Answer to the letter to the editor by J. Finsterer concerning "A case of fatal multi-organ inflammation following COVID-19 vaccination" by H. Nushida et al. (https://doi.org/10.1016/j.legalmed.2023.102244.)

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Running head: Sudden death after COVID-19 vaccination

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We are pleased to respond to the letter to the editor regarding our article titled "A case of fatal multi-organ inflammation following COVID-19 vaccination" [1]. The author has presented several concerns regarding our work [2], many of which have been acknowledged and addressed in the original manuscript.

We diagnosed vaccine-related multi-organ inflammation based on the absence of bacterial or viral infection, lack of a medical history suggestive of autoimmune disease, no allergic reaction, and no drug exposure other than the vaccine. Myopericarditis, a form of multi-organ inflammation, was considered the cause of death. Alternative causes were ruled out during this process.

Arrhythmias derived from the atrium are not atrial fibrillation or atrial flutter but are due to direct inflammation of the stimulatory conduction system, such as complete atrioventricular block.

Takotsubo cardiomyopathy, myocardial infarction, and ventricular fibrillation were excluded because there was no histological fibrosis or necrosis of the myocardium in the left or right ventricles.

Autopsy revealed no coronary artery sclerosis, stenosis, occlusion, or pulmonary artery emboli. Blood tests at the emergency hospital revealed only mild inflammatory findings and no evidence of active cardiac failure: CRP = 0.94 mg/dL, procalcitonin = 0.13 ng/mL, and BNP = 7.5 pg/mL.
There had been no recovery of heartbeat since the arrival of the rescue team, and no ECG confirmation.

As for meningitis and encephalitis, the cerebrospinal fluid(CSF) was visually watery clear, and histologically, there was no lymphocytic or other inflammatory cell infiltrate in the subarachnoid space or subpial tissue, and only a mild lymphocytic infiltrate in the hippocampus, as described in the paper; therefore, fatal meningitis or encephalitis was ruled out. In addition, the inflammatory findings in the brain were very mild compared with those in other organs; therefore, there was little reason to suspect an epileptic focus.

As for vaccine-induced immune thrombotic thrombocytopenia (VITT), platelet counts were not available because blood counts could not be

performed at the emergency hospital. However, no thrombi were found in the superior sagittal sinus, transverse sinus, portal vein, pulmonary vein, or renal vein at autopsy, and no microthrombi were found in any of the organs histologically. Thus, anti-PF-4 antibodies were not measured, and VITT was also negative.

The pathophysiology of this case was systemic inflammation, similar to that of multisystem inflammatory syndrome in children (MIS-C), however, MIS-C is a post COVID-19 infection. According to the CDC definition of MIS-C, fever is persistent[3], in our case, postmortem examination revealed that the inflammatory findings were systemic and not very serious. If our patient had been able to follow the clinical course of the disease without death, it is possible that would have fitted the definition of MIS-C. We believe that this case is useful because it histologically shows that the COVID-19 vaccine can cause systemic inflammation.

We thank the authors for providing feedback regarding our article. We agree that this case report has substantial limitations for clinical diagnosis because of the lack of sufficient clinical data. However, we were able to obtain considerable information through forensic autopsies. We hope that our report

will advance research on the adverse reactions to COVID-19 vaccines.

Reference

[1] Nushida H., Ito A., Kurata H., Umemoto H., Tokunaga I., Iseki H., Nishimura A. A case of fatal multi-organ inflammation following COVID-19 vaccination. Leg Med (Tokyo)

[2] J. Finsterer, Before blaming SARS-CoV-2 vaccination for unexpected death from atrial myocarditis, rule out alternative pathophysiologies, Leg Med (Tokyo). 2023 May 5;63:102266. doi: 10.1016/j.legalmed.2023.102266.

[3] Centers for Disease Control and Prevention, About MIS, U.S. Department of Health & Human Services, https://www.cdc.gov/mis/about.html.