Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 5 Article 22

2024

An Unlikely Cause of Chest Pain: Recurrent Takotsubo Cardiomyopathy

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CASE REPORT

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Abstract

Takotsubo cardiomyopathy is described as transient, ventricular dysfunction. A relatively rare pathology accounting for 0.02% of hospitalizations, recurrent episodes are even less common, occurring at 1−6%. Here, we present a case of an elderly woman presenting with multiple, recurrent episodes of takotsubo cardiomyopathy. Similarities and differences between our case and others presented in literature are compared. Our case highlights the importance of maintaining a broad differential when presented with multiple episodes of recurrent, acute heart failure in the setting of chest pain and ST segment elevations.

Keywords: Takotsubo cardiomyopathy, Acute coronary syndrome, ST elevation, Heart failure, Apical myocardial ballooning

1. Introduction

Takotsubo Cardiomyopathy (TC), characterized by transient left ventricular dysfunction with apical ballooning, was initially identified in 1990, though its roots may extend back to the 1950s.[1,2] Also known as Stress Cardiomyopathy, TC is typically precipitated by an acute stressor, either emotional or physical, leading to Left ventricular (LV) dilation and heart failure. The condition is generally considered benign, with most patients achieving full recovery of their LV function.[3] However, recent accounts have demonstrated a possible association with prolonged cardiac dysfunction and worse outcomes.[2] TC presents with symptoms similar to those of Acute Coronary Syndrome (ACS), necessitating coronary angiography to rule out life-threatening obstructions prior to diagnosis.[3] TC is more commonly observed in female patients and often associated with stressful conditions where elevated catecholamine levels induce LV dysfunction. Management primarily involves supportive care, with a small percentage of patients progressing to cardiogenic shock.[4] Recurrence of TC is rare, estimated at 1−6%, with "super recurrences" (defined as ≥2 TC recurrences) being exceptionally uncommon.[5,6] The proposed pathophysiological mechanism of recurrent TC involves a catecholamine surge leading to transient myocardial contractility and dysfunction.[7] Kato et al. sought to determine patient risk factors associated with recurrent TC through a retrospective analysis of 1400 patients diagnosed with TC.[8] Interestingly, diabetes mellitus and hypercholesterolemia were more prevalent in those with recurrent TC, whereas those with significant cardiovascular risk factors were not associated with recurrent TC.[8] Underlying psychiatric and neurological pathologies, including anxiety, seizure, cerebrovascular disease, and migraine disorder, were observed more frequently in those with recurrent TC.[8] This study highlights important risk factors associated with TC.[8] Herein,

Received 18 April 2024; revised 6 June 2024; accepted 19 June 2024.
Available online 9 September 2024

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https://doi.org/10.55729/2000-9666.1394

we present a unique case of TC recurrence thrice over a six-year period, shedding light on the intermittent recovery of LV systolic function.

2. Case presentation

A 70-year-old female with a medical history of chronic anxiety, recurrent panic attacks, depression, gastroparesis, hyperlipidemia, hypertension, hypothyroidism, and peripheral neuropathy presented to the emergency department (ED) with complaints of chest pain. A 12-lead electrocardiogram (EKG) demonstrated ST segment elevation, concerning for an ST-segment elevation myocardial infarction (STEMI). Consequently, due to concern for ACS, the patient underwent emergent coronary angiography, revealing patent coronary arteries without evidence of obstructive disease, although mild LV dysfunction was observed. Notable electrocardiographic changes and regional myocardial abnormality were noted involving the mid to distal anteroapex and inferoapex. Left ventriculogram revealed classic mid to distal anteroapical, apical and inferolateral akinesis consistent with takotsubo cardiomyopathy. Subsequent transthoracic echocardiography corroborated the presence of mild LV dysfunction, characterized by septal hypokinesis, leading to a diagnosis of idiopathic acute systolic heart failure, with plans for outpatient follow-up. Management included aggressive afterload reduction therapy with lisinopril, carvedilol, atorvastatin, and aspirin therapy along with a follow up echocardiography to assess left ventricular dysfunction.

Three months later, follow-up transthoracic echocardiography indicated a decline in LV systolic function, with the LV ejection fraction decreasing to 35% with evidence of hypokinesis affecting the apex, posterolateral wall of the LV, and distal septum. Considering this pattern of systolic dysfunction, a repeat coronary angiography was performed, confirming the absence of significant coronary artery disease. Consequently, a presumptive diagnosis of takotsubo cardiomyopathy was made based on these characteristic echocardiography findings, and the patient was initiated on guideline-directed medical therapy. Over a two-year period, the patient exhibited improvement in cardiac function, as evidenced by a recovery of the LV ejection fraction to 50–55%, documented on follow-up transthoracic echocardiography and normal findings on nuclear stress testing.

Six years later, the patient presented to the emergency department with shortness of breath and cough. She was found to have sepsis secondary to community-acquired pneumonia for which she was started on antibiotic therapy. The patient was also found to have evidence of volume overload concerning for acute heart failure exacerbation. Cardiac biomarkers were elevated, including troponins and BNP, and she was started on IV furosemide for diuretic therapy. A transthoracic echocardiogram (TTE) revealed a newly reduced LV ejection fraction of 25–30% (Fig. 1, Video 1 [https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1394&window=additional_files&context=jchimp]). Given the patient's presentation, clinical course, and characteristic echocardiography findings, she was deemed to have recurrent takotsubo cardiomyopathy and her medical therapy was optimized. At the six-month follow-up, repeat transthoracic echocardiography demonstrated a recovery of LV ejection fraction to 55%. Diagnostic catheterization revealed patent arteries without occlusion (Fig. 2). At the patient's most recent presentation for her follow up, she reported doing well. Table 1 below further outlines the patient's progression and recovery of her election fraction associated with recurrent TC episodes. She continues to be managed supportively and symptomatically.

Glossary

TC	Takotsubo cardiomyopathy
LV	Left ventricular
ACS	Acute coronary syndrome
ED	Emergency department
EKG	Electrocardiogram
STEMI	ST-segment elevation myocardial infarction
ARB	Angiotensin receptor blockers
ACE	Angiotensin converting enzyme inhibitor
BNP	Brain natriuretic peptide
SNPs	Single nucleotide polymorphisms

3. Discussion

Takotsubo cardiomyopathy is described in literature as a transient myocardial wall-motion abnormality typically observed at the myocardial apex.[9] This acute cardiomyopathy is commonly associated with physical and/or emotional stressors. Recovery and resolution of ejection fraction and wall-motion abnormalities typically occur after removal of initial stressor.[10] Unlike typical case presentation with a singular episode of TC, our case is unique and highlights the possibility of multiple, recurrent episodes of TC. Shaw et al. sought to further identify those patients at risk for recurrent episodes.[6] This prospective study followed up 506 patients with a diagnosis of TC from a United States healthcare center comprised of 91% women and an average age of 68 years old. Statistically significant differences

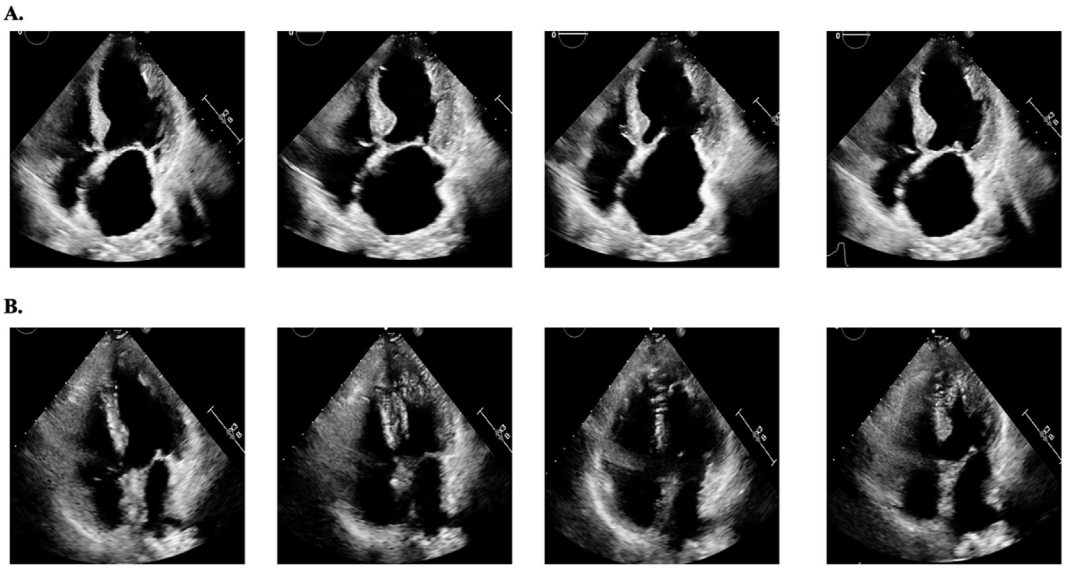

Fig. 1. A. Transthoracic echocardiography images six years after initial episode of Takotsubo cardiomyopathy, illustrating several depressed left ventricular ejection fraction of 25–30% by visual estimation. Wall motion is consistent with stress-induced takotsubo cardiomyopathy with preservation of basal wall motion. Of note, transthoracic echocardiography one year prior revealed a hyperdynamic left ventricle with an ejection fraction of 65%. B. Transthoracic echocardiography images illustrating recovery of left ventricular ejection fraction. Visual assessment of ejection fraction estimated to be 55% with normal biventricular size and systolic volume.

between those with a single TC episodes and recurrent episodes (more than or equal to 2) included a younger age at presentation, higher peak troponin levels (2.08 ng/mL), nadir ejection fraction of 20–30%, diagnosis of depression and/or anxiety and a cancer diagnosis.[6] Although not statistically significant, apical ballooning of the myocardium was also noted in those with two or more recurrent episodes. Our case showed many similarities to those recurrent TC cases outlined above, including a significantly elevated troponin level at initial presentation, nadir LV ejection fraction of 25% and concurrent diagnosis of anxiety and depression. Apical ballooning of the myocardium was also seen in our case. These overlapping similarities observed in patients with recurrent TC can provide clinical clues to help predict future occurrences of TC. Early identification is vital, as TC has been shown to lead

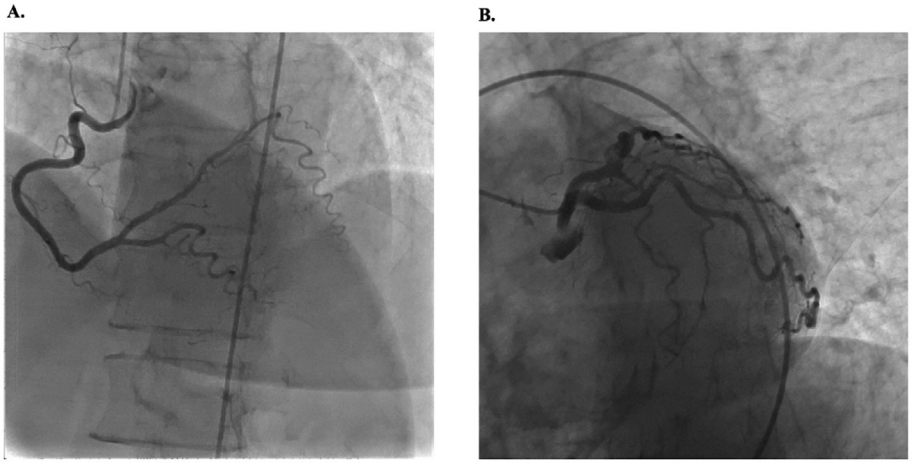

Fig. 2. A. Cardiac catheterization of the right coronary artery revealed patent vasculature without occlusions or obstructive disease at a follow-up visit after an episode of takotsubo cardiomyopathy. B. Angiography view of the left anterior descending artery and left circumflex artery during the same cardiac catheterization revealing similar findings as the right sided vasculature. Findings on this angiography are notably different from those on initial cardiac catheterization during initial takotsubo episode six years prior, which noted classic mid to distal anteroapical, apical and inferoapical akinesis consistent with takotsubo cardiomyopathy on left ventriculogram.

Table 1. Display of events, investigation and subsequent management of each hospital presentation and follow up monitoring the progression and eventual recovery of the patient's recurrent takotsubo cardiomyopathy.

Event	Investigation	Management
• ED presentation with chest pain • ST elevations involving mid to distal anteroapex and inferoapex	• Coronary angiography: absence of ischemic disease; notable LV dysfunction • Left ventriculogram: mid to distal anteroapical, apical and inferolateral akinesis • TTE: mild left ventricular dysfunction with septal hypokinesis	• Outpatient cardiology follow-up • Afterload reduction with lisinopril, Coreg, statin, and aspirin therapy • Follow up echocardiography
• Follow up echocardiography 3 months later	• TTE: reduction in left ventricular systolic function (35%) with apex, posterolateral wall and distal septal hypokinesis • Coronary angiography: absence of ischemic disease	• Continued on Lisinopril, Coreg, statin, and aspirin therapy • Follow up echocardiography
• Follow up echocardiography 2 years later	• TTE: recovered left ventricular ejection fraction (55%)	• Continued on Lisinopril, Coreg, statin, and aspirin therapy
• ED presentation with shortness of breath and cough 6 years later	• TTE: newly reduced left ventricular ejection fraction of 25–30% • Found to have sepsis secondary to community acquired pneumonia	• Diuresis with IV Lasix • Continued on Lisinopril, Coreg, statin, and aspirin therapy • Follow up TTE
• Follow up TTE 6 months later	• TTE: recovered ejection fraction (55%) • Diagnostic cardiac catheterization: absence of ischemic disease	• Continued on Lisinopril, Coreg, statin, and aspirin therapy

to long-term cardiac complications and in some cases, cardiogenic shock, sudden cardiac arrest, and cardiac rupture.[2,4]

Due to complications associated with TC outlined above, proper treatment is important. Initial management is typically supportive.[11] Concurrent presentations associated with TC include anginal chest pain, hypertension, and hypotension.[12] In such cases, nitrates, beta blockers, angiotensin receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitor and/or fluid resuscitation may be indicated.[12] 10% of cases have been observed to develop cardiogenic shock. In these cases, inotropes such as dobutamine, along with fluid resuscitation, may be indicated for treatment.[12] In other cases, patients may present with concurrent left outflow tract obstruction. In these cases, inotropes should be avoided, and beta blocker pharmacotherapy is often used.[12] In our case, each presentation was treated with supportive management. TTE and heart catheterization revealed concurrent pulmonary hypertension and beta blocker therapy was administered appropriately. To date, there are no approved preventative medications for TC.[9] After an episode of TC, ACE inhibitors, ARB, beta blockers and diuretic therapy should be considered for three months.[9] The Takotsubo International Registry recommends administration of an ACE inhibitor or ARB as studies showed a one-year survival benefit at follow-up along with a decreased rate of reoccurrence, although low.[9] Of note, no survival benefit was noted at one year in those managed with beta blockers therapy. Due to the low rate of TC recurrence, other studies recommend against prophylactic therapy.[9] Lisinopril 2.5 mg daily was initiated at her most recent visit, and she has not experienced recurrent TC since administration. Further studies are warranted to explore the benefit of preventative and prophylactic therapy. An important but often overlooked contributing cause of TC are anxiety and depression. Corrigan et al. performed a retrospective review of four consecutive cases of TC at a tertiary care center and found that each patient case had a historical psychiatric diagnosis of Alzheimer's dementia with associated psychotic features, adjustment disorder, major depressive disorder and/or bipolar 1 disorder.[10] Each episode of TC was found to directly follow an exacerbation of the concurrent psychiatric illness.[10] As psychiatric illnesses are relatively common and found in about 21.6% of the public, further optimization of the psychiatric condition may play an important role in prevention of TC.[11]

Early detection of TC is imperative due to overlapping similarities at presentation with ACS. At first presentation, EKG, basic metabolic panel, TSH,

cardiac enzyme biomarkers and brain natriuretic peptide (BNP) levels are typically obtained.[1] Most patients will also undergo invasive angiography to rule out ACS. In patients ultimately diagnosed with TC, angiography typically reveals non-occluded coronary arteries, as seen in our patient at initial presentation (Fig. 1). To date, the Mayo Clinic diagnostic criteria is the most reliable method to diagnose TC and requires the following criteria: transient left ventricular dysfunction, absence of obstructive coronary artery disease, presence of acute ST changes/T wave abnormalities on EKG and absence of pheochromocytoma or myocarditis.[1,3] Our patient met these diagnostic criteria. Although not needed for diagnosis, myocardial perfusion scan (MPS) can be performed to further differentiate from ACS.[9] Our patient underwent MPS at later presentation to rule out ACS, which was unremarkable, consistent with recovery from a TC episode.

Future research should focus on predisposing patient factors that may place them at higher risk for development of TC. Few studies have explored genetic predispositions. Lau et al. isolated a CD36 deficiency, a human adipocyte progenitor, in a patient with recurrent TC.[13] This study suggests that this patient population may be more likely to develop recurrent TC.[13] To further explore genetic predispositions, a genome-wide associated study (GWAS) was conducted on 96 patients with known TC.[14] 18 loci were identified during this study and found to have single nucleotide polymorphisms (SNPs) that were found to be associated with blood pressure and thyroid disease.[14] Nono et al. performed an analysis of L41Q amino acid polymorphism of the GRK5 gene, a protein coupled receptor kinase.[15] Patients with TC were found to have a higher frequency of this polymorphism compared to those without TC.[15] Future studies should focus on specific genetic variations between patients to determine if specific treatment options can be tailored towards these genetic polymorphisms for treatment of TC.

4. Conclusion

Takotsubo cardiomyopathy is an important pathology that requires prompt identification due to many similarities at presentation to ACS. Management is with supportive therapy and tailored towards concurrent presenting conditions, including hypertension, heart failure, hypovolemia, and in some cases, cardiogenic shock.[12] We presented a rare case of recurrent takotsubo cardiomyopathy, with studies outlining a prevalence of 1–6% for repeated episodes.[6] To date, supportive management is the treatment of choice and there are no preventative therapies.[6] Clinicians should maintain a broad differential when presented with cases of recurrent cardiomyopathy and always consider recurrent TC. As our case highlighted, long-term goal directed therapy is imperative for recovery of ejection fraction associated with recurrent cases. Future studies should focus on potential treatment options to reduce the risk of reoccurrence with the added benefit of increasing survival.

Ethical statement

The authors confirm the current research is accurate, this work is original and the authors confirm that all appropriate co-authors have been documented on the manuscript.

Funding

None.

Conflict of interest

There are no conflicts of interests.

Appendix

Video 1: Transthoracic echocardiogram six years after initial episode of Takotsubo cardiomyopathy. Again, an ejection fraction of 25-30% was visualized. This video further highlights akinesis of the apical and ventricular regions with preservation of the basal wall motion.

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