Quadruple episodes of takotsubo cardiomyopathy: a case report

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Background

Takotsubo syndrome (TTS) is characterized by transient left ventricular (LV) dysfunction, often preceded by emotional or physical trigger. The recurrence of TTS has been investigated, however, cases of multiple recurrences are scarcely reported.

Case summary

A 79-year-old woman was admitted to the hospital with the complaint of dyspnoea following emotional stress. Electrocardiogram showed terminal T-wave inversion with QT interval prolongation in anterior leads. Transthoracic echocardiogram revealed severe hypokinesis of mid- and apical-anterior segments. She was diagnosed with focal TTS. After 3 months, she complained of orthopnoea subsequent to upper-respiratory infection. Coronary angiography (CAG) depicted normal coronary arteries. She had recurrence of TTS with bi-ventricular dysfunction, and complicated cardiac collapse requiring intra-aortic balloon pumping. One month after the second episode, she had dyspnoea after herpes zoster infection. She was diagnosed with recurrence of focal TTS. After 4 months, she complained of central chest pain without evident trigger factors. CAG showed no coronary artery stenosis, and left ventriculography revealed mid-inferior and apical segment akinesis. She was diagnosed with the 4th occurrence of TTS.

Discussion

We describe the case of an elderly female experiencing quadruple episodes of TTS with various triggers, LV dysfunctions and severities in a short period of 10 months. Although multiple recurrences of TTS is rare, it can occur with variable trigger factors and patterns of myocardial dysfunction. An analysis of multiple recurrences could aid in clarifying the pathophysiology of TTS.

Keywords

Takotsubo syndrome • Stress induced cardiomyopathy • Recurrence • Multiple • Case report

Learning points

• Takotsubo syndrome (TTS) can recur on multiple occasions, with various triggers and different areas of the myocardium being affected on each occasion.
• For several months after TTS, the affected patients may be at risk of a further episode. Elucidating the recurrence of TTS may aid understanding of the pathophysiology.

Introduction

Takotsubo syndrome (TTS) is characterized by transient left ventricular (LV) dysfunction, often preceded by emotional or physical trigger. Although several pathophysologies have been proposed in the onset of TTS, including multi-vessel coronary spasm, microvascular dysfunction and sympathetic abnormality, the definite cause of TTS is undetermined. Various abnormal findings of
electrocardiogram (ECG) and ventricular wall motion could occur in the early phase of TTS, and ventricular contraction usually improves within 1 or 2 weeks. According to the International Takotsubo Registry, the rate of recurrent TTS was 4.7% with a wide time interval ranging from 1 month to 9 years after the initial event. Multiple recurrences were extremely rare in 0.26–0.35% of patients experiencing TTS. We report the case of an elderly female with quadruple episodes of TTS with various triggers, LV dysfunctions and severities in 10 months.

### Timeline

| Time                  | Events                                                                                                                                 |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| First takotsubo syndrome (TTS) | She had paroxysmal nocturnal dyspnoea following an emotional stress event. Electrocardiogram (ECG) showed terminal T-wave inversion with QT interval prolongation in anterior leads. Transthoracic echocardiography (TTE) revealed severe hypokinesis of mid- and apical-anterior segments. Coronary computed tomography angiography depicted no coronary stenosis. |
| Three months later: second TTS | She had sudden orthopnoea after upper-respiratory infection. ECG showed marked symmetrical giant negative T-wave with QT interval prolongation in anterior leads. TTE revealed broad akinesis in mid- and apical-left ventricle with right ventricular dysfunction. Coronary angiography (CAG) showed no occlusive coronary artery. |
| Five months later: third TTS | She had dyspnoea after herpes zoster infection. ECG showed terminal T-wave inversion in anterior leads. TTE revealed mild hypokinesis in mid- and apical-anteroseptal segments. CAG depicted normal coronary arteries. |
| Ten months later: forth TTS | She experienced central chest pain without a specific trigger. ECG showed ST-segment elevation in inferior leads. CAG showed no coronary artery stenosis, and left ventriculography revealed akinesis of mid-inferior and apical segments. |

### Case presentation

A 79-year-old woman was admitted to the emergency department with complaints of dyspnoea the day before the first anniversary of her husband’s death. She had been affected with persistent atrial fibrillation, taking bisoprolol and apixaban. An initial ECG showed no significant ST-T segment change. Her serum troponin T, creatine kinase (CK), and CK-MB were within normal range. However, transthoracic echocardiogram (TTE) revealed severe hypokinesis of mid- and apical-anterior segments with reduced LV ejection fraction (LVEF) of 45%. Chest X-ray showed bilateral pleural effusion. The next day after admission, a follow-up ECG showed terminal T-wave inversion with QT interval prolongation in leads V1 through V5 (Figure 1). Coronary computed tomography angiography found no significant coronary stenosis. One week later, TTE demonstrated normal LV wall motion, and she was diagnosed with focal type TTS based on the specific findings of ECG and TTE.

Three months after the first hospital admission, she had sore throat and cough. Three days after the onset of the symptoms, she suddenly had orthopnoea. Her blood pressure was 154/104 mmHg with tachycardia of 122 beat per minute, and respiration was accelerated at 32 per minute. On physical examination, we recognized jugular vein dilatation, gallop rhythm, and peripheral coldness. Chest X-ray showed acute pulmonary oedema, and ECG showed ST-segment elevation in leads V2 through V3 and terminal T-wave inversion in leads V2 through V6. TTE revealed broad akinesis in mid- and apical-left ventricle with akinesis of right ventricle (Figure 2; Video 1). LVEF was significantly reduced to 23%, and neither LV outflow tract obstruction nor mitral regurgitation were observed. Her serum troponin T was slightly elevated to 0.088 ng/mL, though CK and CK-MB were within normal range. Emergent coronary angiography (CAG) showed no occlusive coronary artery (Figure 2). She was diagnosed with recurrent TTS, which complicated bi-ventricular dysfunction. Although we had started a vasodilator drug and respiratory support using non-invasive positive pressure ventilation, she haemodynamically collapsed, and required low dose of norepinephrine and dobutamine with support of intra-aortic balloon pumping. The following day after the admission, ECG showed marked symmetrical giant negative T-wave with QT interval prolongation in leads V2 through V6 (Figure 1). We had temporarily prescribed enalapril after stabilization of circulatory collapse, but discontinued it due to an occurrence of hyperkalaemia. After 2 weeks, her bi-ventricular dysfunction was completely normalized (Figure 2; Video 2). 

99mTc-tetrofosmin and 123I-beta-methyl iodophenyl-pentadecanoic acid dual myocardial single-photon emission computed tomography (SPECT) demonstrated a preserved whole perfusion of left ventricle and defect of fat acid metabolism in mid-anterior and apical segments (Figure 3). Computed tomography showed no findings of subarachnoid haemorrhage and pheochromocytoma. She was discharged on day 22.

One month after the second discharge, she suffered from herpes zoster on her back. Two days after the onset of zoster, she presented with dyspnoea, and chest X-ray showed bilateral pleural effusion. ECG showed terminal T wave inversion in leads V2 through V6 (Figure 1). TTE revealed mild hypokinesis in mid- and apical-anteroapical segments, leading to reduced LVEF of 48% (Figure 2). Right ventricular function was preserved. CAG depicted normal coronary arteries, and myocardial biopsy showed no specific findings. She was treated with intravenous diuretics, and TTE showed complete recovery of the LV wall motion on day 10. She was diagnosed with focal type TTS. Metanephrine titration on 24h urine was within normal range. 123I-meta-iodo benzyl guanidine (MIBG) SPECT and fluoro deoxy glucose positron emission tomography detected no evidence of pheochromocytoma and...
paraganglioma. She was discharged with enalapril, spironolactone and carvedilol.

Four months after the third discharge, she suddenly complained of central chest pain. The triggered stress was not identified. On admission, ECG showed ST-segment elevation in leads I, III, and aVF (Figure 1), and her serum troponin T was increased to 2.00 ng/mL. CAG showed no coronary artery stenosis, and left ventriculography revealed akinesia of mid-inferior and apical segments indicating apical ballooning (LVEF: 50%). The next day following the admission, ST-segment elevation was normalized. Normal LV wall motion was regained after 1 week. The diagnosis of quadruple TTS was established. No more recurrence was recognized after 6 months from the last recurrence.

**Figure 1** Electrocardiogram. Electrocardiogram of the patient with quadruple takotsubo syndrome.

**Figure 2** Transthoracic echocardiography and coronary angiography. Transthoracic echocardiography of the patient during the second and third episode of takotsubo syndrome (dashed lines: hypokinesis or akinesis); no occlusive coronary arteries were found during the second episode.
Discussion

We reported the case of an elderly female who had quadruple episodes of TTS in a short period of 10 months. Although the recurrence of TTS is infrequent, multiple recurrences of TTS could occur, and its trigger and myocardial dysfunction are variable.

TTS is estimated to recur in 4.7–11.4% of patients with initial TTS.3–6 The time interval after the initial event to recurrence was wide from 1 month to 9 years.3,5 Among the patients with recurrence, half of them had different type of trigger compared with the preceding event.3,4 In our case, she experienced first recurrence of TTS 3 months after the initial episode. The triggers of each recurrence were diverse, including one emotional, two physical and one undetected. It is reported that 65–80% of recurrent cases presented the same form of LV dysfunction as the previous episode.3,4 Our case presented with various forms of TTS: one apical ballooning, one bi-ventricular type, and two focal types. Previous studies reported equivalent prognosis among various LV wall motion abnormalities,5 however, the right ventricular involvement was associated with adverse clinical course.7 In our case, bi-ventricular dysfunction at the second episode led to cardiac shock requiring intra-aortic balloon pumping. The International Takotsubo Registry reported that neurological disorder and psychiatric disorder were associated with the

![Video 1](image1.png) **Video 1** Broad akinesis in mid- and apical-left ventricle.

![Video 2](image2.png) **Video 2** Normalized left ventricular wall motion.

![Figure 3](image3.png) **Figure 3** Dual single-photon emission computed tomography. Upper panels: 99mTc-tetrofosmin accumulates the whole regions of left ventricle. Lower panels: 123I-beta-methyl iodophenyl-pentadecanoic acid defects in the apical-anterior and mid to apical inferoseptum segments (asterisks).
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Lead author biography

Takashi Hiruma is a clinical trainee at the Department of Cardiology, Sakakibara Heart Institute, Tokyo since 2019. He graduated from the Faculty of Medicine, Gunma University in 2017 and completed his internal medicine training at Toranomon Hospital, Tokyo.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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Conclusion

We experienced a case of quadruple episodes of TTS in a short period of 10 months. A case with multiple recurrences indicates the diversity of TTS, and its elucidation should aid in clarifying the pathophysiology of TTS.

Call to action: Further studies are needed to understand the pathophysiology of TTS and the factors influencing recurrence.
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