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Case Report

An autopsy case report of aortic dissection complicated with histiolympocytic pericarditis and aortic inflammation after mRNA COVID-19 vaccination

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ABSTRACT

A male in his 90 s consulted a doctor because he experienced several days of general fatigue and dyspnea. He was diagnosed with heart failure, and diuretic medications taken for 3 days relieved his symptoms. However, he was found dead on the morning of the fourth day after consultation. He had received a third dose of coronavirus disease 2019 (COVID-19) vaccine approximately 2 weeks before death. An autopsy revealed dissection of the ascending aorta and pericardial hemotamponade. The heart showed a white villous surface, and the pericardium was fibrously thick. Microscopic examination revealed pericarditis with predominantly macrophage and lymphocyte infiltration. These histological findings were compatible with those of post-vaccination myocarditis. To the best of our knowledge, histopathologically proven pericarditis after COVID-19 vaccination has not been reported. In the present case, extended inflammation of the aortic adventitia was a possible cause of aortic wall fragility followed by dissection.

1. Introduction

In December 2020, the Japanese Ministry of Health, Labour and Welfare authorized the emergency use of two mRNA vaccines, BNT162b2 (produced by Pfizer-BioNTech) and mRNA-1273 (produced by Moderna), to control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease, coronavirus disease 2019 (COVID-19). These vaccines encode the SARS-CoV-2 spike protein and have excellent efficacy and safety profiles. However, they can cause mild adverse reactions such as injection site pain, fatigue, and headache, as well as rare but more severe side effects such as thromboembolism, myocarditis, and pericarditis \cite{1}. Because of the low incidence of severe side effects and difficulty in obtaining biopsy samples, histologically confirmed pericarditis has not been reported as a vaccine-related outcome.

2. Case presentation

2.1. Case history

A Japanese male in his 90 s consulted a doctor because he experienced several days of general fatigue and dyspnea. His legs were edematous, and chest X-ray showed right pleural effusion. Elevated N-terminal pro-brain natriuretic peptide (NT-pro BNP; 3,706 pg/mL) and C-reactive protein (47.9 mg/L) were detected. The electrocardiogram results showed no abnormal change. He was diagnosed with heart failure but refused hospital admission. The patient was prescribed a 3-day course of diuretic medication, which relieved his symptoms and decreased the NT-pro BNP level. The patient was found lifeless in his kitchen on the morning of the fourth day after consulting the doctor. He had received a third dose of BNT162b2 approximately 2 weeks before death. No previous illness was reported. He did not have a history of smoking or habitual alcohol consumption. A police investigation at the man’s home revealed no suspicious activity.
2.2. Autopsy findings

A medical examiner found no external abnormalities, including in the left deltoid injection site; therefore, an autopsy was performed 35 h postmortem. The deceased was 156 cm in height and weighed 52 kg. The pericardial sac was filled with dark red clots (Fig. 1A). The ascending aorta had a 2.5 cm intimal tear at 4 cm above the aortic annulus (Fig. 1B). The aortic media was dissected, and the adventitia was perforated within the pericardial cavity. The heart weighed 458 g and had a white villous surface (Fig. 1C). Coronary arteries showed mild atherosclerosis. Disrupted coronary artery plaques, coronary aneurysms, and pulmonary emboli were not detected.

2.3. Microscopic examination

Microscopic examination revealed fibrously thick epicardium with...
inflammatory cell infiltration predominantly composed of macrophages and lymphocytes (Fig. 2A and 2B). Minimal necrosis of the outermost layer of the myocardium in the left lateral wall was also detected. There were no thrombi or multinuclear giant cells. Immunohistochemistry analysis of CD3, CD4, CD8, CD68, and CD79a confirmed macrophages, cytotoxic T lymphocytes, and B lymphocytes in the lesion (Fig. 2C). A PCR assay for SARS-CoV-2 detection was not conducted because all tissue samples were fixed in formalin solution. The pericardial membrane was thick with fibrin deposition and hypertrophic fibroblasts. Macrophages and lymphocytes were also detected in the membrane (Fig. 3).

The aortic root was dissected at the collagenous lesion; it showed inflammatory cell infiltration in the tunica media (Fig. 4A and 4B). Medial elastic fibers were shown to be disrupted in Elastica van Gieson.
stain (Fig. 4C). Immunohistochemical assay revealed macrophage and T- and B-cell infiltration in the aortic wall (Fig. 4D).

2.4. Laboratory testing

Laboratory examinations of the femoral blood were negative for antibodies to parvovirus-B19, cytomegalovirus, coxsackie virus-A4, ECHO virus-11 and –14, adenovirus, and influenza A (H1N1 and H3N2) and B (B-1 and B-2) viruses. A neutralization test for ECHO virus-9 was positive at a titer of 32. The serum was positive for anti-SARS-CoV-2 spike protein IgG antibody (583 AU/mL). Headspace gas chromatography revealed no ethanol in the venous blood, urine, or cerebrospinal fluid.

3. Discussion

Acute pericarditis is the inflammation of the visceral and parietal pericardium. Because the pericardial sac contains the heart and the roots of great vessels, pericarditis inflammation can extend to the aortic wall. Acute pericarditis has a variety of causes, such as viral and bacterial infection, systemic lupus erythematosus, rheumatoid arthritis, neoplastic disease, radiation, and trauma [2]. In the clinical setting, pericarditis is diagnosed using several clinical manifestations and criteria, such as pericardial friction rub, laboratory testing, electrocardiogram, echocardiogram, and other imaging modalities. Histopathological findings are often not used in the diagnosis owing to the difficulty of the sampling procedure—pericardial samples can only be obtained surgically. Although pericardioscopy-guided percutaneous biopsy of the pericardium has been reported without major complications [3], this procedure is technically challenging, and an experienced operator is necessary. To the best of our knowledge, this is the first case report of histologically proven pericarditis after COVID-19 vaccination.

SARS-CoV-2 vaccines have been associated with rare, but sometimes fatal, cardiovascular side effects such as thromboembolism, myocarditis/pericarditis, arrhythmia, and cardiomyopathy [4–9]. Fazollahi et al. [6] summarized the features of seven pericarditis cases after vaccination from case reports and case series. The median case age was 37 years (range: 21 to 80), and 71.4 % were men. The median time from vaccination to onset of the first symptom was 4 days (range: 1 to 11). None of the described cases had died. Diaz et al. [8] reported 37 pericarditis cases from over 2 million individuals who received a COVID-19 vaccine (35 received an mRNA vaccine; 2 received a vector-based vaccine). In their report, the median age was 59 years (interquartile range: 46–69), 73 % were men, and the latent period was 20 days (interquartile range: 6–41). Although no mortality was reported, 13 patients (35.1 %) were admitted to the hospital, and the median length of stay was 1 day. Two-thirds of the cases were treated in the outpatient setting, mainly with colchicine and non-steroidal anti-inflammatory drugs. These two series found a generally favorable prognosis of pericarditis after COVID-19 vaccination.

Several investigators have described the histopathological findings of myocarditis after COVID-19 vaccination, which showed abundant macrophage and T-cell infiltration [6,10,11,12]. These features are similar to those of SARS-CoV-2 infection-associated myocarditis [13–16]. The involvement of eosinophils and B lymphocytes has also been reported [10,17]. The abovementioned histopathological findings of post-vaccination myocarditis are compatible with those of our pericarditis case. Although a direct causal relationship between COVID-19 mRNA vaccination and pericarditis cannot be definitively established in the present case, no other causes were identified from the autopsy findings and laboratory results. A serological examination for virus detection has limited value because it cannot distinguish past infections from the most recent infection. Therefore, we cannot completely rule out a viral etiology.

Although the pathophysiology remains unknown, several hypotheses for the occurrence of post-vaccination myocarditis have been suggested [8]. One hypothesis is that a highly induced antibody response in young people can elicit a response similar to that of multisystem inflammatory syndrome in children with SARS-CoV-2 infection. However, a case of myocarditis without anti-SARS-CoV-2 spike protein antibodies after COVID-19 vaccination has been reported [12]. The present patient developed pericarditis after a third dose of COVID-19 vaccine, and mildly elevated IgG antibodies were detected in the postmortem autopsy sample. Cross-reactive antibodies and a non-specific innate inflammatory response have also been hypothesized. Furthermore, RNA (as opposed to the translated protein) is a potent immunogen and produces a bystander or adjuvant effect, although pericarditis after vaccination with a viral vector-based vaccine has also been reported [8,18].

We presumed that death in the present case was caused by pericarditis-induced fragility of the aortic wall followed by cardiac tamponade. Diuretic medications improved the patient’s status of heart failure due to pericarditis; however, inflammation extending to the adventitia was a possible cause of aortic dissection. In this case, the deceased was aware of developing symptoms of heart failure approximately 1 week after receiving the BNT162b2 vaccine. The time between vaccination and death was approximately 2 weeks. The fibrosly thick pericardial membrane was consistent with this time course.

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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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