REVIEW ARTICLE

Myocarditis Associated with COVID19: A Review of Myocarditis in the COVID19 Era

Megha Patel DO[1]; Daniel McGraw MD[1]; Danyal M Khan MD[2]
[1]Department of Graduate Medical Education, Nicklaus Children's Hospital, Miami, Florida
[2]Department of Cardiology, Nicklaus Children's Hospital, Miami, Florida

ABSTRACT

As the Coronavirus disease 2019 (COVID-19) pandemic has evolved, uncertainty regarding the potential for myocarditis associated with COVID-19 infection has instilled collective anxiety. In the same vein, MIS-c is a well-publicized and particularly dreaded consequence of COVID-19 infection that most often presents with clinically significant myocarditis. Yet another factor is myocarditis following mRNA-based vaccination against COVID-19. This has posed additional challenges for providers, not only concerning patient care but also for vaccine counseling for all patients. As research regarding myocarditis in the COVID-19 era progresses, our understanding of myocarditis associated with COVID-19 continues to expand. The most accurate and current information must be available for our providers regarding myocarditis in COVID-19 infection, its different types, and its management. In our review, we hope to arm providers with the knowledge necessary for optimal care of patients affected with COVID-19-associated myocarditis.

INTRODUCTION

The novel coronavirus causes coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially presented in December 2019 and later declared a world pandemic. In initial COVID-19 studies, the pediatric population exhibited milder symptoms. However, over time, significant complications of COVID-19 infection were brought to light.

Myocarditis is an inflammation of the myocardium. The most common etiologies of myocarditis are infectious, immune-mediated, or toxic agents. Myocardial injury affects all age ranges and is associated with increased morbidity and mortality, including pediatric intensive care units (PICU) admissions, inotropic support, and mechanical ventilation. Viral illnesses, such as Influenza viruses, enterovirus, adenovirus, and HHV-6, are the most commonly implicated with myocarditis.[1] SARS-COV-2 represents a novel infectious etiology of myocarditis.

Furthermore, in the months following the emergence of SARS-COV-2, a newly recognized phenomenon related to this infection was reported. Characterized by hyper-inflammation and multi-organ involvement, specifically in the pediatric population, it was called multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome (PIMS).[2] Additionally, myocarditis related to COVID-19 vaccination has been identified, posing unique challenges for providers.

In this review article, we aim to summarize the current knowledge about myocarditis in the pediatric population related to SARS-CoV-2, including acute infection, MIS-C, and following vaccination, to provide insight into further understanding and clinical practice management.

PATHOPHYSIOLOGY

Myocarditis secondary to viral infections has been widely described. The mechanism of myocardial damage is not fully understood, but several theories exist about how SARS-CoV-2 causes myocarditis: 1. Direct myocardial injury with viral entry.[2] Hypoxia-induced myocardial ischemia, and 3. Systemic inflammatory response with up-regulation of the host immune system and cytokine storm.[3-4] In reality, myocarditis is likely a combination of the above mechanisms.

Direct myocardial injury in viral illness has been documented with another SARS virus. In the 2003-2004 Toronto SARS outbreak, SARS-CoV viral RNA was found in 35% (7/20) of autopsied human heart samples in deceased patients with confirmed SARS-CoV infection.[5] Likewise, The Middle East Respiratory Syndrome Coronavirus has also been identified as a causative agent of myocarditis in adults.[6] SARS-COV-2 manipulates the host ACE2 receptor to facilitate viral entry. Viral particles of SARS-CoV-2 have been found in the cardiac myocytes of patients with COVID-19 myocarditis.[3]

Hypoxia-induced myocardial injury is another component of myocarditis related to COVID-19 infection. The respiratory disease commonly seen with infection causes systemic hypoxia with increased metabolic demand and anaerobic metabolism in the cardiac myocyte. This increased demand can lead to hypoxia and cell necrosis.[4]

Finally, an exaggerated systemic inflammatory response with cytokine storm further exacerbates myocardial injury. The inflammatory cascade is activated, leading to cytokine storm and cell-mediated cytotoxicity.[4] Thus, damage to the myocardium occurs secondary to the effect of the cytokine storm. This mechanism of cytokine storm has been shown to play a direct role in MIS-C.[4]

EVALUATION AND DIAGNOSIS

Diagnosis of myocarditis is based on histological, immunological, and immune-histochemical criteria. The gold standard for diagnosis of myocarditis is an endomyocardial biopsy. According to the Dallas criteria, the diagnosis of myocarditis requires inflammatory infiltrate in cardiac myocytes with associated myocardial damage.[7] However, due to the invasive nature of the procedure, it is rarely used in diagnosis. More frequently used is the Lake Louis criteria, which define acute myocarditis with four major criteria: 1) symptoms of clinical findings of acute myocardial damage, 2) evidence of structural cardiac abnormality in the absence of other cause, 3) enhancement on cardiac MRI, and 4) presence of inflammatory cells or positive viral genome on endomyocardial biopsy.[8]

Myocarditis is most often diagnosed clinically. The key in the evaluation is to identify if a patient has had exposure to COVID-19. Patients typically present with chest pain and palpitation. Other signs and symptoms may also include acute cardiac dysfunction such as dyspnea, exercise intolerance, syncopal episode, tachypnea, unexplained tachycardia, hepatomegaly, or gallop rhythm.[1,9] For patients with a concerning presentation, further testing is indicated.

Myocarditis can be identified in the emergency room by measuring point-of-care troponin levels. Myocarditis is the most common cause of elevated Troponin I and Troponin T in the pediatric population. Brain natriuretic peptide (BNP)/N-terminal pro-b-type natriuretic peptide (NT-proBNP) are cardiac biomarkers that are quantitative markers of heart failure. In the right clinical scenario, they can help confirm the diagnosis of myocarditis.

Patients with myocarditis frequently have an abnormal electrocardiogram (ECG). However, these changes may be nonspecific. ECG abnormalities include ST-segment elevation or depression, atrioventricular block, and premature ventricular contractions (PVC).[10] Normal cardiac biomarkers (creatine kinase (CK), CK-MB, cardiac troponin T, and troponin I), systemic inflammatory markers (Erythrocyte sedimentation rate and C-reactive protein), and ECG effectively rule out myocarditis. Chest radiography at the time of diagnosis can have nonspecific patterns, including cardiomegaly, pulmonary vascular congestion, and possible pleural effusion[1].

An echocardiogram may show cardiac dysfunction, wall motion abnormalities, mitral regurgitation, and pericardial effusion.[11] In patients with pericardial involvement, also assess the patient for pericarditis. Pericarditis is an inflammation of the pericardium and requires the presence of two of the following to diagnose: chest pain, pericardial friction rub on physical examination, ECG changes including ST-segment changes and/or PR-depression, and new or worsening pericardial effusion.[12] In an acute presentation of myocarditis, Cardiac MRI can show inflammation with edema. Cardiac MRI is a non-invasive method of diagnosis that is starting to be used more frequently due to its high sensitivity and specificity for myocarditis.[13]

Any patient with suspected myocarditis should have a pediatric cardiology consultation. Patients with greater than three days of fever have clinical features of Kawasaki disease, such as rash or conjunctivitis, and patients who present in shock or heart failure should increase concerns for MIS-C and require additional investigation.

ISOLATED VIRAL MYOCARDITIS IN COVID-19

Myocarditis has been reported in the pediatric population as the first clinical presentation of COVID-19.[4] Early in the pandemic, Dong et al. found myocardial injury and heart failure occurring in 0.6% (12/2135) of reported pediatric patients with COVID-19.[14] Garot and coworkers reported a case of fulminant myocarditis in an 18-year-old male patient with COVID-19 infection characterized by ST segment changes, hemodynamic instability requiring inotropes, elevated troponin, and BNP. He was treated with acetaminophen, antibiotics, and hydroxychloroquine with clinical recovery by day 15.[15] Gnecci et al. reported a case of COVID-19 myocarditis in a 16-year-old male with ST-segment elevations, elevated troponin levels, and echocardiography showing hypokinesis of the left ventricle.[15] He was treated with ibuprofen, hydroxychloroquine, and antiviral therapy, with improvement in troponin levels and ST segment by day eight.[16] Kesici et al. reported a two-year-old patient with COVID-19 myocarditis who presented in cardiogenic shock with elevated troponin T, severe left ventricular failure on echocardiogram, and required extracorporeal membrane oxygenation (ECMO). This patient subsequently developed dilated cardiomyopathy, and a biopsy taken during ECMO cannulation showed cardiac tissue positive for SARS-CoV-2 via RT-PCR.[17] In a single-center retrospective study of 27 children with acute myocarditis conducted from January 2018 to November 2020, 7/27 (26%) showed evidence of SARS-CoV-2 exposure.[18] Six of seven individuals were diagnosed with MIS-C and one with isolated myocarditis. In this study, patients with isolated or MIS-C-associated myocarditis related to SARS-CoV-2 had better clinical courses, shorter duration of inotropic medications, and shorter ICU stay.[18]

Currently, there are no approved anti-viral treatments for COVID-19 myocarditis. Treatment focuses on decreasing myocardial injury secondary to inflammation. In practice, immunotherapies, including IVIG and corticosteroids, are frequently used in pediatric patients with myocarditis. Drucker et al. investigated IVIG in pediatric myocarditis. They demonstrated echocardiographic and survival benefits with IVIG. They recommended a dose of 2g/kg of IVIG.[19] The use of corticosteroids in the setting of myocarditis has been studied more extensively in adults than in the pediatric population. However, studies regarding steroid therapy have been inconclusive to date[11]. Similarly, the use of NSAIDs in myocarditis remains controversial.

Isolated myocarditis in pediatric patients associated with COVID-19 infection seems rare and often appears early in the clinical history. The incidence of isolated COVID-19 myocarditis remains unknown. Most patients with isolated COVID-19 myocarditis recover cardiac function, but there is a risk of progression to cardiac failure or sudden cardiac death. Hence, early recognition of these patients is important for practitioners.

MIS-C RELATED MYOCARDITIS

MIS-C is a potential sequela of COVID-19 infection. This syndrome presents with fevers, gastrointestinal symptoms, and features of myocarditis. The Centers for Disease Control defines MIS-C with the following features: patients under 21 years of age with fever plus two or more of the following: abdominal pain, conjunctivitis, diarrhea, signs of hypotension, skin rash, and/or emesis.[2] As of March 2022, 7450 cases of MISC were reported, with a median age of 9 years of age and 63 MIS-C-related deaths.[2]

While not required for diagnosis, MIS-C is primarily associated with myocarditis. In a systematic review of 255 patients with MIS-C, most children had negative RT-PCR but positive serum levels of anti-SARS-CoV-2 antibodies[20], demonstrating that MIS-C is more likely a post-viral inflammatory disease rather than a continued infection. In this same study, 75.3% of patients with MIS-C had findings suggestive of myocarditis. In another study at two Italian pediatric referral centers, a cohort of 294 children, MIS-C was documented in 46 patients. Of those with MIS-C, cardiac manifestations were seen in 97.8%, ventricular dysfunction in 59%, and pericarditis in 69%, the most common.[21] By one-year follow-up, all patients had recovered, and no cardiac abnormalities were recorded.[21] Furthermore, in a meta-analysis of 773 patients, left ventricular systolic dysfunction was seen in 55.3% of patients.[2] Across studies, the most common findings in MIS-C-related myocarditis are elevated cardiac biomarkers and left ventricular dysfunction via echocardiogram. *Vukomanovic et al.* noted that patients with acute myocarditis related to SARS-CoV-2 had higher systemic inflammatory markers and a wider variety of clinical presentations when compared to myocarditis not associated with SARS-COV-2.[18] Interestingly, these patients also had a shorter duration of inotropic drug use and a quicker recovery of left ventricular function.[18]

Management of MIS-C requires admission to tertiary care centers offering PICU and subspecialty services.[4,20] PICU admission rates up to 75.6% were noted, with up to 56.4% of patients presenting in shock requiring inotropic support.[20] The risk of cardiac decompensation can be minimized by prompt diagnosis and treatment. Across four tertiary academic centers, COVID-19 myocarditis in previously healthy children was characterized by systemic inflammation and vasodilatory shock yet tended to be less severe than in other causes of myocarditis.[9] Matsubara and investigators noted in their early follow-up study at 5.2 days +/- 3 days intervals that most patients with MIS-C had returned to normal left ventricular function.[22] With prompt diagnosis and treatment, Myocarditis associated with MIS-C has a good prognosis and relatively rapid return of cardiac function.[4,18]

COVID-19 VACCINE ASSOCIATED MYOCARDITIS

Historically, cardiac adverse events, including myocarditis and pericarditis, have been recognized as possible side effects of vaccinations such as smallpox and influenza vaccination.[23] As vaccination against SARS-CoV-2 emerged, it was identified as an additional cause

of myocarditis.

During the months following the emergence of the SARS-CoV-2, vaccine research, including adverse effect monitoring, reached unprecedented levels. The pre-existing Vaccine Adverse Event Reporting System (VAERS) database was used to identify myocarditis as an adverse effect of the mRNA-based COVID-19 vaccines. The CDC noted that cases occurred predominantly in adolescents and young adults, more often in males than females, more often following the second dose than the first, and typically within four days of vaccination.[24] Current CDC guidance details an association between myocarditis and mRNA-based vaccines, namely the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) and the Moderna COVID-19 vaccine (Spikevax). Similar associations have not reliably been seen with the viral DNA-based Johnson and Johnson COVID-19 vaccine (Janssen).[24]

As with other forms of myocarditis, presenting symptoms include acute chest pain, shortness of breath, and palpitations. Patients with these symptoms should be evaluated for myocarditis in conjunction with a history of mRNA-based COVID-19 vaccination within the preceding seven days. Together with evaluation for vaccine-associated myocarditis, the workup should include diagnostics aimed at other causes of myocarditis, including SARS-CoV-2 PCR, SARS-CoV-2 antibodies, and testing for other viral pathogens, such as a comprehensive viral panel.

Thus far, the typical hospital course of those with COVID-19 vaccine-associated myocarditis has been shown to be mild, with quick clinical recovery and excellent short-term outcomes.[25] A multi-center survey study of mRNA COVID-19 vaccine-associated myocarditis across 57 institutions looked at variability in diagnosis, management, and follow-up in adolescents with COVID-19 vaccine-associated myocarditis.[25] First-line treatment across the institutes was NSAIDs followed by steroids and IVIG, respectively. In practice, NSAIDs remain the mainstay of treatment.

As with viral-induced myocarditis, the SARS-CoV-2 vaccination-induced myocarditis can predispose patients to arrhythmias. One-third of the institutions in the multi-center survey study previously mentioned also reported patients with new-onset rhythm disturbances.[25] Thus, having a close follow-up with these patients becomes essential. Further studies are needed to understand the long-term implications and pathophysiology of vaccine-associated myocarditis. The authors do not recommend repeat vaccination with an mRNA vaccine. For patients above 18 years of age, a viral DNA-based vaccination is an acceptable alternative.

FOLLOW-UP

Patients with COVID-19-associated myocarditis usually have partial or complete recovery of cardiac function, but there is a risk of progression to arrhythmias and cardiac failure. The timing for follow-up depends on the severity of myocardial dysfunction at presentation. As exercise can trigger arrhythmias, the American College of Cardiology recommends that athletes diagnosed with myocarditis should refrain from exercise for at least three to six months after diagnosis.[26] While there is no expert consensus on follow-up studies, cardiologists may obtain a cardiac stress test at a three to six-month follow-up to determine if the patient is safe to return to exercise. 66% of institutes in a multi-center survey study of mRNA COVID-19 vaccine-associated myocarditis across 57 institutions recommended a stress test before returning to full activity.[25] Many cardiologists also obtain a cardiac MRI to evaluate the extent of residual inflammation and/or scarring to help with the clearance for sports and for prognosis. If the patient continues with ongoing inflammation on imaging, they are recommended to continue refraining from exercise until resolution.

CONCLUSION

Providers should be aware of the variety of presentations of myocarditis associated with COVID-19. Isolated myocarditis with COVID-19 appears rare, while MIS-C is more commonly described in the literature. In addition, myocarditis in relation to SARS-CoV-2 vaccination has also been reported. With prompt diagnosis and initiation of treatment, COVID-19-associated myocarditis has favorable outcomes. Even so, this population has a risk of sudden cardiac death. Therefore, providers should be aware of the potential cardiac manifestations of SARS-CoV-2 infection and vaccination in the pediatric population, as well as basic initial management and when to refer to a specialist.

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