

Takotsubo Cardiomyopathy Presenting with QT Prolongation and Torsade de Pointes in a Patient with Coronavirus Disease 2019

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Coronavirus disease 2019 (COVID-19) is associated with cardiovascular complications; however, Takotsubo cardiomyopathy (TCM) with QT prolongation and Torsade de pointes has been reported only rarely. We present a case of TCM after QT prolongation and Torsade de pointes. A 58-year-old woman was admitted because of COVID-19-related pneumonia. Seven days after admission, she developed sudden loss of consciousness without any indication of cardiovascular disease. A monitoring electrocardiogram indicated Torsade de pointes and a prolonged QT interval. Emergency cardiac catheterization revealed TCM. She was treated with favipiravir and steroids, followed by rehabilitation, and her condition improved. To detect asymptomatic TCM, routine electrocardiography screening should be considered for patients with COVID-19. (*J Nippon Med Sch* 2024; 91: 124–128)

Key words: COVID-19, Takotsubo cardiomyopathy, QT prolongation, Torsade de pointes, pacing

Introduction

The clinical spectrum for coronavirus disease 2019 (COVID-19) ranges from absence of symptoms to severe symptoms. Cardiovascular complications of COVID-19 include acute myocardial infarction, myocarditis, cardiomyopathy, and venous thrombosis¹. However, Takotsubo cardiomyopathy (TCM) presenting with QT prolongation and Torsade de pointes (TdP) has been reported only rarely. We describe a case of TCM with QT prolongation and TdP in a patient with COVID-19.

Case Report

A 58-year-old woman presented to our hospital with fever (body temperature, 38.6°C), loss of appetite, and deoxygenation (oxygen saturation, 89% in room air). She was positive for COVID-19 on a real-time reverse transcription-polymerase chain reaction assay of a nasopharyngeal swab specimen. Chest computed tomography revealed ground-glass and band-like opacities in the pulmonary dorsal lobe, which were consistent with COVID-19 pneumonia. Chest X-ray did not show cardiomegaly (cardiothoracic ratio, 49%). The patient was admitted to

the quarantine ward.

On day 1 of hospitalization, we initiated oxygen administration and prescribed remdesivir. On day 3, remdesivir was switched to favipiravir because of the risk of worsening kidney function. On day 5, dexamethasone was administered. On day 7, she developed sudden loss of consciousness. A monitoring electrocardiogram (ECG) showed repetitive TdP (**Fig. 1**). Sinus rhythm spontaneously recovered; however, repetitive non-sustained VTs were observed. Twelve-lead ECG demonstrated an inverted T-wave in broad leads and a prolonged QT interval: QTc of 615 msec (**Fig. 1**). Levels of the electrolytes potassium, magnesium, and calcium were 3.0 mEq/L, 1.8 mEq/L, and 9.7 mEq/L, respectively. Although hypokalemia was observed, it was not an acute change. On admission day, the potassium level was 2.1 mEq/L because of a history of diarrhea. After admission, potassium was carefully supplemented. The patient was not taking any drugs that could cause QT prolongation. After she was transferred to the intensive care unit, her heart rate gradually decreased to approximately 40 beats/min (**Fig. 2**). Laboratory data showed elevation of troponin

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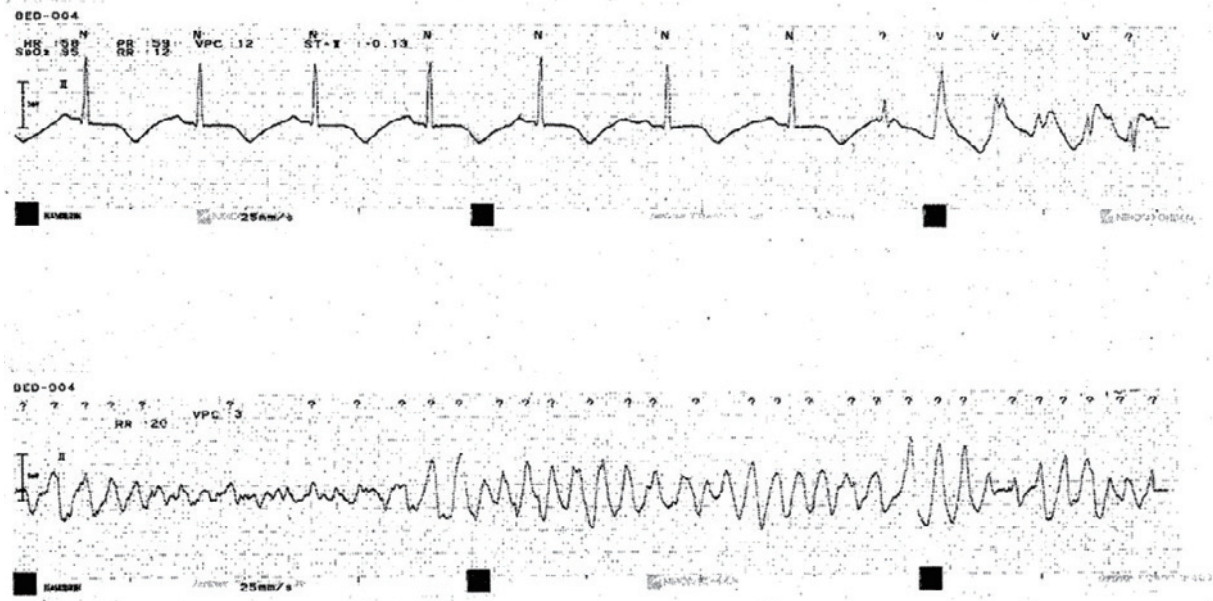


Fig. 1 Monitoring ECG showed marked QT interval prolongation (QTc 615ms) following Torsade de pointes

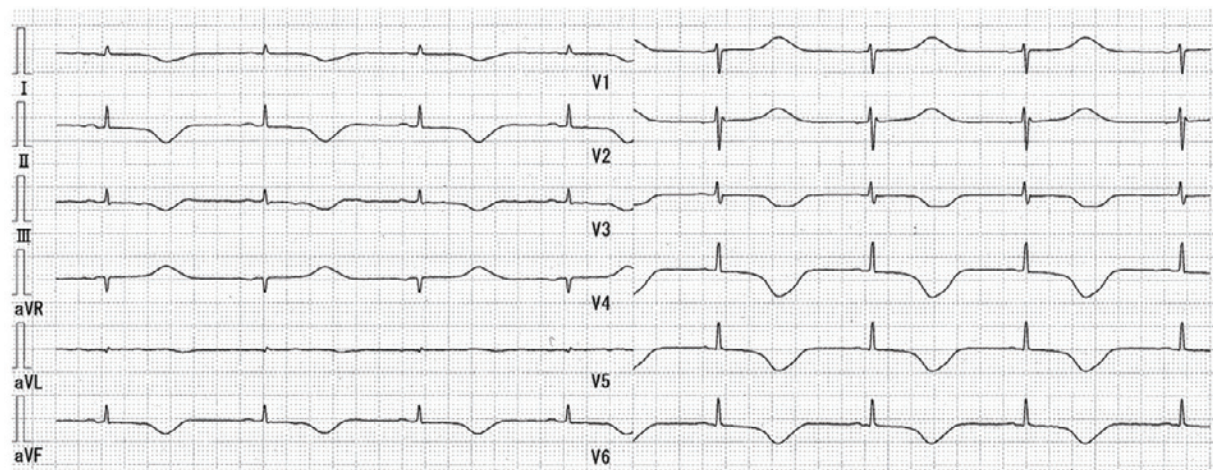


Fig. 2 Surface ECG showed marked bradycardia and QT interval prolongation (QTc 647ms)

levels (high-sensitivity troponin I, 524.4 pg/mL). On the basis of ECG findings and laboratory data, we performed emergent coronary angiography to rule out acute coronary syndrome. However, there were no stenotic lesions in the coronary arteries. Left ventriculography showed mid-to-apical ballooning wall motion (Fig. 3, Supplementary video: https://doi.org/10.1272/jnms.JNMS.2023_90-607). We diagnosed TCM presenting with QT prolongation and TdP in the setting of COVID-19. Because bradycardia was a likely precipitating factor for TdP, backup temporary pacing was inserted and completely prevented TdP. The QTc interval was 577 msec during backup pacing. The patient's clinical condition gradually improved during treatment with favipiravir and steroids. On day 24 of hospitalization, she was moved to a neighboring

nursing home for rehabilitation. ECG demonstrated T-wave recovery, and the QTc interval was 413 msec. Transthoracic echocardiography showed restoration of normal wall motion on day 25 of hospitalization.

We obtained written informed consent from the patient to publish this case.

Discussion

This was a case of TCM complicated by TdP with QT prolongation in the setting of COVID-19. Giustino et al.² reported a 4.2% incidence rate of TCM in patients with COVID-19. However, in most cases, TCM was diagnosed based only on electrocardiography and echocardiography findings, without cardiac catheterization such as coronary angiography and left ventriculography. We performed

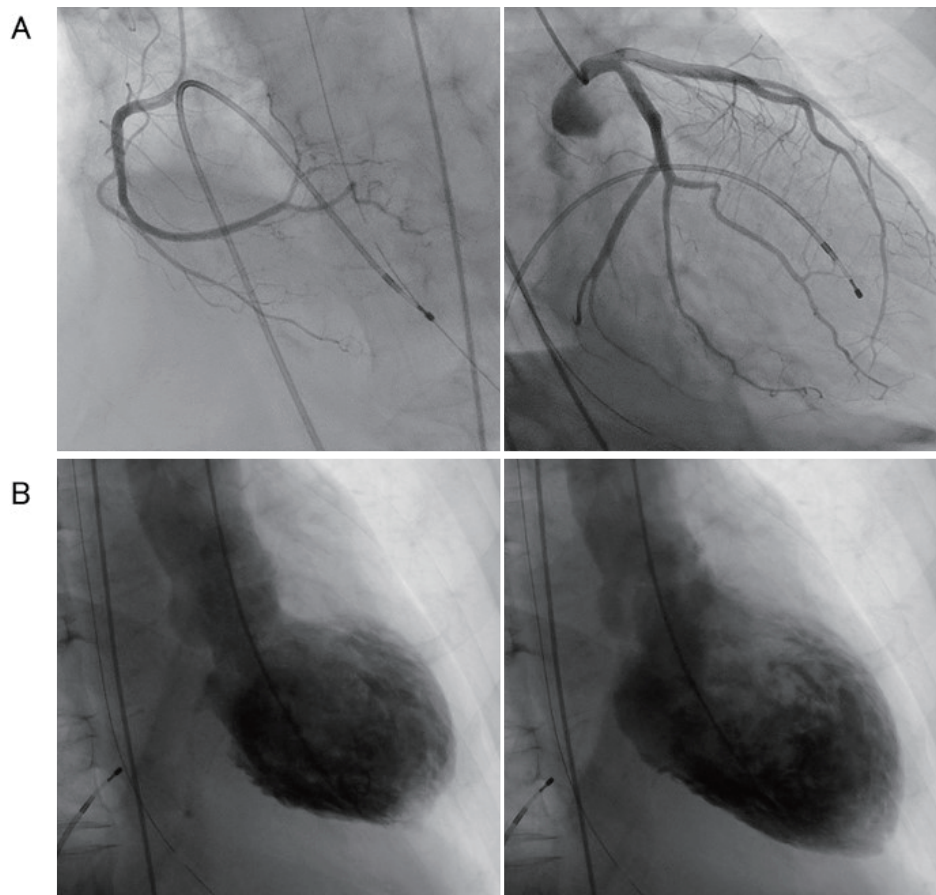


Fig. 3 Coronary angiography revealed no significant organic stenosis (A)
Left ventriculography showed severe hypokinesis at apical site; Takotsubo-like wall motion (B)

cardiac catheterization to accurately diagnose TCM.

Imran et al.³ reported that 25 (54.3%) of 46 patients with TCM showed a QT prolongation of >470 ms for men and >480 ms for women. Prolongation of the QT interval in patients with TCM is an independent predictive factor for development of ventricular arrhythmia. The pathophysiological mechanism underlying QT prolongation in TCM is likely multifactorial. Postulated mechanisms include catecholamine-induced myocardial damage, myocardial stunning, coronary vasospasm, oxidative stress, and genetic factors. Moreover, reduced repolarization reserve between the endocardial and epicardial layers and intramyocardial calcium overload likely caused QT prolongation.

TCM was probably the primary cause of QT prolongation in our patient. However, hypokalemia might also affect QT prolongation even if it gradually recovered from baseline. We ruled out drugs with a potential risk of QT prolongation leading to TdP. The cause of QT prolongation could be multifactorial. We believe that possible risk factors for QT prolongation associated with COVID-19

infection should be examined. ECG is recommended before administration of drugs such as remdesivir.

TCM is associated with TdP in more than 8% of cases⁴. The mechanism has been described as a pause-dependent short-long-short coupling that triggers TdP in acquired long QT syndrome⁴. The mechanism responsible for TdP might be triggered activity in our case because there was no marked R-R interval variability at TdP initiation.

Bradycardia is a significant detrimental factor that causes TdP via early afterdepolarization. In our case, TdP disappeared after ventricular overdrive pacing. Therefore, bradycardia is an important factor for TdP.

Sinus bradycardia occurs in approximately 8% of patients with COVID-19⁵. The pathophysiology of sinus bradycardia in COVID-19 is associated with several conditions, including direct viral injury of cardiac cells, hyperinflammatory status, hypoxemia, imbalance of the autonomic nervous system, and drug effects⁶. With respect to drug effects, our patient did not receive hydroxychloroquine or azithromycin. A previous case study reported marked acute sinus bradycardia immediately af-

ter initiation of remdesivir⁷. In our case, there was no relationship between sinus bradycardia and remdesivir use, because sinus bradycardia was observed 4 days after stopping remdesivir.

Capoferri et al.⁸ reported that relative bradycardia was observed in 58% of patients with COVID-19. High levels of inflammatory cytokines such as interleukin-6, which are common in patients with COVID-19, were reported to increase vagal tone and decrease heart rate variability⁹. The present case might involve complications of relative bradycardia caused by COVID-19-related pneumonia.

Seven days after admission, TCM was diagnosed after TdP episodes in our patient. The exact date of TCM onset is unclear because the patient did not show any signs of cardiovascular complications, such as heart failure or chest pain. TCM is also known as stress cardiomyopathy. Patients with COVID-19 are under severe physical, mental, and social stress and can therefore develop TCM. A recent study reported a significant positive association between COVID-19 and the increasing number of out-of-hospital cardiac arrests¹⁰. TCM after TdP might be a reason for the association with out-of-hospital cardiac arrest. Our patient did not undergo routine ECG because patients with COVID-19 undergo minimal screening testing, to limit the risk of spreading COVID-19. However, ECG can be performed in patients with COVID-19 to rule out TCM. When ECG suggests TCM, even when no symptoms are present, patients should be hospitalized to monitor ECG changes, because the QT interval might be longest several days after diagnosis, and TdP can be observed in patients complicated with sinus bradycardia¹¹.

Limitations

Since the present patient did not undergo ECG on admission, we could not determine the timing of TCM onset and QT prolongation. QT prolongation might have happened first, and TCM developed after the TdP event. However, there were no obvious indicators of QT prolongation except TCM. Moreover, during TdP, the patient did not need advanced resuscitation procedures, such as epinephrine administration, which could cause TCM.

Conclusions

This case of TCM presenting with QT prolongation and TdP suggests that routine ECG screening is useful for excluding asymptomatic TCM in patients with COVID-19. Patients with TCM in the setting of COVID-19 should be hospitalized to monitor progression of QT prolongation involving TdP.

Data availability statement: The data in this study are available from the corresponding author upon reasonable request.

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Conflict of Interest: The authors declare no conflict of interest.

References

1. Coromilas EJ, Kochav S, Goldenthal I, et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ Arrhythm Electrophysiol.* 2021 Mar;14(3):e009458.
2. Giustino G, Croft LB, Oates CP, et al. Takotsubo cardiomyopathy in COVID-19. *J Am Coll Cardiol.* 2020 Aug 4; 76(5):628–9.
3. Imran TF, Rahman I, Dikdan S, et al. QT prolongation and clinical outcomes in patients with takotsubo cardiomyopathy. *Pacing Clin Electrophysiol.* 2016 Jun;39(6):607–11.
4. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, et al. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. *Heart Rhythm.* 2011 Apr;8(4):555–61.
5. Gopinathannair R, Merchant FM, Lakkireddy DR, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. *J Interv Card Electrophysiol.* 2020 Nov;59(2):329–36.
6. Goette A, Patscheke M, Henschke F, Hammwohner M. COVID-19-induced cytokine release syndrome associated with pulmonary vein thromboses, atrial cardiomyopathy, and arterial intima inflammation. *TH Open.* 2020 Sep 26;4(3):e271–9.
7. Gubitosa JC, Kakar P, Gerula C, et al. Marked sinus bradycardia associated with remdesivir in COVID-19: a case and literature review. *JACC Case Rep.* 2020 Nov 18;2(14):2260–4.
8. Capoferri G, Osthoff M, Egli A, Stoeckle M, Bassetti S. Relative bradycardia in patients with COVID-19. *Clin Microbiol Infect.* 2021 Feb;27(2):295–6.
9. Hajiasgharzadeh K, Mirnajafi-Zadeh J, Mani AR. Interleukin-6 impairs chronotropic responsiveness to cholinergic stimulation and decreases heart rate variability in mice. *Eur J Pharmacol.* 2011 Dec 30;673(1-3):70–7.
10. Baldi E, Sechi GM, Mare C, et al. Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy. *N Engl J Med.* 2020 Jul 30;383(5):496–8.
11. Chinitz JS, Goyal R, Harding M, et al. Bradyarrhythmias in patients with COVID-19: marker of poor prognosis? *Pacing Clin Electrophysiol.* 2020 Oct;43(10):1199–204.

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