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BRIEF COMMUNICATION

The application of cardiac magnetic resonance imaging (CMR) in myocarditis after COVID-19 vaccines : Case series from single medical center in Taiwan

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Abstract

During the coronavirus disease 2019 (COVID-19) pandemic, reports of vaccine-induced myocarditis, particularly messenger ribonucleic acid (mRNA)-based myocarditis, were widely spread. This case series describes various cases of COVID-19 vaccine-induced myocarditis confirmed by cardiac magnetic resonance imaging (MRI), including those who were administered rare protein-based vaccines. Eleven patients comprising eight males and three females with suspected myocarditis underwent cardiac MRI at Taichung Veterans General Hospital between October 2021 and May 2022. The median age of the patients was 33.5 years old (range: 22-57 years). The onset of myocarditis was mainly observed following mRNA vaccine inoculation. One patient received the MVC-COV1901 vaccine, a unique protein-based COVID-19 vaccine in Taiwan, and met the 2018 Lake Louise Criteria for the diagnosis of myocarditis, confirmed by cardiac MRI. Most patients reported chest discomfort after receiving various vaccine types. Among four patients with reduced left ventricular ejection fraction (LVEF), two showed LVEF restoration during the follow-up period, and the other two were lost to follow-up. Cardiac MRI characterizes myocardial features such as edema, inflammation, and fibrosis, and has been proven to diagnose myocarditis accurately with a sensitivity of 87.5% and a specificity of 96.2% according to the 2018 Lake Louise criteria. This diagnosis was achieved without invasive procedures such as endomyocardial biopsy or coronary angiography.

Keywords: Coronavirus disease 2019; Females; Myocarditis; Vaccine-associated perimyocarditis; Veterans

1. INTRODUCTION

Acute myocarditis has been reported after vaccination with messenger ribonucleic acid (mRNA) vaccines (BNT162b2 or mRNA-1273) for coronavirus disease 2019 (COVID-19).[1] Myocarditis and pericarditis have been reported to mainly occur in young adult males aged 5 to 39 years, usually within 0 to 7 days after receiving the second dose of COVID-19 mRNA vaccines.[2,3]

The MVC-COV1901 COVID-19 vaccine is a protein-based subunit vaccine that contains recombinant spike protein (S-2P) as the antigen and is adjuvanted with CpG 1018 and aluminum hydroxide.[4] In Taiwan, MVC-COV1901 has been approved for emergency use by the Taiwan Food and Drug Administration, Ministry of Health and Welfare for adults above 18 years.[5,6]

Few cases of acute myocarditis have been reported in association with the protein-based subunit COVID-19 vaccinations.[7,8] Here, we report a case series involving 11 patients who developed symptoms of myocarditis after receiving the Taiwan-approved COVID-19 vaccination and fulfilled the imaging diagnostic criteria confirmed by cardiovascular magnetic resonance imaging (MRI).

2. CARDIAC MAGNETIC RESONANCE IMAGING (CMR) PROTOCOL

CMR images were obtained using a 1.5-Tesla scanner (Avanto; Siemens Medical Imaging, Erlangen, Germany) with a

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cardiac-phased array receiver surface coil and electrocardiography (ECG) gating. Cine imaging was performed using a steady-state free precession sequence (echo time [TE]: 1.1-1.3 millisecond, repetition time [TR]: 35-37 millisecond) to capture a stack of 5 or 8 mm thick short-axis slices covering the entire ventricular area, as well as long-axis slices. In contrast, we utilized a gradient-echo sequence to minimize the artifacts in patients with implantable devices. Myocardial T1 mapping was performed using an ECG-triggered modified look-locker inversion-recovery (MOLLI) pulse sequence before and 10 to 15 minutes following the intravenous administration of gadobutrol (Gadovist, Bayer, Germany) at a dose of 0.15 mmol/kg as a contrast agent. The MOLLI T1 mapping protocol employed 5(3)3 (native) and 4(1)3(1)2 (post-contrast) sampling schemes (voxel size: 1.4×1.4×8 mm).[9] The T2 mapping protocol involved a T2-prepared steady-state free precession sequence with a voxel size of 1.87×1.87×8 mm.[10] Late gadolinium enhancement (LGE) images were captured 10 to 15 minutes after the intravenous administration of gadobutrol, and an inversion-recovery gradient-echo pulse sequence was used to individually adjust the inversion time according to the results of TI scout scans to optimize the nulling of the normal myocardium (TI: 285-380 millisecond).[11] The field of view was set at 320×320 mm following the standard (adjustments were made depending on the patient size; the typical voxel size of the images was 0.9×0.9×8 mm, the TE was 1.1-1.3 millisecond, and the TR was 500-700 millisecond). All patients provided informed consent and were monitored throughout the procedures. The presence of LGE was confirmed in two spatial orientations, and the researcher was blinded to the clinical data.

3. CASE PRESENTATION

This retrospective case series includes 11 cases of MRI-confirmed myocarditis following COVID-19 vaccine inoculation. The median age of the patients was 33.5 years (22-57 years), with eight of them (72.7%) being male. The patients reported chest discomfort after receiving various types of vaccination. Three patients experienced chest discomfort after the first dose of the mRNA vaccine injection (BNT162b2 or mRNA-1273), whereas four patients experienced it after the second dose. The other four patients developed symptoms after the third dose of immunization. One patient received three doses of the MVC-COV1901 vaccine, whereas the others received the AZD1222 vaccine as either their first or second dose. Baseline characteristics, initial symptoms, cardiac enzyme levels, and specific vaccine types are presented in Table 1.

Briefly, most patients presented with chest tightness, dyspnea, and palpitations. Some patients experienced headaches and general malaise, and one patient presented with acute gastroenteritis. In our study cohort, patients showed symptoms of early onset within 24 hours postvaccination and symptoms of late onset up to 3 weeks postvaccination. Four (36%) patients did not exhibit elevated troponin levels, which contradicts the previous literature[11] indicating elevated troponin I levels among approximately 98% of patients with mRNA-based COVID-19 vaccination-related myocarditis. Table 2 shows the cardiac MRI findings according to the 2018 Lake Louise Criteria.[12]

A 29-year old male (case 3 in Table 1) without underlying comorbidities experienced left anterior chest tightness 3 days prior to presenting to our emergency department. He remained in his usual state of health until receiving the third dose of the MVC-COV1901 vaccine. The patient was not infected with COVID-19, which was confirmed by SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction. ECG revealed sinus rhythm, a biphasic T wave at lead V3, and T wave inversion throughout leads V4 to V6. Blood tests revealed elevated levels of cardiac

Table 1

Baseline characteristics of study cohort

Case	Age, gender	1st vaccine	2nd vaccine	3rd vaccine	Symptoms of boost dose	Vaccine before symptoms	Time from vaccine to presentation	Symptoms and signs	hsTnT, ng/mL	LVEF at admission	LVEF at follow-up
1	40, male	mRNA-1273	mRNA-1273	MVC-COV1901	2	mRNA-1273	2 d	Fever, palpitation, tachycardia	5.42	56% (echo) 61% (MRI)	65% (echo) 1 mo later
2	52, female	AZD1222	AZD1222	BNT162b2	3	BNT162b2	1 d	Chest tightness and pain	3.72	52% (echo) 52% (MRI)	
3	29, male	MVC-COV1901	MVC-COV1901	MVC-COV1901	3	MVC-COV1901	22 d	Chest tightness	447.3	50% (echo) 53% (MRI)	61% (echo) 6 mo later
4	30, male	AZD1222	BNT162b2	mRNA-1273	3	mRNA-1273	3 d	Dyspnea	21.34	28% (echo) 23% (MRI)	54% (echo) 8 mo later
5	57, male	BNT162b2	BNT162b2	BNT162b2	1	BNT162b2	1 d	Palpitation, chest tightness, dizziness	12.76	51% (echo) 53% (MRI)	
6	22, male	BNT162b2	mRNA-1273	x	2	mRNA-1273	1 d	Chest tightness, dizziness	3064	61% (echo) 48% (MRI)	56% (echo) 4 mo later
7	47, male	BNT162b2	BNT162b2	mRNA-1273	2	BNT162b2	75 d	Diarrhea, epigastric pain	2394	50% (echo) 51% (MRI)	56% (echo) 4 mo later
8	34, female	mRNA-1273	mRNA-1273	mRNA-1273	2	mRNA-1273	1 d	Dyspnea, palpitation	112.1	36% (echo) 32% (MRI)	
9	44, female	AZD1222	AZD1222	BNT162b2	3	BNT162b2	1 d	Chest tightness, headache, general malaise	3.71	57% (echo) 58% MRI	
10	33, male	mRNA-1273	x	x	1	mRNA-1273	20 d	Chest tightness, palpitation	18.62	32% (echo) 29% (MRI)	52% (echo) 1 y later
11	22, male	BNT162b2	x	x	1	BNT162b2	23 d	Left chest and arm numbness	5.42	43% (echo) 49% (MRI)	

LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid.

Table 2

Cardiac MRI findings

Case	MRI acquisition: days after symptoms onset	LVEF	LV end-diastolic volume index	RVEF	T1-weighted images and mapping	Late gadolinium enhancement	T2-weighted images and mapping	Pericardial effusions
1	31	61	69.2	59.7	+	+ Focal		+
2	23	52	89.8	54.3	+ (1028 ± 108 ms) Focal	-	+ (50 ± 8 ms)	-
3	7	53	93.7	44	+ (1031 ± 81 ms) Focal	+ Apical anterior, anteroseptal, inferior	+ (52 ± 11 ms)	+
4	48	23	120.9	17.5	+ (1050 ± 74 ms) Diffused	+ Diffused	+	+
5	21	53	61.4	55.4	+ (1035 ± 97 ms) Focal	+ Focal	+ (51 ± 8 ms) Focal	+
6	3	48	124.2	41.92	+ (1049 ± 118 ms) Focal	+ Apical anterior and inferior	+ (51 ± 8 ms) Focal apex (54 ± 7 ms)	+
7	3	51	154.78	42.44	+ (1046 ± 99 ms) Focal	+ Basal lateral (transmural)	+ (50 ± 9 ms) Lateral (57 ms)	_
8	77	32	182.29	22.95	+ (1058 ± 56 ms)	+ Patchy	– (49 ± 5 ms)	+
9	18	58	124.63	51.85	+ (1044 ± 118 ms) Focal	+ RV insertion point	– (50 ± 10 ms)	+
10	61	29	285.13	29.42	+ (1045 ± 47 ms)	+ (Septal > lateral)	+ (52 + 13 ms)	-
11	26	49	159.6	28.65	+ (1025 ± 137 ms) Focal inferior wall 1075 ms	+ (Linear at inferior epicardial wall)	+ (52 + 11 ms)	-

LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

enzymes (peak creatine kinase: 123 U/L, Troponin-T: 458.90 ng/L) and N-terminal pro B-type natriuretic peptide (460.40 pg/mL). No common viral infections associated with myocarditis (herpes simplex virus, adenovirus, Epstein-Barr virus antibody, or cytomegalovirus tests were negative) were observed. Transthoracic echocardiography revealed mild hypokinesia over the inferior wall of the basal to mid-left ventricle (LV) with preserved LV ejection fraction (LVEF: 50%). Cardiac MRI showed preserved LV systolic function and patchy subepicardial delayed enhancement at the apical anterior, anteroseptal, and inferior walls of the LV, with focal elevated native T1 value (mean: 1031 ± 81 millisecond, apex: 1066 ± 66 millisecond) and diffused high T2 value (52 ± 11 millisecond) (Fig. 1). The patient refused coronary angiography due to the symptom relief. Post-myocarditis treatment included a prescription of Valsartan 80 mg (one tablet daily). Follow-up echocardiography was performed 5 months after symptom onset, and recovery of LV wall motion was confirmed (LVEF, 61%).

4. DISCUSSION

This case series included 11 patients with a cardiac MRI-based diagnosis of myocarditis after COVID-19 vaccination.

Cardiac inflammation, commonly reported after mRNA COVID-19 vaccination, has prompted warnings from the WHO Global Advisory Committee on Vaccine Safety (GACVS).[13] A meta-analysis of COVID-19 vaccine recipients revealed a higher myocarditis incidence with mRNA vaccines compared to non-mRNA types (22.6 vs 7.9 cases per million vaccine doses).[14] In the United Kingdom, myocarditis after mRNA Covid-19 vaccination was estimated at 10 to 30 patients per 1 000 000 doses, based on their event of press.[15] The prevalence of myocarditis increased following the second dose, particularly among young males, which was consistent across data collected from Isarel,[16] Canada,[17] and Taiwan.[18]

Although the mechanism of post Covid-19 mRNA vaccination-induced cardiac inflammation is unclear, the possible underlying pathogenesis is the autoimmune cross-reactivity that antibodies to SARS-CoV-2 spike glycoproteins attack myocardial contractile proteins, such as myocardial α-myosin heavy chain.[19] Despite nucleoside-modified mRNA not being a live virus or DNA, a complex interplay of the aberrant immune response, hormonal differences, and associated proinflammatory cascades is also hypothesized.[20,21]

Myocarditis induced by non-mRNA COVID-19 vaccines has rarely been reported due to its relatively lower incidence rate.[14] In our case series, one patient received a protein-based subunit COVID-19 vaccine (MVC-COV1901). However, the mechanism underlying this protein-based COVID-19 vaccine remains unknown. One of the cases developed acute myocarditis after NVX-CoV2373 vaccination, and endomyocardial biopsy (EMB) showed elevated $CD4^+$ T cell presentation.[6] Similar to the mRNA vaccine, the NVX-CoV2373 COVID-19 vaccine elicits a $CD4^+$ T cell response, fostering heart-specific autoimmunity.[22,23]

The gold standard method for the diagnosis of myocarditis is tissue-proof EMB. The Dallas criteria define myocarditis based on inflammatory infiltration and associated myocyte necrosis with or without damages unrelated to an ischemic event.[24] However, sampling errors, variations in histological interpretation, and EMB complications limit its diagnostic utility. Cardiac MRI provides a comprehensive noninvasive assessment of the myocardium and serves as an appropriate tool for patients without high-risk features of myocarditis in clinical presentations, as observed in most cases of COVID-19 vaccine-related myocarditis.[25] According to the revised Lake Louise criteria 2018, tissue characterization identified on cardiac MRI has good performance in diagnosing acute myocarditis with a sensitivity of 87.5% and specificity of 96.2%.[12] Notably, cardiac MRI identified the diseased myocardium in four patients with typical angina symptoms; however, no elevation was observed in troponin levels (cases 1, 2, 9, and 11).

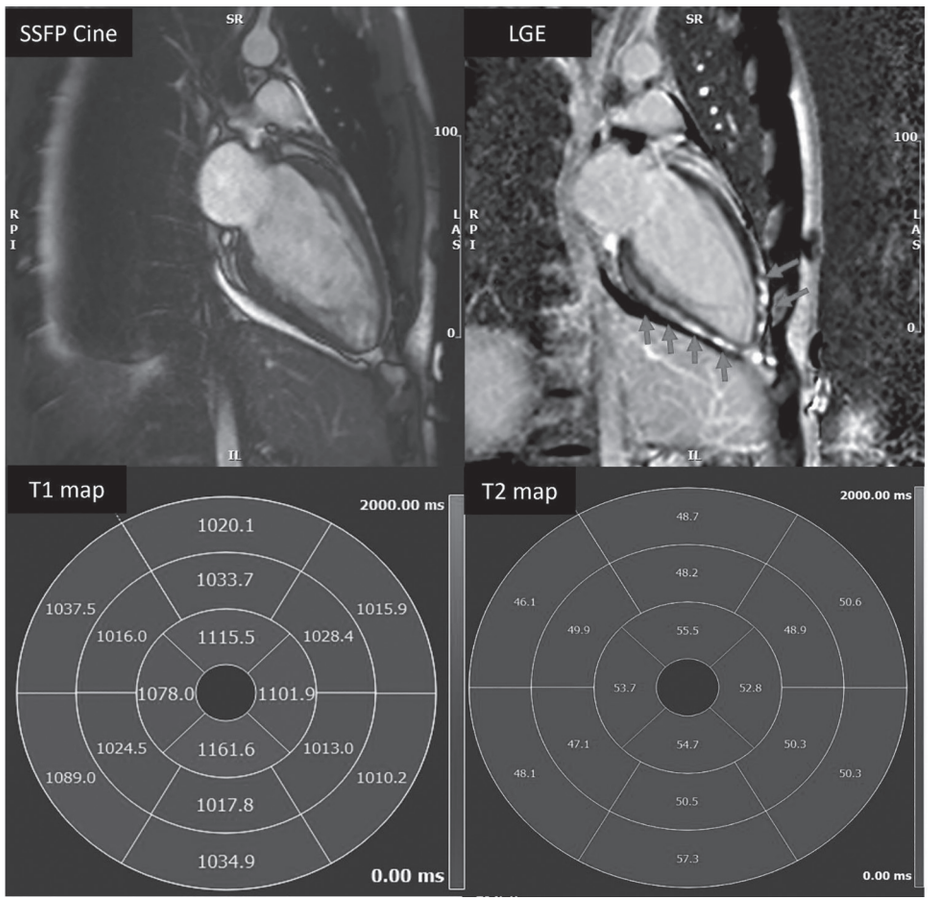

Fig. 1 SSFP image (two chamber view) shows presence of pericardial effusions; Late gadolinium enhancement at apical anterior wall of LV, and inferior wall at basal to apical wall of LV; bull-eye T1 polar map showed elevation of native T1 value, especially at LV apex; focal elevation of T2 value at LV apex. LV = left ventricular; SSFP= steady-state free precision.

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