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Short communication

Myocarditis following COVID-19 vaccination – A case series

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ABSTRACT

There have been reports of myocarditis following COVID-19 vaccination. We surveyed all hospitalized military personnel in the Isareli Defense Forces during the period of the COVID-19 vaccination operation (12/28/2021–3/7/2021) for diagnosed myocarditis. We identified 7 cases of myocarditis with symptoms starting in the first week after the second dose of COVID-19 Pfizer-BioNTech vaccine. One case of myocarditis diagnosed 10 days after the second dose of the vaccine was not included. These 8 cases comprise of all events of myocarditis diagnosed in military personnel during this time period. All patients were young and generally healthy. All had mild disease with no sequalae. The incidence of myocarditis in the week following a second dose of the vaccine was 5.07/100,000 people vaccinated. Due to the nature of this report no causality could be established. Clinicians should be aware of the possibility of myocarditis following Pfizer-BioNTech vaccination. True incidence rates should be further investigated.

1. Introduction

Myocardial injury has been shown to be prevalent in hospitalized COVID-19 patients, reaching up to 36% of them.[1] The pathogenetic pathway of this myocardial injury in COVID-19 patients is not yet determined, but evidence supporting direct infection of myocytes or epithelial cells are sparse to lacking, and it is thought that cardiac injury might occur due to inflammatory system hyperactivation and release of inflammatory mediators.[2] Myocardial injury has also been observed in recovered COVID-19, PCR negative, patients. This might be part of the Multisystem Inflammatory Syndrome in Adults (MIS-A) or as a standalone phenomenon. [3,4].

Recent studies have reported on myocarditis events following COVID-19 vaccination. Marshall and colleagues described 7 cases of myocarditis in adolescents within 4 days following the second dose of the Pfizer-BioNTech COVID-19 vaccine. [5] Montgomery and colleagues reported on 23 cases of myocarditis in the US military following a second dose of the Pfizer-BioNTech COVID-19 vaccine. [6] they concluded that the incidence of myocarditis after COVID-19 was higher than expected in comparison to incidence following vaccination. Abu Mouch and colleagues reported on 6 myocarditis patients hospitalized in an Israeli hospital after a second dose of Pfizer-BioNTech vaccination, 5 of them within 72 h of the vaccination. [7] Larson and colleagues reported on 8 cases of myocarditis in an Italian hospital. [8] It is worth mentioning that one patient in their report presented with myocarditis after the first dose of the vaccine, but that patient previously recovered from COVID-19. Rosner and colleagues reported on 7 cases of myocarditis after COVID-19 vaccination [9]. Kim and colleagues report on 4 cases of myocarditis following COVID-19 vaccination, identified during a study researching vaccine associated myocarditis. [10] it is noteworthy that one of the cases reported in their article was a 70 year old female, the only female in all articles mentioned here.

On March 1st 2021, the Israeli Ministry of Health published incidence data on myocarditis following COVID-19 vaccinations. [11] The incidence rate of myocarditis in the 90 days following the second dose of the vaccine was 6.7 per 1,000,000, whereas the incidence following the first dose was much lower (0.6/1,000,000).

The Israeli Defense Forces (IDF) have provided COVID-19 vaccinations to its personnel, in a dedicated campaign that started on the 28th of December 2020. All vaccines used were of Pfizer-BioNTech manufacture. In this time frame more 158,000 IDF personnel received a single dose, and 138,000 received the second dose of the vaccine. In this study we monitored all personnel vaccinated up until March 1th 2021 and up to a week post vaccination for the diagnosis of myocarditis. Therefore, the follow up period ended on March 7th 2021.

The IDF Medical Corps have a robust and comprehensive monitoring system of hospitalized personnel. This ensures that no soldier is hospitalized without the Medical Corps knowledge and

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follow up. Since all cases of diagnosed myocarditis are hospitalized, the IDF Medical Corps have full knowledge of these cases. We identified 8 cases of myocarditis in the study follow-up period. All were diagnosed in patients that received COVID-19 vaccination. In one case symptom started more than 10 days after vaccination, and was not included in this report. Another case was clinically diagnosed as myocarditis, but the diagnosis was annulled on review due to lack of ECG, echocardiography, or MRI findings and only borderline Troponin levels. This case was not considered as myocarditis for the purpose of this report.

All data relating to the cases were based on clinical records. No tests were performed as part of this study. Informed consent was not obtained. This is in accordance with Israeli law which exempt publication of case reports with no identifying data from the need for informed consent or ethical approval.

2. Cases

All seven cases were males. Demographic, clinical data for the seven cases are presented in Table 1. All but one (patient no. 3) had chest pain on presentation to the emergency department. All but one (patient no. 5) reported fatigue or malaise. Two patients reported headaches, two reported abdominal pain, and two reported fever. All patients had elevated troponin and CRP levels, in three patients where CPK was measured it was elevated. All patients were SARS-CoV2 PCR negative. Two patients were evaluated for COVID-19 antibodies, both had evidence of vaccine associated immunity (positive Anti-S, negative Anti-N antibodies). All but one (no. 3) had typical ECG changes. In two patient the echocardiography was abnormal. Two patients underwent cardiac CT, and three underwent cardiac MRI, all had abnormal findings, typical for myocarditis. All patients had a mild to moderate disease. Hospitalization duration ranged 1–5 days. None of the patients suffered from clinical acute heart failure, and all had normal cardiac function and imaging following hospitalization. All treatments were short-termed and were discontinued on discharge or shortly after.

3. Discussion

The IDF Medical Corps provided 138,000 personnel with two doses of Pfizer-BioNTech COVID-19 vaccines in the time of this report follow-up. We identified eight cases of myocarditis in the follow up period, seven of them within one week of the second dose of the vaccine, on which we report here. As this is a purely observational report, we cannot assume causality between vaccination and incidence of myocarditis. Nevertheless, our report is unique in the fact that we due to the strict surveillance system of the IDF on hospitalized personnel, we can estimate incidence rates of myocarditis following COVID-19 vaccinations. In our report, myocarditis incidence in the week following the second dose of the vaccine was 5.07 per 100,000 people vaccinated. Due to national security, we cannot detail the number of personnel in the IDF, thus we cannot present the total myocarditis incidence in this time period as well of background incidence of diagnosed myocarditis in the IDF.

The number of myocarditis cases in the IDF in the years 2107–2020 was reported to the Israeli Ministry of Health in the beginning of 2021, as part of the background incidence report in the Ministry's effort to examine the association of myocarditis to the COVID-19 vaccines [unpublished data]. The report included all diagnosed cases of myocarditis in the years 2017–2020. In the years 2017–2019 the number of diagnosed myocarditis cases was 33–38 per year. It is worth mentioning that 2020 was an exceptional year with total number of myocarditis cases of 18 (reasons for this occurrence are subject to further research). On extrapolation of the number of myocarditis cases in our study's follow-up period to a year's time (69 days of follow-up, that is between the 28th of December 2020 to the 7th of March 2021, to 365 days) we reach 42.3 cases/year. This estimate is higher than the highest occurrence of myocarditis cases in previous years. Furthermore, the number of diagnosed myocarditis cases between January-February of 2020 was 6, less than the number of cases in our report, which was 8, although the time period was not exactly the same, and the small number of cases warrant caution when comparisons are made. It is worth mentioning that although all our patients described here are males, the population that was vaccinated include a large proportion of females. we do not have data concerning male–female ratios of background incidence of diagnosed myocarditis in our population, thus no comparison could be made.

The Ministry of Health in Israel published data concerning the incidence of myocarditis occurring within 90 days of COVID-19 vaccination. [11] The data are valid up until 1st March 2021. The incidence described after the second dose is 6.7/1,000,000. It is difficult to compare these data to our findings as the time period following vaccination is different. The report does not specify temporal distribution of these instances of myocarditis. The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom published its report concerning adverse events reported following COVID-19 vaccines. [12] The report is based on voluntary reporting system, and does not include active data collection of adverse events. The report includes 16 events of myocarditis out of 11.2 million first doses and 6.8 million second doses of the Pfizer-BioNTech vaccine. Because of the different methodology of data collection, it is impossible to compare it to our findings.

Montgomery and colleagues reported on 23 military personnel diagnosed with myocarditis up to 4 days after a second dose of the Pfizer-BioNTech COVID-19 vaccine. [6] Although not presented, according to the data in their report the incidence of diagnosed myocarditis after the second dose of the vaccine can be calculated as 3.49 per 100,000 people vaccinated (data regarding military service members only). This incidence is lower than the incidence we found in our report, but higher than estimated based on voluntary reporting systems.

In all published case series of myocarditis following COVID-19 vaccinations, findings are mostly similar. Chest pain is by far the most prevalent presenting symptoms, accompanied by fever, malaise, and other typical symptoms associated with myocarditis. [5–10,13]. Most patients reported on, but not all, presented with symptoms within the first week of a second dose of the vaccine. However, there is a report of myocarditis presenting after the first dose of the vaccine, although the patient described has previously recovered from COVID-19. [8] Usually, cardiac enzymes were elevated, and typical findings were found in ECG, and imaging studies. These findings are concurrent with our report. As in our report, all case series mentioned are observational in nature, and cannot establish causality between the vaccines and appearance of myocarditis, although temporal association cannot be disregarded. Due to the nature of the case series mentioned, incidence of myocarditis could not be reliably estimated.

It is important to note that all patients reported on in published case series from various locals, and age ranges, but one, were males. The case series cited, added to our report describe 62 cases of myocarditis following COVID-19 vaccination. Only one of these was a female. Myocarditis is more prevalent in males. [10] However, the extreme male predominance in published reports, raises a question whether there is a pathogenetic reason for it. In our opinion this question should be investigated in future research.

Table 1
Demographic, clinical features, treatments, and outcomes of 7 patients reported with myocarditis post second dose of COVID-19 vaccination.

No.	Age (yrs), sex	Underlying medical condition	Clinical signs and symptoms	No. of days following second dose of vaccination	Laboratory studies- peak (normal ranges)	Imaging/ other diagnostic study	treatments	length of stay / Outcome and follow-up
1	20, male	attention deficit and hyperactivity disorder	fatigue, headache, abdominal pain, chest pain radiating to right arm, perspiration					
	1	**Troponin-I** – 22,000 ng/L (0–50)						
CPK – 337 IU/L (46–171)								
CRP- 58.54 mg/L (<0.03–5)								
SARS-CoV-2 rt-PCR- negative	**ECG**- ST elevation, leads I, AVL, V1-6, PR elevation on AVR.							
Echocardiography- hypokinesis of the apex. LV EF was 45%.								
Cardiac catheterization - normal coronary arteries.								
Cardiac spectral CT -sub epicardial focal enhancement of the lateral wall and septum of the inferior wall, No pericardial or pleural effusion.	Bisoprolol, Ramipril	4 days/ discharged with normal LV function.						
2	19, male	Celiac disease	abdominal pain and fatigue, chest pain	1	**Troponin-I** – 15,000 ng/ dL (0–50)			
CRP – 9 mg/L (<0.03–5)								
LDH- 643 U/L (208–378)								
SARS-CoV-2 rt-PCR- negative								
COVID-19 S IgG AB- positive **COVID-19 N IgG AB** - negative	**ECG**- ST elevation, inferior leads, reciprocal depression on leads I and AVL.							
CXR- no pleural effusion.								
Echocardiography- normal LV and RV sizes and normal systolic function with EFof 60% and no pericardial effusion.								
Cardiac CT - late adherence through the lateral wall, the inferior basal wall, the apex and middle part of the septum.								
	Bisoprolol, Ramipril	4 days/ no symptoms and decreasing Troponin levels.						
3	19, male	allergic asthma						
	fatigue, throat pain, dizziness	1	**Troponin-I** – 15,527 ng/dL (0–50)					
CRP- 44 mg/L (<0.03–5)								
SARS-CoV-2 rt-PCR- negative	**ECG**-normal sinus rhythm							
CXR-no pleural effusion								
Echocardiography- normal LV and RV sizes and function. LV EF – 60%.								
24-hour ECG Holter- relatively short QTc (0.33 msec), few premature ventricular contractions with no significant events.								
Cardiac MRI (two weeks after discharge) -LV EF – 51% and late subepicardial and mesocardiac enhancement of 5% of LV walls.	Bisoprolol, Ramipril	4 days/ after admission with no symptoms.						

(*continued on next page*)

Table 1 (*continued*)

No.	Age (yrs), sex	Underlying medical condition	Clinical signs and symptoms	No. of days following second dose of vaccination	Laboratory studies- peak (normal ranges)	Imaging/ other diagnostic study	treatments	length of stay / Outcome and follow-up
4 **CPK-** 358 IU/L (30–200) **CRP** – 7 mg/L (0.2–5) **SARS-CoV-2 rt-PCR**- negative **Echocardiography**- normal LV function, minimal pericardial effusion.	22, male **ECG**- ST elevation I, II, III, AVF, V3-6 leads. Colchicine, Ibuprofen	none 4 days/ Troponin levels 4 days after discharge were within normal limits. Echocardiography 1 month after discharged showed normal LV function.	chest pain radiating to the left arm, fatigue	5	**Troponin-I** – 6000 ng/ Dl			
5 **CPK** – 381 IU/L (⟨195) **CRP** – 58.1 mg/L (0.2–5) **SARS-CoV-2 rt-PCR**- negative **CXR**-normal. **Echocardiography** -normal LV and RV functions with EF reaching 60%. **Cardiac MRI-** normal LV size with normal systolic function (EF = 63%), normal RV size with normal systolic function (EF = 65%). Myocardial edema and late gadolinium enhancement were noted in the basal LV and subepicardial myocardium.	24, male **ECG**- diffuse ST segment elevation in septal and lateral leads, and PR segment depressions in inferior leads. Colchicine, Ibuprofen	none 1 day/ clinical improvement.	squeezing chest pain and dyspnea	2	**Troponin**-T –409 ng/L (positive)			
6 **CRP** – 120 mg/L (0–5). **SARS-CoV-2 rt-PCR**- negative **Echocardiography**- moderate global LV dysfunction, LV EF of 38–42%, and normal RV size and function. **Cardiac MRI**- dilated LV (60 mm), mild to moderate systolic dysfunction (EF = 42%), normal RV size with mild systolic dysfunction (EF = 44%). Late gadolinium enhancement in the subepicardial and midmyocardium, along the lateral wall, infero-basal wall and mid- and basal septum involving 8% of myocardial mass. Enhancement was evident diffusely in the peri card.	21, male **ECG**- sinus tachycardia and findings consistent with LV hypertrophy. Colchicine, Bisoprolol	s/p myocarditis 5 years ago. 2 days/ ECG and Troponin levels taken after discharge were normal.	fever and malaise, squeezing chest pain radiating to the back	5	**Troponin-T-** 2300 ng/ L (0–20),			

Table 1 (*continued*)

No.	Age (yrs), sex	Underlying medical condition	Clinical signs and symptoms	No. of days following second dose of vaccination	Laboratory studies- peak (normal ranges)	Imaging/ other diagnostic study	treatments	length of stay / Outcome and follow-up
7	18, male	none	stabbing chest pain aggravated by lying down, myalgia, headache, malaise	2	**Troponin-T** – 33 ng/L (0–14)			
CRP – 4 mg/L (0.02–0.5) **SARS-CoV-2 rt-PCR**-negative **COVID-19 S IgG AB**- positive **COVID-19 N IgG AB** - negative	**ECG**- diffuse ST segment elevation associated with ST segment depression in AVR and PR segment depression.							
Echocardiography- normal LV and RV function	Colchicine	5 days/ discharged after decrease in Troponin levels and no symptoms						

Abbreviations: CRP- c-reactive protein, **CPK**- Creatine Phospho-Kinase, **LDH**- lactate dehydrogenase, **LV**- Left ventricle, **RV**-right ventricle, **EF**- ejection fraction, **CT**- computed tomography, **ECG**- electrocardiogram, **CXR**- chest x-ray, **AB**- antibody, **MRI** – magnetic resonance imaging, **Temp.**- temperature, **HR**- heart rate, **SPO2**- oxygen saturation, **BP**- blood pressure. **S**/P-status post.

It was shown by Kawakami and colleagues that in COVID-19 patients who suffered from myocarditis-like syndrome, there was little histological evidence of myocarditis, thus they suggest that myocardial injury is the correct term in these cases.[2] There are several possible pathogenetic pathways for this injury, one of them is suggested to be the inflammatory process associated with SARS-CoV-2 infection and the ensuing "cytokine storm". [2] Myocarditis/ myocardial injury was also evident in COVID-19 recovered patients, as part of the MIS-A. [3,4] In these cases inflammatory system involvement is also suggested. [4,14]. We suggest that such a response of the immune system might be elicited after a COVID-19 vaccine, and be the cause of myocarditis/myocardial injury in adults. The finding that myocarditis was diagnosed only after the second dose might support this theory, but this hypothesis needs to be examined in further studies.

It is interesting to note that all our patients but one had chest pain on presentation. In the medical literature the rate of chest pain as part of the clinical presentation of myocarditis varies, as most patients are asymptomatic, and was described as reaching up to 32%. [15] This might imply that a large portion of cases with myocarditis go undiagnosed in this time period in our population. Post vaccination symptoms, especially after the second dose are common, with fatigue, fever, muscle pain among the leading complaints [16]. One can argue that a portion of those might have electrocardiographic, laboratory or imaging findings consistent with myocarditis, but this assumption needs to be examined in prospective studies.

Our study has inherent limitation. Firstly, it is a case series and as stated previously, no causality can be assumed or established due to its observatory nature. Secondly, as stated, although the IDF Medical Corps has a robust surveillance system, true incidence could not be determined due to the specific clinical presentation in our cases, which might not be indicative of all other cases with less suggestive clinical expression.

4. Conclusions

We describe a series of myocarditis cases in patients following Pfizer-BioNTech COVID-19 vaccine. The unique nature of our study allows the estimation of the incidence of myocarditis following COVID-19 vaccination, although it is important to note that we cannot establish causality. The incidence of diagnosed myocarditis in our population was low, but there is a possibility the true incidence of myocarditis following COVID-19 vaccination is higher. Further studies should examine the true incidence, as well as the possible pathogenetic pathways. In the mean-time clinicians should be aware to the possibility of post COVID-19 vaccination myocarditis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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