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Myocarditis following Coronavirus vaccination

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ABSTRACT

Introduction: Myocarditis is an adverse reaction discovered after the marketing of SARS-CoV-2 mRNA vaccines. Nevertheless, this effect is not mentioned as an adverse reaction in the summary of product characteristics of other types of vaccines against this disease.

Objective: In this work, we aim to present the cases of myocarditis after vaccination against COVID-19 reported to the national Tunisian centre of pharmacovigilance.

Method: We present the cases of myocarditis reported after the COVID-19 vaccination. All cases are diagnosed according to Brighton’s case definition of myocarditis. The vaccines causality assessment was estimated by the French imputability updated method of Bégaud et al.

Results: We included five patients. The sex ratio (M/F) was 4. The mean age was 30 years. All patients had no notable cardiovascular history and did not report any significant past medical history. The onset of symptoms was two days post-vaccination in three patients. The predominant reported symptoms are chest pain and dyspnea in the five cases. Cardiac magnetic resonance imaging (MRI) confirmed the myocarditis diagnosis in four patients (not performed for one patient).

All cases were classified as definitive cases according to the Brighton case definition of myocarditis. No patient required hospitalization in a cardiac intensive care unit. All the patients recovered from acute myocarditis within a few days.

Conclusion: Reported cases of myocarditis post-COVID-19 vaccination in our population are rare, not severe, and have a quick favorable outcome.

Introduction

Myocarditis refers to the clinical and histological manifestations of a wide spectrum of pathological immunologic processes in the heart tissues. The immune response in the heart leads to structural and functional aberrations in cardiomyocytes, which result in contraction impairment, chamber stiffening, or conduction system disorder. Acute myocarditis is often linked to non-specific symptoms (chest pain, dyspnea, or palpitations) or occasionally asymptomatic.

The main etiologies of myocarditis are viral infections. Non-infectious etiologies of myocarditis are rare and are usually reported with systemic inflammatory conditions such as eosinophilic myocarditis, giant-cell myocarditis, or hypersensitivity myocarditis related to a drug or vaccine administration [1]. Even though myocarditis after vaccination was reported in the literature after many vaccines, mostly the smallpox vaccine, affirming causality, remains elusive [2].

Recently, after the worldwide mass administration of SARS-CoV-2 vaccines, there have been a few reports of myocarditis after the mRNA COVID-19 vaccine [3, 4]. That adverse event observed after the commercialization of mRNA vaccines was not initially described in the safety data or detected in the clinical trials prior to their commercialization. Afterward, myocarditis was considered an adverse reaction to mRNA vaccines.

Nevertheless, even when some cases of myocarditis were reported after other SARS-CoV-2 vaccines such as viral vector vaccines [1, 5], it was not mentioned as an adverse reaction in their summary of product characteristics of the other types of COVID19 vaccines.

Herein, we present the cases of myocarditis following vaccination against COVID-19 reported to the department of collection and analysis of adverse events of the National Pharmacovigilance Center of Tunisia.

Method

Data were collected retrospectively from the database of the department of collection and analysis of adverse events of the National Cen-
ter of Pharmacovigilance of Tunisia. We included reported cases of myocarditis that occurred after the COVID19 vaccination administration that were notified between March 2021 and October 2021.

All cases of myocarditis were defined according to Brighton’s case definition. The Brighton Collaboration was established in 2000 with the aim of developing globally accepted standardized case definitions for adverse events following immunizations as well as guidelines for the collection, analysis and presentation of surveillance data. The Brighton’s case definition for a definitive case of myocarditis is illustrated in Fig. 1 [6].

The vaccines causality assessment was evaluated according to the French imputability updated method which classifies adverse events from 10 to 16 [7].

Results

We included five patients. The gender ratio (M/F) was 4. The mean age was 30 years. All patients had no notable cardiovascular history and did not report any significant medical history or prior COVID-19 infection.

The symptoms onset delay was two days post-vaccination in three patients. The predominant reported symptoms were chest pain for all patients and dyspnea in four patients. Other reported symptoms included fever, asthenia, and myalgia. The median hospitalization duration was three days (ranging between two and five days). Laboratory tests performed during the acute presentation showed an elevated troponin I and C-reactive protein (CRP) elevation for all patients included in this study. Electrocardiogram (ECG) findings reported were diffused ST-elevation (in three patients) and non-specific ST-T changes (two patients). Patients with ST-elevation had no coronary artery obstruction on coronary angiography. Echocardiogram revealed decreased ejection fraction (EF) of less than 50% in three patients. No pericardial effusion was noted in echocardiographic findings for all patients. Cardiac magnetic resonance imaging (MRI) confirmed the myocarditis diagnosis in four patients (not performed for one patient). Nasopharyngeal SARS-CoV-2 PCR (for two patients) and rapid antigenic test (for three patients) were negatives for all patients.

According to this data, all cases were classified as definitive cases according to the Brighton case definition of myocarditis. No patient required hospitalization in a cardiac intensive care unit. Four patients received nonsteroidal anti-inflammatory drugs. Three of them received ibuprofen (20 to 30 mg/Kg as daily dose) for 5 to seven days and one patient received piroxicam (20mg daily) for five days. All the patients recovered from acute myocarditis within a few days.

Taking into account the chronological and semiological data, the five cases were scored I1 (doubtful) in one case and I2 (likely) in four cases according to the French updated imputability method.

The results are summarized in Table 1

Discussion

Post-vaccination myocarditis has been sporadically reported in the literature. With the introduction of new vaccines over the years, myocarditis remains rarely reported adverse event after vaccines (0.1% of reported adverse events). These reports revealed no further or unanticipated safety concerns [2].

Myocarditis reports concerned mostly influenza, tetanus, human papillomavirus, and hepatitis B vaccines. Nevertheless, the association was not as assertive as with the smallpox vaccine. Engler RJM et al. suggested, in their prospective observational cohort study, a higher clinical myocarditis relative risk following smallpox and influenza vaccination of 200-times than the published background rate [8].

Wide-scale clinical trials of mRNA vaccines in more than 70,000 individuals in the United States demonstrated good safety profiles [9].

After Emergency Use Authorization was given by the Food and Drug Administration (FDA) for both mRNA vaccines Pfizer-BioNTech and Moderna and after their administration, to a large worldwide population, adverse reactions not seen during clinical trials were reported to the Vaccine Adverse Event Reporting System (VAERS) such as proven myocarditis [10].

Myocarditis following COVID-19 vaccination’s data reported to the VAERS showed a high incidence of post-mRNA vaccination myocarditis in males less than 30 years of age [11]. Our study also showed that the incidence of myocarditis was mostly noticed in youth males post mRNA vaccination.

Myocarditis is always subject to gender biases. There is a broad agreement in the literature that myocarditis has a male gender tendency (sex ratio (M/F) is about 3.5:1). That was attributed to cardioprotective factors reaching higher levels in women, as well as the testosterone impact on the immune response and its role in the enhancement of viral replication in the myocarditis that was proven in in-vitro procedures. In addition, previous studies argue that estrogens boost an immunoregulatory response within the heart tissues that limitate further cardiomyocyte damage and as a result myocarditis progression [12,13].

Though myocarditis does have autoimmune components, this is notably at odds with autoimmune diseases commonly among women [13,14].

A Meta-analysis of clinical presentation and outcomes of myocarditis post mRNA vaccination found that 88.5% of the patients developed symptoms after the second dose with a median onset delay of two days post-vaccination. No significant past medical history was reported in 81.2% of these patients. Also, no prior COVID-19 infection was detected in 91.3% of included patients [15]. In our study, we have reported three cases of acute myocarditis occurred after the second dose of the mRNA-COVID-19 vaccine with a delay of two days, all in young males, with no past medical history. In agreement with these results, Li M et al have shown that the incidence rate of myocarditis following the second dose of mRNA vaccination was twice more elevated than the first dose [5].

Chest pain/tightness (100%), followed by fever (44.9%), myalgia (23.2%), chills (21.7%), and dyspnea (18.8%) were the principal clinical symptoms in most reported cases in the literature [15]. In our study, all the patients presented with chest pain followed by dyspnea (in 4/5).

A study on a large population analyzing background incidence rates of medical conditions for the safety assessment of COVID-19 vaccines has shown that the increased risk of myocarditis is only recognized for mRNA vaccines and not for viral vector vaccines [16]. That casts doubt on the imputability of the viral vector vaccine in the genesis of myocarditis in the 5th case in our study. In this case, symptoms were presented 21 days following the 1st dose of viral vector vaccine (Astrazeneca®) and the case was scored I1 according to the updated French
imputability method. Also, to uphold the safety of viral vector vaccines regarding myocarditis, some authors recommend viral vector vaccines as an alternative for patients at high risk of myocarditis or for those who have had myocarditis after the first dose of mRNA vaccine [5].

The myocarditis prognosis seems good. In fact, in the meta-analysis study, the outcome was reported in 87% of the patients who all progressed favorably [15]. All our patients recovered and were discharged from the hospital with no complications.

The mechanism of mRNA vaccines myocarditis is not yet elucidated [5]. Previous studies suggested different pathological explanations. Li et al evoked that an autoantibody generation occurs after receiving mRNA vaccines. Autoantibodies recognize the self-cells, including cardiomyocytes, as non-self-cells and will try to destroy them, and this will contribute to the development of myocarditis [5].

Otherwise, once the mRNA stimulates an adaptive immune response to recognize and eradicate the virus expressing spike protein. However, mRNA molecules can be immunogenic and stimulate the innate immune system, which will destroy the mRNA before it reaches target cells, blocking antibody production. The activation of this immune response is usually mild and transient and was reported more commonly among the younger population probably due to increased immunogenicity in younger people and more often after the second dose. While, in individuals with genetic predisposition, the aberrant immune response to mRNA may not be regulated leading to systemic inflammatory reactions. In fact, the mRNA in the vaccine will be detected as an antigen causing the activation of proinflammatory cascades and immunologic pathways that may play a role in the genesis of myocarditis as an outcome of a systemic reaction [15,17].

The main limitation of our study is the small sample size. However, this was the only reported cases of myocarditis following COVID-19 vaccination on a national scale. This fact may be explained by two possible hypothesis either the lack of notification to the pharmacovigilance department or the limited population vaccinated with an mRNA in Tunisia comparing to other populations reported in published data.

**Conclusion**

In summary, we highlight that while the clinical presentation and chronological association suggest the possibility of vaccine-associated myocarditis in our patients, we cannot conclude definitively that the COVID-19 vaccine was causative or that other etiologies for myocarditis can be definitively excluded. Nevertheless, clinicians should be suspicious of myocarditis in recently vaccinated patients with symptoms consistent with this diagnosis. Moreover, further researches must be needed to illuminate cardiovascular medicine by identifying the pathophysiology behind myocarditis post-vaccination and outlining the approach of care. It is still essential to evaluate the risk of COVID-19 vaccines in view of the persistence of the pandemic and the constant appearance of new variants.

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**Declarations of Competing Interest**

None

**Data availability**

No data was used for the research described in the article.

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**Table 1**

Summary of reported data for all patients.

| Age (years) | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|-------------|-----------|-----------|-----------|-----------|-----------|
| Sex         | Male      | Male      | Male      | Male      | Female    |
| Vaccine     | mRNA      | mRNA      | mRNA      | mRNA      | Viral vector |
| Pfizer-BioNTech® | Moderna® | Moderna® | Moderna® | Moderna® |
| Vaccine dose | 1st       | 2nd       | 2nd       | 2nd       | 1st       |
| Onset delay (days) | 7 | 2 | 2 | 2 | 21 |
| Electrocardiogram abnormalities | + | + | + | + | + |
| Troponine I (µg/L) (Normal values <0.1 µg/L) | 125.6 | 165.7 | 223.65 | 146.33 | 632.6 |
| C-reactive protein (mg/L) (Normal < 8 mg/L) | 66 | 124 | 87 | 117 | 141 |
| Ejection fraction (%) | conserved | conserved | <50% | <50% | <50% |
| Cardiac MRI compatible with myocarditis | + | + | + | + | Not performed |
| Imputability score | 12 | 12 | 12 | 12 | 11 |