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Review

COVID-19 mRNA vaccine-induced myocarditis

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ABSTRACT

Myocarditis is an inflammatory condition of the myocardium that develops secondary to various etiological factors; it is a disease with complications and mortality. Although the causes are infectious, immune-mediated, and drug-toxin exposure, it can also develop after exposed to the coronavirus 2 and coronavirus disease 2019 (COVID-19) vaccines, which recently affected the world and caused severe acute respiratory syndrome. In addition to clinical and laboratory findings, imaging methods, such as echocardiography, computed tomography angiography, and cardiac magnetic resonance imaging, play a significant role in diagnosis. In this article, myocarditis overview, diagnostic methods, post-COVID, and post-vaccine myocarditis were reviewed.

Keywords: Computed tomography, coronavirus, COVID-19, magnetic resonance imaging, mRNA vaccines, myocarditis.

Myocarditis is an inflammatory condition that can affect the myocardium in a focal or widespread manner. According to accepted histological, immunological, and immunohistochemical criteria, myocarditis is a relatively common but potentially fatal inflammatory disease of the myocardium. It is a significant cause of sudden cardiac death (SCD), first unexplained dilated cardiomyopathy (DCM), and heart failure (HF). It affects millions of individuals globally, particularly children and young male adults. Dilated cardiomyopathy is present in approximately 30% of cases.[1-3] The majority of myocarditis studies show a male predominance and a median age of about 42 years for individuals with lymphocytic myocarditis.[1,4,5]

In addition to clinical and laboratory findings, imaging methods provide a very useful contribution to the diagnosis of myocarditis. In particular, magnetic resonance imaging (MRI) plays an important role in clinical diagnosis and treatment evaluation due to its high soft tissue and spatial resolution, and its various sequence and advanced imaging possibilities. Although there are numerous etiological causes of myocarditis, coronavirus disease 2019 (COVID-19) has recently emerged as one of the leading causes. Furthermore, some cases have been reported to have post-vaccine myocarditis.[6,7]

This review article discussed the general definition of myocarditis, diagnostic methods, and post-vaccine myocarditis.

MYOCARDITIS

Etiology

Myocarditis can be caused on by a number of relevant reasons, including infections (bacterial, spirochaetal, fungal, protozoal, parasitic, viral), immune-mediated diseases, toxins, heavy metals (Copper, iron, lead), hormones (Phaeochromocytoma), vitamin-B1 deficiency, radiation, electric shock, and medication exposure.[2,8,9]

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Classification of myocarditis

Myocarditis can be classified into four different categories including fulminant myocarditis (17%), acute (non-fulminant) myocarditis (65%), chronic active myocarditis (11%), and chronic persistent myocarditis (7%). Acute myocarditis is the most common type of myocarditis and is characterized by a clinically slower onset, mild cardiovascular impairment, and incomplete recovery. It occasionally leads to heart failure, cardiac dysfunction, and, less commonly death. Histologically, there are inflammatory infiltrates which are active or borderline active and disappear completely.[10-16]

The onset of fulminant myocarditis is extremely sudden. Class IV heart failure symptoms that appear suddenly and are unexplained, with a normal-sized or left ventricular (LV) dilation may go away completely on their own or quickly deteriorate and result in death from severe cardiac compromise. Some people may experience heart failure, early cardiogenic shock, or unstable arrhythmias symptoms. Histologically, there are numerous active sites of inflammatory infiltration in the early stages of the disease. Patients with elevated N-terminal pro-B-type natriuretic peptide, reduced left ventricular ejection fraction, and conduction abnormalities at admission are more likely to have a fulminant course of acute myocarditis. In adult patients with acute viral myocarditis, a prolonged PR interval and enlarged QRS complex at admission are separate risk factors for fulminant myocarditis.[17-20]

Chronic active myocarditis usually progresses to only mild or moderate cardiac dysfunction and presents similarly to acute myocarditis. Persistent fibrosis is present histologically, which may indicate chronic inflammatory alterations. Chronic active myocarditis develops gradually, beginning with mild ventricular dysfunction and progressing to active or borderline myocarditis on biopsy. The restrictive cardiomyopathy generally occurs two to four years after the presentation in these patients due to persistent inflammation and fibrosis. In an experimental study, it has been demonstrated that SAP-IFN [signaling lymphocyte activation molecules (SLAM)-associated protein interferon (IFN)] gamma (γ) transgenic mice spontaneously develop chronic active myocarditis [characterized by infiltration of T cells, macrophages, and dendritic cells and by expression of monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, IL-12, and tumor necrosis factor alpha (TNF-α)], which eventually results in the development of severe cardiomyopathy. SAP-IFN-transgenic mice constitutively express IFN- in their livers and demonstrate significantly elevated cytokine serum concentration.[11,12,14,15,19,21-24]

Chronic persistent myocarditis (7%) is characterized by subtle onset. Despite other cardiovascular symptoms such as chest discomfort or palpitation, it is defined by a persistent histologic infiltration, frequently with foci of myocyte necrosis, but without ventricular failure or cardiovascular impairment.[25]

It should be noted that the majority of this classification has a clinical focus.

Laboratory findings

- Complete blood count: Leukocytosis is a prevalent condition. Eosinophilia may be a sign of eosinophilic myocarditis.[2,14,19]
- Although acute phase reactants such as erythrocyte sedimentation rates, and C-reactive protein have low specificity for myocarditis, their elevation is useful in monitoring clinical progression or therapy response. Furthermore, the elevated levels of novel biomarkers such as TNF-α, interleukins such as IL-10, interferon-γ, serum-soluble Fas, and soluble Fas ligand, and microRNAs indicate a poor prognosis.[23,26-31]
- There was no connection between virus serology and endomyocardial biopsy (EMB) results, and current recommendations do not support measuring viral antibody titers.[2,32-36]
- Numerous cases of acute myocarditis result in elevated levels of cardiac troponins, creatine kinase, and myoglobin; however, cardiac markers and enzymes are not limited to cardiac inflammatory diseases. In all patients, cardiac troponin should be assessed. In contrast to cardiac troponin I or T, which is raised in at least 50% of patients with biopsy-proven

myocarditis, creatinine kinase is elevated in only 7.5% of individuals with myocarditis. Myoglobin expression correlates with the duration and severity of acute myocarditis. Acute cases may benefit from significantly elevated cardiac markers and enzymes, but their absence does not rule out myocarditis. Additionally, as demonstrated by cardiac MRI studies, normalization of cardiac parameters after three months does not indicate convalescence.[37-41]

Diagnosis

Non-invasive diagnostic methods

- Electrocardiography (ECG): The ECG is a widely used tool for diagnostic screening that can identify ST-segment abnormalities despite having a low (47%) sensitivity for myocarditis. For all patients with clinically suspected myocarditis, a 12-lead ECG should be performed. These ST elevations are often widespread and concave. Pericarditis can also coexist with myocarditis, which manifests as diffuse ST elevations and PR-depressions on the ECG. Patients with inflammatory heart disease may experience supraventricular and ventricular arrhythmias, atrial or ventricular conduction delays, or both. Heart transplantation or cardiac death was found to be independently predicted by a prolonged QRS duration of more than 120 milliseconds. Heart failure symptoms are due to LV systolic and diastolic dysfunction induced by a virus. Acute coronary syndrome, which might include sudden onset of angina, ECG alterations (ST-elevation or T-wave inversions), and an increase in heart-specific enzymes such as troponin or creatinine kinase, can manifest in some patients. An examination of the echocardiogram frequently identifies LV failure in varying degrees. In a patient with a newly developed third-degree heart block, myocarditis should always be ruled out.[2,18,42-46]

- Echocardiography, also known as transthoracic heart ultrasonography, is a non-invasive diagnostic technique that uses ultrasonic waves to identify and diagnose diseases. For the assessment of heart anatomy and function in individuals suspected of having myocarditis, echocardiography is the first-choice and most often employed imaging modality. Particularly in children who may have reduced cooperativity or hemodynamic instability, real-time imaging and mobility are essential components for quickly assessing the severity of cardiovascular damage. It is a common practice for patients with suspected myocarditis to rule out other possible causes of heart failure, search for intracardiac thrombus and related valvular disease (e.g. functional valvular regurgitation), and assess the level of left ventricular dysfunction or enlargement, and track the effectiveness of treatment. It also reveals pericardial abnormalities, ejection fraction, the presence of pericardial fluid, and localized wall motion abnormalities.[47-51]

- Cardiac scintigraphy and positron emission tomography: With a high sensitivity of 92% (antimyosin scintigraphy (indium III-monoclonal antimyosin antibody) makes it easier to detect myocardial inflammation; nevertheless, it has a low specificity and positive predictive value (13%, 45%, respectively). On the other hand, positron emission tomography employing 18-fluorodeoxyglucose and gallium-67 (Ga-67) scanning, which were both developed more recently, are highly sensitive to detecting significant myocardial cellular infiltration. It is mostly utilized during the acute stage of sarcoidosis and to track the course of the condition.[2,52-54] In patients with dilated cardiomyopathy, gallium scanning has a sensitivity of 36% and a specificity of 98% for detecting myocarditis. Ga-67 scanning demonstrated a sensitivity of 44%, specificity of 100%, and a positive predictive value of 58% in identifying inflammatory myocarditis when the endomyocardial biopsy was employed as the diagnostic gold standard.[53,55,56]

- Coronary computed tomography angiography (CCTA) is a low-risk, reliable, logistically straightforward non-invasive, and safer technique for the diagnosis or exclusion of diseases including coronary

artery disease (CAD), pulmonary embolism, valvular and aortic diseases (e.g. aortic dissection); in the assessment of the anatomy of coronary arteries and veins, congenital heart disease mainly to plan interventional or surgical procedures. In recent years thanks to many technical advancements, including wider detectors with increased coverage, shorter rotation times, prospective ECG-triggering, low tube voltage scanning, tube current modulation, and iterative reconstruction approaches, have improved the quality and efficiency of cardiac CTA image acquisition. Coronary CTA has demonstrated value in the early rule out of acute coronary syndrome in low-risk patients who arrive with acute chest pain. The median per-patient sensitivity and specificity across numerous meta-analyses on the reliability of CCTA with contemporary (at least 64-slice) computed tomography systems were 98% and 90%, respectively. Nearly all investigations show that the high sensitivity is represented by a very high negative predictive value of 95 to 100%. As a negative CCTA of appropriate quality virtually excludes obstructive CAD and considerably decreases unnecessary invasive procedures, CCTA has evolved into a gatekeeper to the catheterization laboratory.[57-59]

- Cardiac MRI has become the non-invasive standard procedure for the diagnosis and monitoring of myocarditis patients. It is a particularly appealing potential approach because of the precision and repeatability of cardiac structure evaluation, the special capability of non-invasive tissue characterization, and the absence of ionizing radiation. When used to confirm or establish the diagnosis of myocarditis, screen for subclinical cases, stratify patients for risk based on known independent prognostic factors such as left ventricular ejection fraction, end-systolic volume, and degree of myocardial edema, predict the prognosis, and track the effectiveness of treatment during follow-up, it offers valuable information. By utilizing gadolinium contrast material at the late phase [late gadolinium enhancement (LGE)], it demonstrates necrosis and fibrosis. Although LGE imaging can detect the injured cardiac area, it cannot distinguish between acute and chronic inflammation.[2,3,19,60]

Invasive diagnostic method

- Quantitative (invasive) coronary angiography (QCA): Since the clinical presentation of myocarditis can mimic myocardial infarction (i.e., pseudo-infarct pattern), especially if there are focal wall motion abnormalities and localizing electrocardiographic changes, coronary angiography is frequently recommended to rule out coronary artery disease as the cause of new-onset heart failure. Rather than directly assessing the condition of interest (in this case, atherosclerotic disease), QCA relies on lumen blockage to infer its existence and severity. In circumstances of exterior vascular remodeling, traditional angiography usually underestimates the burden of atherosclerotic disease compared to intravascular ultrasonography or optical coherence tomography. Also, QCA does not correlate well together with intravascular ultrasonography on the severity of stenosis, while both technologies allow for thorough vascular assessment as opposed to conventional angiography's limited, two-dimensional projections.[2,15,19,61,62]
- The gold standard for diagnosis is an EMB, however, this procedure is underutilized in clinical practice. As a result, the diagnosis is frequently made using a combination of a compatible clinical presentation, non-invasive biomarkers, and imaging findings.[2]

CORONAVIRUS INFECTIOUS DISEASE 2019

Coronavirus disease 2019 is a respiratory viral illness that was originally identified in Wuhan, China, and has since spread to every country around the globe, resulting in a pandemic. Initial epidemiologic data show that roughly 80% of COVID-19 patients are asymptomatic or have

moderate symptoms, despite the fact that there are infections and deaths from the SARS-CoV-2. On the other hand, in the remaining instances, patients may experience severe respiratory illness accompanied by a systemic inflammatory response and multiorgan failure, necessitating critical care therapy. Although pneumonia is the most frequent clinical symptom of COVID-19, other cardiovascular problems have also been observed.[63]

Similar to SARS-CoV-1, the novel SARS-CoV-2 virus is composed of an outer envelope and a single-stranded RNA of around 30 kilobases, which encodes for a number of structural and nonstructural proteins. More than 80% of the genome has reportedly been found to be identical to the original SARS-CoV-1. The spike protein (S), the membrane protein (M), the envelope protein (E), and the nucleocapsid protein (N) are examples of structural proteins. Angiotensin-converting enzyme 2 (ACE2) is used by SARS-CoV-2 and SARS-CoV-1 as an entrance receptor in humans through the binding of their outer surface spike S protein. A human cellular protease called transmembrane protease, serine2, also primes the S protein of SARS-CoV-2. SARS-CoV-2 infection is more likely to affect cells that express ACE2, such as type II alveolar cells in the lungs.[64-68]

Toll-like receptor 4 (TLR4) is an innate immune receptor found on the cell surface that detects pathogen-associated molecular patterns (PAMPs), such as viral proteins, and causes the release of type I interferons and proinflammatory cytokines to fight infection. In addition to immune cells, it is expressed in cells that are found in the tissue. Recently, it has been suggested that the spike protein has the highest protein-protein interaction with TLR4, whereas ACE2, the reported entrance receptor for SARS-CoV-2, is only found on 1-2% of the cells in the lungs or has a low pulmonary expression. Other TLRs, such as TLR3, are tethered to intracellular endosomes and detect double-stranded RNA patterns from encroaching pathogens after they have entered the cells. TLR4, in contrast, is expressed both at the cell surface (main site), where it detects viral proteins before they enter the cell, and in endosomes, where it is activated by a different signaling route. Initiating inflammatory responses through TLR4 is crucial, and overstimulating it can be harmful and cause hyperinflammation. As with ischemia-reperfusion damage, atherosclerosis, hypertension, cancer, and neuropsychiatric and neurodegenerative disorders, dysregulation of TLR4 signaling has been demonstrated to contribute to the onset and/or development of a number of diseases. Additionally, TLR4 plays a crucial role in the activation of the host immune system in response to infectious disorders such as bacterial, fungal, and viral infections as well as malaria.[68-74]

Although various mechanisms of myocardial injury are being proposed, the pathogenetic processes underlying cardiovascular problems in SARS-CoV-2 remain unknown. Viral invasion-induced macrophage activation may cause an aberrant immune-mediated host response that results in a cytokine storm. High plasma concentrations of certain cytokines, such as IL-2, IL-6, IL-7, IL-10, and TNF-α, may trigger a systemic inflammatory response that is accompanied by myocardial cell apoptosis or necrosis as well as hypercoagulability. These cytokines, in summary, the immune activation in severe COVID-19 infection is likely sufficient to cause disseminated intravascular coagulation (DIC), microvascular dysfunction, and myocardial damage, upregulating tissue factor expression and causing a prothrombotic condition.[75-79]

Myofibrillar lysis is a hallmark of histological damage, and viral particles were seen in interstitial cytopathic macrophages but not inside the myocytes. A number of cells, including pneumocytes, macrophages, enterocytes, cardiac myocytes, pericytes, and endothelial cells, display the ACE2, a surface protein that promotes viral entrance into the target cells. Endothelial cells in the heart and other organs are directly infected with a virus and widely inflamed. Coronary circulatory dysfunction and increased vasoconstriction in myocardial tissue may be caused by widespread endothelial inflammation and pericyte damage. Myocardial injury, defined in COVID-19 as an elevated troponin level over the upper reference range coupled with ECG and/or echocardiographic abnormalities, is quite common and is linked to a poorer prognosis and more severe illness. Cardiac damage is thought to be primarily

caused by thrombotic events, and microvascular and endothelial dysfunction.[80-83]

Incidence of myocarditis in COVID-19

The prevalence of myocarditis in COVID-19 patients is unknown, in part because early studies frequently lacked the precise diagnostic tools needed to detect myocarditis. Some claimed that myocarditis was a factor in up to 7% of COVID-19-related deaths.[84]

Myocarditis diagnosis based on MRI findings

The Consensus Criteria for cardiac MR (CMR) imaging in Myocardial Inflammation or known as the Lake Louise Criteria (LLC), were established in 2009.[85] A combination of the three distinct cardiac MRI methods indicated above should be used to base CMR findings on the LLC.[2,85,86] The Lake Louise Criteria employs early gadolinium enhancement (EGE), LGE, and T2-weighted ratio as tissue-based CMR indicators. These parameters evaluate myocardial edema, hyperemia/capillary leak, and fibrosis/necrosis. Quantitative imaging using T1 and T2 mapping has significantly improved since the founding of LLC in determining diffuse myocardial damage. If at least two of the following conditions are met, CMR data are likely to indicate myocardial inflammation:

- An increase in myocardial signal intensity in T2-weighted images corresponds to edema.
- Increased global cardiac EGE ratio in T1-weighted images (before and after contrast injection) between the myocardium and skeletal muscle.
- Inversion recovery-prepared gadolinium-enhanced T1-weighted images show at least one focal lesion with non-ischaemic regional distribution: The subepicardial is affected but not the subendocardial layer.

However, recently published revised LLC following the introduction of myocardial mapping and redefining imaging, makes diagnosis in accordance with the occurrence of both T1 parameter (extracellular volume values, presence of LGE, increased T1 mapping) and T2 parameter (hyperintensity in T2-weighted short-tau inversion recovery or increased T2 mapping values).[36] In diagnosis of acute myocarditis, revised LLC have improved diagnostic performance of CMR, particularly for atypical clinical presentation.[87]

Myocardial inflammation causes intracellular edema, hyperemia with capillary leakage, and eventually permanent injury in myocarditis, which begins with an initial attack from either direct injury or activation of the natural immune system. Late gadolinium enhancement imaging gives an assessment of irreversible harm in the LLC criteria, whereas EGE and T2-weighted imaging provide an assessment of inflammation and edema. However, since EGE and T2-weighted images are prone to abnormalities and misunderstanding, applying the LLC criteria in routine clinical practice is difficult. When LLC components are pooled univariately, LGE has the top point estimate for diagnostic accuracy and that is the key driver of LLC performance, owing to its high specificity in patients with permanent injury or necrosis. Because gadolinium contrast material can only examine the extracellular region, LGE cannot identify intracellular edema, which is also considered to occur in the early stages of myocarditis. As a result, LGE has limited sensitivity for detecting modest edema and reversible damage associated with the early stages of inflammation. Therefore, when compared to LGE alone, the combination of three factors (EGE, LGE, and the T2- weighted ratio) boosts the sensitivity of the LLC. Also, extracellular volume (ECV) estimates and native T1 and T2 mapping have both been demonstrated to add to the diagnostic knowledge available to myocarditis patients.[86,88,89]

Advanced CMR imaging in myocarditis

- T2-mapping: Free water content is typically found through T2-mapping. This characteristic may be useful for staging and tracking recovery since T2 relaxation times are particularly high during the acute phase of myocarditis and progressively normalize over months. T2-mapping is thought to be the only method that effectively distinguishes between myocarditis and non-inflammatory cardiomyopathies confirmed by endomyocardial biopsy in individuals with symptoms persisting longer than two weeks. Also, in a study

using phantoms and participants without a history of cardiac disease, high-spatial-resolution three-dimensional (3D) whole-heart T2-mapping demonstrated high intrasession and intersession reproducibility and helps provide T2 myocardial characterization in agreement with the clinical two-dimensional (2D) reference while enabling 3D assessment of focal disease with greater confidence.[86,90,91]

- Extracellular volume mapping: It is frequently employed as a stand-in marker for fibrosis because there is a link between myocardial inflammation and fibrosis. It can identify extracellular growth resulting from ongoing inflammation. When compared to LGE, ECV's key advantage is its capacity to evaluate diffuse fibrosis and inflammation outside of localized foci of fibrosis. Combine ECV and LGE to raise diagnostic accuracy to 90%. In particular, by detecting diffuse myocardial damage in patients with negative LGE, global ECV can raise sensitivity. Also, ECV is a particular parameter for extracellular expansion that can assess amyloid accumulation and cardiac involvement in myocardial inflammation, which has greater ECV values.[88,92-94]
- Native T1-mapping can identify different stages of myocarditis since edema and extracellular expansion both cause T1 prolongation. It is reliant on extracellular/interstitial as well as intracellular variables. When the ideal cutoff is selected, native T1 delivers great sensitivity and specificity during the acute phases of myocarditis, when edema is most common. Native T1 prolongation, however, loses its myocarditis-specificity when the initial inflammation fades and fibrosis progresses. Since many heart diseases lead to widespread fibrosis, native T1 has difficulty differentiating between inflammatory and noninflammatory causes in individuals with persistent symptoms.[89,95-97]

COVID-19 messenger RNA-based vaccines

Several coronavirus vaccines, including messenger RNA (mRNA)-based vaccines such as Pfizer-BioNTech, Moderna, recombinant adenoviral vector vaccines such as Johnson and Johnson/Janssen, Oxford-AstraZeneca, and Sputnik V), and inactivated whole viral vaccinations, are now being delivered across the world (i.e. Sinovac Biotech and Sinopharm). COVID-19 mRNA immunization and myocarditis have now been linked in a number of case reports, case series, and retrospective investigations.[7,98,99] In the adult population the mean age of patients was 29.34±12.94 (range, 16 to 68) years, and in adolescents mean age of patients was 17.2±1.0 (range, 16 to 19) years.[6,7] In a study investigating the link between myocarditis and pericarditis following COVID-19 vaccination, males comprise the majority of the cases (85.5%). Most patients with reported cases of vaccine-associated myocarditis/pericarditis received Pfizer-BioNTech (69%); the remaining patients received Moderna (25.7%), Janssen Johnson and Johnson (4.1%), and AstraZeneca (1.03%). The average number of days it took for symptoms to appear after vaccination was 3.8±4.5, with symptoms appearing in 75% of people after the second dose. The most typical manifestations include dyspnea, myalgias, fever, and chest pain. The vast majority of patients who initially had myocarditis and pericarditis made a full recovery and were released.[7]

Myocarditis caused by COVID-19 is thought to have pathogenesis that is partially related to the cardiotropism of the SARS-CoV-2 spike protein, which enters cells through the ACE2 receptors on cardiomyocytes. Both the Moderna and Pfizer-BioNTech vaccines take advantage of the spike protein's mRNA sequences, which have the potential to be a therapeutic target and cause myocarditis.[100]

According to the revised LLC diagnosis can be made. Depending on the specific situation, patients with active myocarditis may need to be followed up. Due to the localized nature of the early stages of the disease, CMR investigations performed in the first few days of myocarditis may be less sensitive than those performed one week after the onset of clinical symptoms. Persistent CMR indicators for inflammation four weeks after initiation have predictive significance. In order to distinguish uncomplicated myocardial involvement in a systemic viral disease

from a complicated course with the viral or auto-immunological disease, follow-up at least four weeks after the onset of the disease may be beneficial. In the first few days following infection, viral clearance is often complete, and tissue inflammation shouldn't linger more than two to three weeks.[85,101]

The prognosis and course of myocarditis are completely determined by the etiology, clinical manifestations, and stage of the disease. Even though the pathogenesis of myocarditis should be the primary target of treatment, only a small number of trials with inflammatory heart diseases like sarcoidosis and giant cell myocarditis have shown the effectiveness of a particular causative medication. In those individuals, further conventional heart failure medication is typically advised due to the high incidence of LV dysfunction. Standard heart failure therapy consists of diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists. In general, calcium-channel blockers are not advised to treat acute heart failure. Patients with apical aneurysms with thrombus (e.g., Chagas disease, atrial fibrillation, and past embolic episodes) are typically advised to take anticoagulation to avoid thromboembolic events.[49,102,103]

Colchicine and non-steroidal anti-inflammatory medications have become standard first-line treatments for pericarditis.[104-108]

Beta-blockers, amiodarone, and sotalol are used as first-line therapies for the treatment of arrhythmia. When there is a cardiac block or bradyarrhythmia, permanent pacemakers are employed.[13,49,109,110]

It has been demonstrated that high dose intravenous immunoglobulin (IVIG) affects the immunological and inflammatory response in a range of systemic autoimmune diseases, including sarcoidosis or systemic lupus erythematosus. In contrast, there was no change in LV function between patients receiving IVIG and those getting a placebo in patients with recent-onset myocarditis and DCM. However, the use of IVIG is not currently advised by the European Society of Cardiology.[111-114]

A therapy with acyclovir, ganciclovir, and valacyclovir may be explored in individuals with herpes virus infection in situations when other treatments have failed, despite the fact that their clinical efficacy in treating myocarditis is uncertain. Interferon therapy purges enteroviral and adenoviral genomes in individuals with LV dysfunction. Remdesivir, an antiviral drug, was also proved to be effective at preventing and lessening disease severity in the Middle East respiratory syndrome (MERS) coronavirus in primates, as well as at speeding up recovery in patients hospitalized with COVID-19.[2,8,115-117]

Based on the encouraging findings of multiple trials, immunosuppressive medication is now only seen as a possibility for virus-negative patients. Steroid and azathioprine therapy may possibly be a future treatment option for B19V-related diseases.[118]

The most frequently used treatments in the case studies were non-steroidal anti-inflammatory drugs, colchicine, and steroids, indicating that the management of post-COVID-19 vaccine myocarditis complies with current recommendations. The effectiveness of anti-inflammatory medications supports the hypothesis that COVID-19 vaccine-associated myocarditis (C-VAM) autoimmunity and molecular mimicry coexist.[7]

In conclusion, myocarditis is an inflammatory condition of the myocardium that can also develop after receiving the second dose of mRNA COVID-19 vaccines. The majority of patients lacked a significant cardiovascular disease or COVID-19 infection history. Myocarditis and pericarditis are more common in males. More patients who experienced the symptoms had two doses of the vaccine (compared to one). Myocardial inflammation is caused by cell-mediated immune reactions against the vaccine's active ingredients. Immunosuppressants and anti-inflammatory medications can be used to manage the condition. Myocarditis and pericarditis should be considered a likely diagnosis in patients who received the COVID-19 vaccination, especially in males who develop suspicious symptoms within a few days of the second dose of the mRNA vaccines.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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