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Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military

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IMPORTANCE Myocarditis has been reported with COVID-19 but is not clearly recognized as a possible adverse event following COVID-19 vaccination.

OBJECTIVE To describe myocarditis presenting after COVID-19 vaccination within the Military Health System.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case series studied patients within the US Military Health System who experienced myocarditis after COVID-19 vaccination between January and April 2021. Patients who sought care for chest pain following COVID-19 vaccination and were subsequently diagnosed with clinical myocarditis were included.

EXPOSURE Receipt of a messenger RNA (mRNA) COVID-19 vaccine between January 1 and April 30, 2021.

MAIN OUTCOMES AND MEASURES Clinical diagnosis of myocarditis after COVID-19 vaccination in the absence of other identified causes.

RESULTS A total of 23 male patients (22 currently serving in the military and 1 retiree; median [range] age, 25 [20-51] years) presented with acute onset of marked chest pain within 4 days after receipt of an mRNA COVID-19 vaccine. All military members were previously healthy with a high level of fitness. Seven received the BNT162b2-mRNA vaccine and 16 received the mRNA-1273 vaccine. A total of 20 patients had symptom onset following the second dose of an appropriately spaced 2-dose series. All patients had significantly elevated cardiac troponin levels. Among 8 patients who underwent cardiac magnetic resonance imaging within the acute phase of illness, all had findings consistent with the clinical diagnosis of myocarditis. Additional testing did not identify other etiologies for myocarditis, including acute COVID-19 and other infections, ischemic injury, or underlying autoimmune conditions. All patients received brief supportive care and were recovered or recovering at the time of this report. The military administered more than 2.8 million doses of mRNA COVID-19 vaccine in this period. While the observed number of myocarditis cases was small, the number was higher than expected among male military members after a second vaccine dose.

CONCLUSIONS AND RELEVANCE In this case series, myocarditis occurred in previously healthy military patients with similar clinical presentations following receipt of an mRNA COVID-19 vaccine. Further surveillance and evaluation of this adverse event following immunization is warranted. Potential for rare vaccine-related adverse events must be considered in the context of the well-established risk of morbidity, including cardiac injury, following COVID-19 infection.

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Myocarditis is a heterogeneous disease with diverse clinical patterns, etiologies, and therapeutic responses, reflecting inflammatory injury to myocardial tissue in the absence of ischemia.[1] While viral infections, now including SARS-CoV-2, are the most common triggers of the disease, some myocarditis cases are associated with certain drugs and vaccine exposures.[1] With the exception of cases following live-attenuated smallpox vaccine in the military population,[2] myocarditis as an adverse event following immunization is described in rare published case reports and infrequent submissions to the Vaccine Adverse Events Reporting System (VAERS).[3,4]

Serious adverse events associated with receipt of new vaccines targeting COVID-19 are of high interest to the public and to public health vaccine safety surveillance. We describe a series of 23 individuals who developed probable hypersensitivity myocarditis in temporal association with COVID-19 messenger RNA (mRNA) vaccination.

Key Points

Question Should myocarditis be considered a potential adverse event following immunization with messenger RNA (mRNA) COVID-19 vaccines?

Findings In this case series of 23 male patients, including 22 previously healthy military members, myocarditis was identified within 4 days of receipt of a COVID-19 vaccine. For most patients (n = 20), the diagnosis was made after the second dose of mRNA COVID-19 vaccine; these episodes occurred against the backdrop of 2.8 million doses of mRNA COVID-19 vaccines administered.

Meaning Vigilance for rare adverse events, including myocarditis, after COVID-19 vaccination is warranted but should not diminish overall confidence in vaccination during the current pandemic.

Methods

The US military initiated COVID-19 vaccination following US Centers for Disease Control and Prevention (CDC)–defined phased distribution in December 2020. Adverse events following immunizations were identified from referrals to Defense Health Agency clinical specialists and through review of VAERS reports. Retrospective review of cases was conducted in accordance with the Walter Reed National Military Medical Center Institutional Review Board–approved protocol, "Adverse Events Following Immunization: Case Definitions and Outcomes Retrospective Review," and exempt from formal consent procedures.

Results

A total of 23 male patients (22 currently serving in the military and 1 retiree; median [range] age, 25 [20-51] years) were evaluated between January and April 2021 for acute-onset chest pain following mRNA COVID-19 vaccination. Care was provided in 15 distinct geographic locations globally with varying diagnostic evaluations. Each patient had a final diagnosis of myocarditis without infectious, ischemic, or autoimmune etiologies identified. Diagnoses were reviewed by an adjudication process and met the CDC case definition criteria for probable myocarditis (**Table 1**). A total of 8 patients had cardiac magnetic resonance imaging (cMRI) with T2 weighting showing subepicardial late gadolinium enhancement and/or focal myocardial edema, consistent with Lake Louise criteria for myocarditis.[1] The eFigure in the Supplement exemplifies cMRI findings for one of these patients.

The demographic and clinical characteristics of patients are summarized in **Table 2**. All military service members were physically fit by military standards and lacking any known history of cardiac disease, significant cardiac risk factors, or exposure to cardiotoxic agents. All patients presented with acute chest pain and significantly elevated cardiac troponin levels (10-fold to 400-fold the upper limits of their respective reference ranges). Their symptoms began within 12 to 96 hours following immunization with an mRNA COVID-19 vaccine. Sixteen had received the mRNA-1273 vaccine (Moderna), and 7 had received the BNT162b2-mRNA vaccine (Pfizer-BioNTech). For all but 3 patients, the second dose of vaccine preceded their myocarditis presentations. Among the 3 patients presenting after an initial vaccine dose, all had confirmed COVID-19 infection more than 2 months prior to vaccination.

All patients underwent electrocardiography and echocardiography (Table 2). Abnormal electrocardiography findings were recorded in 19 patients (83%); findings included ST-segment elevations, T-wave inversions, and nonspecific ST changes. Echocardiography in 4 patients (17%) demonstrated reduced left ventricular ejection fractions (40% to 50%).

Table 1. Case Definition Criteria for Myocarditis Following Immunization[a]

Suspected case	Probable case	Confirmed case
Dyspnea, palpitations, or chest pain of probable cardiac origin, with either one of the following: A. ECG abnormalities beyond normal variants, not documented previously, including: • ST-segment/T-wave abnormalities • Paroxysmal or sustained atrial or ventricular arrhythmias • AV nodal conduction delays or intraventricular conduction defects • Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy B. Focal or diffuse depressed LV function of indeterminate age identified by an imaging study	Meets criteria for suspected myocarditis, in the absence of other likely cause of symptoms, in addition to one of the following: A. Elevated cardiac enzymes (troponin-I, troponin-T, or creatine kinase-MB) B. New-onset or increased degree of severity of focal or diffuse depressed LV function by imaging C. Abnormal imaging findings indicating myocardial inflammation (cardiac MRI with gadolinium, gallium-67 scanning, antimyosin antibody scanning)	Histopathologic evidence of myocarditis by endomyocardial biopsy or autopsy

Abbreviations: ECG, electrocardiography; LV, left ventricular; MRI, magnetic resonance imaging.

[a] This definition was originally developed to evaluate cardiac events after smallpox vaccine. The definition is currently being reviewed by the international Brighton Collaboration for application to COVID-19 vaccine.

Table 2. Demographic and Clinical Characteristics of 23 Military Health System Patients With Myocarditis Following COVID-19 Vaccination, January-April 2021

Characteristic	No. (%)
Age, median (range), y	25 (20-51)
Sex	
Male	23 (100)
Female	0
Military status	
Currently serving	22 (96)
Retired	1 (4)
Proximate vaccine dose	
Second mRNA-1273 dose	14 (61)
Second BNT162b2-mRNA dose	6 (26)
First mRNA-1273 dose	2 (9)
First BNT162b2-mRNA dose	1 (4)
Time to symptom onset, mean (range), h	50 (12-96)
Troponin level[a]	
Elevated	23 (100)
Not elevated	0
Electrocardiogram findings[b]	
Abnormal	19 (83)
Normal	4 (17)
Echocardiogram findings[c]	
LVEF <50%	4 (17)
LVEF ≥50%	19 (83)
Coronary artery imaging	
Abnormal	0
Normal	16 (70)
Not performed	7 (30)
Cardiac MRI[d]	
Abnormal	8 (35)
Normal	0
Not performed	15 (65)
SARS-CoV-2 PCR findings at presentation	
Positive	0
Negative	19 (83)
Not performed	4 (17)
Other viral testing at presentation[e]	
Positive	0
Negative	13 (57)
Not performed	10 (43)
History of prior SARS-CoV-2 infection	
Positive	3 (13)
Negative	20 (87)

Abbreviations: LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; mRNA, messenger RNA; PCR, polymerase chain reaction.

[a] Inconsistencies in troponin types and laboratory sensitivity of testing preclude reporting combined quantified results.

[b] Electrocardiogram findings included ST elevations, T-wave inversions, and nonspecific ST changes.

[c] Echocardiogram findings are reported as LVEF; no structural abnormalities were noted in any patients.

[d] All abnormal cardiac MRIs reportedly met current Lake Louise criteria for myocarditis, with subepicardial late gadolinium enhancement and/or focal myocardial edema.

[e] Testing for other acute viral infections varied in each case; panels included some or all of these pathogens: coxsackie viruses, cytomegalovirus, Epstein-Barr virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, herpes simplex virus, human herpesvirus 6, HIV, influenza viruses, and parvoviruses.

Table 3. Expected vs Observed Cases of Myocarditis in Military Health System Patients Based on Number of Messenger RNA (mRNA) COVID-19 Vaccine Doses Administered

Doses of mRNA COVID-19 vaccine (through April 30, 2021)	No. of myocarditis cases	
	Expected[a]	Observed
2 810 000 Total doses	2 to 52	23
1 065 000 Second doses	1 to 20	20
544 000 Second doses to military members	0 to 10	19
436 000 Second doses to male military members	0 to 8	19

[a] Expected number is based on an expected annual incidence ranging from 1 per 100 000 person-years to 22 per 100 000 person-years[5,6] presenting within a 30-day period after vaccination.

No structural abnormalities were noted on any echocardiograms. A total of 16 patients underwent coronary artery imaging (11 had cardiac catheterization and 5 had coronary computed tomography angiography); none showed evidence of coronary artery disease.

Nineteen patients had respiratory specimens tested for SARS-CoV-2 by polymerase chain reaction at the time of presentation; none had evidence of acute SARS-CoV-2 infection. There were no positive findings among 13 patients who were tested for other infections, nor among 9 patients who were tested for autoimmune diseases.

Cardiac symptoms resolved within 1 week of onset for 16 patients. Seven patients continued to have chest discomfort at the time of this report; follow-up is ongoing.

The number of doses of mRNA COVID-19 vaccine administered by the Military Health System through April 30, 2021, is shown in **Table 3**. Overall, 2 810 000 doses were administered; 1 065 000 second doses were administered; 544 000 second doses were administered to military service members; and 436 000 second doses were administered to male military service members. The expected number of myocarditis cases occurring in a 30-day period after vaccination may be estimated using an international incidence of 22 cases per 100 000 person-years[5] or a US incidence of 1 to 10 cases per 100 000 person-years.[6] Observed numbers of myocarditis in the Military Health System were higher than some estimates of expected numbers, especially when considering the subset of the population who were military service members who received second doses of an mRNA COVID-19 vaccine (Table 3).

Discussion

In this case series, we describe 23 patients with clinical evidence of myocarditis following mRNA COVID-19 vaccination and meeting the CDC case definition for probable myocarditis. Eight patients had cMRI findings consistent with myocarditis. All patients in this series reflect substantial similarities in demographic characteristics, proximate vaccine dose, onset interval, and character of vaccine-associated myocarditis. The consistent pattern of clinical presentation, rapid recovery, and absence of evidence of other causes support the diagnosis of hypersensitivity myocarditis. Without myocardial

biopsy, histology cannot be defined, but the clinical course suggests eosinophilic hypersensitivity myocarditis as described in the context of other drug-associated and vaccine-associated myocarditis.[1-3] Presentation after second vaccine dose or, in 3 patients, when vaccination followed SARS-CoV-2 infection, suggests that prior exposure was relevant in the hypersensitivity response.

With the exception of the smallpox vaccine, immunizations are rarely associated with hypersensitivity myocarditis. The spectrum of clinical presentation and reliance on patients seeking health care and on health care professionals recognizing a rare vaccine-associated adverse event limits determination of the true incidence of this condition.[7] In contrast to passive case finding, Engler et al[2] reported a significantly higher incidence of myocarditis and pericarditis after smallpox vaccination through active prospective follow-up of vaccinated participants. They noted that 60% of these patients would not have sought medical care for symptoms outside of the study protocol.[2] Recognition of vaccine-associated myocarditis is clinically important since diagnosis impacts management, recommendations for exercise, and monitoring for cardiomyopathy.[8]

Notably, myocarditis cases were not reported following vaccination in clinical trials of current COVID-19 vaccines.[9,10] Adverse cardiac events of any kind were reported in less than 0.1% of trial participants, and rates were not higher in recipients of vaccine compared with placebo. The inability to identify rare adverse events is understandable in preauthorization testing since fewer than 20 000 participants received a vaccine in each trial.

Background rates of myocarditis in the general population are variable and may be challenging to determine. As noted, a global estimate of incidence is 22 cases per 100 000 person-years.[5] More recent estimates of US incidence are lower (1 to 10 cases per 100 000 person-years) and may be more appropriate for estimating expected rates of diagnoses in evaluations of immunization safety.[6] Applying both the US and global background incidence to the population vaccinated by the US military yields a range of expected numbers of cases of myocarditis in this period (Table 3). The observed number of male military members who experienced myocarditis after their second dose of mRNA vaccine, while relatively small, is substantially higher than the expected number.

Finally, it is important to frame concerns about potential vaccine-associated myocarditis within the context of the current pandemic. Infection with SARS-CoV-2 is a clear cause of serious cardiac injury in many patients.[11] The mechanism of injury may be direct infection, an immune-mediated response, or a combination of direct or indirect effects. Prevalence of cardiac injury may be as high as 60% in seriously ill patients. Notably, nearly 1% of highly fit athletes with mild COVID-19 infection have evidence of myocarditis on cMRI.[12,13] Given that COVID-19 vaccines are remarkably effective at preventing infection, any risk of rare adverse events following immunization must be carefully weighed against the very substantial benefit of vaccination.

Limitations

Important limitations to this case series should be considered. Passive surveillance, even when stimulated by global attention on vaccine safety, may not identify all cases. The patients described in this report were identified in a brief period of observation after vaccine implementation from a cohort of essential workers who are not necessarily representative of the general population. Clinical evaluations varied and did not include complete testing in some patients who received care in different hospitals and in different countries. In particular, consistent application of cMRI and thorough viral testing would have strengthened clinical conclusions. This early report is also unable to describe longer-term outcomes among these patients. Despite limitations of this review, it is notable that the clinical presentations of these 23 patients appear consistent with other recent case reports of myocarditis after second doses of mRNA COVID-19 vaccines.[14,15]

Conclusions

We report a case series of probable hypersensitivity myocarditis with consistent temporal association to receipt of an mRNA COVID-19 vaccine. While the true incidence of this adverse event is unknown at this time, the presentation pattern and clinical course suggest an association with an inflammatory response to vaccination. Increased attention to myocarditis as a potential adverse event following immunization is warranted. Recognition of the substantial morbidity associated with COVID-19 infection, including risk of cardiac injury, and the strong effectiveness of immunization in preventing infection provide important context for this topic. Concerns about rare adverse events following immunization should not diminish overall confidence in the value of vaccination.

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Study concept and design: Montgomery, Ryan, McClenathan, Collins, Hrncir, Herring.
Acquisition, analysis, or interpretation of data: Montgomery, Ryan, Engler, Hoffman, McClenathan, Loran, Hrncir, Herring, Platzer, Adams, Sanou, Cooper.
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