with this disease. At magnetic resonance imaging, myocarditis can be diagnosed in up to 60% patients in the short-term follow up after SARS-CoV-2 infection. A few ultrastructural studies have detected SARS-CoV-2 in endothelial cells, macrophages, neutrophils, fibroblasts, and inside cardiomyocytes. Shortness of breath, fever, cough, and precordial chest pain are the main clinical symptoms; in half patients, ground glass opacities in chest X-ray are also observed, although oxygen saturation may be normal. COVID-19 myocarditis may occur in a patient with no past cardiac history and may alternatively be a late phenomenon in the course of the disease. COVID-19 myocarditis can also affect children and adolescents; acute heart failure is the predominant clinical manifestation, including fulminant myocarditis, in this population. Elevated troponin blood levels are observed in the majority of patients. Abnormal electrocardiogram findings – usually ST-segment changes and inverted T waves – can be detected in at least 25% of cases. Abnormal echocardiography can be found in 3% of cases and left ventricular systolic dysfunction can be found in 67% of such cases. The clinical course of COVID-19 myocarditis is usually benign with most patients recovering from the myocardial insult. Non-steroidal anti-inflammatory drugs are the treatment for noncomplicated cases; colchicine is added in case of associated pericarditis. Corticosteroids have largely been used. Mechanical support is lifesaving in cases of cardiogenic shock. Post-vaccination myocarditis is very rare, and less frequently found than COVID-19 myocarditis.
Conclusions: Although relative rare, myocarditis may be a serious complication of COVID-19 illness.

Key words SARS-CoV-2, COVID-19, myocarditis.

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**Correspondence to: Reinaldo B. Bestetti, Faculty of Medicine, Universidade de Ribeirão Preto (UNAERP), Av. Costabile Romano 2201, 14096-900 San Paulo, Brazil.*
Tel.: +55.1636037031. E-mail: rbestetti44@gmail.com.br

Introduction

SARS-CoV-2, the etiologic agent of COVID-19 pandemic, has caused at least 676 million cases of COVID-19 throughout the world as of March of 2023, with a death rate of almost 7 million people.[1] Since 2020, SARS-CoV-2 has suffered several mutations, and the new variants, especially the Omicron variant, the dominant strain at this time,[2] has been associated with a less severe disease than the Delta variant,[3] which preceded the appearance of the Omicron variant,[2] as well as the ancestral strain.

About 13 billion vaccine doses have been given from around the world as March, 2023.[1] New medications have been shown to favorably impact on dismal prognosis of vulnerable people with COVID-19.[3] Collectively, these findings account, at least in part, for the reduced death rate of COVID-19 from 115.6 per 100,000 people in 2021 to 61.3 per 100,000 people in 2022.[4] However, the SARS-CoV-2 has not been eradicated. Unvaccinated (roughly about 20% of the population in

the USA) and vulnerable people, mainly the immunocompromised patients, continue to be at high risk of death or hospitalization due to COVID-19.[3]

Heart injury detected by elevated troponin blood levels (ETBL) has been found in about 8% to 36% of patients with COVID-19 illness.[5-8] ETBL are an independent predictor of all-cause mortality for patients with COVID-19 illness,[8] and more frequently found in patients with severe than in those with mild to moderate COVID-19 ailment.[9] Nevertheless, ETBL are not synonymous with the diagnosis of COVID-19 myocarditis, as they can be found in several types of cardiac disease and in patients with pneumonia.[10]

An international registry study including hospitalized patients with COVID-19 from February, 2020 to April, 2021 shows that the prevalence of myocarditis as detected by clinical findings, magnetic resonance imaging (MRI) or endomyocardial biopsies (EMB) is about 4/1000 patients.[11] A population-based study has estimated the prevalence of COVID-19 myocarditis around 45/100.000 people, similar to that found in hospitalized patients.[12] However, the prevalence in the follow-up of COVID-19 patients may be higher. A prospective study carried out 71 days on average following recovery from COVID-19 illness with cardiac MRI showed ongoing myocarditis in 60 (60%) patients.[13]

Accordingly, the aim of this paper is to provide an overview about morphological, pathophysiological, clinical aspects, clinical course, and potential therapeutics for patients with COVID-19 myocarditis.

Morphological and histopathological aspects

The incidence of active or borderline myocarditis varies from 7% to 33% in autopsy studies carried out in patients with COVID-19 illness.[14-19] In a 12-case series of complete autopsy, borderline myocarditis was observed in 1 (8%) out of 12 patients as an incidental finding.[15] In 21 autopsied cases, lymphocytic myocarditis has been detected in 3 (14%) patients with no association with ETBL. In that study, increased interstitial macrophage infiltration not accompanied by myocyte necrosis was observed in 18 (86%) patients, thus suggesting that this high concentration of myocardial macrophages would be the consequence of elevated systemic levels of pro-inflammatory cytokines.[16] Another case series enrolling 14 autopsied patients show active lymphocytic myocarditis in 1 (7%) out of 14 patients.[17]

A *post-mortem* study enrolled 15 patients with COVID-19: 12 of them with active disease and 3 with cleared disease (a negative genetic test at the time of autopsy or before death, but having a previous positive confirmatory genetic test). Active lymphocytic myocarditis was present in 5 (33%) patients. Interestingly, nonocclusive fibrin microthrombi was detected in 12 (80%) patients with COVID-19 illness. No virus was detected at ultrastructural examination.[18] A recent overview on 277 autopsy cases performed in patients with COVID-19 illness has shown active myocarditis in 20 (7%) patients and borderline myocarditis in 35 (13%) patients. Interestingly, small vessel coronary thrombi were observed in 30 (11%) patients.[19] A review on 201 cases (9 by EMB, 192 by autopsy) showed that 14 (7%) patients had myocarditis; 9 active (4.5%), and 5 (2.5%) borderline myocarditis.[20]

Endomyocardial biopsies have been performed in patients with suspected COVID-19 myocarditis. Sala *et al.*[21] reported a case consistent with SARS-CoV-2 acute myocarditis; diffuse interstitial oedema with scattered foci of myocardial necrosis were observed at histopathological examination. A patient with fulminant myocarditis underwent EMB, and the histological study revealed a borderline myocarditis and vacuolated macrophages. Ultrastructural study revealed viral particles consistent with SARS-CoV-2 in interstitial cells, but not inside myocytes.[22] Dolhnikoff *et al*. described a case of a 11-year-old child who developed the multisystem inflammatory syndrome and acute respiratory distress syndrome with ETBL. Histopathology revealed active myocarditis. Electron microscopy revealed SARS-CoV-2 particles in the interstitium, and inside cardiomyocytes, endothelial cells, macrophages, neutrophils, and fibroblasts.[23]

An endomyocardial study performed in 104 patients revealed that 5 (5%) were positive for SARS-CoV-2 genome detection; two patients had acute myocarditis (one active myocarditis; one borderline myocarditis). The other three patients had a diagnosis of inflammatory cardiomyopathy (myocarditis with left ventricular systolic dysfunction). Immunohistochemical showed marked myocardial inflammation involving small vessels leading to arterial obliteration.[24]

The mechanism associated with SARS-CoV-2-induced myocarditis in patients with COVID-19 illness is still controversial and multifactorial. Because the virus can occasionally be seen inside the myocardium, a direct virus effect disrupting myocytes has been postulated.[23] Intracellular components released in view of myocyte necrosis, leading to epitopes similar to viral antigens, presented by major histocompatibility complex, has also been suggested as a cause of an autoimmune myocarditis.[25] Another possibility would be endothelial dysfunction, but no firm evidence has been demonstrated.[20] A cytokine storm mediated by increased plasma levels of interleukin-6 might lead to myocardial fibrosis.[25] Thrombotic microangiopathy might also play a role in the pathogenesis of COVID-19 myocarditis.[12]

A quantification of viral load in the heart of 39 autopsied patients showed a copy number >1000 copies per µg RNA of SARS-CoV-2, which is considered clinically significant, in 16 (41%) of them. In addition, in situ hybridization of SARS-CoV-2 revealed that the virus was not inside the myocytes, but in the myocardial interstitial cells. Furthermore, an increased expression of pro-inflammatory myocardial cytokines was observed in patients with >1000 copies per µg RNA SARS-CoV-2. No mononuclear cell infiltrate was detected in the myocardium of such patients.[26] Taken together; these findings suggest that cytokine may play a pivotal role in the pathogenesis of SARS-CoV-2-induced myocarditis.[25]

Clinical features of COVID-19 myocarditis

The clinical picture of COVID-19 myocarditis varies from clinically mild to fulminant myocarditis. Systematic reviews in patients with COVID-19 myocarditis showed shortness of breath in 75% to 82% of patients, fever in 55% to 83%, cough in 55%, and chest pain in 55% of patients.[11,27,28] Shortness of breath and cough are more frequently observed in patients with concomitant pneumonia.[11] However, COVID-19 myocarditis can be diagnosed in patient with no past cardiac history and normal electrocardiogram (ECG).[29] Moreover, myocarditis may be a late phenomenon in SARS-CoV-2 infection; it may appear one to three weeks after hospital discharge without cardiac symptoms.[30,31] Fulminant myocarditis usually appears in patients with severe COVID-19 illness;[22] in a series of 54 patients, fulminant myocarditis was diagnosed in about 39% of them.[11]

COVID-19 myocarditis may affect children and adolescents as well. The clinical picture is usually heart failure with no previous symptom indicative of SARS-CoV-2 infection, including no lung involvement.[32] Myocarditis may also appear in adolescents with clear SARS-CoV-2 infection manifested by fever and glass opacities in the chest X-ray.[33] Fulminant myocarditis during the course of an acute infection manifested by fever and heart failure has also been observed in such pediatric patients.[34]

Among the laboratory tests, patients with COVID-19 myocarditis show ETBL in 91% of cases;[27] usually, they are 20-fold the normal values.[11] Elevated white blood count and C-Reactive Protein blood levels can also be observed, especially in patients with concomitant pneumonia.[11]

Ground glass opacities in the chest X-ray can be seen in 67% of cases.[28] Although oxygen desaturation is frequently found in patients with concomitant pneumonia,[11] it is important to emphasize that the oxygen saturation may be normal in those patients without pneumonia.[28] Conversely, the acute respiratory distress syndrome is usually seen only in patients with concomitant pneumonia.[11]

Abnormalities in the 12-lead ECG seen in patients with COVID-19 myocarditis can be found in at least 25% of cases,[27] being higher in patients with pneumonia than in those without.[11] Such abnormalities are comprised of sinus tachycardia, left ventricular hypertrophy, bi-atrial enlargement,[35] ST-T segment elevation,[36] T wave changes,[6,28] localized,[33] or diffuse,[37] low voltage of the QRS-complex,[30] multiple premature ventricular contractions,[38] and ventricular tachycardia.[39] Atrial fibrillation can be observed in about 13% of patients, and ST-T elevation in 26% of cases.[11] Malignant arrhythmias developed more frequently in patients with ETBL than in those without.[8]

At echocardiography, myocarditis has been diagnosed in 3% of patients.[40] Left ventricular dilatation (LVD) can be observed in 67% of such patients,[28] left ventricular systolic dysfunction (LVSD) in 60% to 67%,[27,28] and pericardial effusion from 33% to 46% of cases.[11, 28] Usually, LVD and LVSD are mild.[11] Increased E/E' at tissue Doppler imaging and reduced left ventricle longitudinal strain at speckle tracking echocardiography, which correlates with myocardial oedema at cutaneous radiation injury, also contribute to the diagnosis of myocarditis.[41]

Magnetic resonance imaging is useful to diagnose acute myocarditis according to the updated Lake Louise criteria – the presence of either myocardial oedema or myocardial injury in 90% of patients with COVID-19 ailment.[11,42] Nonetheless, only 8% of patients had both conditions.[11] MRI reveals diffuse myocardial oedema frequently,[21,43] but late gadolinium enhancement indicative of myocardial necrosis may be,[30,31] or may not be present.[21] In fact, late gadolinium enhancement compatible with myocardial fibrosis affects only 4% of patients with or without ETBL.[43] Pericardial effusion and LVSD can also be found. Patients recovered from the acute infection but with precordial chest pain, palpitations or chest distress have been found to have myocardial oedema and myocardial fibrosis in 54% and 31% of cases, respectively.[44]

It is important to emphasize that myocarditis/inflammatory cardiomyopathy (ETBL along with reduced biventricular function) may also be found in children and adolescents with the multisystem inflammatory syndrome caused by SARS-CoV-2 infection. This syndrome affects patients less than 21years of age, but more than half patients are >10-year-old. These patients may show cutaneous rash, conjunctivitis, oral lesions, fever, and abdominal pain. Coronary artery dilatation, as observed in Kawasaki disease, may be seen; however, myocardial dysfunction is not usually observed in Kawasaki disease.[45]

Differential diagnosis

COVID-19 myocarditis should be clinically differentiated from several cardiac diseases in view of different treatment possibilities. COVID-19 myocarditis should be differentiated from stress-induced cardiomyopathy. Demertzis *et al.* described a patient with SARS-CoV-2 infection with ETBL, and a transthoracic echocardiogram with a transitory systolic ballooning of the basal segment of the left ventricle consistent with stress-induced cardiomyopathy.[46] Sang III *et al*. reported a case of 58-year-old woman who presented with respiratory distress caused by the 2009 H1N1 influenza and SASRS-CoV-2 infection, ETBL, and impairment of the left ventricular apex disproportional to that seen in the basal regions at echocardiography consistent with stress-induced cardiomyopathy. [47]

De Vita *et al.* reported a case of a woman who present with COVID-19, which had delivered a baby one month ago. She presented with ETBL, left ventricular dilatation and LVSD. MRI failed to show either tissue oedema or myocardial fibrosis, both consistent with acute myocarditis. Therefore, the diagnosis of peripartum cardiomyopathy was raised.[48]

COVID-19 myocarditis must also be differentiated from obstructive coronary disease-induced acute heart failure. A 56-year-old man presented to a hospital complaining of shortness of breath, ETBL, a new left bundle branch block in the resting ECG, diffuse bilateral patchy airspace opacities through the lungs at chest X-ray, and LVSD at echocardiography. A presumptive diagnosis of COVID-19 myocarditis was done. He progressed to shock and was transferred to another institution where he was placed on a venous extracorporeal membrane oxygenation.

Polymerase chain reaction for SASRS-CoV-2 infection was negative, and a coronary angiogram disclosed a 99% obstruction in the left anterior descending coronary artery.[49]

Clinical course

The clinical course of COVID-19 myocarditis is characterized by recovery from the myocardial insult in most patients.[21,24,29-36,50-53] Cardiac tamponade and cardiogenic shock,[52,54] usually secondary to fulminant myocarditis,[55,56] are the most frequent complications of COVID-19 myocarditis illness. Overall, the death fatality rate is 5% to 7% during hospital stay, and it is higher in patients with concomitant pneumonia in comparison with those without.[11]

In a retrospective analysis of the cause of death in 150 patients in China, acute myocarditis with cardiogenic shock was the cause of death in 5 (7%) patients, and myocarditis with respiratory failure caused the death of 22 (33%) patients.[57] Up to 70% of patients are treated in a critical care unit, and 18% of them need mechanical circulatory support. The median hospital stay is 13 days. Mortality in a 4-month follow up is 7%; nevertheless, it is higher in patients with pneumonia (15%) in comparison with those without (0%).[11]

Fulminant myocarditis has also been observed in an unvaccinated patient with normal C reactive protein with mild myocardial inflammatory infiltrate, thus suggesting that myocarditis may be the consequence of direct cytotoxic viral effect rather than an autoimmune mechanism.[58]

Even though the Omicron variant causes less aggressive disease, fulminant myocarditis has been observed in an unvaccinated 66-year-olf female associated with Omicron BA.2 lineage. Endomyocardial biopsy showed only mild interstitial inflammatory cell infiltration without necrosis, but immunostaining revealed diffuse CD3+ T lymphocytes and interstitial CD68+ macrophages infiltration. She was treated with tocilizumab with good results.[59]

Management

At the present, no evidence-based medicine support has been available for the treatment of COVID-19 myocarditis. Hospitalization is indicated in patients with mild to moderate COVID-19 myocarditis.[12] The clinical treatment of COVID-19 myocarditis may be supportive with anti-inflammatory drugs in non-complicated cases.[51] In those with LVSD, the standard treatment for congestive heart failure (CHF) has been used.[24,29,31] Nevertheless, low dose of betablocker is advised in patients with severe LVSD because this drug may provoke cardiogenic shock in such patients.[12] Colchicine has been added to cases with associated pericardial effusion or in those with associated acute respiratory distress syndrome.[52,55]

Corticosteroids have been given to many patients with COVID-19 myocarditis regardless of the severity of the clinical picture.[6,30,36,37,52,55] Overall, about 59% of patients with COVID-19 myocarditis have been treated with either oral or intravenous corticosteroids.[11] Immunoglobulin may be added to the therapeutic regimen in patients with severe COVID-19 myocarditis,[6,36,53] and it has been used in up to 19% of patients with this condition.[11] Tocilizumab has been used in up to 9% of patients with COVID-19.[11,55] Antiviral treatment has also been used in the treatment of COVID-19 myocarditis.[6,21,30,53] In an international registry, antiviral drugs, especially ritonavir/lopinavir, were used in about 21% of cases.[11]

Patients with fulminant COVID-19 myocarditis should be referred to a center with expertise in the treatment of this condition, especially with the use of mechanical circulatory support, particularly with V-A extracorporeal membrane oxygenation.[12] In patients with cardiogenic shock due to COVID-19 myocarditis, vasopressors and inotropes have been used in 39% and 33% of cases, respectively.[11] Mechanical support can be used in up to 17-18% of cases if drugs did not stabilize hemodynamic conditions.[11,27] Intra-aortic balloon pump can be used in the treatment of cardiogenic shock in patients with this condition,[56] but extra corporeal membrane oxygenation is life-saving in many patients with fulminant COVID-19 myocarditis.[6,22,53,56]

Patients who recovered from myocarditis regardless of the clinical picture severity should not perform physical exercise for 3 to 6 months. After that, the performance of physical exercise, especially in high-performance athletes and high-school athletes, will depend on the lack of symptoms, normal troponin levels, normal left ventricular function, and lack of arrhythmias. However, cardiac MRI might still reveal abnormalities consistent with myocarditis in up to 59% of such patients. In this circumstance, physical exercise performance should be postponed.[12]

Post-vaccination myocarditis

Vaccination against SARS-CoV-2 with mRNA vaccines can rarely be associated with myocarditis. Overall, the risk of mRNA vaccine-induced myocarditis is about 5 cases/100,000 patients, affecting mainly male from 16 to 30 years (11 to 15 cases/100,000 subjects). In general, myocarditis is more frequently observed 30 days after the second dose of mRNA vaccine. In 95% of cases, myocarditis has a benign clinical course. However, fulminant myocarditis has been observed in one patient from more than 5 million vaccinated people. Conversely, the risk of myocarditis in unvaccinated people is about 1/10,857 patients. Clearly, the risk of myocarditis is higher in people with SARS-CoV-2 infection than in those vaccinated with mRNA vaccine against SARS-CoV-2.[60]

A series of 8 cases with post-vaccination myocarditis has been reported in detail. Of interest, all patients presented with chest pain, and five patients had fever. ETBL were increased in all patients at presentation. One patient, who had myocarditis after two days of the first dose, had previous experienced SARS-CoV-2 infection; endomyocardial biopsy showed no active myocarditis. The remaining patients had myocarditis 2-4 days following the second dose. At echocardiography, segmental wall

motion abnormalities were found in five patients, and generalized hypokinesis in the remaining three patients. MRI showed delayed gadolinium enhancement and oedema in all patients. The clinical course was benign in all patients.[61]

Interestingly, injection with mRNA vaccine in patients with previous history of myocarditis previously to the SARS-CoV-2 infection appears not to pose patients at greater risk of myocarditis. In fact, in a series of 34 cases, only one patient developed myocarditis two days following vaccination with good clinical course.[62]

Conclusions

Myocarditis may affect up to 4,5% of patients with COVID-19 illness diagnosed clinically, and in up to 33% of patients at autopsy. SARS-CoV-2 has been found in interstitial and endothelial cells, as well as inside cardiomyocytes. In about half patients, COVID-19 myocarditis has been found associated with ground glass opacities in the chest X-ray, although it can be either detected late in the course of the disease or in patients without symptoms consistent with COVID-19 illness. Precordial chest pain, ETBL, ST-T wave changes, left ventricular systolic dysfunction, and left ventricular dilatation at echocardiography are prominent diagnostic cues. The clinical course is usually benign, although some patients can present with fulminant myocarditis, including pediatric patients. The treatment of COVID-19 myocarditis is not supported by evidence-based medicine. Nonsteroidal anti-inflammatory drugs, standard treatment for CHF, and glucocorticoids have been used in the real-world. In patients with fulminant myocarditis, besides vasopressor and inotropic drugs, mechanical circulatory support, particularly extracorporeal membrane oxygenation, can be saving-life.

Contributions

RBB, designed the work, data acquisition, analysis and interpretation of data for the work, wrote the manuscript draft, final approval of the manuscript to be published; RFD, data acquisition, analysis and interpretation of data for the work, critical review of the manuscript for important intellectual content, final approval of the manuscript to be published; LPP, analysis and interpretation of data for the work; critical review of the manuscript for important intellectual content; final approval of the manuscript to be published. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare no conflict of interest.

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