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CASE REPORT
Other

A case report of takotsubo syndrome complicated by ischaemic stroke: the clinical dilemma of anticoagulation

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Background Takotsubo syndrome (TTS) is an acute and transient heart failure syndrome due to reversible myocardial dysfunction characterized by a wide spectrum of possible clinical scenarios. About one-fifth of TTS patients experience adverse in-hospital events. Thromboembolic complications, especially stroke, have been reported, albeit in a minority of patients.

Case summary A 69-year-old woman presented to our emergency department for dyspnoea after a family quarrel. Electrocardiogram revealed ST-segment elevation in anterolateral leads and laboratory exams showed a slight elevation of high-sensitivity cardiac troponin. The patient was treated according to current guidelines on ST-elevation myocardial infarction and referred to the cath lab. Urgent coronary angiography revealed normal coronary arteries. Based on the patient profile and instrumental findings, a diagnosis of TTS was hypothesized. After 6 days, the patient developed dysarthria and right hemiparesis under therapy with aspirin, whilst low molecular weight heparin had been previously withdrawn. Transthoracic echocardiography (TTE) revealed persisting apical akinesia and a subtle intraventricular thrombus. Head computed tomography and magnetic resonance imaging detected focal areas of ischaemic necrosis resembling diffuse cardioembolic lesions. Anticoagulation therapy was started and regular TTE showed complete recovery of myocardial systolic function and absence of ventricular thrombi at 1-month follow-up. The patient fully recovered speech after 5 months.

Discussion This challenging case reinforces current recommendations to administer antithrombotic therapy in TTS patients with extensive apical dysfunction up to complete or near-complete recovery of myocardial contractility, regardless of the presence of atrial fibrillation, and highlights the importance of close TTE monitoring during the acute phase.

Keywords Takotsubo syndrome • Intraventricular thrombosis • Ischaemic stroke • Cardioembolism • Case report

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Learning points

- Takotsubo syndrome (TTS) is an acute and reversible heart failure syndrome associated with adverse in-hospital events in about one-fifth of the patients. Intraventricular thrombosis complicated by ischaemic stroke has also been reported, albeit in a minority of cases.
- Up to date, there is a knowledge gap in literature regarding the appropriate therapeutic strategy in order to prevent thromboembolic complications in TTS patients.
- Current case suggests adopting anticoagulation therapy in case of extensive apical akinesia and typical apical ballooning pattern, even in presence of sinus rhythm. Such therapy should be prolonged, especially in patients at high risk for developing thromboembolic events, until complete or near-complete recovery of myocardial function whereas bleeding risk is acceptable.

Introduction

Takotsubo syndrome (TTS) is an acute and transient heart failure syndrome characterized by a wide spectrum of possible clinical scenarios. Pathophysiology of TTS is still unclear. High levels of serum catecholamines may have a key role in the genesis of reversible myocardial dysfunction.[1] Genetic, endocrine and inflammatory factors seem to be accountable for increased adrenergic stimulation.[1] A stressful event, emotional or physical, usually precedes TTS onset, although no trigger event can be identified in one-third of the patients.[1] Common clinical picture is characterized by symptoms (e.g. chest pain, dyspnoea, palpitations and syncope), electrocardiogram (ECG) changes and increased troponin levels, often mimicking acute coronary syndrome despite normal coronary arteries. Ventricular wall motion abnormalities most commonly involve apical segments (apical ballooning variant); less frequent phenotypes are the midventricular, basal and focal forms.[1] The peculiarity of this syndrome is the extensive myocardial dysfunction, irrespective of regional distribution, involving territories supplied by different coronary arteries (circumferential pattern). Although TTS is reversible, with complete recovery of myocardial contractility within days or weeks, in about one-fifth of the patients it is associated with adverse in-hospital events including heart failure, cardiogenic shock, and life-threatening arrhythmias.[2,3] Furthermore, embolic complications, especially stroke, have been reported, albeit in a minority of patients.[2] We report the case of a patient with TTS and typical apical ballooning pattern complicated by intraventricular thrombosis and ischaemic stroke.

Timeline

	Patient without cardiovascular risk factors. Anamnesis of mitral valve prolapse, colon cancer successfully treated 3 years before, anxiety occasionally treated with anxiolytic drugs.
Day 1	Onset of dyspnoea after a family quarrel. Systolic murmur 2/6 Levine scale with systolic click and crackles at both lung bases. ST-segment elevation in anterolateral leads and prolonged QTc interval value. Elevated levels of markers of myocardial injury. Extensive akinesia of apical segments. Normal coronary arteries at angiography.
Days 2–3	Close clinical observation in cardiologic intensive care unit. Administration of anticoagulation therapy.
Day 4	The patient is transferred into the cardiology unit. Anticoagulation therapy is stopped.
Day 6	The patient develops dysarthria and right hemiparesis. Head computed tomography (CT): small hypodense area at cortico-subcortical site of left parietal lobe.
Day 7	Sudden disappearance of spontaneous speech. Head CT: additional hypodense ischaemic area localized at cortex of the precentral gyrus, no hyperdense area. Echocardiography: small left ventricular thrombus and persistence of apical akinesia. Anticoagulation therapy is started.
Day 8	Head magnetic resonance imaging (MRI): ischaemic stroke with cardioembolic lesions mainly involving the left parietal and frontal lobes.
Day 10	Marked recovery of systolic function. Reduction of thrombus size.
Day 13	The patient is transferred into a neurological rehabilitation institute.
1-month follow-up	Marked improvement of neurological disorders. Electrocardiogram (ECG): diffuse negative T-waves. Echocardiography: normal left ventricular ejection fraction and absence of apical thrombi.
3-month follow-up	Only mild dysarthria persisted. ECG: normalization of ST-T segment. Cardiac MRI: complete recovery of left ventricular systolic function.
5-month follow-up	Complete recovery of speech disorders.

Case presentation

A 69-year-old Caucasian woman presented to our emergency department with a 2-h history of dyspnoea, following a family quarrel. Her past medical history included mitral valve prolapse with mild mitral regurgitation diagnosed in young age and colon cancer successfully treated by surgery and chemotherapy 3 years before. The patient suffered from anxiety, occasionally treated with anxiolytic drugs. Physical exam revealed apical systolic murmur 2/6 Levine scale with systolic click and crackles at both lung bases. Blood pressure was 110/70 mmHg, heart rate 73 b.p.m., respiratory rate 22 b.p.m., and

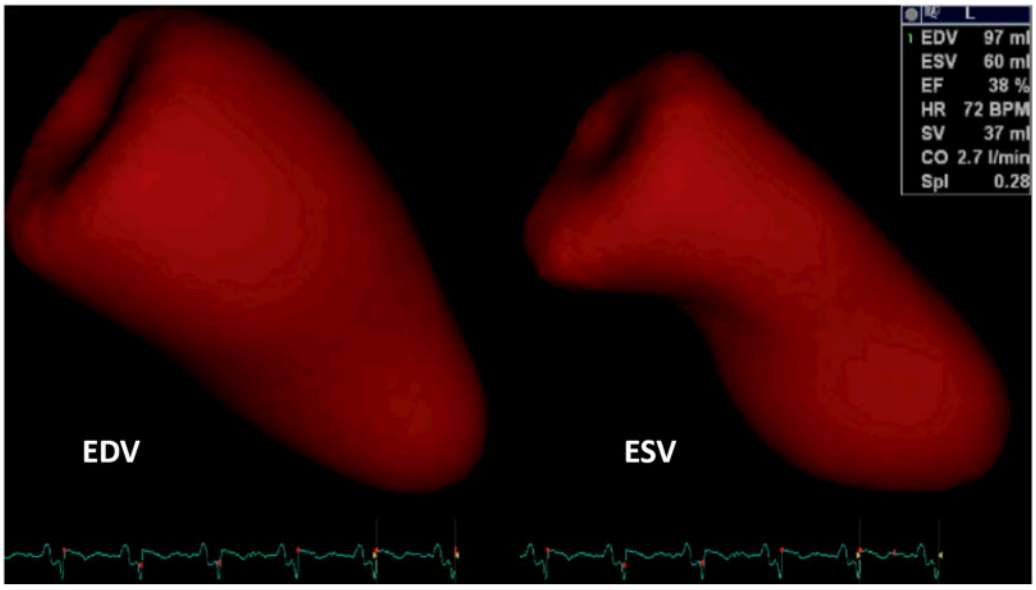
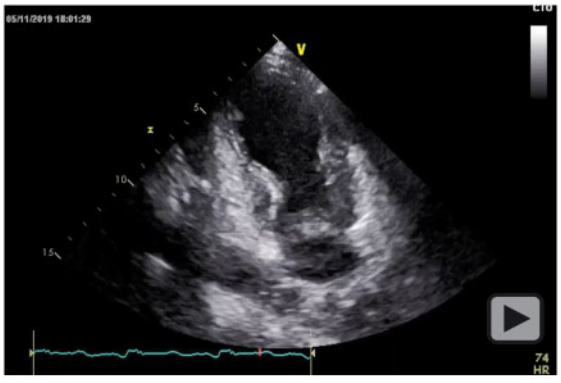
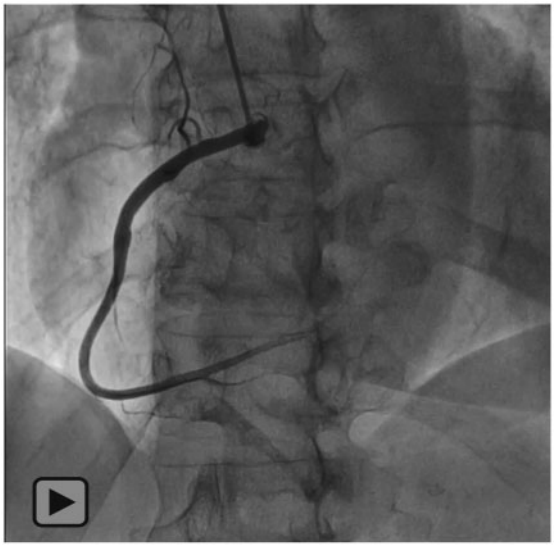


Figure 1 Three-dimensional echocardiographic reconstruction of the left ventricle in end-diastole (left panel) and end-systole (right panel) with apical ballooning morphology. EDV, end-diastolic volume; ESV, end-systolic volume.

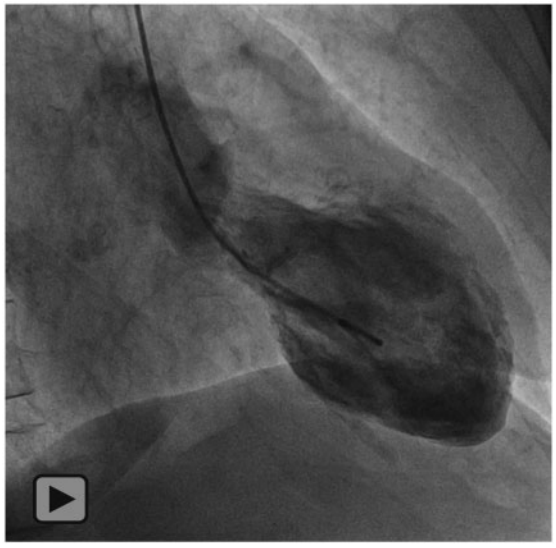


Video 1 Two-dimensional transthoracic echocardiography, 4-chamber, 2-chamber and long-axis view respectively, showing extensive apical akinesia during the acute phase of takotsubo syndrome.



Video 2 Normal coronary arteries can be appreciated at left and right coronary angiography.

O_2 saturation 96%. The ECG showed sinus rhythm, ST-segment elevation up to 1.5 mm in lateral and anterior leads and prolonged QTc interval (496 ms). Increased high-sensitivity cardiac troponin (937 ng/L—URL 20 ng/L) and no other abnormalities were detected on blood sample analysis. Haemoglobin (13.8 g/dL), white blood cells (7.8×10^3/μL), platelets (189×10^3/μL), prothrombin time (12.3 s), and activated partial thromboplastin time (31 s) were within normal range. Transthoracic echocardiography (TTE) showed reduced left ventricular ejection fraction (LVEF, 38%) due to akinesia of cardiac apex (*Figure 1*; *Video 1*). The patient was immediately referred to the cath lab with an initial diagnosis of ST-elevation myocardial infarction and treated with unfractionated heparin 5000 IU i.v. and dual antiplatelet therapy (aspirin 250 mg i.v. and ticagrelor 180 mg *per os*) according to current guidelines.[4] Unexpectedly, coronary angiography revealed normal coronary arteries while left ventriculography confirmed the echo finding of extensive systolic dysfunction of the apical segments with hyperkinesia of the basal segments resembling 'takotsubo' morphology (*Figure 2*; *Videos 2* and *3*).[5–7] Considering the preceding trigger event and the apical akinesia despite normal coronary arteries, the suspicion of typical TTS arose. This hypothesis was reinforced by an InterTAK diagnostic score value of >70. The patient remained under close clinical observation in the intensive care unit



Video 3 Left ventriculography right anterior oblique at 30° in end-systole showing typical apical ballooning pattern resembling the Japanese pot 'takotsubo'.

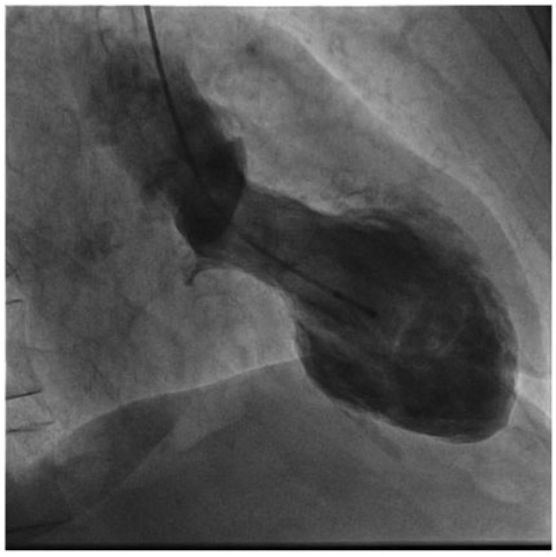


Figure 2 Left ventriculography, right anterior oblique at 30° in end-systole showing typical apical ballooning pattern resembling the Japanese pot named 'takotsubo'.

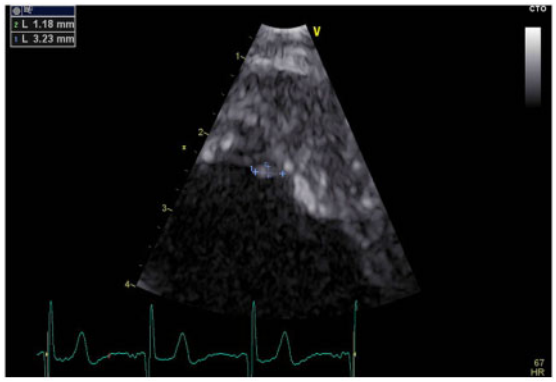


Figure 3 Zoom of modified apical short-axis view demonstrating apical thrombus attached to the left ventricular lateral wall.

for 2 days receiving the following therapy: low molecular weight heparin (LMWH) 6000 IU s.c. twice daily, aspirin 100 mg/day, metoprolol 50 mg twice daily, ramipril 2.5 mg/day. Due to signs of heart failure, furosemide 20 mg i.v. twice daily was added. On the 4th day of hospitalization, the patient was transferred to the cardiology unit. Therapy remained unchanged, except for LMWH which was withdrawn. Two days later, the patient developed dysarthria and right hemiparesis. Head computed tomography (CT) scan revealed a small hypodense area at the cortico-subcortical site of the left parietal lobe. The day after, due to sudden disappearance of spontaneous speech, a new head CT was performed, revealing an additional ischaemic hypodense area localized at the cortex of the precentral gyrus, whilst no hyperdense area suggestive of ongoing intracranial haemorrhage was detected. TTE showed persisting apical akinesia and detected a small apical thrombus (1.2 mm × 3.2 mm) attached to the apical segment of the left ventricular (LV) lateral wall (*Figure 3*; Supplementary material online, *Video S1*). Therefore, anticoagulation therapy with acenocoumarol *per os* was started, with dose adjustment according to periodic laboratory testing of international normalized ratio. At 72 h from the onset of neurological symptoms, head magnetic resonance imaging (MRI) confirmed the diagnosis of ischaemic stroke showing diffuse cardioembolic lesions mainly involving the left parietal and frontal lobes (*Figure 4*). Ten days after hospitalization, LV systolic function improved significatively (LVEF 48%) and the size of the apical thrombus appeared reduced (Supplementary material online, *Video S2*). Owing to the persistence of the neurological disorders, the patient was transferred 3 days later to a neurological rehabilitation institute, in stable haemodynamic conditions. At 1-month follow-up, she was asymptomatic, hemiparesis was no more detectable and dysarthria was slowly but significantly improving. The ECG showed only diffuse negative T-waves. TTE showed normal LVEF (58%) and no apical thrombus (Supplementary material online, *Video S3*). At 3-month follow-up, the patient was in good clinical conditions. Speech had further improved, albeit still slower than normal. No more ST-T segment abnormalities were identifiable at ECG. Cardiac MRI confirmed the complete recovery of LV systolic function and the absence of thrombi (Supplementary material online, *Video S4*). No areas of oedema or late gadolinium enhancement were appreciated (*Figure 5*). Therefore, anticoagulation therapy was withdrawn. At 5-month follow-up, the patient fully recovered speech without any relevant symptoms.

Discussion

The prevalence of intraventricular thrombosis and embolism in TTS patients ranges from 2.2% to 3.3%.[8–10] In the largest international registry on TTS, the InterTAK registry, intraventricular thrombosis

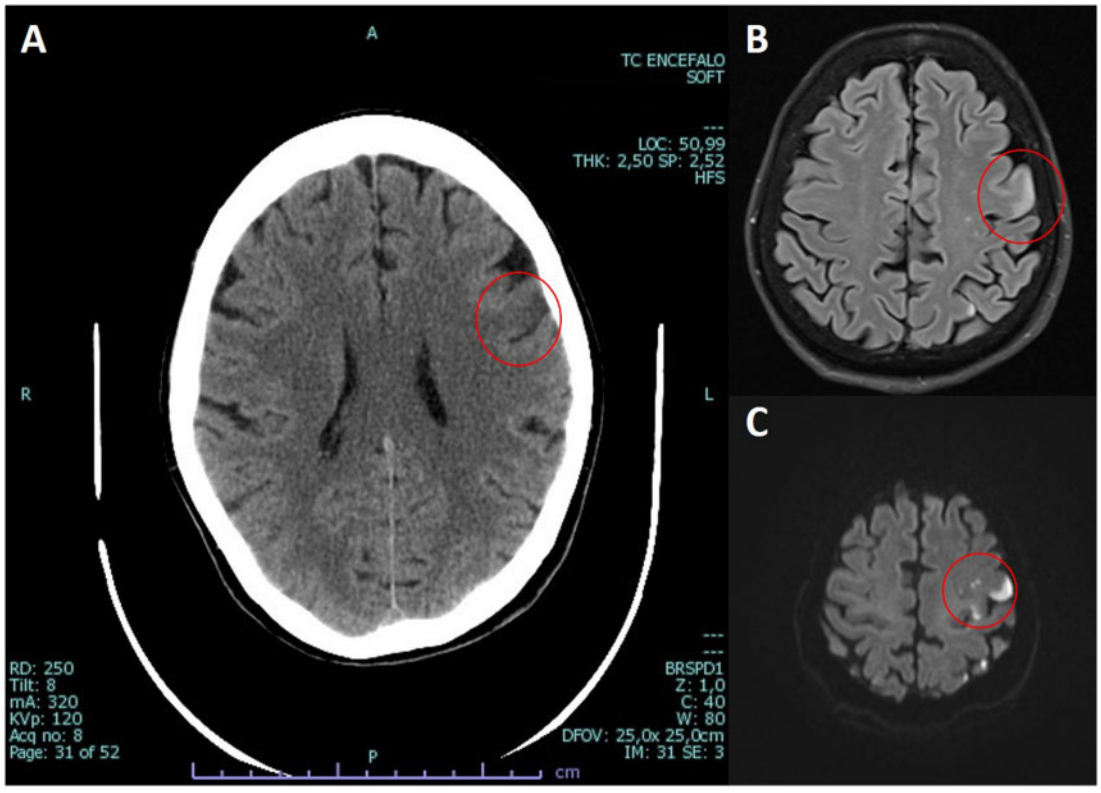


Figure 4 Focal ischaemic necrosis (red circles) mainly involving the left frontal and parietal lobes by head computed tomography (*A*); T2 TIRM Dark fluid magnetic resonance imaging (*B*); diffusion-weighted magnetic resonance imaging (*C*).

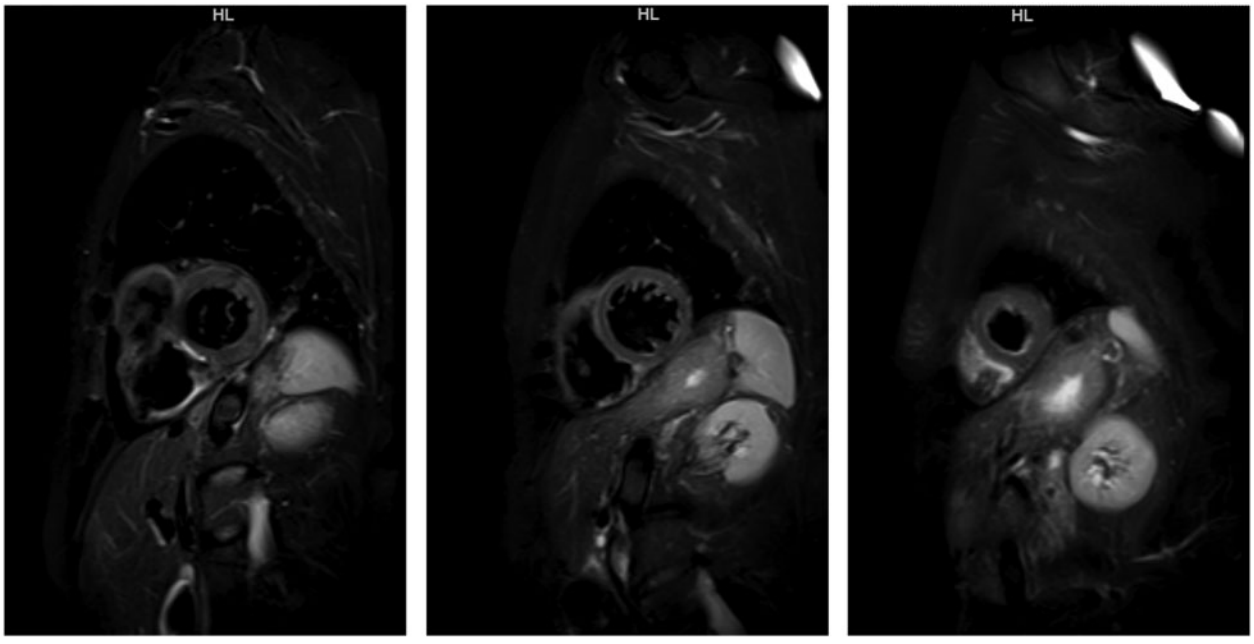
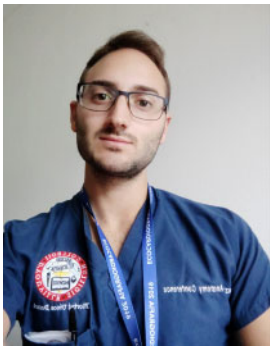


Figure 5 No area of myocardial oedema can be detected by black blood T2-weighted inversion-recovery cardiac magnetic resonance imaging at 3-month follow-up.

and/or embolism were reported in 56 (3.3%) of 1676 patients. Of note, in this subgroup, ischaemic stroke occurred in 13 patients and in 3 patients with LV thrombi. Determinants of thromboembolic complications were the apical ballooning phenotype, previous vascular disease, LVEF ≤30% and white blood cell count on admission $>10 \times 10^3$ cells/μL.[8] Usually, apical thrombi have been detected during the first week after hospitalization, especially within the first 48 h.[8] Furthermore, it has been demonstrated that TTS patients with elevated CHA_2DS_2-VASc score at admission are more prone to develop major adverse cardiac and cerebrovascular events at long-term FU, regardless of the presence of atrial fibrillation.[11] Current recommendations based on expert opinion suggest using anticoagulation therapy in TTS patients with extensive myocardial akinesia and a typical apical ballooning pattern.[2,12] Up to date, there is a persisting knowledge gap in the literature about the most appropriate treatment to adopt and its duration.[13] In the present case, the persistence of extensive myocardial dysfunction induced marked reduction of intraventricular systolic flow velocity leading to intraventricular thrombosis. Early interruption of LMWH probably favoured both thrombus formation and cerebral embolism. In fact, ischaemic stroke occurred on the 6th day of hospitalization despite sinus rhythm. This challenging case reinforces the recommendation to administer anticoagulation therapy up to complete or near-complete recovery of ventricular contractile function in TTS patients with apical ballooning, especially in those at high risk for developing thromboembolic events, if bleeding risk is acceptable. In addition, this case highlights the crucial importance of close echocardiographic monitoring in the acute phase of TTS in order to evaluate myocardial contractile recovery and to detect early LV thrombi. Future prospective randomized studies should be scheduled to select patients with TTS at higher risk of thromboembolic complications and to establish an appropriate anticoagulation therapy.

Lead author biography



Giuseppe Iuliano, MD, graduated at University of Salerno, Italy, after 3 years of training at the echo lab of University Hospital San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy. He completed a fellowship in echocardiography at Hospital de Santa Maria, Lisbon, Portugal. Currently, he is resident in Cardiovascular Disease at University of Salerno. His research interests include cardiomyopathies, especially takotsubo syndrome and Fabry disease, and the application of novel imaging techniques in diagnosis and treatment of structural heart diseases.

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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