

A case report of recurrent takotsubo cardiomyopathy including the rare ‘inverted’ form

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Background

Takotsubo cardiomyopathy (TC) is a disease that causes transient left ventricular (LV) dysfunction in multiple vascular territories in the absence of coronary artery disease. Takotsubo cardiomyopathy is typically associated with dilation and dyskinesia of the apical and mid-LV segments induced by acute emotional and/or physical stress. Here, we present a case of recurrent TC including one episode of inverted TC, which is a rare form where dyskinesia occurs in the basal segments with sparing of the apical segments.

Case summary

A 53-year-old female patient with a background history of chronic stress and anxiety was admitted with three episodes of recurrent TC over 4 years. The first episode in 2017 was triggered by an acute stressful event, but no major triggers were identified for the subsequent episodes. Although the first and third episodes displayed the signs of classical TC, the second episode was an inverted TC. Full cardiac function was restored after each episode. She now takes prognostic heart failure medications long term and mental health teams are trying to support her emotional wellbeing.

Discussion

This patient displayed a rare disease course involving three recurrent episodes of TC, including one instance of its inverted form. Although psychiatric conditions and emotional stress are acknowledged as risk factors for TC, further research is needed to assess whether mental health treatment following TC can prevent disease recurrence.

Keywords

Takotsubo • Inverted takotsubo cardiomyopathy • Recurrent takotsubo cardiomyopathy • Echocardiography • Cardiac MRI • Case report

ESC Curriculum

2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 2.1 Imaging modalities • 4.3 Mitral regurgitation • 6.5 Cardiomyopathy

Learning points

- Recognition of the clinical and imaging features of inverted takotsubo cardiomyopathy (TC).
- Recognize the effects of long-term emotional stress and anxiety on the potential recurrence of TC and the lasting deleterious effects this may have on cardiac function.

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Introduction

Takotsubo cardiomyopathy (TC) is a disease characterized by transient abnormalities in left ventricular (LV) wall motion without coronary ischaemia.¹ Takotsubo cardiomyopathy was first reported in a cohort of Japanese women in 1983 as a transient apical myopathy induced by emotional and/or physical stress.^{2,3} Its name comes from the ballooning of the apical LV segment, which makes the heart look like a Japanese pot used to trap octopi, known as a Takotsubo.³ Inverted TC is one of many variants of the disease and was first described in 2010.¹ This variant is characterized by transient abnormalities within the basal segments of the LV and sparing of the apical segments.^{1,2} For a true diagnosis of inverted TC to be made, these features must exist within multiple vascular territories and in the absence of coronary artery disease, pheochromocytoma, or myocarditis.² Diagnosis is usually confirmed by left ventriculography or non-invasive cardiac imaging.⁴

Inverted TC has been shown to account for 1–2.2% of all TC cases.^{5,6} Whilst TC classically presents in post-menopausal women,⁷ inverted TC has been shown to occur more frequently in younger women compared with other forms of the disease.² Inverted TC can also present with syncope, nausea, abdominal pain, and indigestion.² Although TC does not reoccur in most cases and patients typically do not suffer from long-lasting cardiac disease,^{7,8} instances of patients suffering more than two episodes of the disease have been reported.^{9,10}

Timeline

Section	Date	Event
Cardiac history	June 2017	The patient presented with cardiac chest pain after an altercation with a work colleague. She had minor ECG changes but elevated troponins. Coronary angiogram revealed no arterial disease and classical TC was seen on TTE. Cardiac MRI scan 3 weeks post-discharge showed normal cardiac function with no gadolinium enhancement or myocarditis.
	October 2017	The patient suffered an exacerbation of anxiety associated with palpitations and chest pain. She presented to the ED and discharged after serial troponins were normal, her ECG showed normal sinus rhythm, and 24 h telemetry showed no arrhythmias.
	March 2021	The patient was admitted again with cardiac chest pain, this time without an acute stress trigger. ECG showed minor non-specific changes but elevated troponin T. An echocardiogram showed dilation and hypokinesia of all basal to mid-LV segments with a moderately impaired ejection fraction as well as moderate mitral regurgitation. A cardiac MR scan during admission showed hypokinesia of the basal–mid LV segments. A repeat coronary angiogram was normal and a diagnosis of inverted takotsubo cardiomyopathy was made. A repeat TTE 4 weeks post-discharge showed full recovery of cardiac function and resolution of the mitral regurgitation.
	June 2021	The patient presented to ED with central crushing chest pain without an acute stress trigger. ECGs showed new T-wave inversion in lead V6 and troponin T was elevated. Her echocardiogram during admission showed classical TC. Four weeks post-discharge, her TTE displayed normal LV systolic function.

ECG, electrocardiogram; ED, emergency department, MRI, magnetic resonance imaging; TTE, transthoracic echocardiogram.

Case presentation

A 53-year-old female first presented in June 2017 with chest pain, ST-elevation in the lateral ECG leads, and a troponin I elevated at

6996 ng/L. Her past medical history included a meningioma excision in 2014, hypertension, hypercholesterolaemia, irritable bowel syndrome, and she was an ex-smoker. Her social history included chronically high levels of emotional stress and anxiety, particularly surrounding her work, and on the day of admission, she reported having an altercation with a work colleague. On examination, the patient displayed a respiratory rate of 18, sinus tachycardia with a heart rate of 133 b.p.m., normal heart sounds, and oxygen saturation of 95% on room air. The patient's chest was clear on auscultation and her initial chest X-ray (CXR) displayed no pulmonary consolidation. A repeat CXR 2 h later, however, showed worsening peri-hilar opacities suggestive of worsening pulmonary oedema.

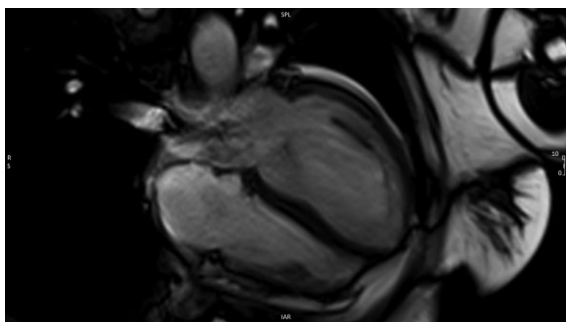
Coronary angiography was normal (see [Supplementary material online, Videos S1 and S2](#)) and a transthoracic echocardiogram (TTE) showed ballooning of the LV apex with dyskinesia of the mid and apical segments. A diagnosis of classical TC was, therefore, made and the patient was commenced on daily 2.5 mg bisoprolol and 5 mg ramipril. Three weeks later, a cardiac magnetic resonance (cMR) scan confirmed the complete functional recovery of the LV, no late Gadolinium enhancement, and no evidence of myocarditis. All cMR scans performed for this case used a 3 T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) and images were analysed with reference to expert consensus reported in the *Journal of Cardiovascular Magnetic Resonance*.¹¹ The patient was referred for counselling and stress management following discharge.

In March 2021, now aged 56, the patient presented again to the emergency department with chest pain. On this occasion, she denied any acute stress/exercise triggers. Her troponin T was raised at

239 ng/L and her electrocardiogram (ECG) showed inferolateral ST depression. She displayed a normal CXR and a normal plasma metanephrine level of 203 pmol/L. A TTE showed akinesia in all basal and mid-LV segments, an ejection fraction (EF) of 45%, and moderate mitral regurgitation (MR) (see [Supplementary material online, Video S3](#)). The apical LV segments, however, were normal. A cMR scan ([Video 1](#)) with T2 mapping ([Figure 1](#)) and late gadolinium

enhancement (Figure 2) carried out 48 h later confirmed the wall motion abnormalities seen on TTE. The cMR revealed basal LV dilation with an EF of 46%, raised T1 and T2 values in the basal LV segments, and faint mid-wall type of gadolinium hyperenhancement in the basal inferior wall segment. The patient underwent a repeat coronary angiogram (see [Supplementary material online, Videos S4 and S5](#)), which showed unobstructed coronary arteries and a diagnosis of inverted TC was made. The patient remained stable on the ward and was discharged with daily 25 mg eplerenone in addition to her regular 2.5 mg bisoprolol and 5 mg ramipril. A repeat TTE in April 2021 showed full recovery of LV function (Video 2). The patient was counselled about managing her emotional stress and anxiety and her general practitioner was advised to refer her for cognitive behavioural therapy to help prevent further episodes of TC.

Two months later, in June 2021, the patient presented for a third time with severe chest pain, shortness of breath, palpitations, and light-headedness. Her ECG showed a new T-wave inversion in lead V6, but there were no dynamic changes on repeat traces. Her troponin T was elevated at 926 ng/L and an admission CXR showed no abnormalities. A TTE showed classical TC again with apical and mid-segment dyskinesia and severe LV impairment (Video 3). The patient recovered well on the ward following treatment with intravenous furosemide and 4 weeks post-discharge, she had no shortness of breath, chest pain, or peripheral oedema. A TTE at this follow-up showed normal LV systolic function and no evidence of valvular disease (see [Supplementary material online, Video S6](#)). The patient's regular 40 mg oral furosemide was,



Video 1 Cardiac magnetic resonance following inverted takotsubo cardiomyopathy in March 2021. Steady-state free precession cardiac magnetic resonance cine imaging (four-chamber view) following inverted takotsubo cardiomyopathy in March 2021. Cardiac magnetic resonance revealed hypokinesia of the basal and mid-segments of the left ventricle. The apical left ventricular segments showed normokinesia. The left ventricle was dilated (end-diastolic volume index = 102 mL/m²) and displayed mild systolic dysfunction (ejection fraction = 46%). The left and right atria and right ventricle were normal and there was no focal or generalized myocardial hypertrophy. The patient also showed a new, mild mitral regurgitation (regurgitant flow ratio = 13%). All cardiac magnetic resonance scans performed for this case used a 3 T scanner (MAGNETOM Skyra, Siemens Healthcare) and images were analysed with reference to expert consensus reported in the *Journal of Cardiovascular Magnetic Resonance*.¹¹

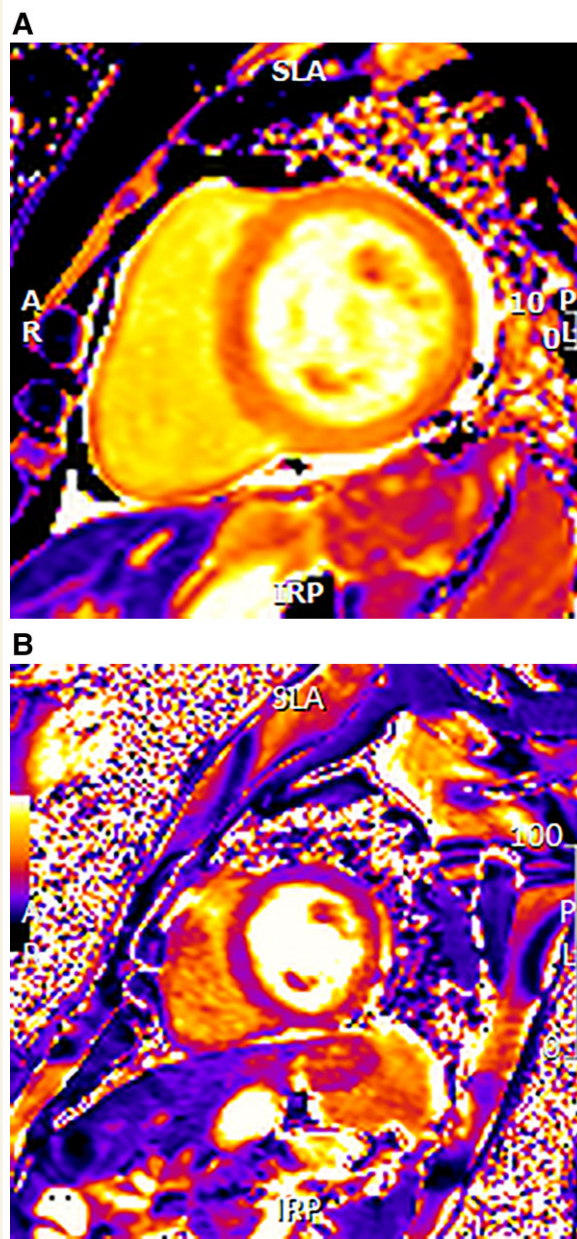


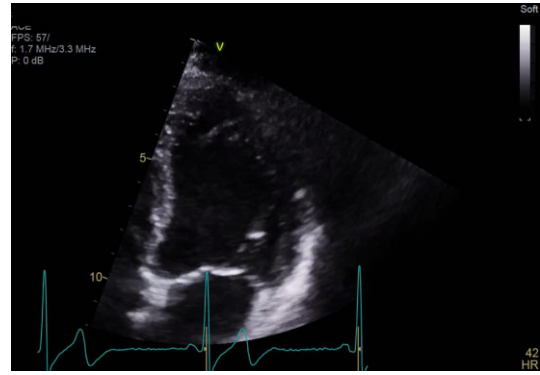
Figure 1 Cardiac magnetic resonance T2 mapping and native T1 mapping in March 2021. Cardiac magnetic resonance T2 mapping (T2-prepared steady-state free precession) basal short-axis view (A) showed significantly increased T2 values in the basal segments (up to 65 ms in the basal inferolateral segments and 59 ms in the basal anteroseptum) compared with the mid-segments (which were normal, having all T2 values <45 ms). Corresponding native T1 mapping (MODified Look-Locker Inversion Recovery) basal short-axis view (B) showed T1 values significantly increased in the basal segments (up to 1470 ms in the basal inferior) compared with the mid-segments (which were normal, having all native T1 values <1300 ms). All cardiac magnetic resonance scans performed for this case used a 3 T scanner (MAGNETOM Skyra, Siemens Healthcare) and images were analysed with reference to expert consensus reported in the *Journal of Cardiovascular Magnetic Resonance*.¹¹



Figure 2 Late gadolinium enhancement during cardiac magnetic resonance in March 2021. Late gadolinium enhancement imaging two-chamber view (acquired 10 min after intravenous injection of 0.2 mmol/kg gadolinium-based contrast agent using a phase-sensitive inversion-recovery gradient-echo sequence) showed faint mid-wall type of hyperenhancement in the basal inferior wall segment. Cardiac magnetic resonance T2 mapping (T2-prepared steady-state free precession) basal short-axis view (A) showed significantly increased T2 values in the basal segments (up to 65 ms in the basal inferolateral segments and 59 ms in the basal anteroseptum) compared with the mid-segments (which were normal, having all T2 values <45 ms). Corresponding native T1 mapping (MODified Look-Locker Inversion Recovery) basal short-axis view (B) showed T1 values significantly increased in the basal segments (up to 1470 ms in the basal inferior) compared with the mid-segments (which were normal, having all native T1 values <1300 ms). All cardiac magnetic resonance scans performed for this case used a 3 T scanner (MAGNETOM Skyra, Siemens Healthcare) and images were analysed with reference to expert consensus reported in the *Journal of Cardiovascular Magnetic Resonance*.¹¹

therefore, stopped and since she displayed bradycardia in the community, bisoprolol was switched to 10 mg propranolol. Following this switch, however, the patient complained of nausea and vomiting and so she was switched back to bisoprolol at half her initial dose. In October 2021, Holter monitoring revealed an average heart rate of 57 b.p.m. with a range of 44–97 b.p.m. Episodes of ventricular ectopic beats and supraventricular ectopic beats were noted and the patient experienced palpitations during a single episode of frequent ventricular ectopic beats. No other concerning cardiac symptoms were noted and a decision to continue with daily 1.25 mg bisoprolol was made.

During each admission, the admitting physicians treated the patient as having acute coronary syndrome (ACS) until a diagnosis of TC was confirmed. She also required LV supportive therapies such as diuretics, beta-blockade, angiotensin-converting enzyme inhibitors, and aldosterone antagonists. These medications were discontinued after she



Video 2 April 2021 transthoracic echocardiogram: apical four-chamber view 4 weeks after the second takotsubo cardiomyopathy episode. A follow-up transthoracic echocardiogram performed 4 weeks after the second episode of takotsubo cardiomyopathy showed full recovery of left ventricular function.



Video 3 June 2021 transthoracic echocardiogram: apical four-chamber view during the third takotsubo cardiomyopathy episode. Transthoracic echocardiogram during admission in June 2021 showed apical and mid-segment akinesia in the classical form of takotsubo cardiomyopathy.

recovered from her first episode but she is now regularly taking bisoprolol and ramipril.

Discussion

We present a case of a patient who had three episodes of recurrent TC within the space of 4 years. The prevalence of TC recurrence has been shown to be 4.7% from the largest reported InterTak registry of 1402 patients.¹² In this registry, there was no observed difference in triggers or patterns of ballooning in the recurrence groups, but the incidence of diabetes and hypercholesterolaemia was lower. A meta-analysis of 1664 patients found that those with severe disease at initial presentation were more likely to suffer a recurrence.¹³ Other factors associated with TC recurrence include female gender,

low body mass index, mid-ventricular hyper-contractility, and close proximity to the initial presentation.¹⁴ In the large multi-centre German Italian Stress Cardiomyopathy (GEIST) registry of 749 patients, El-Battraway *et al.*¹⁵ showed that just 30 patients (4%) suffered a recurrence of TC and only 1 patient had more than two episodes. The InterTAK registry reported 5 patients (0.3%) with multiple recurrences¹² and a study of 100 patients in New Zealand found that just one suffered more than a single episode of TC recurrence.¹⁶ Having more than two episodes of TC, as in our case, is, therefore, exceedingly rare.

The patient presented in this report also had an episode of inverted TC in between two presentations of classical TC. Although instances of different patterns of LV ballooning during recurrent presentations have been reported in both the large registries and in case reports, the inverted pattern is rare.^{9,12,15} In the InterTAK registry, inverted TC was seen in 0.3% of patients.¹² In the GEIST registry, 20% of the recurrence group displayed different patterns of cardiac ballooning and dyskinesia at subsequent presentations.¹⁵ Only 2.3% of patients in this registry presented with inverted TC at first presentation and none presented with this variant at a second presentation, demonstrating that inverted TC remains an extremely rare pattern during recurrent episodes.¹⁵ The basal TC episode in our patient was associated with significant transient functional MR, presumably because of the important mechanistic contribution from the LV basal and mid-segments subtending the papillary muscles.

Our case also demonstrates that TC is not always precipitated by acute emotional or physical stress, which is the classical teaching in this disease. In the GEIST registry, 70% of patients had a preceding acute stress event and in the recurrence group, physical stress was more prevalent than emotional stress.¹⁵ Similar findings were reported in the InterTAK registry.¹² Although the majority of TC patients do not experience long-term cardiac sequelae,⁸ it is not always a benign course. Acute complications including cardiogenic shock or even death have been reported. Quevedo and Khoueir¹⁷ reported a case where recurrent episodes of TC were associated with ventricular fibrillation, highlighting the importance of preventing repeat episodes of the disease. Templin *et al.*³ showed that patients with TC were more likely to have concurrent psychiatric disorders when compared with patients with ACS. This has also been highlighted in the InterTAK registry, which showed that neurological and psychological diseases are independent predictors of TC recurrence.¹² Chronic stress and anxiety were also associated with recurrent TC in another case report.¹⁸ Although psychiatric conditions and emotional stress are acknowledged as risk factors for TC,^{3,12,19} there is currently no evidence supporting the use of psychiatric treatments in order to prevent disease recurrence. Psychological care and support following TC could represent a therapeutic target and requires further research.

Conclusions

The occurrence of more than two episodes of TC is rare. In this case study, not only did our patient have three episodes of TC, the second episode was of an inverted TC pattern. Due to its rarity, experience in recognizing and managing patients with inverted TC can be

challenging. This case report, therefore, provides key learning opportunities about this condition.

Lead author biography



I am an academic foundation doctor at Manchester University NHS Foundation Trust and have completed Bachelor's degree qualifications in Medicine and Surgery and Medical Science from the University of Birmingham. I am developing my clinical and research interests and I hope to incorporate academia at each stage of my career. Outside of work, I enjoy playing football, keeping

fit, and playing music, especially jazz and soul. In addition, my passions for promoting wellbeing and widening access within medicine have led me to volunteer for the UK registered charities You Okay, Doc? and African Caribbean Medical Mentors.

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 have obtained verbal and written patient consent in accordance with COPE guidelines.

Conflict of interest: None declared.

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