Review Article,

Myocarditis Associated With COVID-19 Infection and Mrna Vaccination: A Review Article

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Abstract:

Coronavirus disease 2019 (Covid-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Initially, COVID-19 was considered a respiratory illness, but later on, it was found out that this disease can affect many organ systems. Cardiovascular manifestations of this disease include myocarditis, heart failure, myocardial infarction, and thromboembolism. Myocarditis related to COVID-19 is thought to be due to the direct viral injury and host immune response. The cases of myocarditis after the COVID-19 mRNA vaccine have been reported in the literature as well. COVID-19 myocarditis can present as chest pain, shortness of breath, acute heart failure, arrhythmia, and possibly death. The initial workup should include an electrocardiogram (ECG) and troponins if myocarditis is suspected.

Further screening should be done if troponins are elevated, or the patient has ECG changes concerning myocardial damage. Noninvasive imaging that helps to diagnose COVID-19 myocarditis includes echocardiograms, computerized tomographic (CT) with contrast, and cardiac magnetic resonance imaging (CMR). An endomyocardial biopsy (EMB) can be performed if the diagnosis remains unclear. Initial treatment of COVID-19 myocarditis is mainly supportive, and intravenous immunoglobulin (IVIG) and corticosteroid may be effective, particularly in fulminant myocarditis. If the patient develops life-threatening arrhythmias or shock, advanced mechanical support is required. Early intervention is a critical factor in decreasing morbidity and mortality. Further research is needed to determine the efficacy of different treatment modalities, including IVIG and corticosteroids, in patients with COVID-19 myocarditis.

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-COV2) caused a pandemic that first emerged in Hubei, a province of China [1], and later spread to Spain, Iran, the United States of America (USA), the United Kingdom (UK) and then spread all over the world with each region having a different kind of strain. The World health organization (WHO) declared Coronavirus disease

2019 (Covid-19) a global pandemic in March 2020 [2]. The first strain emerged after China was Alpha in the UK in September 2020. Another strain, namely Beta, was identified in South Africa in May 2020. Then another variant named Gamma emerged in Brazil in November 2020. Another deadly variant called Delta wreaked havoc in India in the latter half of 2020. From November 2021 to date, a new variant of omicron has been identified in various countries involving the UK, USA, Australia, South Asia, and even New Zealand, which was deemed COVID free during the first half of 2021.

Initially, people presented with symptoms involving the lower respiratory tract causing cough, dyspnea, pulmonary fibrosis, atelectasis, and ground glass appearance on imaging modalities. Later on, it presented with symptoms of multiorgan involvement, likewise myalgias, diarrhea, abdominal cramps, nausea, vomiting, headache, alopecia, ageusia, anosmia, and cardiovascular symptoms specifically involving the heart. Cardiac involvement presenting as myocarditis has accounted for the majority of cardiac injuries. Early diagnosis of myocarditis is crucial as untreated myocarditis can progress to congestive heart failure, cardiogenic shock, and fatal arrhythmias. This article aims to present an updated overview of the pathophysiology, epidemiology, diagnosis, treatment, and prognosis of COVID-19 infection-induced myocarditis.

Literature review:

Epidemiology:
The incidence of viral myocarditis is 22/100,000 [4]; however, the true incidence of COVID-19 induced myocarditis is unclear for various reasons. In one meta-analysis, 8% of patients with COVID-19 were diagnosed with myocardial injury [5]. The true incidence of COVID-19 myocarditis is underestimated as many patients with COVID-19 may have no symptoms or only minor symptoms. The reporting rates of myocarditis in females were lower than those in males younger than 50. Most ethnicities were disproportionately affected, and death due to COVID-19 is more in the African-American population than in any other race in America [6]; this may be explained due to genetic predisposition to poorer cardiac outcomes.

Pathophysiology and clinical presentation of COVID-19 induced myocarditis: Myocarditis is an inflammation of cardiac myocytes, which can be infectious or noninfectious. The worldwide most common cause of myocarditis is a viral infection. Previously the COVID-19 pandemic emerged with respiratory symptoms; recently, cases have been reported with heart problems, including myocarditis.

SARS-COV2 belongs to the family of Coronavirus, which is a positive sense, single-stranded RNA enveloped virus. The structure of SARS-COV2 includes four structural proteins [7]; these proteins include Spike(S), Membrane (M), Encapsulated (E), and Nucleocapsid (N)[8]. S protein has two subunits (S1 and S2) and significantly contributes to stimulating immune response [9]. M proteins are involved in pathogenesis [10], E plays a role in viral replication [11], and N is involved in transcription and synthesis [12].

The SARS-CoV-2 virus gains entry into the cells by binding to the angiotensin-converting enzyme (ACE) 2 receptor. These receptors are highly expressed in type II alveolar cells of the respiratory tract and are responsible for the respiratory manifestation of COVID-19. These receptors are also found in cardiac myocytes; therefore, it is possible that SARS-CoV-2 can infect cardiac myocytes leading to viral myocarditis [13]. The virus's entry into host cells by binding to the ACE 2 receptors leads to the activation of proinflammatory cytokines such as interleukin-6 (IL-6), Interleukin-10 (IL-10), and Tumor Necrosis Factor-alpha (TNF alpha) [14]. These mediators will cause inflammatory changes in the lungs, heart, and many other organs, leading to a multiorgan failure (figure 1).
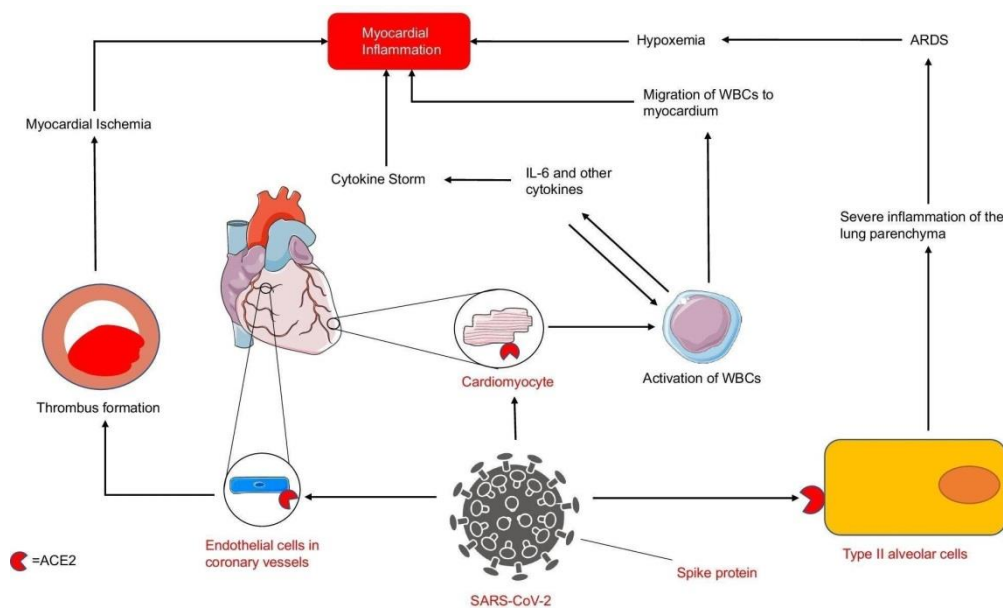
Figure 1: Proposed mechanisms of myocarditis in patients with SARS-COV2 infection Source of figure is reference [14]

Another proposed mechanism of myocardial damage is an infection of endothelial cells in the heart; this theory was supported by identifying the SARS-CoV-2 within the endothelial cells of the myocardium [13]. By infecting endothelial cells of the coronary vessels, the SARS-CoV-2 increases the risk of thrombus formation resulting in myocardial ischemia and injury. An alternative way SARS-CoV-2 can cause myocardial damage is by hypoxia. COVID-19 pneumonia causes severe acute respiratory distress syndrome (ARDS), resulting in hypoxemia. Eventually, hypoxemia results in the myocardial oxygen demand and supply mismatch resulting in myocardial inflammation [14].

COVID-19 mRNA vaccine associated myocarditis:
The risk of myocardial injury is not limited to viral infection. There are many COVID-19 mRNA vaccine-induced myocarditis cases, but the incidence is much lower than COVID-19-associated myocarditis and cardiac damage. According to case series studies from the USA, myocarditis rates are near 0.3-5.0 cases per 100,000 vaccinated people; meanwhile, the reported incidence of COVID-19-associated myocarditis and cardiac damage was 1,000-4,000/100,000 people with SARS-CoV-2 infection. The highest incidence of myocarditis

was after administering the second dose of mRNA vaccines, and young male adults (aged 12-39) were affected predominantly [15]. The mechanism proposed is a delayed hypersensitivity reaction induced by T lymphocytes. 2-3 days after the first vaccine dose, the immune system gets sensitized; however, after the second dose, it goes into the effector phase leading to the release of inflammatory cytokines into the myocardium. The cytokine infiltration can further activate the immune cells to migrate to the myocyte leading to further inflammation [15-16]. Another proposed mechanism for COVID-19 mRNA vaccine-induced myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and cardiac protein. The antibodies against spike protein may cross-react with cardiac protein, including myocardial α-myosin heavy chain resulting in myocardial injury and inflammation [15-16].

Diagnosis of COVID-19 associated myocarditis:
When there is a suspicion of COVID-19 myocarditis based on history and physical examination, various blood tests and imaging can be performed for further screening. The blood workup includes inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, and lactate

dehydrogenase (LDH) [14,17]. These tests are nonspecific for myocarditis as they are infection markers and can be elevated without myocarditis. The cardiac enzymes such as N-terminal pro B type natriuretic peptide (NT-proBNP) and troponin levels are usually elevated in a patient with COVID-19 induced myocarditis. The baseline level of these cardiac enzymes should be obtained to trend during the hospital course. However, these enzymes have poor sensitivity; therefore, a normal troponin does not exclude myocarditis [14].

Commonly seen electrocardiogram (ECG) changes in a patient with myocarditis include sinus tachycardia (most common), ST elevation/depression, PR depression, T wave inversions, nonspecific T wave changes, QT prolongation, new onset of bundle branch block, atrioventricular nodal block, and tachycardia/bradycardia arrhythmias [14,17]. However, most of the ECG changes are nonspecific, and the absence of these changes cannot wholly exclude myocarditis, but if ECG changes are present, they are helpful to assess underlying possible myocardial damage and identify the presence of arrhythmia which are more common in fulminant cases of myocarditis.

The commonly used imaging modalities for diagnosing COVID-19 myocarditis are cardiac magnetic resonance imaging (CMR), echocardiogram, and computerized cardiac tomography (CT) with contrast. Echocardiogram changes seen in patients with COVID-19 myocarditis are usually nonspecific, and it includes hypokinesis, pericardial effusion dilatation of the cardiac chambers, increased wall thickness, and reduced ejection fraction.

CMR is the best non-invasive test for diagnosing COVID-19 myocarditis as it has high sensitivity. The results of the CMR are interpreted according to the Lake Louise criteria. This criterion uses T2-based imaging, early gadolinium enhancement, and late gadolinium enhancement imaging to identify myocardial edema, hyperemia/capillary leakage, and myocardial fibrosis/necrosis [18]. The limitation of CMR includes hours of availability, patient hemodynamic stability, and the requirement for a thorough cleaning, given the infection is very contagious [17]. If the CMR is not feasible for the above reasons, then in those

situations, cardiac CT with contrast can be considered.

The gold standard test for diagnosing myocarditis is an endomyocardial biopsy (EMB). The biopsy sample should be sent for Immunohistochemistry and genomic testing to identify SARS-CoV-2 RNA within the myocardium cells. The limitation of EMB includes the risk of acquiring infection as the disease is very contagious, availability of expertise, and false-negative results because of patchy inflammation of the myocardium [14,17].

Management of COVID-19 induced myocarditis:

The management of COVID-19 induced myocarditis involves treating underlying inflammation and complications resulting from myocarditis.

Concrete guidelines for the treatment of COVID-19 induced myocarditis are still being developed as we understand more and more about the disease; however, management of acute viral myocarditis can mostly still be valid regardless of the etiology. Initial management of myocarditis is largely supportive but may necessitate the administration of inotropes and vasopressors and mechanical ventilation for hemodynamically unstable such as cardiogenic shock.

Chronic therapy of COVID-19 induced myocarditis depends largely on the complication developed. If all causes were excluded, COVID-19 infection was determined to be the cause of myocarditis. In that case, anti-inflammatory agents (corticosteroids, intravenous immunoglobulins (IVIG), tocilizumab (Actemra), and anakinra) can be used [32].

Management of Specific Complications of Covid-19 myocarditis:

- Management of Heart Failure:

Treatment of specific complications such as myocarditis-induced heart failure initially includes angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [20], beta-blockers (only in chronic heart failure) (21), and aldosterone receptor antagonists (spironolactone and eplerenone) [22]. Neprilysin Inhibitor (Sacubitril/Valsartan), funny channel (If channel) inhibitor (Ivabradine), and vasodilators like isosorbide dinitrate and Hydralazine can be used if no improvement was obtained with the initial

therapeutic triad. The use of beta-blockers in the acute phase of heart failure induced by myocarditis is contraindicated due to its negative inotropic effects [23-24].

- Management of Fulminant Myocarditis:

Fulminant myocarditis management involves implementing the initial management protocol for cardiogenic shock, which includes administration of inotropes and/or vasopressors and mechanical ventilation. Longer-term management involves mechanical circulatory interventions such as extracorporeal membrane oxygenation (ECMO), ventricular assist device, or anintra-aortic balloon pump [IABP].

- Management of Arrhythmias Caused by COVID Myocarditis:

Management of arrhythmias caused by COVID myocarditis includes cardiac monitoring by telemetry, and treatment depends on the type of underlying arrhythmia. Brady arrhythmias are treated with 0.5 mg intravenous atropine every 3 to 5 minutes to a maximum total dose of 3 mg or may require implantation of a cardiac pacemaker. Tachyarrhythmias are treated by vagal maneuvers, cardio version, or medications such as beta-blockers and verapamil or surgically by catheter ablation, implantable cardioverter-defibrillator (ICD), Maze procedure, and/or overdrive pacing, which works by pacing the patient's heart at a rate faster than the intrinsic rhythm.

Treatment of atrial fibrillation includes drugs for rate control (beta-blockers and verapamil or diltiazem) and rhythm control (flecainide, propafenone, quinidine, sotalol, amiodarone, and dronedarone), despite their efficacy, antiarrhythmic drugs aren't used for all patients with arrhythmias and may cause serious side effects [26].

Roles of specific drugs in COVID-19 myocarditis:

A) Tocilizumab:
The role of Tocilizumab, an anti–interleukin-6 (IL-6) receptor monoclonal antibody used in the treatment of rheumatoid arthritis, was associated with improved outcomes in COVID-19 patients with raised IL-6 levels. It most likely reduces myocardial inflammation in the setting of a cytokine storm [27]. Anakinra is an interleukin 1 (IL-1) inhibitor that has a similar effect on

myocarditis by decreasing the level of inflammatory cytokines.

B) Corticosteroids:
The role of corticosteroids in the management of COVID-19 myocarditis remains less evident, while steroids are known to reduce inflammation by decreasing the expression of proinflammatory cytokines; it has been linked with higher mortality and increased length of stay in some COVID-19 pneumonia patients in a systematic review and meta-analysis which involved 5270 patients [28]. On the other hand, in some studies, corticosteroids have also been shown to decrease mortality, especially in patients with complicated diseases who may benefit from corticosteroids' effects on their overall health condition rather than just myocarditis [29].

A Systematic review by Kamarullah et al. revealed that the use of corticosteroids to treat COVID-19 induced acute myocarditis was associated with improved outcomes [30]. But the systematic review had 18 case reports from 18 different studies rather than a randomized control trial. Similarly, a systematic review by Sawalha et al. revealed similar results [31], but the review also consisted of 14 case reports. The level of evidence provided by the systematic review of case reports is poor; therefore, we need a randomized controlled clinical trial to determine the efficacy of corticosteroids in patients with COVID-19 induced myocarditis.

C) IVIG:
IVIG has been proven beneficial in treating COVID-19 myocarditis, specifically in patients with fulminant myocarditis. IVIG has an anti-inflammatory effect, and it decreases cardiac inflammation by down-regulating the production of cytokines [14]. IVIG also facilitates the clearance of the pathogen from the myocardium. A meta-analysis revealed that IVIG use in patients with COVID-19 myocarditis was associated with a significant reduction in mortality and improved left ventricular ejection fraction [31]. Explicitly in patients with fulminant myocarditis, IVIG use was associated with a substantial increase in survival rate [14, 32].

D) Colchicine:

The cytokine storm plays an important role in COVID-19 myocarditis. Colchicine decreases inflammation by inhibiting tubular information, thus inhibiting neutrophil chemotaxis; therefore, the use of colchicine may provide positive outcomes [32].

Role of mechanical circulatory support in Management of Covid-19 Myocarditis:

Mechanical circulatory support devices such as intra-aortic balloon pumps and ECMO can be considered for patients presenting with cardiogenic shock as a complication of fulminant myocarditis, not responding to inotropes/vasopressors [33-34]. The venoarterial ECMO pumps back the oxygenated blood to the femoral artery and bypasses the lung and heart, thus decreasing the load on the heart in case of myocarditis regardless of the reason [33-35].

The intra-aortic balloon pump is to act as a one-way valve by directing blood away from the heart by inflating when the heart relaxes to prevent the backflow of blood from the aorta into the LV and deflating when the heart contracts to allow the pumping of blood from the LV into the systemic circulation thus minimizing the heart failure symptoms caused by myocarditis [36].

Long term cardiovascular effects of COVID-19 infection and Prognosis:

The prognosis of Covid-19 induced myocarditis depends mainly on the presence of comorbidities and the overall health state of the patient; the information on Covid-19 and its long term effects on the heart is limited, but it has been proposed that different forms of long term damage can occur such as fibrosis and remodeling which increase the risk for future arrhythmias and heart failure (37). Dilated cardiomyopathy is another potential long-term complication of myocarditis in genetically susceptible individuals (38). Several case studies also note a relationship between COVID-19 and postural tachycardia syndrome (POTS) (39).

COVID-19 myocarditis carries a high risk of mortality. In one systematic review, Haussner et al. reported that the mortality rate was 14% in patients with COVID-19 myocarditis. The risk factor associated with poor outcomes includes old age, diabetes mellitus, hypertension, obesity, asthma/COPD, and cardiovascular disease [40].

Conclusion:

COVID-19 myocarditis is a known complication of the SARS-CoV-2 virus. The timely diagnosis of COVID-19 myocarditis is imperative as it is associated with high morbidity and mortality. It may be challenging to diagnose COVID-19 myocarditis as symptoms can resemble COVID-19 pneumonia. If there is a suspicion of myocarditis, the ECG and troponin should be drawn. CMR and EMB can be done to confirm the diagnosis. The clinician should also look for long-term complications of COVID-19 myocarditis such as POTS, dilated cardiomyopathy, and arrhythmias. There are no specific guidelines for the treatment of COVID-19 myocarditis, but the use of corticosteroids and IVIG has seemed to be beneficial in individual cases in systematic reviews. There is a need to conduct randomized control trials to assess the safety and efficacy of corticosteroids, IVIG, and immunomodulators in the management of COVID-19 induced myocarditis.

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