Features and follow-up of patients affected by noninflammatory myocarditis after coronavirus disease 2019 vaccination
Sara Corradetti\textsuperscript{a}, Matteo Sclafani\textsuperscript{a}, Raffaella Mistrulli\textsuperscript{a}, Giovanna Gallo\textsuperscript{a}, Erika Pagannone\textsuperscript{a}, Marco Di Girolamo\textsuperscript{b}, Camillo Autore\textsuperscript{a}, Allegra Battistoni\textsuperscript{a} and Massimo Volpe\textsuperscript{a}

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\textsuperscript{a}Department of Clinical and Molecular Medicine and \textsuperscript{b}Department of Radiology, Sant’Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, Azienda Ospedaliero Universitaria Sant’Andrea, Rome, Italy

Correspondence to Allegra Battistoni, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, Azienda Ospedaliero Universitaria Sant’Andrea, Via di Grottarossa 1035-1039, 00189 Rome, Italy
Tel: +39 633779979; e-mail: allegra.battistoni@uniroma1.it

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To the Editor

Although acute myocarditis has not been described as an adverse event in landmark trials of coronavirus disease 2019 (COVID-19) vaccines, it has been frequently reported as a rare complication in the real world.\textsuperscript{1–6} The prognosis of this self-limiting condition is generally good, but little is known about the long-term outcomes.\textsuperscript{2} This work aims to report a single-center experience giving new insights into this topic.

Methods

We describe four cases diagnosed with myocarditis\textsuperscript{7} at Sant’Andrea Hospital in Rome, Italy, within 24–96 h after receiving a dose of COVID-19 vaccination between 1 August and 15 October 2021. All patients underwent blood tests, ECG and echocardiography at the time of presentation. All patients underwent cardiovascular magnetic resonance (CMR) within a few weeks from the onset of symptoms. All patients received an outpatient evaluation including ECG and echocardiography after a median of 6 months. Follow-up CMR at 6 months was performed and compared with the previous one in all four patients.

Results

Key characteristics of each case are included in Table 1. All patients had chest pain and elevated troponin levels on presentation to the emergency department. Serum C-reactive protein levels were very low and procalcitonin levels were in the normal range in all but one patient. None developed an increase in white blood cell count or changes in erythrocyte sedimentation rate. Abnormal ECG findings were recorded only in one patient presenting nonspecific ST changes. Echocardiography demonstrated preserved left ventricular (LV) ejection fraction (EF) and no regional wall motion abnormalities in all patients; pericardial effusion was present in three patients. The two patients who underwent CMR within 4 weeks of symptom onset had findings of myocardial edema with one having also late gadolinium enhancement (LGE). Conversely, the two CMRs performed after 4 weeks of onset showed LGE without myocardial edema. Hospitalization ranged 3–4 days. All patients were treated with NSAIDs, beta blockers and ACEi. None of the patients had in-hospital sustained arrhythmias or suffered from clinical acute heart failure, and all had normal cardiac function at discharge. All were asymptomatic and had not complications or rehospitalizations during follow-up. After 6 months from the onset, none had persistent ECG changes or echocardiographic alterations and inflammatory biomarkers were in the normal range. On 6 months, follow-up, CMR findings of myocardial edema disappeared in all cases, but areas of LGE present in the acute phase persisted almost unchanged in terms of extent and distribution.

Comment

Acute myocarditis following COVID-19 vaccination is a well defined clinical entity characterized in most cases by a presentation with chest pain and troponin I elevation without impairment of left ventricular ejection fraction (LVEF) and a benign in-hospital course.\textsuperscript{8,9} An atypical finding compared with other forms of myocarditis\textsuperscript{3} and in previously reported vaccine-associated\textsuperscript{10–12} is the prevalent absence of inflammatory serological changes, suggesting a noninflammatory pathophysiology.

With respect to the CMR findings, all patients in acute phase met at least one of the two updated 2018 Lake Louise CMR main criteria for acute myocarditis.\textsuperscript{13} Of note, sub-epicardial LGE was a frequent finding and persisted mostly unchanged after a follow-up of 6 months. In non-vaccine-associated myocarditis, the presence of LGE is generally associated with increased risk of adverse cardiovascular events during follow-up. However, data are
Table 1  Key characteristics of patients with acute myocarditis following coronavirus disease 2019 vaccination

| Case 1 | Case 2 | Case 3 | Case 4 |
|--------|--------|--------|--------|
| **Age (years)** | 39 | 20 | 54 | 21 |
| **Gender** | Male | Male | Female | Female |
| **Coronary artery disease risk factors** | No | No | Hypertension, dyslipidemia | No |
| **Cardiovascular history** | Previous myocarditis | No | No | No |
| **Known prior COVID-19 infection** | No | No | No | Yes |
| **Symptoms** | Chest pain, generalized malaise | Chest pain | Chest pain, dyspnea | Chest pain, dyspnea, fever |
| **COVID19 vaccine doses prior to symptom onset** | 1 | 1 | 1 | 2 |
| **COVID19 vaccine manufacturer** | Johnson & Johnson | Moderna | Pfizer | Pfizer |
| **Days from vaccination to symptom onset** | 3 | 3 | 2 | 2 |
| **SARS-COV-2 PCR testing** | Negative | Negative | Negative | Negative |
| **Serum hsTnI (pg/ml)** | 5734 | 9313 | 158 | 390 |
| **Serum BNP (pg/ml)** | 43 | Not obtained | 64 | Not obtained |
| **Serum CRP (mg/dl)** | 0.02 | 0.02 | 0.12 | 0.06 |
| **Serum PCT (ng/ml)** | 0.02 | 0.02 | 0.02 | 0.02 |
| **Serum ESR (mm/h)** | 17 | 2 | 12 | 8 |
| **ECG** | No abnormal findings | No abnormal findings | Nonspecific ST changes | No abnormal findings |
| **TTE LVEF (%)** | 57 | 63 | 61 | 58 |
| **Pericardial effusion** | No | Yes | Yes | No |
| **Anatomic coronary artery assessment** | Not obtained | Nonobstructive (ICA) | Nonobstructive (ICA) | Not obtained |
| **Time from clinical onset to first CMR** | 4 weeks | 4 weeks | 4 weeks | 2 weeks |
| **First CMR findings** | LGE with sub-epicardial distribution in the mid-basal inferolateral wall (not present in the previous CMR) | LGE with mesocardial distribution in the mid-apical inferolateral wall | Focal edema with sub-epicardial distribution in the basal lateral wall | LGE with sub-epicardial distribution in the basal inferolateral wall |
| **Oxygen support** | No | No | No | No |
| **Length of stay (days)** | 4 | 3 | 2 | 2 |
| **Discharge medications (in addition to chronic therapy)** | Ibuprofen | Aspirin | Ibuprofen | Aspirin |
| **Follow-up** | 6 months | 6 months | 6 months | 2 months |
| **Time from clinical onset to second CMR** | 6 months | 6 months | 6 months | 6 months |
| **Second CMR findings** | LGE with sub-epicardial distribution in the mid-basal inferolateral wall unchanged | LGE with mesocardial distribution in the mid-apical inferolateral wall unchanged | No edema | LGE with sub-epicardial distribution in the basal inferolateral wall unchanged |

BNP, brain natriuretic peptide (normal range 0–65 pg/ml); CMR, cardiovascular magnetic resonance; CRP, C-reactive protein (normal range 0–0.5 mg/dl); COVID-19, the coronavirus disease of 2019; ESR, erythrocyte sedimentation rate (normal range 2–25 mm/h); hsTnI, high-sensitivity troponin I (normal range 0–34 pg/ml); ICA, invasive coronary angiography; LGE, late gadolinium enhancement; PCT, procalcitonin (normal range <0.05 ng/ml); TTE LVEF, transthoracic left ventricular ejection fraction.
Cardiovascular magnetic resonance findings. (a) Case 1 CMR on acute phase: PSIR sequences. Short-axis view, basal segments. The image shows a linear area of LGE with sub-epicardial distribution in the inferolateral wall (arrow). (b) Case 1 CMR after 6 months of follow-up: PSIR sequences. Short-axis view, basal segments. The image shows the persistence of pericardial enhancement (+) and linear sub-epicardial LGE in the inferolateral wall of left ventricle (arrow). (c) Case 2 CMR on acute phase: PSIR sequences. Long-axis view. The image shows an area of LGE with mesocardial distribution in the mid-apical inferolateral wall (arrows). (d) Case 2 CMR after 6 months of follow-up: PSIR sequences. Long-axis view. The image shows the persistence of the area of LGE with mesocardial distribution in the mid-apical inferolateral wall (arrows). (e) Case 3 CMR on acute phase: STIR sequences. Short-axis view. The image shows focal edema with sub-epicardial distribution in the basal lateral wall (arrow). (f) Case 3 CMR after 6 months of follow-up: STIR sequences. Short-axis view, basal segments. The image shows the dissolution/disappearance of the myocardial edema previously detected in the lateral wall. (g) Case 4 CMR on acute phase: PSIR sequences. Short-axis view. The image shows a linear area of LGE with sub-epicardial distribution in the basal inferolateral wall (arrow). (h) Case 4 CMR after 6 months of follow-up: PSIR sequences. Short-axis view, basal segments. The image shows the persistence of linear area of LGE. CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement.
lacking with regard to the prognostic significance of persistent LGE in the absence of severe LV dysfunction and remodeling. In this setting, prolonged clinical and instrumental follow-up is recommended as these findings may reflect the extensive myocardial derangement potentially leading to future evolution to LV remodeling or late arrhythmias. Interestingly, the localization of LGE to the inferolateral LV segments on CMR was similarly seen in other case series and seems to carry a better prognosis compared with LGE localized to the septal segments. Nevertheless, further investigations are needed to determine the prognostic impact of these findings in the context of myocarditis following COVID-19 vaccination (Fig. 1).

Conflicts of interest
There are no conflicts of interest.

References
1 Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021; 385:1078–1090.
2 Medha G, Ishita R, Dwayne M, et al. Myocarditis post SARS-CoV-2 vaccination: a systematic review. QJM 2022;115:2531–2533; [Epub ahead of print].
3 Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA 2022; 327:331–340.
4 Díaz GA, Parsons GT, Gering SK, et al. Myocarditis and pericarditis after vaccination for COVID-19. JAMA 2021; 326:1210–1212.
5 Block JP, Boehmer TK, Forrest CB, et al. Cardiac complications after SARS-CoV-2 infection and mRNA COVID-19 vaccination - PCORnet, United States, January 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022; 71:517–523.
6 Patone M, Mei WX, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2022; 28:410–422.
7 Calbuto ALP, Fankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013; 34:2636–2648; Online ahead of print.
8 Sinagra G, Poncari A, Merlo M, et al. Miocarditi, pericarditi e vaccino a mRNA contro il COVID-19. Expert opinion della Società Italiana di Cardiologia. G Ital Cardiol 2021; 22:894–899.
9 Luk A, Clarke B, Dahdah N, et al. Myocarditis and pericarditis after COVID-19 mRNA vaccination: practical considerations for care providers. Can J Cardiol 2021; 37:1629–1634.
10 Kim HW, Jenista ER, Wendell DC, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 2021; 6:1196–1201.
11 Patel YR, Louis DW, Atalay M, et al. Cardiovascular magnetic resonance findings in young adult patients with acute myocarditis following mRNA COVID-19 vaccination: a case series. J Cardiovasc Magn Reson 2021; 23:101.
12 Truong DT, Dionne A, Muniz JC, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults. Circulation 2022; 145:345–356.
13 Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018; 72:3158–3176.
14 Sinagra G, Anzini M, Pereira NL, et al. Myocarditis in clinical practice. Mayo Clin Proc 2016; 91:1256–1266.
15 Aquaro GD, Perfetti M, Camasta G, et al. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. J Am Coll Cardiol 2017; 70:1977–1987.