Recurrent Takotsubo cardiomyopathy with variable regional involvement

**INTRODUCTION**

Takotsubo cardiomyopathy (TCM), a stress-induced cardiomyopathy, is a well-recognized cause of left ventricular dysfunction. It commonly presents similar to acute coronary syndrome with chest, dyspnoea, and electrocardiographic changes consistent with ischaemia and elevations of cardiac markers. Takotsubo cardiomyopathy often presents with acute myocardial stunning without evidence of coronary artery disease or atherosclerotic disease that is out of proportion to the demonstrated disease. Takotsubo cardiomyopathy has characteristic left ventriculographic and radiographic findings — including left ventricular hypokinesis, adjacent areas of hyperkinesis, and variable regional involvement (i.e. apical, mid-ventricular, or basal ballooning patterns). Recurrent disease can occur and is often found to have similar ventricular wall dysfunction patterns. However, we present an uncommon case of possible recurrent Takotsubo cardiomyopathy that was found to have variable regional involvement.

**CASE PRESENTATION**

A 57-year-old woman with history of hypothyroidism, vertigo, and chronic back pain presented to the emergency department complaining of dizziness and nausea. She was bradycardic (50 - 60bpm) and hypotensive (78/48mmHg), but responsive to fluid resuscitation. Initial workup included comprehensive metabolic panel, complete blood count, lactic acid, troponin, electrocardiogram, thyroid studies, and urinalysis; all were unremarkable. After thorough assessment (including inpatient evaluation by the electrophysiologist and extensive workup by Neurology, Cardiology, and Otolaryngology), the patient’s presenting symptoms were thought to be visual vertigo with accompanying hypotension and bradycardia secondary to medication effects (Tizanidine).

On hospital day 3, however, the patient became delirious and was found to be tachycardic (120 - 130bpm) and hypotensive (69/45mmHg). An electrocardiogram demonstrated new ST-segment elevations in leads I and aVL (Figure 1). Troponin I was 2.74ng/ml (<0.05ng/ml), and brain natriuretic peptide was 3.631pg/ml (<100pg/ml). The patient was taken for an emergent coronary angiogram, which revealed 70% stenosis of the left circumflex, and 2 drug eluting stents were placed (Figure 2). A left ventriculogram and transthoracic echocardiogram (TTE) demonstrated akinesis of the mid and basal segments with preserved apical contractility and a severely reduced ejection fraction of 15 - 20%, which was disproportionate to the patient’s ischaemic event (Figure 3).
Considering the patient’s clinical presentation as well as her incongruent angiography and TTE findings, there was suspicion of stress-induced cardiomyopathy confounded by her coronary artery disease. She was started on a beta blocker, ace inhibitor, and dual anti-platelet therapy, and was discharged. On follow-up, 4 weeks later, she reported full recovery and was able to return to work full-time. Repeat TTE demonstrated normal left ventricular function with an ejection fraction of 67%, without any wall motion or valvular abnormalities, furthering suspicion of an apical sparing variant of TCM.

Approximately 2 months after her admission, the patient returned to the emergency department with complaints of dizziness and nausea. She was again found to be hypotensive (50/30mmHg) and bradycardic (40 - 50bpm), but not responsive to fluid resuscitation. An ECG demonstrated ST-elevations in leads I and aVL (Figure 1). Peak troponin I was 1.35ng/ml (<0.05ng/ml), and BNP was 125pg/ml (<100pg/ml).

She underwent another emergent coronary angiogram that revealed patent left circumflex stent and no changes in remaining coronary arteries (Figure 2). Left ventriculogram and

**FIGURE 1:** First episode of Takotsubo with lateral ST-segment elevation with mildly prolonged QTc (top), and second episode of Takotsubo with lateral ST-segment elevation with normal QTc (bottom).
TTE revealed left ventricular dysfunction with akinesis of the mid-apical segments with hyperdynamic basal function and an ejection fraction of 30%, suggestive of an apical variant of TCM (Figure 3). Repeat TTE obtained 4 days later showed resolution of the wall motion abnormalities and normalization of the ejection fraction to 61%. In both instances, an extensive history and physical was obtained, but no physical, emotional or psychological stressor could be elucidated to cause the recurrent Takotsubo cardiomyopathy.

**DISCUSSION**

Over the decades, different ballooning variants of TCM have been described, e.g. mid-ventricular ballooning with basal and apical hyperkinesia (14.6%), basal ballooning with apical hyperkinesia (2.2%), and focal segmental ballooning (1.5%). While a formal definition for TCM has not been established, diagnosis is often made by pathognomonic wall motion abnormalities that are not associated with significant coronary artery disease or not explained by a single coronary artery distribution, transient ECG abnormalities, or troponin elevations (along with...
absence of other possible causes such as pheochromocytoma or myocarditis). Treatment of TCM focuses on supportive care that anticipates recovery of left ventricular function, which is seen in days or weeks. Studies have shown that the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers may improve survival. 

FIGURE 3: A: First episode of Takotsubo with mid and basal variant diastole, B: mid and basal variant systole, C: second episode of Takotsubo with apical variant diastole, and D: apical variant systole.
While the exact mechanism remains unclear, increased catecholamine release is suspected to have an important role in pathophysiology. One study found a 2- to 3-fold increase in plasma catecholamine levels in patients with TCM compared with patients presenting with an acute myocardial infarction and a similar degree of clinical heart failure. Another study found higher serum catecholamine levels in patients with subarachnoid haemorrhage and transient LV dysfunction was compared with those without LV dysfunction. Many mechanisms have been proposed, including catecholamine cardiotoxicity, wrapping of left anterior descending artery, transient multivessel coronary vasospasm, coronary microvascular dysfunction, direct myocyte injury, and beta receptor gradient distribution.

However, some previously proposed theories would not explain variable regional involvement. For instance, a study found higher densities of β2 receptors in the left ventricular apex compared to the base; in contrast, higher expression of sympathetic nerve terminals was found at the base compared to the apex. Therefore, it has been thought that wall motion abnormalities may reflect differences of adrenergic receptor distribution. Other proposed theories include the idea that excessive epinephrine release results in a negative feedback mechanism of the β2 receptors, leading to a negative inotropic response and causing myocardial stunning of that region. While these theories may be able to explain recurrent disease with similar regional involvement, they would not explain variable left ventricular involvement – as seen with the presented patient in this case report. Furthermore, progression to cardiogenic shock is a rare complication in Takotsubo, without an identifiable trigger experienced by our patient during both admissions. The short-term prognosis is typically unfavourable in those that experience cardiogenic shock during the course of Takotsubo.

In the case of our 57-year-old woman with 2 recurrent episodes of TCM, the first and second occurrences had no identifiable triggers. The first episode of TCM was clouded by a finding of 70% stenosis in the left circumflex, which was subsequently stented. A large area of stenosis in a distribution of a coronary artery can cause regional wall motion abnormalities. However, the authors would argue that the extensive wall motion abnormalities observed in the ventriculogram would argue against the stenosis as the cause of the ballooning, since it extends past 1 coronary artery distribution; rather, this patient had a true TCM in the first episode. Given that a repeat coronary angiogram during the repeat episode showed no coronary re-stenosis, it highly likely that the second episode represented a true TCM which was a different variant of TCM.

Cardiac magnetic resonance imaging using late gadolinium enhancement is a technique used to characterise the myocardium. The patient had several confounding differentials, including acute coronary syndrome and myocarditis that may have been differentiated on cardiac magnetic resonance imaging – however, this was not performed in this case.

In ischaemic heart disease the gadolinium enhancement starts in the subendocardium and extends to the epicardium as injury progresses. T2 mapping has been used to detect myocardial oedema, which indicates inflammation that can be suggestive of myocarditis.

**CONCLUSION**

Takotsubo cardiomyopathy is a rare cause of left ventricular dysfunction in the general population. It presents with symptoms similar to acute coronary syndrome. Multiple forms of Takotsubo exist, but two separate forms rarely present in the same patient without a known trigger – even after an exhaustive search for a trigger. The exact pathophysiology of reoccurrence of Takotsubo is unknown, but any effort to find a known trigger should accompany every occurrence because of the poor outcomes associated with the acute phase of Takotsubo cardiomyopathy.

**Conflict of interest:** none declared.

**REFERENCES**