

Histopathological characteristics of myocarditis following COVID-19 vaccination: a scoping review

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Abstract

Introduction: Cases of myocarditis in people vaccinated against COVID-19 have been reported in the recent years. Nevertheless, the histopathological features and the pathomechanisms in these cases are still unclear. Hence, a scoping review of existing literature was performed to discover the histopathological features of myocarditis induced by the above-mentioned vaccine. **Methods:** A search was performed in the PubMed, Scopus and EMBASE databases to retrieve the relevant records, involving analyses of biopsy and autopsy specimens. Baseline characteristics of the patients and the histopathological characteristics of the respective specimens were extracted and recorded. **Results:** Overall, 24 case reports and case series (involving a total of 54 patients) were included in this scoping review. The following signs of inflammation were present in the specimens: lymphocyte infiltration (64.8%), eosinophilic infiltration (29.6%), neutrophil infiltration (3.7%) and giant-cell formation (1.9%). Other features included myocardial tissue necrosis (20.4%), the presence of the SARS-CoV-2 spike protein (16.7%) and microthrombosis (3.7%). **Conclusions:** The histopathological characteristics of SARS-CoV-2 vaccine-induced myocarditis were heterogenous, the only common characteristic was the presence of lymphocyte infiltration in more than half of the cases. Studies of unreported past cases may provide further insights into the topic.

Keywords: histopathology · COVID-19 vaccine · mRNA vaccines · myocarditis · myocardial inflammation

Citation

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Introduction

Myocarditis is a rare but serious condition where the heart muscle (myocardium) becomes inflamed [1]. According to the histopathological standard for diagnosing myocarditis (the Dallas criteria), myocarditis is defined as an inflammatory infiltration of the myocardium with or without fibrosis of the tissue [2]. Although the latter disease is not generally life-threatening and doesn't cause permanent damage to the myocardium, it can lead to hospitalization and increased risk of developing arrhythmias [3].

Since early 2021, several cases of myocarditis have been reported in people following vaccination against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, particularly in those vaccinated with mRNA vaccines [4-5]. Interestingly, most patients who developed myocarditis presented some common patterns, including the onset of the disease in an average of 2-3 days after receiving the second dose of the SARS-CoV-2 vaccine [6]. Nonetheless, most cases of post-vaccination myocarditis were diagnosed based on medical imaging techniques or laboratory examinations, therefore not enough data and systemic descriptions were available to comprehend the pathophysiology of this condition [7-8]. Hence, there is a significant need for the analysis of biopsy or necropsy specimens of the myocardia of patients with inflammatory cardiomyopathy after receiving the SARS-CoV-2 vaccine. Moreover, according to the proposals of the World Health Organization, it is necessary to systematically evaluate the adverse effects of vaccines [9]. The aim of this study was to conduct a scoping review of the available literature in order to investigate the histopathological features of the myocarditis following SARS-CoV-2 vaccination.

Material and methods

A scoping review was conducted according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines with the aim of answering the following research question: "what are the histopathological characteristics of myocarditis following vaccination against SARS-CoV-2, as described in the available literature?" [10]. We systematically searched the PubMed, Scopus and EMBASE electronic databases for English-language articles published from inception until April 2023. The following keywords in combination with Boolean operators (AND, OR) were used in the electronic search: "myocarditis", "inflammatory cardiomyopathy", "histolog*", "histopatholog*", "anatomopatholog*", "surgical pathology", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "coronavirus disease 19", "COVID-19", "vaccine" and "vaccination".

The inclusion criteria were: case report, case series or observational study reporting the biopsy or necropsy results of patients with myocarditis occurring after the SARS-CoV-2 vaccination. We used the citation manager EndNote (Clarivate, Philadelphia USA and London UK) to remove duplicate records. All remaining records were screened for eligibility based on their titles and abstracts. Finally, we obtained the full-text versions of the remaining records and assessed them in detail.

Data extraction and statistical analyses

Data was extracted from all included studies regarding the number of patients, their gender, the number of vaccine doses they received prior to the onset of myocarditis, the type of vaccine they received, their medical history, the type of specimen taken (biopsy sample or necrotomy specimen) and the histopathological features found within the myocardial specimens. The extracted data was processed and presented using descriptive statistics. All statistical processes were performed using the STATA software package version 17.0 (StataCorp LLC, College Station USA).

Results

The database search retrieved a total of 179 records, of which 94 remained after the duplicates were removed. During the title and abstract screening, a total of 55 citations were deemed ineligible due to irrelevance to the research question. Once the full-text versions of the remaining articles were assessed, 15 were excluded (see Figure 1 for details). Hence, a total of 24 studies were finally included in the review, all of which were case reports and case series [11-34].

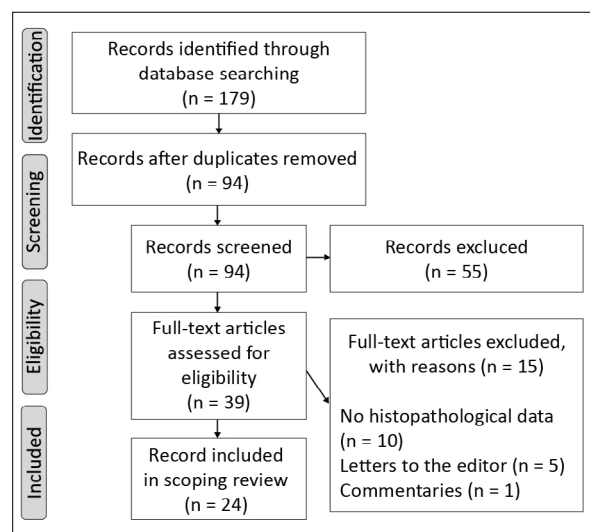


Figure 1. PRISMA diagram of our systematic review

Overall, the included studies described a total of 54 patients who presented with myocarditis after obtaining a dose of the SARS-CoV-2 vaccine. The baseline characteristics and vaccination information of the patients have been recorded in Table 1. Most of the included patients were healthy with no prior history of serious disease and 7 had prior history of myopericarditis, thyroiditis, diabetes mellitus, Parkinson’s disease and glioblastoma [22, 24, 26-28, 31-32]. Moreover, all patients expect 2, developed myocarditis after receiving either the first or the second dose of the vaccine [23-24]. It is also worth mentioning that majority of the patients who developed myocarditis received an mRNA vaccine.

Table 1. Baseline characteristics of patients in the included studies

VARIABLES	
Total number of patients (n)	54
Mean age (years) ± standard deviation	40.9 ± 17.3
Gender	
Male (n)	35
Female (n)	19
Vaccine doses received prior to myocarditis	
One dose (n)	21
Two doses (n)	31
Three doses (n)	2
Type of vaccine received	
Messenger RNA (n)	49
Viral vector (n)	4
Viral subunit (n)	1
Special health conditions	
Prior history of myopericarditis (n)	1
Thyroiditis (n)	3
Diabetes mellitus (n)	1
Parkinson’s disease (n)	1
Glioblastoma (n)	1

All of the specimens (43 from endomyocardial biopsy and 11 from necropsy) in the included studies had undergone anatomopathological analysis. In all the specimens, myocarditis was characterized by inflammatory infiltration, namely lymphocyte infiltration (64.8%), eosinophilic infiltration (29.6%), neutrophile infiltration (3.7%) and giant-cell formation (1.9%). In some specimens, myocardial tissue necrosis was also observed, which was previously reported, particularly in patients with viral myocarditis [35]. Histochemical analyses also revealed that in 16.7% of the specimens, the SARS-CoV-2 spike protein was present. It is also necessary to mention that in 2 specimens, microthrombi were also present and it is known that micro-

thrombosis is associated with SARS-CoV-2 [12, 25, 36]. Table 2 summarizes the histopathological features of the myocardial specimens in the included studies.

Table 2. Histopathological features of myocardial specimens in the included studies

	FREQUENCY (n)	PERCENTAGE (%)
Specimen type		
Endomyocardial biopsy	43	79.6
Necropsy	11	20.4
Lymphocyte infiltration	35	64.8
Eosinophilic infiltration	16	29.6
Neutrophile infiltration	2	3.7
Giant-cell formation	1	1.9
Myocardial tissue necrosis	11	20.4
SARS-CoV-2 spike protein in myocardium	9	16.7
Microthrombosis	2	3.7

Discussion

As seen in this scoping review, the histopathological features of the inflamed myocardia after COVID-19 vaccination vary from case to case. The only prevalent feature amongst the cases was the lymphocytic nature of the myocardial inflammation. Interestingly, the most common type of viral myocarditis is lymphocytic myocarditis as well [37]. Therefore, this histopathological finding may possibly indicate the involvement of the virus in the formation of post-vaccine myocarditis. Indeed, one of the proposed mechanisms is the leakage of vaccine nanoparticles into the bloodstream, which subsequently reach the myocardial cells and cause viral protein expression [38]. The presence of the SARS-CoV-2 spike protein in some of the specimens included in this review may also further support this theory.

Although the present scoping review was performed according to the PRISMA-ScR guidelines it has several significant limitations. First, most included records were case reports, yielding only a small number of included patients and thus decreasing the reliability of the results. Moreover, many of the articles did not provide details of the histopathological characteristics and therefore, possible additional characteristics may not have been recorded in

this review. Lastly, since the search was limited to articles written in the English language, valuable reports written in other languages might have been excluded.

past cases may shed some more light on the histopathological features of myocarditis induced by vaccination against SARS-CoV-2.

Conclusions

Our review demonstrated that myocarditis accompanied with inflammatory infiltration and sometimes myocardial necrosis rarely occurs in patients who were vaccinated against COVID-19, particularly with the novel mRNA vaccines. Further studies are required to validate our results. In particular, retrospective cohort studies of unreported

Conflicts of interest

None to report.

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