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CASE REPORT

# Takotsubo cardiomyopathy associated with rupture of the left ventricular apex: assessment of histopathological features of a fatal case and literature review

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**Abstract** Takotsubo cardiomyopathy, also known as "broken heart syndrome," is a cardiac entity characterized by transient left ventricular dysfunction without obstructive atherosclerotic coronary artery disease. An episode of emotional stress is believed to act as a trigger in the development of this syndrome, which typically occurs in female patients. We report a fatal case of a previously healthy 70-year-old woman who suffered an out-of-hospital cardiac arrest and cardiac rupture during emotional distress, due to Takotsubo cardiomyopathy. Ventricular rupture with Takotsubo cardiomyopathy is rare, but our case emphasizes the importance of dealing with this serious and potentially life-threatening disease. Takotsubo cardiomyopathy should be considered as a differential diagnosis in cases of early-developing heart failure, and clinicians should subsequently use adequate diagnostic and therapeutic options.

**Keywords** Takotsubo cardiomyopathy · Ventricular rupture · Stress cardiomyopathy · Emotional stress

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## Introduction

Takotsubo cardiomyopathy (TCM), also known as apical ballooning syndrome, "broken heart syndrome," and stress cardiomyopathy [1], is a mimic of acute coronary syndrome and typically occurs following physical or emotional distress. TCM is a transient wall motion abnormality of the left ventricular (LV) apex accompanied by emotional and/or physical stress that has usually completely recovered. Left ventriculography during systole in patients with TCM exhibits a shape similar to a "Takotsubo"—a Japanese word for a narrow-necked, round-bottom pot used to catch octopuses. Although TCM is a relatively new syndrome, the number of reported cases is increasing rapidly. Acute heart failure and cardiogenic shock are the two most frequent complications of TCM; however, ventricular arrhythmias may also occur. In 2006, the American Heart Association included this disease as an acquired cardiomyopathy [2]. In the present report, we describe a rare fatal case of TCM, paying particular attention to the pathological characteristics of one of its complications, ventricular rupture (VR). VR is associated with rapid clinical decline and is uniformly lethal when not surgically repaired.

According to previously published retrospective reviews, patients with TCM account for approximately 2 % of all patients with suspected acute coronary syndrome [3]. Furthermore, 90 % of these patients are postmenopausal women [4]. Some studies have indicated that the average age of patients with TCM is 68 years, although children or young adults may also be affected [5]. The most widely accepted diagnostic criterion was described by the Mayo Clinic in 2004 [6]; this criterion was modified in 2008 by Prasad et al. [7]. Kawai et al. [8] classified TCM as a syndrome of unknown etiology, characterized by acute

balloon-like dilation of the LV apex. The most common symptoms listed in the diagnostic criteria are chest pain and dyspnea. In rare cases, patients with TCM develop palpitations, nausea, vomiting, syncope, or cardiogenic shock [6–8].

A unique feature of TCM is its relationship with stressful emotional and/or physical events. This characteristic has been described in nearly two-thirds of patients with TCM [9]. Unlike acute coronary syndrome, which commonly occurs in the early morning, TCM most frequently occurs in the afternoon in association with stressful events. Notably, no specific coronary lesions are detected in patients with TCM [10]. The clinical outcome in patients with TCM is generally favorable; however, VR is often fatal unless expeditiously recognized and surgically repaired. The underlying mechanism of VR in TCM remains incompletely understood. To the best of our knowledge, only 11 case reports describe TCM with VR; all were published from 2004 to 2009 [11] and described rare cases of TCM associated with fatal rupture of the LV apex.

## Case presentation

Our case involves a healthy 70-year-old woman without any cardiovascular risk factors. She had no chronic illnesses and received no medications. Approximately 3 h after a stressful event, the death of her cat, she complained of chest pain and nausea. Her relatives called her physician, who noted a blood pressure of 122/70 mmHg and heart rate of 95 bpm. Her symptoms increasingly worsened over the next few minutes. She was transported to the emergency department of a hospital about 45 min after the first onset of symptoms. Although cardiopulmonary resuscitation was started upon arrival, she had already died. However, it should be noted that the time interval between the stressful event and the onset of the symptoms may not be accurate, due to general confusion during the event and the fact that the woman lived alone.

### Pathological findings

A complete autopsy was carried out, and histological and histochemical methods were employed (Hematoxylin and Eosin, Masson's trichrome).

### Gross examination of the heart

The pericardium was examined and opened. Exploration of the pericardial cavity revealed clinically significant hemopericardium (90 ml) due to cardiac rupture (Fig. 1). The anatomy of the great arteries, pulmonary veins, and

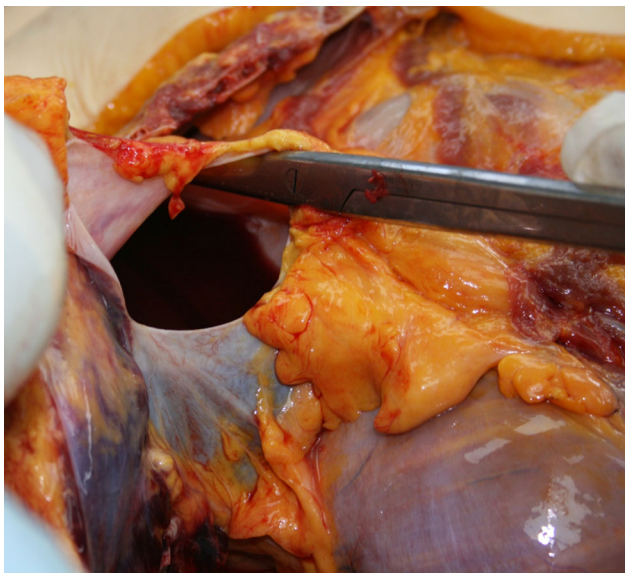

**Fig. 1** Pericardial cavity showing clinically significant hemopericardium due to cardiac rupture

superior and inferior vena cava was examined and found to be normal. These vessels were then transected 3 cm above the aortic and pulmonary valves. The aorta, pulmonary artery, and aortic and pulmonary valves were inspected from above.

### Coronary arteries

The size, shape, position, number, and patency of the coronary ostia were examined. The major epicardial arteries presented right "dominance," and no evidence of intracoronary thrombosis or atherosclerotic plaques was observed.

A complete transverse (short-axis) cut of the heart at the mid-ventricular level followed by parallel slices through the ventricles at 1 cm intervals toward the apex was performed to evaluate the morphology of the walls and cavities.

Once the heart had been emptied of blood, the following measurements were noted. Total heart weight: 363 g; anterior, lateral, and posterior LV free wall thickness: 1.0, 1.1, and 1.2 cm, respectively; free lateral wall thickness of the right ventricle and septum: 0.4 and 1.2 cm, respectively; and transverse and longitudinal heart dimensions: 11.2 and 10.3 cm, respectively.

Hemorrhagic infarction was identified at the LV apex. The infarction extended from the anterior to posterior walls (3.9 × 2.7 cm) and exhibited a 0.4 cm line of ruptured myocardium, which was determined to be the main cause of death (Figs. 2, 3, 4). An acute rupture due to vulnerable plaques in the coronary arteries was ruled out. Histologic

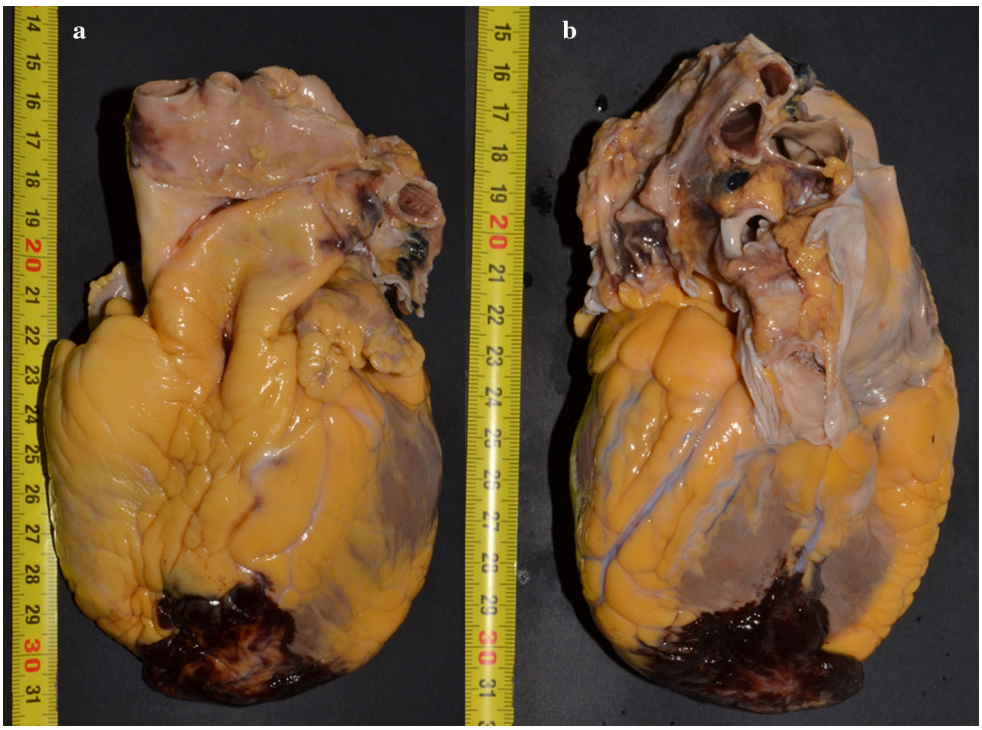


**Fig. 2** Hemorrhagic infarction of the **a** anterior and **b** posterior apex wall

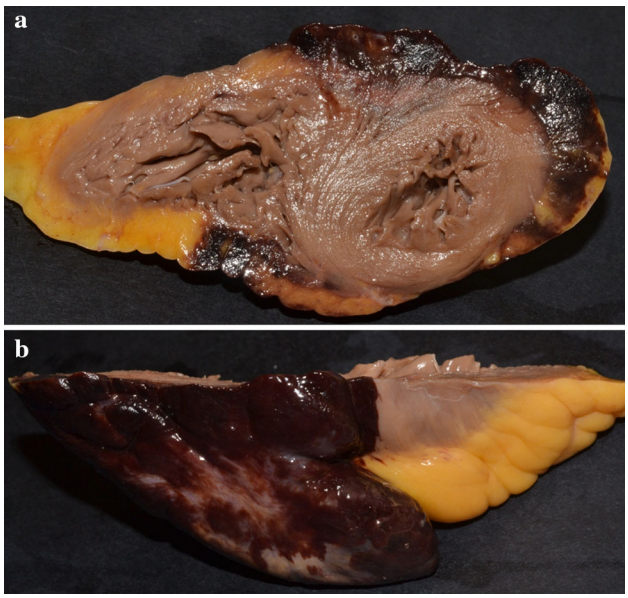


**Fig. 3** Short-axis view of hemorrhagic infarction of the apex

examination of the myocardium revealed diffuse coagulative necrosis of myocytes with a number of foci of contraction bands (Fig. 5a–c), a sign of catecholamine cardiotoxicity. Microscopic examination of the myocardium revealed hypertensive changes with hypertrophied myocyte nuclei. The ischemic hypereosinophilic myocardium contained a large area of coagulative necrosis with neutrophilic infiltration and multiple small areas of "spotty" necrosis (localized death of a few myocytes) with hemorrhagic changes and a form of catecholaminergic myocarditis characterized by a severe mixed inflammatory infiltration of lymphocytes and neutrophils associated with localized areas of fibrosis (Fig. 6).

Histological examination of the brain, lungs, kidneys, liver, stomach wall, and intestine revealed nonspecific findings.

## Discussion

TCM is an uncommon but well recognized condition that is often initially misdiagnosed as acute coronary syndrome because patients typically present with chest pain and dyspnea [12]. The exact pathogenesis of TCM is unknown. Various hypotheses have been suggested and discussed, including coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, reperfusion injury following acute coronary syndrome, myocardial microinfarction, and abnormalities in cardiac fatty acid metabolism. Catecholamine-induced cardiotoxicity and microvascular dysfunction are currently the most supported theories.

The role of catecholamines seems to be central to the pathophysiology of TCM. Catecholamines lead to multiple potentially relevant direct and indirect effects on the brain,

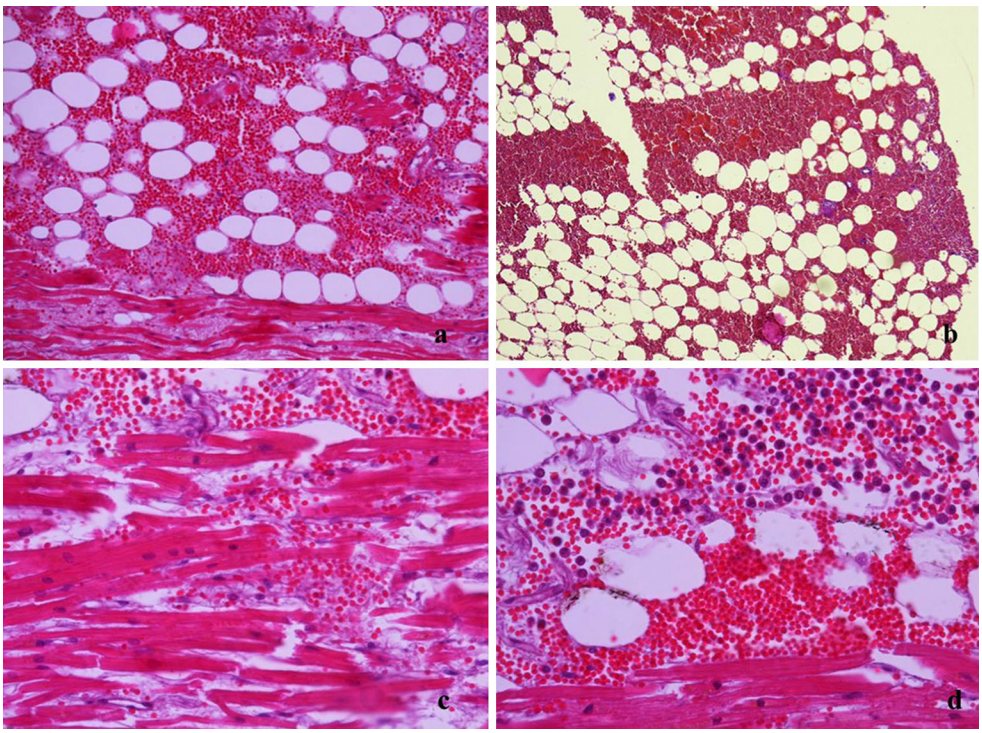


**Fig. 4** Microscopic findings. Large hemorrhagic area. **a** Hematoxylin and Eosin, ×100 magnification; **b** Masson's trichrome, ×100 magnification). **c** Magnification of acute myocardial interstitial erythrocyte infiltration and edema. **d** Epicardial granulocytes (Hematoxylin and Eosin, ×100 magnification)

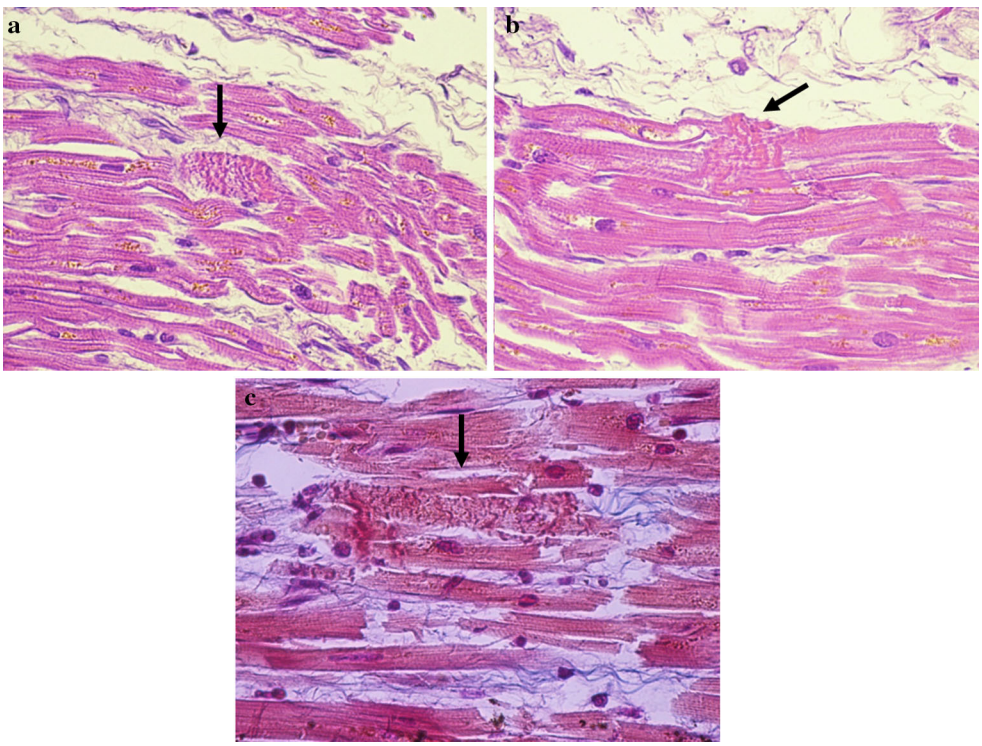


**Fig. 5** Focus of myocytes coagulative necrosis with contraction bands foci (*arrows*). **a**, **b** Hematoxylin and Eosin, ×400 magnification; **c** Masson's trichrome, ×400 magnification)

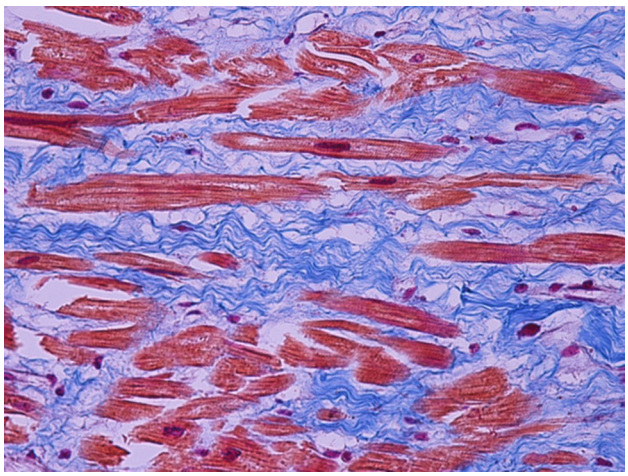

**Fig. 6** Microscopic view of areas of interstitial fibrosis (Masson's trichrome, ×100 magnification)

systemic vasculature, coronary vasculature, and myocardium [13]. Wittstein et al. [14] found that the serum catecholamine concentration was two to three times greater in patients with TCM than in patients with myocardial infarction and reported that serious emotional stress was a precipitating factor. Additionally, exogenously administered catecholamines and pheochromocytoma reportedly cause typical characteristics of TCM, which supports this theory [15].

The pathophysiology of TCM can be considered to develop in two phases. The first starts with increased release of epinephrine and norepinephrine, initiated through activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to a given stress; this is termed HPA gain. The catecholamine concentrations in serum are substantially elevated at presentation in patients with TCM compared with resting levels in the same patients and those in comparable patients with acute heart failure secondary to acute myocardial infarction. These differences suggest the potential for excessive HPA gain and epinephrine release in susceptible individuals [14]. This effect is most relevant for patients with TCM triggered by emotional stress [16].

Myocardial biopsy of patients with TCM shows regions of contraction band necrosis, inflammatory cell infiltration, and localized fibrosis [17]. These changes are caused by direct catecholamine toxicity on the cardiac muscle cells [18]. Morel et al. [19] found that C-reactive protein levels and white blood cell counts increased along with the increase in norepinephrine levels in patients with TCM, inferring that catecholamines produce systemic inflammation via the induction of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6. Several studies have pointed out remarkable myocardial edema with normal perfusion on cardiac magnetic resonance imaging, providing further evidence in support of the inflammation theory [20].

The in-hospital mortality caused by TCM is low (2.5 %), and approximately half of deaths are from cardiac causes [21]. In TCM, acute emotional stress may directly elicit cardiac dysrhythmia by causing an increase in sympathetic outflow [22]. Numerous reports have described that the symptoms of reversible LV dysfunction are similar to those of acute myocardial infarction without coronary artery stenosis [23–26]. More than 90 % of patients with TCM are postmenopausal women. One study investigated whether hormone replacement therapy is effective in female patients with TCM; the authors concluded that a lack of estrogen replacement in the postmenopausal state may predispose women to this cardiomyopathy [27]. Moreover, Ueyama et al. [28] demonstrated that the decrease in LV function was greater in ovariectomized rats subjected to restraint stress than in rats receiving estradiol supplementation. Myocytes express estrogen receptor-α and estrogen receptor-β. According to the theory described by Ueyama et al. [28], estrogen enhances transcription of cardioprotective factors, such as heat shock protein and atrial natriuretic peptide, and in turn protects against the toxic effects of catecholamines, calcium overload, and reduced oxidative stress.

The more frequent presentation of cardiac rupture in postmenopausal women with TCM and acute myocardial infarction could be explain a further pathogenic mechanism: these diseases share the same lack of myocardial free wall compliance because of the interaction between fibrosis diffusion and decreased estrogen levels.

Patients with TCM usually have a good prognosis, and 96 % almost completely recover from their symptoms [29]. The in-hospital mortality rate varies from 1 to 2 % [30]. TCM was previously thought to follow a relatively benign course; however, Sharkey et al. [30] described that approximately 5 % of patients with TCM experienced cardiac arrest. Although their long-term survival rate is the same as that in healthy subjects, patients with TCM have a greater risk of death at the time of initial onset [29]. In one study, the most frequent chief complaint was chest pain (30 %) over 4 years after initial presentation [29]. In the present case, the histopathological analysis demonstrated ischemic necrotic injury and reperfusion changes of the myocytes. Moreover, the presence of granulocytes and lymphocytes in the inflammatory infiltrate supported both the ischemic and catecholaminergic etiology of myocardial injury. VR with TCM is rare [31]; thus, our case emphasizes the importance of treatment of TCM as a serious and potentially life-threatening disease, despite most patients having a benign course.

## Conclusion

Because of the similarity of its presentation and clinical course to those of acute myocardial infarction, TCM should be included as a differential diagnosis for acute myocardial infarction. SCD is an increasingly recognized presentation of TCM. The actual incidence of out-of-hospital cardiac arrest in patients with TCM may be higher than reported because these patients may not survive until hospital arrival and diagnosis. TCM should be considered as a differential diagnosis of SCD among patients who present following major emotional and/or physical stressors. Patients with acute TCM should be monitored closely so that life-threatening arrhythmias may be appropriately treated.

## Key points

1. Takotsubo cardiomyopathy, also known as "broken heart syndrome," is a cardiac entity characterized by transient left ventricular dysfunction without obstructive atherosclerotic coronary artery disease.
2. We report a fatal case of a previously healthy 70-year-old woman who suffered an out-of-hospital cardiac arrest and cardiac rupture during emotional distress, due to Takotsubo cardiomyopathy.
3. An episode of emotional stress is believed to act as a trigger in the development of this syndrome, which typically occurs in female patients. Ventricular rupture with Takotsubo cardiomyopathy is rare, but our case emphasizes the importance of dealing with this serious and potentially life-threatening disease.
4. Takotsubo cardiomyopathy should be considered as a differential diagnosis in cases of early-developing heart failure, and clinicians should subsequently use adequate diagnostic and therapeutic options.

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