INTERNAL MEDICINE

□ CASE REPORT □

Critical Takotsubo Cardiomyopathy Complicated by Ventricular Septal Perforation

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Abstract

An 81-year-old woman was admitted with chest pain. An electrocardiogram demonstrated ST segment elevation in leads II, III and aVF, and echocardiography revealed left ventricular apical asynergy with a left-to-right ventricular shunt. Meanwhile, emergent coronary angiography showed no significant coronary artery stenosis, whereas left ventriculography indicated apical ballooning and a left-to-right ventricular shunt. We therefore diagnosed the patient with Takotsubo cardiomyopathy complicated by ventricular septal perforation and cardiogenic shock. An electrocardiogram disclosed a prolonged QT interval over time, and the patient became hemodynamically stable under treatment with inotropes; however, she suddenly developed fatal ventricular fibrillation three days after hospitalization. Takotsubo cardiomyopathy complicated by ventricular septal perforation is a critical condition that requires careful monitoring.

Key words: Takotsubo cardiomyopathy, apical ballooning, ventricular septal perforation, prolonged QT interval, ventricular fibrillation

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Introduction

In general, Takotsubo cardiomyopathy (TCM) has a good prognosis; however, some patients develop various cardiac complications, including congestive heart failure, left ventricular free wall rupture, ventricular septal perforation (VSP), left ventricular apical thrombosis and ventricular arrhythmias (1). VSP is a rare, but critical, complication of TCM. We herein present a fatal case of TCM complicated by VSP (TCM-VSP).

Case Report

An 81-year-old woman was admitted to our hospital due to acute chest and back pain without either any preceding symptoms or emotional stress. She had been under medical treatment for rheumatoid arthritis and chronic gastritis for over 12 years; however, no heart murmurs were detected prior to admission. On admission, her blood pressure was 93/74 mmHg, her heart rate was 75 beats/min (bpm) with a regular rhythm, her respiratory rate was 23 breaths/min and her peripheral oxygen saturation was 100% under the administration of 10 L/min oxygen via a rebreather mask. A Levine 4/6 pansystolic murmur was audible at the apex. In addition, the D-dimer level was 8.5 μg/mL and the N-terminal pro brain natriuretic peptide (NT-proBNP) level was 2,178 pg/mL, whereas the myocardial enzyme levels were within the normal ranges. An electrocardiogram (ECG) demonstrated ST segment elevation in leads II, III and aVF and negative T-waves in leads V1-6 (Fig. 1). A chest X-ray showed an enlarged cardiac silhouette and lung congestion, and transthoracic echocardiography (TTE) demonstrated left ventricular apical asynergy with a left-to-right ventricular shunt on color-flow Doppler (Fig. 2). In addition, emergent coronary angiography (CAG) revealed no significant coronary artery stenosis (Fig. 3A, B), whereas left ventriculography disclosed apical ballooning with akinesis and basal hyperkinesis. Furthermore, the right ventricle and pulmonary artery were connected via a left-to-right ventricular shunt

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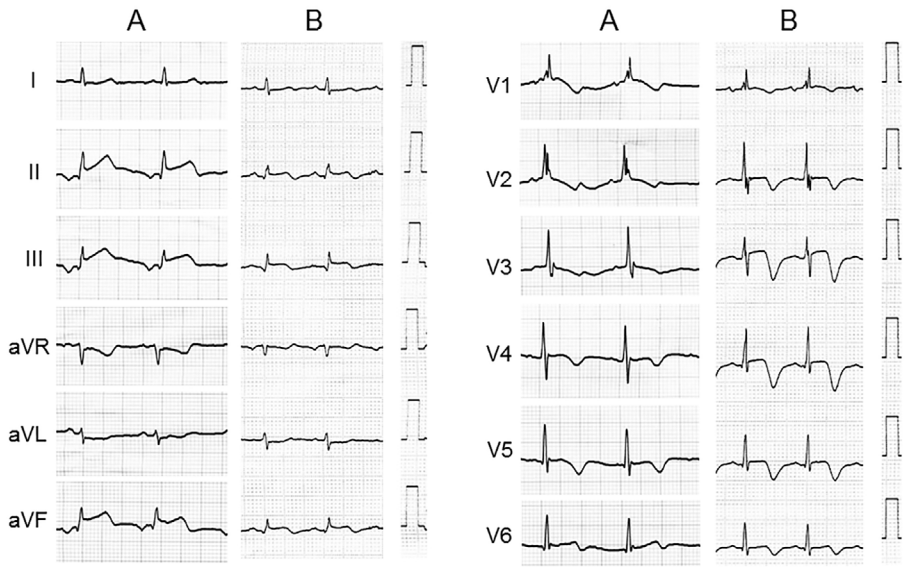

Figure 1. **Time course of the changes in the electrocardiogram (ECG) findings. The ECG obtained on admission (A) demonstrated ST segment elevation in leads II, III and aVF, negative T-waves in leads V1-6 and corrected QT interval (QTc) prolongation (QTc=480 ms). One day after admission (B), an ECG demonstrated remarkable QTc prolongation (QTc=510 ms) with negative T-waves.**

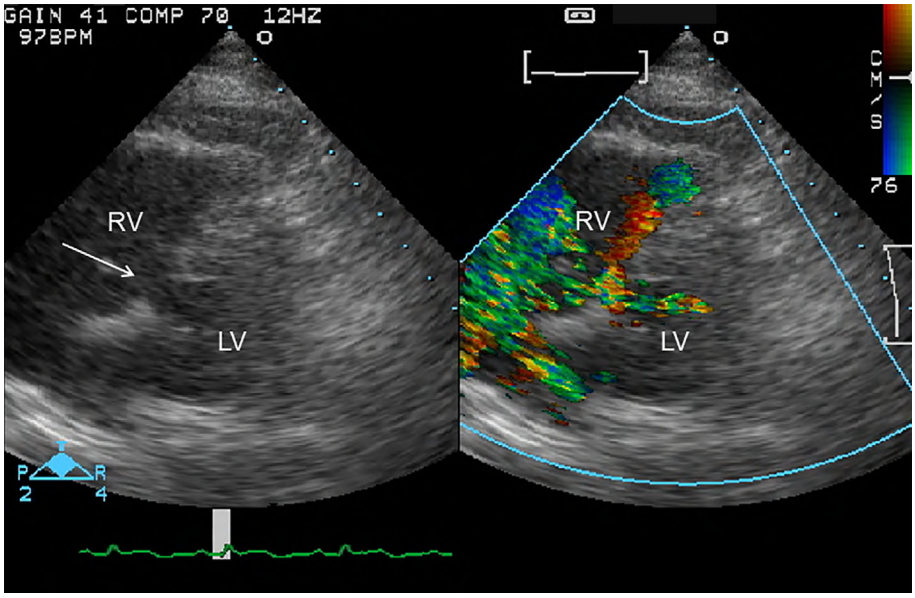

Figure 2. **Transthoracic echocardiography performed on admission in the parasternal short axis view demonstrated a ventricular septal defect (white arrow) and a left-to-right ventricle shunt flow on color-flow Doppler imaging. LV: left ventricle, RV: right ventricle**

(Fig. 3C, D). We thus diagnosed the patient with TCM-VSP. After emergent cardiac catheterization, her blood pressure dropped to 60 mmHg, and the cardiac shock persisted, even after the administration of appropriate fluid resuscitation. Hence, she was transferred to the intensive care unit (ICU) and given inotropes with norepinephrine, after which she became hemodynamically stable, with improvements in her symptoms. Echocardiography subsequently demonstrated a pulmonary to systemic blood flow ratio (Qp/Qs) of 2.82, with no left ventricular outflow tract obstruction. We continued medical management during the early phase of TCM-VSP. However, two hours after admission, the patient exhibited sustained ventricular tachycardia with a cycle length of 270 ms that lasted for approximately 30 seconds and then stopped spontaneously. We therefore initiated treatment with intravenous lidocaine (1,000 mg/day) to prevent ventricular tachycardia. One day after admission, ECG demonstrated a remarkable correction in the QT interval (QTc) prolongation (QTc=510 ms), without hypokalemia (K=5.2 mEq/L). Therapy with inotropes and fluid resuscitation was effective in

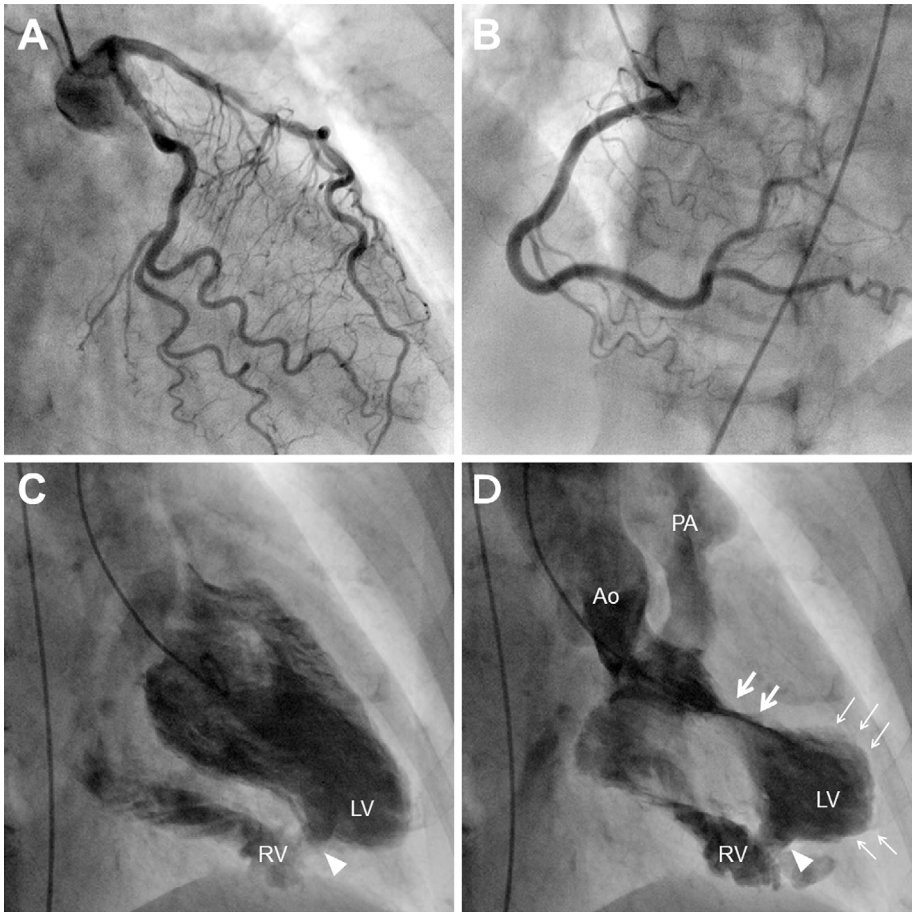

Figure 3. **The right anterior oblique view of left coronary arteriography (A) showed no significant coronary artery stenosis. The left anterior oblique view of right coronary arteriography (B) also showed no significant coronary artery stenosis. The right anterior oblique view of left ventriculography performed during the diastolic phase (C) and systolic phase (D) showed apical ballooning with akinesis (thin white arrows) and basal hyperkinesis (thick white arrows). In addition, the right ventricle and pulmonary artery were connected via a left-to-right ventricular shunt (white arrowhead). PA: pulmonary artery, Ao: aorta. Other abbreviations are the same as in Fig. 2.**

increasing tissue perfusion, after which the dose of the inotropes was gradually decreased in parallel with improvements in the patient's condition. Three days after admission, however, she suddenly lost consciousness due to ventricular fibrillation (VF). Despite applying resuscitation, including repeated electrical defibrillation, she could not be rescued. Postmortem computed tomography demonstrated no specific findings, including cardiac tamponade, massive thoracic or abdominal bleeding or intracranial hemorrhage.

Discussion

TCM is characterized by the presence of acute, transient left ventricular apical wall motion abnormalities associated with emotional or physical stress (2). In a large national inpatient study of 24,701 TCM patients, the majority (21,994, 89.0%) of subjects were women, and most individuals (59.6%) were ≥65 years of age (3). The most common presenting symptom of TCM is chest pain, followed by shortness of breath, and ST segment elevation mimicking acute myocardial infarction (AMI) is commonly detected as an abnormality on ECG (4). During the acute phase, TCM is frequently associated with ST segment depression in the aVR lead and the absence of ST segment elevation in the V1 lead compared with that observed in cases of anterior AMI (5). The opposite side of the aVR lead faces the apical region, which is primarily involved in patients with TCM. During the subacute phase, negative T-waves appear more broadly in subjects with TCM than in those with reperfused anterior AMI (6). In the present case, the detection of ST segment elevation in leads II, III and aVF as well as ST segment depression in the aVR lead and reciprocal changes in leads V1-3 suggests the presence of myocardial damage in the apical and inferior regions in cases of TCM. TCM is diagnosed at a frequency of 0.5-1.2% among all patients and 2.1-4.9% of women presenting with symptoms similar to those of AMI (7-10). Although the underlying pathophysiology remains unknown, several mechanisms have been proposed, including multivessel coronary spasms, coronary microvascular dysfunction, myocarditis, myocardial dysfunc-

Table. Clinical Characteristics in Patients of Takotsubo Cardiomyopathy Complicated with Ventricular Septal Perforation

Reference	14	15	16	Our case
Age (years)	71	73	84	81
Gender	Female	Female	Female	Female
Hypertension	NA	Yes	NA	No
Diabetes mellitus	NA	Yes	NA	No
Blood pressure at admission (mmHg)	NA	110/68	104/82	93/74
Pulmonary congestion	NA	Yes	No	Yes
Cardiogenic shock	Yes	No	Yes	Yes
LVEF (%)	25	49.0	NA	67.2
Qp/Qs	NA	2.96	1.97	2.82
IABP use	Yes	No	No	No
Surgical repair	Yes	Yes	No	No
Outcome	Survival	Survival	Death	Death

LVEF: left ventricle ejection fraction, Qp/Qs: pulmonary to systemic blood flow ratio, IABP: intra-aortic balloon pump, NA: not available

tion mediated via catecholamine-induced damage and a neurogenic stunned myocardium (1, 11).

The prognosis of TCM was previously considered to be favorable. However, according to recently published studies, the in-hospital mortality rate is 4.2-4.5% (3, 12). These reports have demonstrated a male gender and various underlying pre-existing critical illnesses, such as sepsis, cerebrovascular accidents, acute renal failure, respiratory insufficiency, gastrointestinal bleeding and surgical emergencies, to be associated with higher acute mortality in patients with TCM. The in-hospital mortality rate among men is 8.3-8.4%, compared to 2.1-3.6% among women (3, 12), and 10-12% of patients with underlying pre-existing critical illnesses die in the hospital versus only 1% of patients without critical illnesses (3, 12). Therefore, the present case is rare in that the patient was a women with TCM with no pre-existing comorbidities; such patients typically exhibit a survival rate of approximately 99%. Common acute complications associated with the in-hospital mortality of TCM include cardiogenic shock, ventricular arrhythmias and respiratory insufficiency associated with acute congestive heart failure (3). In addition, several cases of ventricular wall rupture including VSP have been reported as rare complications of TCM (13).

In contrast, TCM-VSP has been reported in only three cases according to a search of PubMed in April 2014 (14-16)(Table). All patients were women over 70 years of age, similar to the present patient. Surgical repair was performed to repair the VSP either urgently or after 22 days after the onset of the condition in two patients, both of whom survived (14, 15). However, one patient was reported to have died six hours after admission (16). There are currently no guidelines or recommendations regarding the treatment of TCM-VSP. A previous report of the pathological examinations of a patient with TCM-VSP found that the ventricular septum contained relatively new sites of myocardial infarction in which myocardial nuclei were lost, in addition to hemosiderin deposition (15). These findings suggest the presence of similar underlying mechanisms responsible for VSP in cases of AMI and TCM. According to the American Heart Association (AHA) and American College of Cardiology (ACC) guidelines for the management of ST elevation myocardial infarction (STEMI) (17), the need for emergent surgical repair for VSP in the acute phase should be taken into consideration, even in hemodynamically stable patients. However, the best timing for surgical repair of the VSP in the acute phase remains unclear. A recent large national registry study suggested that a shorter interval between AMI and surgical repair of VSP is associated with a higher operative mortality rate (18). Similarly, it is difficult to determine the best timing for surgery in cases of TCM-VSP.

In the present case, the prolonged QT interval and continuous use of inotropes may have been triggers of the patient's refractory ventricular fibrillation in addition to VSP. ECGs show transient T-wave inversion in most leads with a prolonged QT interval after ST segment elevation in the majority of TCM patients (2, 19), which may reflect the inhomogeneity of left ventricular myocardial edema (20). The degree of QTc prolongation has been reported to be associated with the occurrence of VF and torsades de pointes (TdP) in TCM patients (21). Therefore, physicians should strictly assess the QT interval and remove all triggers associated with a prolonged QT interval, such as drugs, electrolyte imbalances (hypokalemia, hypomagnesemia and hypocalcemia) and bradycardia (22, 23). In addition, the intravenous administration of inotropes, such as epinephrine or dobutamine, may be a trigger for a prolonged QTc interval (24). Furthermore, elevated plasma levels of catecholamine, including epinephrine, norepinephrine and dopamine, have been reported in the acute phase of TCM (25). Based

on the findings of experiments using an immobilization animal model of TCM, abnormal catecholamine dynamics resulting from acute stress are likely associated with characteristic ECG changes and reversible left ventricular apical ballooning (11). Therefore, the intravenous administration of inotropes should be applied carefully to treat cardiac shock or acute pump failure. In conclusion, TCM-VSP is a critical condition that requires optimal treatment and careful monitoring.

The authors state that they have no Conflict of Interest (COI).

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