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LETTER TO THE EDITOR

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Myocarditis after COVID-19 mRNA vaccination in three young adult males: Significance of biopsy in vaccine-associated myocarditis

To the Editor,

Myocarditis following mRNA coronavirus disease 2019 (COVID-19) vaccination predominantly occurred in young males in their teens or twenties within a few days of receiving the second dose of the vaccine.[1] The number of young males in their teens and twenties who experienced myocarditis after receiving the second dose of the Pfizer-BioNTech vaccine was 15.4 and 10.0 per million people, respectively, and the number of those who received the Moderna vaccine was 102.1 and 47.2 per million people, respectively (reported in Japanese). The clinical symptoms were mild in severity, and this young population demonstrated good prognosis.[1] However, because there is limited information on myocarditis confirmed via endomyocardial biopsy (EMB), factors, such as the type of inflammation, tissue responses, and the pathogenesis of this condition in particular, are not well-characterized. Myocarditis is a potentially life-threatening condition. Thus, a comprehensive evaluation is crucial using both detailed imaging studies to determine the morphological and functional abnormalities in the heart as a whole and EMB with tissue characterization of the type of inflammation, in addition to etiological information.

We report three cases of young adult males (aged 19, 24, and 24) who were healthy before receiving the COVID-19 mRNA vaccination and presented to our hospital with severe chest pain within 2–3 days of their second dose of the mRNA-1273 COVID-19 vaccine (Moderna) between July and September 2021. Our institute granted an exemption from requiring ethics approval. Written informed consent for participation in this study was obtained from all three patients. All patients had a high fever of 38°C–39°C (100.8°F–102.2°F) before admission within 1 day of vaccination. On presentation, the electrocardiogram of all patients showed diffuse ST-segment elevation, and their levels of serum troponin T were elevated (0.49–1.03 ng/ml, reference range <0.014). Coronary angiography revealed no stenosis. The left ventricular (LV) systolic function was preserved. All patients reported no prior COVID-19 infection, and they all had negative nasopharyngeal polymerase chain reaction (PCR) results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on admission. Cardiac magnetic resonance (CMR) imaging on hospital days 6–9 revealed a positive nonischemic distribution pattern in early gadolinium enhancement (EGE) images in the lateral wall of the LV in all patients, indicating non-ischemic myocardial injury (Figure S1A). CMR also showed myocardial edema on T2-based images, corresponding with the EGE results (Figure S1B). These findings support the diagnosis of acute myocarditis according to the clinical setting and the CMR criteria. After a few days of observation in the intensive care unit, all patients were discharged home without critical complications. At 1 month follow-up, all patients were completely asymptomatic, and their serum troponin T levels were in the normal range. Patients' characteristics and clinical data are summarized in Table S1. We performed EMB from the right ventricular septum for all patients within 2–3 days of their vaccination (Figure 1). All three patients showed similar histological findings of mild interstitial inflammatory infiltrates that were predominantly composed of macrophages admixed with a few T-cells without adjacency to cardiomyocyte necrosis. Eosinophils were either absent or rarely found. Immunohistochemical expression of tenascin-C (TN-C) was observed in the (sub)endocardium and partially in the interstitium. Human leukocyte antigen (HLA)-DR antigens were diffusely positive on capillary endothelial cells and interstitial infiltrating cells compared with that in other nonmyocarditis cases (immunohistochemistry of three cases in Figure S2). Moderate endomyocardial fibrous thickening and mild interstitial fibrosis of the myocardium were also observed. No viral genomes including SARS-CoV-2 were detected in the myocardium of all EMB specimens by a multivirus real-time PCR system.[2] Although there was no myocyte injury to meet classical myocarditis criteria,[3] these immunohistochemical findings and absence of viral genomes suggested that this was a case of immune-mediated

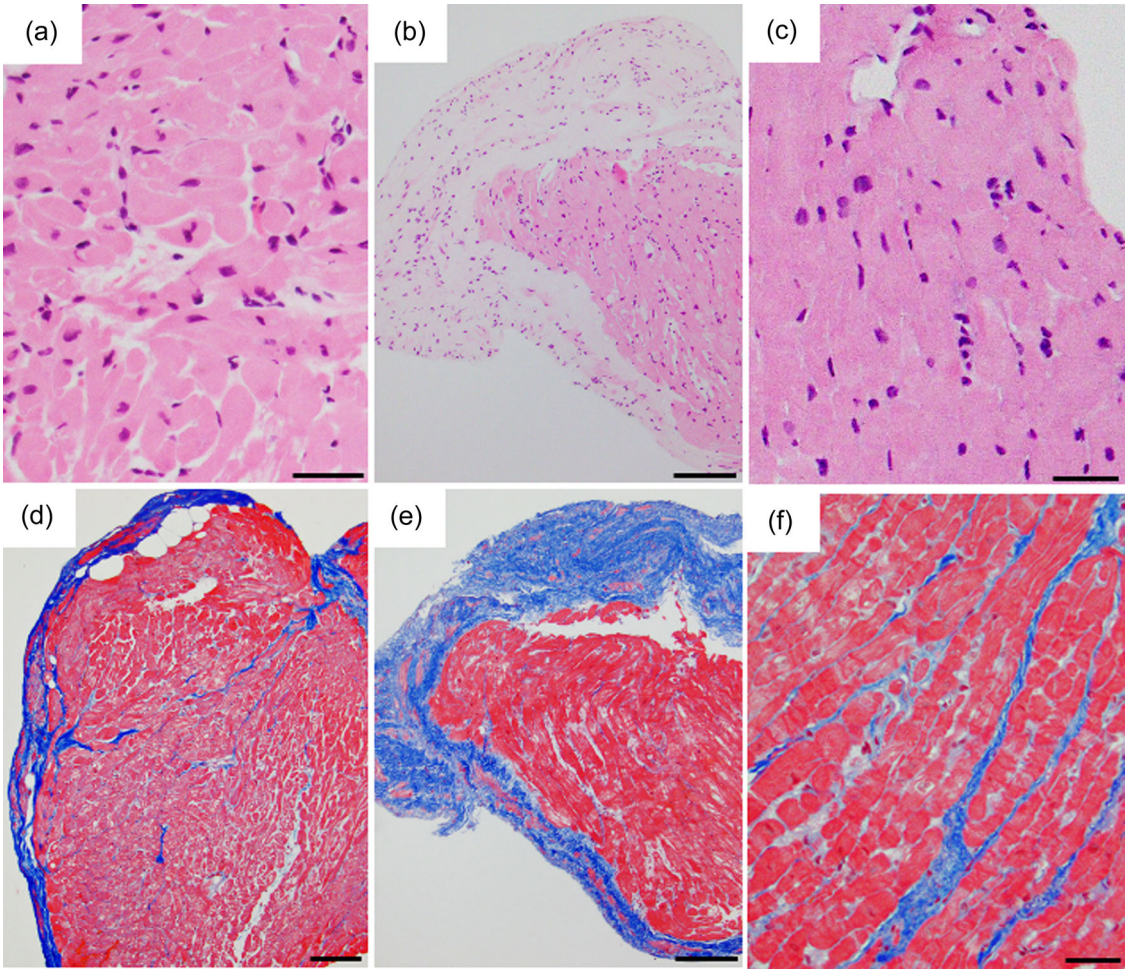

FIGURE 1 Endomyocardial biopsy (EMB) histology of three cases of myocarditis after coronavirus disease 2019 (COVID-19) mRNA vaccination. EMB obtained from the right ventricular septum showed mild inflammation in H&E staining (a–c) in all patients and moderate endomyocardial thickening and mild interstitial fibrosis in Masson's trichrome staining (d–f). (a) and (d); Patient 1. (b) and (e); Patient 2. (c) and (f); Patient 3. Scale bar: 50 μm.

myocarditis (all findings are summarized in Table S2). Although a direct causal relationship could not be made, no other causes were identified and temporal association implicated myocarditis to be associated with COVID-19 mRNA vaccination.

In our case series of young males with myocarditis confirmed on CMR, despite the presence of mild lymphocytic infiltration in the myocardium without the necrosis of adjacent myocytes, additional immunostaining including TN-C and HLA-DR proved immune activation. TN-C expression occurs in response to tissue repair after inflammation, based on the hypothesis that TN-C regulates the pro-inflammatory phenotype of macrophages.[4] HLA-DR antigens are constitutively expressed on human endothelial cells within the heart in cases of inflammation.[5] Most cases of myocarditis associated with COVID-19 vaccination in young people demonstrate a mild clinical course with rapid symptom resolution.[1] The reasons for its predominance in young adults are unknown, and its long-term prognosis is yet to be determined. Therefore, our findings emphasize the importance of histological evaluation for suspected myocarditis following COVID-19 vaccination to confirm the diagnosis and possibly guide therapy by determining the type of inflammation and presence or absence of viral genomes.

In summary, we present a Japanese case series demonstrating the detailed biopsy characteristics of non-fulminant myocarditis after COVID-19 mRNA vaccination in healthy young males who were confirmed to have mild myocarditis with mild myocardial abnormalities via EMB samples. Finally, the immunohistochemical findings and absence of viral genomes suggested the presence of immune-mediated myocarditis.

AUTHOR CONTRIBUTIONS

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DISCLOSURE STATEMENT

None declared.

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SUPPORTING INFORMATION

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