ABSTRACT

Cardiac inflammation in the form of myopericarditis (myocarditis and pericarditis) is a well-known and rare complication of the SARS-COV-2 (COVID-19) vaccination for both the mRNA constructed as well as the Adeno viral based platforms. Myopericarditis following COVID-19 vaccination is a transient phenomenon with very low morbidity and mortality is rare. A high degree of suspicion in younger, vaccinated individuals in the appropriate clinical setting and confirmatory laboratory evaluation leads to the diagnosis. The treatment approach is based on the presence of symptoms and the outcome is excellent although the long-term outlook is unknown at present. In this brief review, the mechanism of action of mRNA and vector based COVID-19 vaccines, the proposed mechanism of pathogenesis of cardiac inflammation following COVID-19 vaccination, diagnosis, therapeutic options, and follow up of patients will be discussed.

Keywords: SARS-COV-2 (COVID-19), Myopericarditis, Inflammation, Virus, Cytokines, Immunity.

INTRODUCTION

The occurrence of pericarditis and myocarditis vary between 2-20 persons to as much as 36.5 persons per million per year [1,2]. The most common causes include viral and idiopathic. The viruses that induce pericarditis and myocarditis include adeno, enterovirus, parvo B 19, herpes, influenza, HIV, hepatitis C, hepatitis B, and corona including SARS-CoV-2 (COVID-19) [1]. After the advent of the SARS-CoV-2 vaccination, pericarditis and myocarditis were recognized as a complication following vaccination [3]. The safety and efficacy of COVID-19 vaccine is well documented [4]. In the Vaccine Adverse Event Reporting System (VAERS), out of 350 million mRNA COVID-19 vaccine administrations, a total of 1991 cases were reported and of those, 1626 were defined as myocardial inflammation, 391 cases had pericarditis, and 684 had pericarditis only [5]. Myopericarditis affected mostly the young between the ages of 12-30 following the 2nd vaccine dose within 7 days of receiving the vaccine as against unvaccinated and those who received the non-mRNA COVID-19 vaccine [6]. It was lower in females below the age of 50 years. mRNA vaccine induced myocarditis was 113 cases per million following the Moderna vaccine and 28 per million following the Pfizer vaccine [6].
absolute risk of pericarditis or myocarditis measured as the incidence rate within a week of COVID-19 vaccination for males between the ages of 18-25 years after the 2nd dose was 2.17 (95% confidence interval [CI] 1.5-3.04 per 100,000 person days) for the Moderna vaccine and 1.71 (CI 1.3-2.2) cases per 100,000 for the Pfizer-BionTech vaccine [7]. It was reported that COVID-19 caused 1000-4000 cases of myocarditis and pericarditis per 100,000 individuals, which is much higher than what is seen as resulting from the COVID-19 vaccination [8]. It is important to note that vaccine associated myopericarditis doesn’t indicate that the vaccine was the etiological agent, it is possible that the adjuvant may have reactivated, elevated, or augmented cardiac inflammation caused by an immune mediated mechanism or a viral infection [9]. Although the incidence of myopericarditis is higher in the vaccinated group versus the unvaccinated group, the absolute risk is small in both groups. In comparison, the risk of myopericarditis is seven times higher in those who are infected with COVID-19 than those who received the vaccine [10].

Pathophysiology of Cardiac Inflammation

Mechanism of mRNA and Adeno virus vector-based vaccine action:

mRNA Vaccine consists of modified mRNA contained within a lipid nanoparticle and is injected intramuscularly. The injected nanoparticle adheres to the host cell, releasing mRNA into the cytoplasm. The mRNA subsequently enters the ribosomes and gets translated into a viral spike protein followed by conversion of spike protein into antigen peptides by proteosomes. The antigen peptides are expressed on the cell membrane via major histocompatibility complex class 1 (MHC-1). MHC-1 interacts with cytotoxic CD8+ T cells. The antigen peptide also penetrates antigen presenting cells (APCs) and are expressed on MHC-2. Interaction between T-cell receptor membrane protein, MHC-2, and CD4+ T cells leads to the production of cytokines such as interleukin 2 (IL 2), IL-4, and IL-5 and resulting in the activation of adaptive immunity as well as humoral immunity via the activation of β cells to produce antibodies against the spike protein of the COVID-19 virus. The innate immune system is also activated when mRNA binds to toll like receptor (TLR), particularly to TLR-7, as well as to MDA-5 (melanoma differentiation-associated protein 5). Both belong to the pattern recognizing receptor family (PRR), resulting in the generation of anti-viral type 1 interferon. On the other hand, Adeno virus vector-based vaccines (AstraZeneca and Johnson & Johnson) contain DNA instead of RNA and operate by similar mechanism to activate the immune system. It is of interest to note that TLR-9 is involved instead of TLR-7 in the activation of the innate immunity in adeno virus vector-based vaccines [11,12].

The proposed mechanism of induction of myopericarditis (figure 1):

The three described mechanisms are immune overactivation (cytokine storm), molecular parody, and gender based hormonal differences.
adaptive immunity can arise resulting in the overexpression of cytokines [9], as well as the generation of toxic granzyme and perforin, reactive oxygen, nitric oxide by macrophages, resulting in damage to surrounding tissues (friendly fire). It is interesting to note that the 2nd dose of the vaccine induced the activation of T cells. Individuals who underwent biopsy for myocarditis following COVID-19 vaccination had high levels of antibodies directed against interleukin-1 receptor antagonist (IL-1RA), which is part of the TLR4/IL-1R signaling family. The TLR4/IL-1R signaling pathway produces IL-1ß, which is upregulated on mast cells and macrophages in males and is essential in initiating myocarditis/pericarditis in animal experiments. Angiotensin-converting enzyme 2 (ACE2)/ trans-membrane protease serine 2 (TMPRSS2) / Neuropilin 1 (NRP1) receptors which are found on mast cells may be directly triggered at the site of vaccination and perhaps at distant sites, such as the heart, following vaccination leading to an autoimmune response [13].

**Molecular parody**

The similarity in molecular pattern between the cardiac myosin and the spike protein of COVID-19 virus may be involved in cardiac inflammation following vaccine administration [14]. Myocarditis represents infective complication rather than vaccine induced consequence.

**Gender based hormonal effect**

The stimulating effect of testosterone in inducing a Th-1 (T-helper cell-1) type of immune response and the inhibitory effect of estrogen on inflammation may explain the male preponderance in the induction of cardiac inflammation during a viral infection such as following SARS-COV-2 and consequently also COVI-19 vaccination [15].

**DIAGNOSIS**

**Clinical presentation**

**Myocarditis and pericarditis**

Myocarditis ensued in men under the age of 40 years whereas pericarditis developed in men under 50 years of age. 95% of individuals who developed myocarditis were white in comparison with 84% who developed pericarditis. 95% of individuals with myocarditis were admitted to the hospital for three days with 10% in the intensive care unit compared with 35% of pericarditis patients admitted to the hospital and 3% in intensive care unit. Most cases of myocarditis fall into category of suspected or probable etiologies.

The onset of clinical presentation varies widely from a few hours to days. Features of myocarditis include asymptomatic or symptoms and signs such as exhaustion, chest pain or pressure, palpitation, malaise, fatigue, arrhythmia, cardiac failure, and cardiogenic shock with a rare incidence of mortality [16].

Acute pericarditis, on the other hand, present with chest pain, pericardial rub, and pericardial effusion [17]. Younger pediatric patients present with irritability, vomiting, poor feeding, tachypnea, and lethargy.

**WORK UP**

**Blood testing**

Elevated B-type natriuretic peptide (BNP), N-terminal B-type natriuretic peptide (NT-pro-BNP), and troponin indicate myocarditis. Polymerase Chain Reaction (PCR) testing is used for viruses that cause myocarditis. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated.

**EKG**

Findings include PQ-segment depression, ST-segment elevation, non-specific ST-segment changes, T-wave inversion, ST-segment inversion, junctional rhythm, sinus tachycardia, supraventricular tachycardia, left bundle branch block (LBB), and rarely ventricular arrhythmia.

**Transthoracic Echocardiography (TTE)**

A third of the patients may show pericardial fluid and decreased left ventricular function.

**Cardiac magnetic resonant imaging (CMR)**

Myocardial edema was noted on T2 recording.

**TREATMENT**

A high level of suspicion is essential for the diagnosis. The diagnosis is based on history, clinical presentation, and appropriate work up as enumerated previously. COVID-19 related cardiac inflammation is a transient and self-limited illness unlike viral induced affliction.

Therapeutic options include non-steroidal anti-inflammatory drugs (NSAIDS), colchicine (anti-inflammatory), and immunomodulation therapy using intravenous immunoglobulin (IVIG) and corticosteroids. Colchicine and immunomodulation are only used in symptomatic and refractory cases [18]. Supportive treatment of heart failure is initiated in those who present with clinical evidence of congestive heart failure.
OUTCOME

Most cases of vaccine induced pericarditis and myocarditis are self-limited and transient. Most cases resolve with normalization of cardiac function. Both morbidity and mortality are extremely low [19]. Activity restriction followed by repeat evaluation is indicated in selected athletes and screening for myocarditis is not indicated in asymptomatic athletes that received COVID 19 vaccine.

COVID-19 VACCINE RECOMMENDATION

Although vaccinated individuals are twice as likely to develop myopericarditis when compared with the unvaccinated group, COVID-19 vaccine benefits outweigh risks. The benefits include prevention of severe infection, hospital admission, death, and reduction in community spread of infection, protection of the most vulnerable population such as immunocompromised individuals, infants, and the geriatric age group as well as preventing overstretching of the health care resources. Hence, vaccine against COVID-19 is recommended in all age groups [20].

Vaccines in autoimmune conditions

Studies provide evidence of no harmful outcomes in patients with autoimmune disease immunized with influenza and pneumococcal vaccination [21]. COVID-19 vaccination is safe for patients with systemic lupus erythematosus [22].

CONCLUSION

Myocarditis represents first and foremost a viral complication that can also arise after vaccination which must induce protection against the infection without inducing infectious disease. The development of myopericarditis following COVID-19 vaccination is rare and is induced by immunological mechanism and a high degree of suspicion is essential to make a diagnosis. The treatment is largely supportive with good prognosis. The benefit of vaccination outweighs the risks and individuals of all age groups must be encouraged to take the vaccine.

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CONFLICT OF INTEREST

None.

REFERENCES

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