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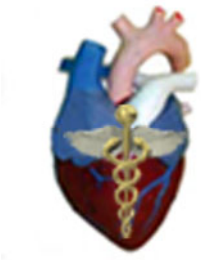

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EDITORIAL

COVID-19 Related Myocarditis: Diagnosis and Management

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Abstract

A comprehensive review of current data on COVID-19 related myocarditis is herein presented. ***Rhythmos 2022;17(2): 25-31***.

Key Words: COVID-19; SARS-CoV-2; acute myocarditis; acute cardiac injury; heart failure; COVID-19 vaccines; endomyocardial biopsy; cardiac magnetic resonance imaging

Abbreviations: COVID-19 = corona virus disease 2019; PCR = polymerase chain reaction; WHO = World Health Organization

Introduction

Although cardiac troponin is elevated in ≥1/3 of patients with COVID-19 infection, with higher levels noted in more severe infections, acute myocarditis had not been definitely confirmed during the initial period of the pandemic.[1-4] In COVID-19 patients, acute myocardial injury, defined by an increased troponin level above the 99th percentile, may be due to ischemic and non-ischemic myocardial processes, including myocardial infarction (MI) type 1, acute coronary syndrome with normal or near-normal coronary arteries (ACS-NNOCA), acute myocarditis, multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults, severe respiratory infection with hypoxia, critical illness and sepsis, systemic inflammation, endothelial injury and "endotheliitis", pulmonary thrombosis and embolism, other prothrombotic and procoagulant responses to COVID-19 infection, cardiac adrenergic hyperstimulation during cytokine storm syndrome, type 2 MI, or Takotsubo syndrome (TTS) (**Table 1**) .[2, 4-10] Since ≥1 of these etiologies may coexist, it may be challenging to identify a specific cause. [11]

Initially, there were limited reports on definite myocarditis caused by SARS-CoV-2 and limited demonstration of direct infection of the myocardium by the virus with viral particles in the myocardium.[12-15]

An initial meta-analysis of 4189 confirmed COVID-19 infected patients from 28 studies showed that acute cardiac injury, defined as high cardiac troponin levels, was more frequent in those with severe, compared to milder, disease (risk ratio - RR 5.99; P<0.001) and was associated with higher mortality (RR 3.85; P<0.001).[16] The authors emphasized the need for cardiac monitoring to prevent myocarditis in patients infected with COVID-19.

Thus, not all cases of elevated cardiac troponin represent typical myocarditis; as mentioned, other mechanisms involve microangiopathy (combined coagulopathy and vasculitis), reduced troponin clearance

in patients with acute kidney injury, type 1 or type 2 MI, and/or systemic inflammatory response with cytokine storm producing cytokine-driven myocardial damage, particularly in the late phases of the disease characterized by acute respiratory distress syndrome, multiorgan failure, and mortality.[4, 17] High cytokine levels may reflect a key cause of myocardial injury in COVID-19, related to direct myocardial injury, endothelial dysfunction, destabilization of coronary plaque, and microthrombogenesis. [4, 7-9]

Table 1. Causes/Mechanisms of High Cardiac Troponin/ Cardiac Injury in Patients with COVID-19 Infection

- *Myocardial ischemia* including typical acute MI
- *ACS-NNOCA* (Acute Coronary Syndrome with Normal or Near-normal Coronary Arteries) / Takotsubo syndrome (TTS)
- *Other non-ischemic etiologies* / severe respiratory infection with hypoxia, critical illness and sepsis, systemic inflammation, endothelial injury and "endotheliitis", pulmonary thrombosis and embolism, other prothrombotic and procoagulant responses to COVID-19 infection, cardiac adrenergic hyperstimulation during cytokine storm syndrome, type 2 MI
- ***Acute myocarditis*** / Cardiomyocyte infection due to the SARS-CoV-2 / Myocardial damage due to the direct viral action
- *Cytokine storm* / cell-mediated cytotoxicity by *activated* CD8 T lymphocytes migrating to the heart and causing myocardial inflammation (IL-6 seems is central mediator of cytokine storm)
- Interferon-mediated hyperactivation of the innate and adaptive immune system, especially in pediatric patients
- *Drug-induced myocarditis* / cardiotoxic antiviral therapies (e.g., chloroquine and hydroxychloroquine)

The pathogenesis of viral myocarditis may involve inflammatory damage mediated by overactivation of the autoimmune system (cytokine storm), direct damage by the virus to the heart; and secondary causes such as fever, hypoxia, etc.[18] It is argued that an endomyocardial biopsy (EMB) is needed to prove COVID-19 myocarditis, while a PCR test from a respiratory sample is not specific.[14, 19] Thus, the commonest mechanism of COVID-19 related myocarditis seems to be immune-mediated inflammatory injury with the viral infection being the initiating factor of myocarditis, while other secondary factors might also occasionally cause myocardial damage.

Cases of clinically suspected COVID-19-induced myocarditis have been corroborated by cardiac magnetic resonance (CMR) or proven by EMB and/or pathology examination on autopsy.[13, 14, 20-23] The CMR findings of myocarditis include subepicardial edema and a late gadolinium-enhanced (LGE) image showing a high intensity signal indicating necrosis in the same region.[22]

Case Series / Systematic Reviews

A case series of 20 critically ill children admitted for shock due to an acute myocarditis (median left ventricular - LV ejection fraction-LVEF 35%; troponin, 269 ng/mL) related to COVID-19 infection, initially presented with intense abdominal pain and fever for 6 days.[24] All children but one needed an inotropic/vasoactive drug support and 8 were intubated. Patients received various therapies including intravenous immunoglobulin with adjuvant corticosteroids, interleukin (IL) 1 receptor antagonist or a monoclonal antibody against IL-6 receptor. All children survived and were afebrile with a full LV function recovery at discharge from the intensive care unit (ICU).

A systematic review of 9 case reports and 2 retrospective studies indicated that COVID-19 myocarditis affected patients aged >50 years with equal gender distribution.[25] Patients presented with dyspnea, cough, fever with hypotension and chest pain. Laboratory findings included leukocytosis, increased C-reactive protein, and respiratory acidosis. All cardiac markers were elevated. Chest X-ray showed bilateral ground glass opacities or bilateral infiltrates, while CMR produced LGE. Electrocardiography demonstrated ST-segment elevation or inverted T waves, while echocardiography revealed reduced LVEF with cardiomegaly or LV hypertrophy. Management with corticosteroids was favored in most cases, followed by antiviral medication. The majority of studies reported either recovery or stable condition.

Another systematic review of COVID-19-related myocarditis reported 14 cases of myocarditis/ myo-pericarditis with a male predominance (58%) and a median age at 50.4 years.[26] The majority of patients did not have a previously identified comorbid condition (50%), but of those with a past medical history, hypertension was most prevalent (33%). Electrocardiographic findings were variable, and troponin was elevated in 91% of cases. Echocardiography, performed in 83% of cases, showed reduced LV function in 60%. Endotracheal intubation was performed in the majority of cases. Glucocorticoids were most commonly used in treatment of myocarditis (58%). The majority of patients survived to discharge (81%) and 85% of those that received steroids survived to discharge.

Another review reported 12 cases of confirmed COVID-19 related myocarditis and 39 with possible myocarditis (median age 55 years; 69% male).[3] The most common presenting symptoms were fever, shortness of breath, cough and chest pain. Electrocardiographic changes included non-specific ST-segment and T-wave changes and ventricular tachycardia. Most patients had elevated cardiac and inflammatory biomarkers. Left ventricular dysfunction and hypokinesis was common. CMR established the diagnosis in 10 patients, with features of cardiac edema and myocardial injury on T1-weighted imaging with LGE; EMB was not available in most cases; only 2 patients had histopathological examination, one with EMB and one by autopsy after sudden death. Some cases required mechanical ventilation and extracorporeal

membrane oxygenation (ECMO); 30% of patients recovered but mortality was high at 27%.

A recent systematic review of 54 case reports and 5 cohorts identified 215 COVID-19 infected patients with myocarditis.[27] Comorbidities included hypertension (51.7%), diabetes (46%), and cardiac comorbidities (15%). Symptoms included cough (62%), fever (60%), shortness of breath (53%), and chest pain (44%). High inflammatory markers were present in 98%, and increased cardiac markers were present in 95% of patients. Cardiomegaly (32.5%) was the most common radiographic finding. ST segment elevation was present in 45% patients and T wave inversion in 7%. CMR imaging disclosed myocardial edema in 83%, with LGE in 64% of patients. In hospital management included azithromycin (25.5%), methyl-prednisolone/ steroids (8.5%), and various other therapies for COVID-19. The most common in-hospital complication included acute respiratory distress syndrome (66%) and cardiogenic shock (14%). Finally, 65% of the patients survived, whereas 32% of patients succumbed to their disease.

A retrospective multicenter study described 25 children admitted to pediatric ICUs for cardiogenic shock, LV dysfunction, and severe inflammatory state (median age at admission 10 years, range, 2-16 years).[28] Comorbidities were present in 28%, including asthma and overweight. Gastrointestinal symptoms were prominent. LVEF was <30% in one-third; 80% required inotropic support with 28% treated with ECMO. Inflammation markers were suggestive of cytokine storm (IL-6 median, 135 pg/mL) and macrophage activation (D-dimer median, 5284 ng/mL). Mean B-type natriuretic peptide (BNP) was elevated (5743 pg/mL). Thirty-one of 35 patients (88%) tested positive for SARS-CoV-2 infection by polymerase chain reaction (PCR) of nasopharyngeal swab or serology. All patients received intravenous immunoglobulin, with adjunctive steroid therapy used in one-third. Left ventricular function was restored in the 25 of 35 of those discharged from the ICU. No patient died, and all patients treated with ECMO were successfully weaned.

Importantly, approximately ≥50% of cases with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 have evidence of myocarditis.[29, 30] Although there is an overlap between this syndrome (MIS-C) and Kawasaki disease, myocardial involvement requiring vasopressor support is more common in MIS-C vs Kawasaki disease (~50% vs 5%). [30]

Differential Diagnosis

A recent report on COVID-19 associated myocarditis suggested two distinct etiologies of primary acute heart failure with equal incidence in patients with COVID-19 infection, viral myocarditis and Takotsubo syndrome (TTS)/cardiomyopathy.[31] COVID-19 myocarditis, TTS cardiomyopathy, and severe COVID-19 can be clinically indistinguishable. All can present with dyspnea and evidence of cardiac injury, although in myocarditis and TTS, this is due to primary LV dysfunction as compared to respiratory failure in severe COVID-19. Direct viral infection (COVID-19-associated myocarditis) differs from COVID-19 respiratory failure by an early shock state, while some patients develop TTS cardiomyopathy. Regardless of etiology, steroids may be a beneficial treatment, similar to other critically ill COVID-19 patients. Finally, evidence of acute cardiac injury including ECG changes and/or high troponin levels in patients with COVID-19 should prompt investigation for concurrent myocarditis.

CMR vs EMB

A definitive diagnosis of myocarditis is based upon findings on EMB, an approach supported by the WHO classification and definition of cardiomyopathies, as well as expert statement and society guidelines.[32, 33] EMB can have added useful and discriminant information, leading to a more accurate diagnosis and better therapeutic options.[34] EMB can contribute to the exclusion of infectious agents or viral genome in the myocardium which is essential for patients who may be candidates for immunosuppressive treatments and can also provide prognostic information. [35] Also, based on animal models, non-specific anti-inflammatory therapy or low-dosage steroids are not advised for patients without histological confirmation of myocarditis, since they could hinder virus clearance.[33]

Although EMB is the gold standard examination to provide histological diagnosis in myocarditis, many patients with suspected myocarditis may not be considered candidates for EMB, mostly due to its invasive nature and its attendant risks. In such circumstances, CMR may be most helpful in the majority of cases (**Table 2**).

Table 2. Diagnostic Testing for COVID-Related Myocarditis

Clinical information and examination
Positive PCR testing for SARS-CoV-2
Recent COVID-19 vaccination
Electrocardiography
Cardiac troponin
Echocardiography
CMR (preferred method)
? Coronary angiography
? EMB *

EMB = endomyocardial biopsy; PCR = polymerase chain reaction

* EMB is not recommended for the routine assessment of patients suspected of having COVID-19 myocarditis and should be limited to cases of severe or refractory heart failure where histological findings may guide therapeutic choices

Indeed, CMR is the gold standard, noninvasive diagnostic tool for suspected myocarditis.[36] CMR findings in typical cases include diffuse edema and subepicardial LGE suggestive of myocyte necrosis. However, absence or minimal amount of LGE has also been observed in COVID-19 patients correlating with the few histological results published to date, reporting limited or absent myocyte necrosis,[15, 37] suggesting an indirect mechanism of myocardial inflammation.[38]

According to a single-center study comprising patients discharged with a COVID-19 diagnosis and myocardial injury as indicated by elevated high-sensitivity troponin T, CMR frequently revealed occult coronary artery disease, high rates of myocarditis-like LGE, and sometimes dual pathology.[39] The lack of edema in these patients suggests that the myocarditis-like scar may be permanent.

A possible mimicker of myocarditis in patients with COVID-19 infection is the multisystem inflammatory syndrome (MIS) which is serious cardiac complication of COVID-19 causing endothelial (endotheliitis) and vascular damage (vasculitis) in the heart and resembling Kawasaki disease, albeit with intact cardiomyocytes.[30, 40]

In a German cohort of 100 patients recently recovered from COVID-19, CMR showed cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis.[41] The most prevalent abnormality was myocardial inflammation (60%), followed by regional scar and pericardial enhancement. EMB in 3 patients with severe findings revealed active lymphocytic inflammation. The authors suggested that these findings indicate the need for ongoing investigation of the long-term cardiovascular consequences of COVID-19.

It is argued by investigators and European and other Guidelines that clinical and laboratory data do not suffice to establish the diagnosis of myocarditis, as myocarditis has a great variability in clinical and radiological patterns of presentation, and only EMB is able to detect the etiology and also provide prognostic information, particularly in cases of viral myocarditis.[34] On the other hand, CMR imaging cannot exclude myocardial infections, whereas EMB provides additional prognostic information. [42] Thus, the combination of CMR and EMB could provide improved diagnostic accuracy by overcoming some limitations of each individual technique and thus may be the best option to enhance the diagnostic yield in the absence of significant coronary artery disease. [43]

As mentioned, cause and effect relationship between SARS-CoV-2 infection and myocarditis is difficult to demonstrate. However, evidence of myocardial inflammation with or without direct cardiomyocyte damage, suggesting different mechanisms responsible for COVID-mediated myocarditis has been recently provided. A systematic review of eligible studies of laboratory confirmed COVID-19 infection and a clinical and/or histological diagnosis of myocarditis by ESC or WHO/ISFC criteria, revealed reports of 38 cases (26 males, 24 aged <50 years) with histological data found in 12 cases (8 EMB and 4 autopsies) and CMR being the main imaging modality to confirm a diagnosis of myocarditis (25 patients).[44] The first histologically proven case was a virus-negative lymphocytic myocarditis; however, biopsy evidence of myocarditis secondary to SARS-CoV-2 cardiotropism has also been shown recently. There was a substantial variability in biventricular systolic function during the acute episode and in therapeutic regimen used. In hospital mortality was 13% (5 patients).

COVID-19 Vaccination Related Myocarditis

Besides COVID-19-related myocarditis, COVID-19 vaccines have also been reported to cause myocarditis.[45-47] However, patients' course and CMR imaging findings of COVID-19 vaccine-related myocarditis are re-assuring as these cases are relatively mild and mostly benign.[45, 48]

A case series of 23 males (median age, 25 years), previously healthy and fit, within the US Military Health System who experienced myocarditis after COVID-19 vaccination (7 after the BNT162b2-mRNA vaccine and 16 after the mRNA-1273 vaccine) indicated that patients presented with acute onset of marked chest pain within 4 days after receipt of an mRNA COVID-19 vaccine.[49] The majority (n=20) had symptom onset following the second dose of the vaccine. All patients had significantly elevated cardiac troponin levels. Among 8 patients who underwent CMR imaging during the acute phase, all had findings consistent with the clinical diagnosis of myocarditis. Additional testing did not identify other etiologies for myocarditis. All patients received brief supportive care and were recovered or recovering at the time of the report. These cases occurred among 2.8 million administered doses of mRNA COVID-19 vaccine in this period.

In keeping with reports indicating that myocarditis following COVID-19 vaccination is often mild, seen more commonly in young healthy males and followed by rapid recovery with conservative treatment, another systematic review of 85 articles comprising 2184 patients showed a predominantly male (73%) and young population (mean age 25.5 ± 14.2 years) experiencing myocarditis with most having received an mRNA-based vaccine (99%).[50] The mean duration from vaccination to symptom onset was 4.01 ± 6.99 days. Chest pain (90%), dyspnea (26%) and fever (12%) were the most common symptoms. Only 2.3% had comorbidities. C-reactive protein (CRP) was elevated in 83% and cardiac troponin in 98% patients. An abnormal ECG was reported in 97% patients with ST-segment elevation being most common (35%). Echocardiographic data were available for 57% of patients, of whom 23% had

reduced LVEF. Nonsteroidal anti-inflammatory agents (77%), steroids (14%) followed by colchicine (7%) were used for treatment. Mortality was reported at 0.5%.

Another review of 40 case reports indicated that the majority of cases were seen in males (90%; mean age 29 years).[51] In 65% of cases, patients had received the BNT162b2 vaccine; 30% of cases were reported with the mRNA-1273 vaccine; and 5% of cases with JNJ-78436735. Of all the cases, 80% were reported after the second dose of the vaccine with either Moderna or Pfizer.

A recent systematic review of 200 cases of possible COVID-19 vaccine-related myocarditis from 52 publications of case reports, with information obtained from 5 vaccine safety surveillance databases, suggested low overall incidence rates of 2-5 per million mRNA vaccines. [52] A higher incidence was reported in younger male populations, with onset of symptoms within a few days, usually after the second dose, although some patients with prior COVID-19 infections had earlier onset, after the first dose. The majority presented with chest pain (98%) and all had high troponin levels; CMR imaging was commonly reported. Clinical course was mild in the majority, with response to anti-inflammatory therapies.

Among >2.5 million vaccinees who received at least 1 dose of the BNT162b2 mRNA vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among males aged 16-29 years; most cases were mild or moderate in severity.[53]

For diagnosis of vaccine-related myocarditis, as for viral myocarditis, CMR has been recommended as a most practical approach, considered the gold standard, non-invasive diagnostic tool for suspected myocarditis, revealing typical mid-subepicardial non-ischemic LGE. [36, 44, 48, 54, 55]

Course and Complications

The clinical course of COVID-19 myocarditis can be benign but also fulminant complicated by arrhythmias and/or sudden cardiac death, heart failure, hypotension and cardiogenic shock (**Table 3**). Indeed, the clinical course of the viral disease may be worrisome with mortality rates up to 10-32%. [3, 26, 27] However, the vaccine-associated cases of acute myocarditis have mostly a benign course and favorable prognosis with mortality rates <1%. [50]

Table 3. Course and complications of COVID-19 Related Myocarditis

- Benign course
- Fulminant course
- Arrhythmias
- Acute heart failure
- Hypotension
- Cardiogenic shock
- Cardiac death (pump failure)
- Sudden death

Management

Management of COVID-19 related myocarditis follows society guidelines indicating etiology-targeted therapy and optimal care of arrhythmia and of heart failure (**Table 4**). [33, 56-58] Immunomodulators are used including dexamethasone, IL-6 inhibitors (tocilizumab, sarilumab), or Janus kinase inhibitors (e.g., baricitinib, tofacitinib). Preferred antiviral therapies include nirmatrelvir with ritonavir; *or* sotrovimab; *r*emdesivir; baricitinib; tocilizumab; sarilumab. Additional therapies include steroids (dexamethasone), anakinra, heparin (prophylactic or therapeutic when there is evidence of thrombosis), treatment of coinfections, use of cardioprotective medications (e.g., β-blocker and angiotensin-converting enzyme inhibitors), and/or antiarrhythmics as needed.

Patients with hemodynamically unstable heart failure should receive current guideline-directed therapies for heart failure in ICUs with respiratory and mechanical cardio-pulmonary support facilities. [56-58] In acute/ fulminant cases with cardiogenic shock and severe LV dysfunction, ventricular assist devices or ECMO may be needed to provide a bridge to transplant or to recovery.

Table 4. Management of COVID-19 Related Myocarditis [56, 57]

Rest
Nonsteroidal anti-inflammatory drugs (myopericarditis)
Colchicine (myopericarditis)
Antiviral agents (tocilizumab/favipiravir/infliximab, etc.)
Immunomodulatory agents (steroids/IV immunoglobulin)
Interleukin-6 inhibitors
Heparin (prophylactic or therapeutic in presence of thrombosis)
Anakinra for refractory cases
Cardioprotective medications (e.g., β-blocker and ACEI)
? High-dose ascorbic acid
? Melatonin
Hemodynamic support (inotropic agents/ vasopressors/ Intra-aortic balloon pumping (IABP)/ ECMO)
Mechanical ventilation
Avoiding or deferring high-intensity physical activity and competitive sports until complete recovery

High-dose IV *vitamin C* may ameliorate cardiac injury through alleviating hyperinflammation in severe and critically ill patients with COVID-19. [59] Also, some findings indicate that *melatonin* may depresses inflammation and oxidative stress, induce antiapoptotic and antifibrotic actions in the damaged myocardium, and favor parasympathetic system dominance sparing energy stores, and has been suggested to alleviate the myocardial injury occurring in COVID-19 in terms of myocarditis, ischemic damage and heart failure. [60]

Conclusion

It seems that investigators have challenged the evidence of definitive EMB/autopsy proof that SARS-CoV-2 causes direct cardiomyocyte damage in association

with histological myocarditis according to ESC/WHO criteria, whereby etiological diagnosis of viral myocarditis is based on histological and immunohistological evidence of nonischemic myocyte necrosis and monolymphocytic infiltration (myocardial inflammation/myocarditis), plus the identification of a specific cardiotropic virus by molecular techniques, in particular PCR/in-situ hybridization, on EMB/autopsy tissue.[61]

However, clinical, epidemiological and imaging data do suggest that SARS-CoV-2 does cause myocarditis in a small/moderate percentage of patients, while it is hypothesized that the rare virus-negative biopsy-proven cases may represent new-onset immune-mediated or latent pre-existing autoimmune forms of myocarditis, triggered or promoted by the hyperinflammatory state of severe COVID-19 infection. Furthermore, several cases of COVID-19 vaccine temporally related myocarditis have also been reported, albeit of a mostly mild course and a favorable prognosis. Although EMB has been the gold standard for a definite diagnosis of myocarditis, CMR has supplanted this invasive tool due to its non-invasive nature and satisfactory diagnostic yield. The clinical course may be worrisome and management of the COVID-19 associated myocarditis seems to be challenging with mortality rates reaching 10% to 32%, whereas the vaccine-associated cases of acute myocarditis have mostly a benign course and favorable prognosis with mortality rates <1%.

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