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Clinical Notes

An adolescent boy with Takotsubo cardiomyopathy after COVID-19 vaccination

Running title: TCM following COVID-19 vaccination

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We herein report the case of a 16-year-old boy with Keans-Sayre syndrome and complete atrioventricular block requiring permanent pacemaker implantation in whom Takotsubo cardiomyopathy developed after the second shot of COVID-10 mRNA vaccination. The patient was diagnosed with Kearns-Sayre syndrome based on findings of psychomotor disorder, progressive extraocular muscle weakness, complete atrioventricular block, and retinitis pigmentosa. A mitochondrial genetic analysis revealed 4.5 kb deletion of mtDNA with 55% heteroplasmy. He had shown developmental regression from 6 years of age and had been bedridden since 10 years of age. He showed impaired speech and language comprehension. He could not move by himself due to quadriplegia and could not eat food by himself. He had been receiving nutritional support through gastrostomy since 12 years of age. He was treated with ubidecarenone, vitamin B1, folic acid and levocarnitine. He also required an anticholinergic agent due to neurogenic bladder and hydrocortisone due to adrenal insufficiency.

At 16 years of age, he had complete atrioventricular block with a heart rate of 40 beats per minute. He therefore underwent implantation of a permanent pacemaker with single chamber pacing. He received the second dose of the BNT162b2 mRNA COVID-19 vaccine 3 months after pacemaker implantation. After 2 days, he was

admitted to our hospital due to persistent low-grade fever, lethargy, insomnia, and anuria. On admission, his heart rate, blood pressure, and systemic oxygen saturation were 60 bpm, 108/71 mmHg, and 99%, respectively. Chest X-ray did not show cardiac dilation.

A laboratory investigation revealed mild liver transaminase elevation (ALT, 174 U/L) with metabolic acidosis (lactate, 3.4 mmol/L). During admission, nocturnal hypertension of systemic blood pressure was continuously observed (130-150 mmHg as systole). He gradually recovered to his pre-admission status. On day 18 of admission, however, continuous electrocardiogram monitoring continuously detected intermittent premature ventricular contractions leading to ventricular tachycardia. His general condition and vital signs were mostly stable, with the exception of mild hypertension. Electrocardiography showed negative T waves in leads II, III, aVF and V_3-V_6. The corrected QT interval (QTc) in lead V5 was prolonged (680 ms) in comparison to that measured 2 months previously (455 ms) under pacemaker rhythm. The decrease of the R wave was unremarkable. Transthoracic eechocardiography showed akinesia of the left ventricular apical segment and hypercontraction of basal parts of the left ventricle with an estimated ejection fraction of 61.1% (Simpson biplanar) (Figure). The laboratory findings demonstrated significant elevation of cardiac troponin (0.110 ng/L [normal

range (NR), <0.014]), NT-proBNP (4,674 pg/mL [NR <55]), and CK-Mb (15.3 ng/mL [NR <3.1]). We did not perform coronary angiography or coronary CT angiography because intravenous sedation was associated with a high risk of complications. He was in lethargic state but his neurological findings were similar to those before vaccination; thus, neurological evaluation by head MRI was not performed. We clinically diagnosed TCM based on the characteristic images in echocardiography, findings in electrocardiography and laboratory data. Electrocardiography findings specific to TCM, such as a decreased R wave or elevation of the ST-segment, were not observed; these findings may have been—at least in part—masked by the artificial pacing after pacemaker implantation. After conservative treatment with bed rest for five days, his vital state gradually recovered along with the disappearance of negative T waves and an almost normal QTc (480 mm) on the electrocardiogram on day 23 of admission. At the time of discharge, the characteristic echocardiographic findings of TCM had already disappeared.

TCM is a transient myocardial disease characterized by hypocontraction of the apex and hypercontraction of the basal segment of the heart, which usually occurs in postmenopausal women after being triggered by physical or mental stressors[1]. Six cases of TCM after COVID-19 vaccination have already been reported. More than half of

those involved women in their 50s or older. In all of these cases, TCM occurred shortly after vaccination (17 hours – 10 days)[2,3]. These patients had various comorbidities but no apparent triggers other than vaccination have been reported [3]. The duration from vaccination to the onset of TCM in the present case was longer in comparison to the previously reported cases. Given that the present patient had difficulties in complaining about his symptoms, TCM could have already developed before the time of the diagnosis. In this case, TCM may have developed under several patient-specific stress situations. First, cardiac dysfunction in TCM is closely related to oxidative stress in the mitochondria and therefore mitochondrial dysfunction in cardiomyocytes due to mitochondrial disease might directly affect energy metabolism[4]. In addition, underlying sympatho-vagal imbalance suggested by consistent anuria and nocturnal hypertension along with anticholinergic drug treatment, might be an additional risk factor for cardiomyopathy[5]. In addition, COVID-19 vaccination can cause an acute immune response, which may influence cardiomyocytes. Lastly, adrenal insufficiency might be undertreated under the multiple stress state. With these risk factors, TCM developed in the patient with mitochondrial disease. The COVID-19 vaccine is widely recommended for high-risk patients, whereas the individual risk factors for adverse reactions after vaccination have not always been fully assessed. Severely handicapped children cannot

express their discomfort or dysesthesia. Therefore, we should carefully assess individual risk factors, and serious life-threatening complications, such as TCM, must be noted before and after COVID-19 vaccination.

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Disclosures

The authors declare no conflict of interest in association with the present study.

Author contributions

H.K. contributed to the diagnosis and treatment management. S.K. provided expert clinical opinions. S.O. wrote the manuscript. T.M. and K.I. clinically reviewed the manuscript and provided technical support. All authors read and approved the final manuscript.

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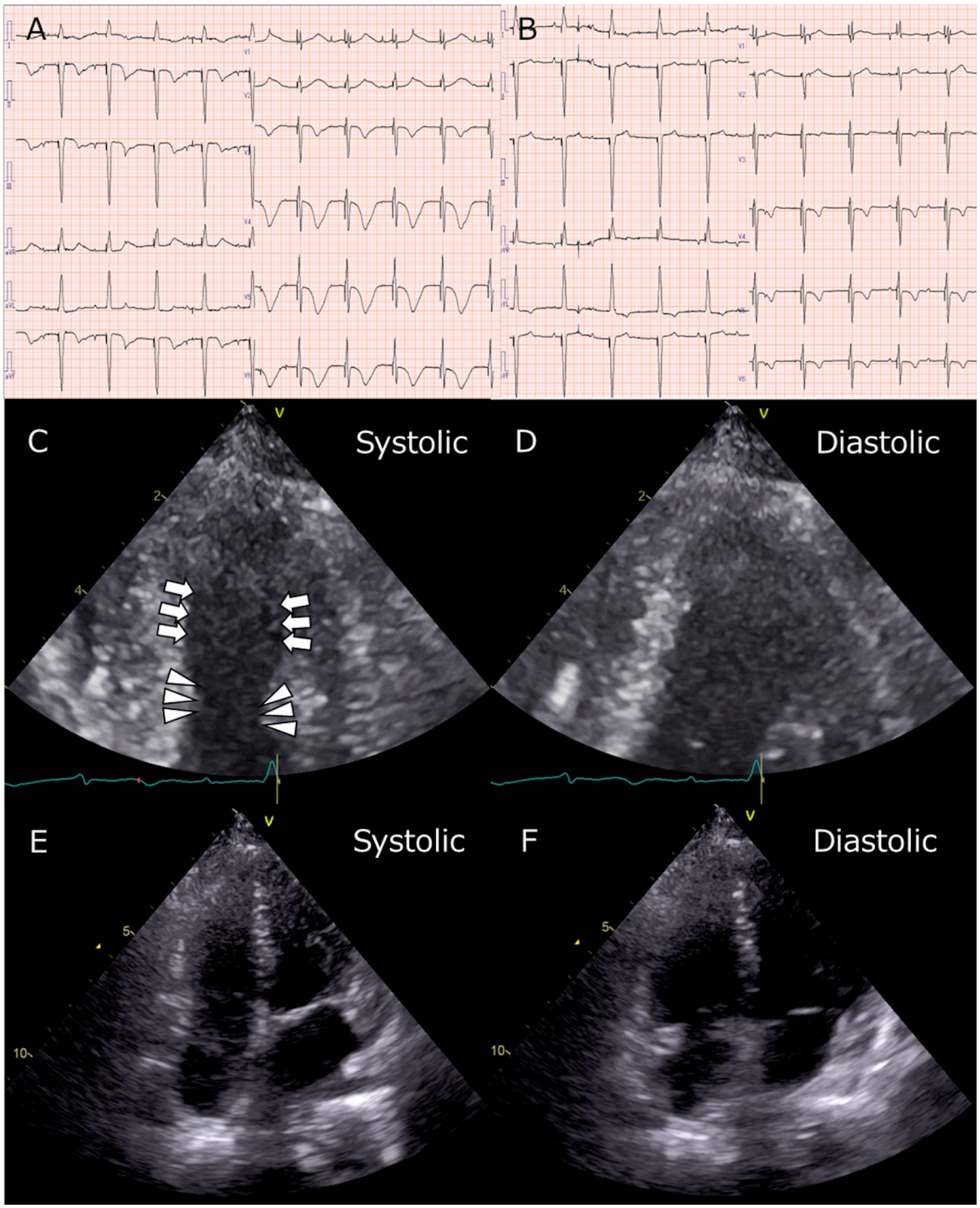
Figure Legend

Figure. Electrocardiography showed negative ST wave changes on day 18 of admission (A), which spontaneously improved before discharge (B). On transthoracic echocardiography, the enlarged four-chamber view of the apex showed hypokinesia of the left ventricular apical segment (arow) and hypercontraction of the basal parts of the left ventricle (arrow head) in the systolic phase (C) in comparison to the diastolic phase (D). Two months before hospitalization, the four-chamber view of the apex showed normal contraction (E) and dilation (F).



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