Tako-Tsubo Syndrome as a Consequence of Transient Ischemic Attack

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An 82-year-old woman presented to the emergency department with chest pain after sustaining a transient ischemic attack 1 week prior to presentation. Electrocardiography revealed ST-segment elevation in leads I, II, aVF, and V3 through V6. Coronary angiography demonstrated nearly normal coronaries but left ventriculography showed apical akinesis and basal hyperkinesis. One month later her follow-up echocardiography showed no wall motion abnormalities. Several reports of tako-tsubo syndrome or transient left ventricular apical ballooning have been described, especially in Japan. We present a case with the typical features of the syndrome after a cerebrovascular accident.

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Key words: Tako-tsubo syndrome • Transient left ventricular apical ballooning • ST-segment elevation myocardial infarction

A novel cardiac syndrome, "tako-tsubo cardiomyopathy," was first described in Japan over 10 years ago. The syndrome mimics ST-segment elevation myocardial infarction (MI) on electrocardiography (ECG) and is characterized by reversible left ventricular apical dysfunction with ballooning. This syndrome is gaining considerable worldwide interest, especially in the United States, and has received increased clinical attention over the last

several years. Theoretical mechanisms have been proposed, including transient sympathetic tone increase, probably at the origin of catecholamine mediated coronary spasm.[1,2]

We present the case of a patient who developed transient left ventricular apical dysfunction 1 week after a transient ischemic attack. In this article we will review the presentation, pathogenesis, and therapy for this syndrome.

Case Report

We admitted an 82-year-old woman for chest pressure typical of myocardial ischemia 1 week after a transient ischemic attack with associated right-sided weakness. She was known to have a poorly controlled hypertension, hyperlipidemia, and colon cancer status post hemicolectomy 20 years ago, but no history of chest pain or coronary artery disease.

On physical examination, pulse rate was 110/min, blood pressure measured 180/94 mm Hg, and the patient was afebrile. Her cardiac exam revealed IV/VI systolic ejection murmur best heard over the apex radiating to the axilla. This murmur was not present 1 week prior. Her other physical findings were unremarkable.

Routine laboratory studies showed a normal complete metabolic panel and blood count. Her cardiac markers revealed a creatine kinase of 155 U/L (CK, normal 55–170 U/L), troponin I of 0.6 ng/mL (normal <0.1), potassium of 3.5 mEq/L (normal 3.6–5.0), aspartate aminotransaminase of 151 U/L (AST, normal 15–46), and alanine aminotransferase of 114 U/L (ALT, normal 7–56).

The initial electrocardiography revealed sinus tachycardia (118 beats/min) with ST-segment elevation in leads, I, II, aVF, and V3 through V6 (Figure 1). Aspirin, heparin, nitroglycerin, and metoprolol therapy were started in the emergency room. Her symptoms improved and the ST-segment changes resolved slowly (Figure 2).

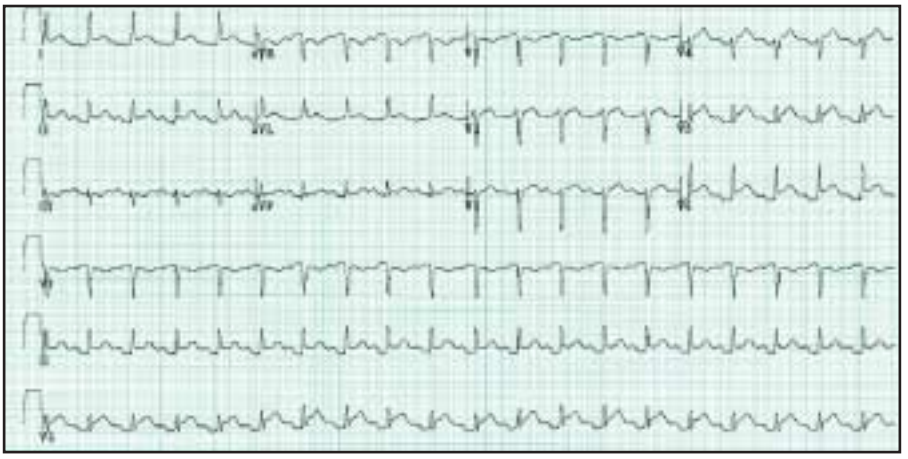
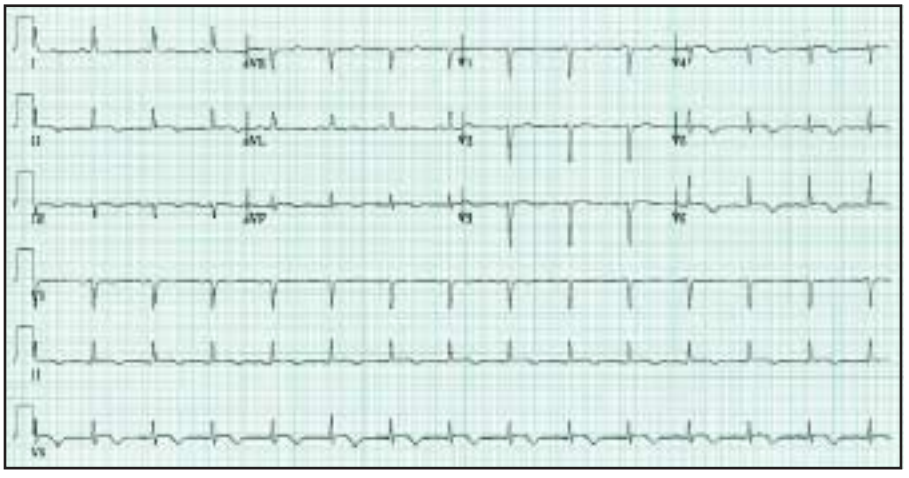


Figure 1. *Electrocardiogram showing sinus tachycardia at 118 beats/min and ST-segment elevation in leads I, II, aVF, and V3 through V6.*

A transthoracic echocardiogram was obtained and showed akinesis of the distal septum, distal inferior wall, apex and distal lateral walls with mild aortic and tricuspid valve regurgitation, and moderate mitral regurgitation. The left ventricular ejection fraction was estimated at 40%. This finding was different from an echocardiogram performed on a previous admission 2 weeks earlier, which had shown normal wall motion with a normal ejection fraction. Her cardiac catheterization the next day revealed minimal atherosclerotic disease (Figures 3, 4), and left ventriculography demonstrated mid and distal segment akinesis with basal hyperkinesis (Figure 5), along with moderate to severe (3+) mitral regurgitation.

The patient remained clinically stable during her hospital stay. Troponin peaked at 10.6 ng/mL. Her discharge medication included aspirin, a

Figure 2. *Electrocardiogram showing return to baseline of the ST segment with T waves inversion in leads I, II, aVF, and V3 through V6.*



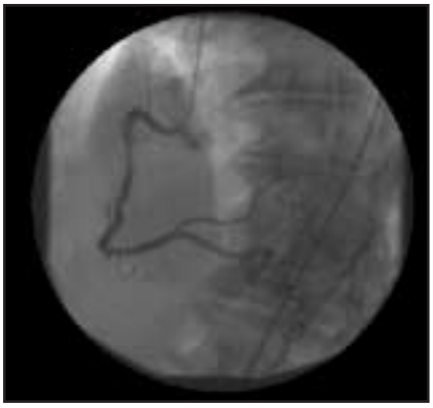


Figure 3. *Angiography showing right coronary artery with minimal disease.*

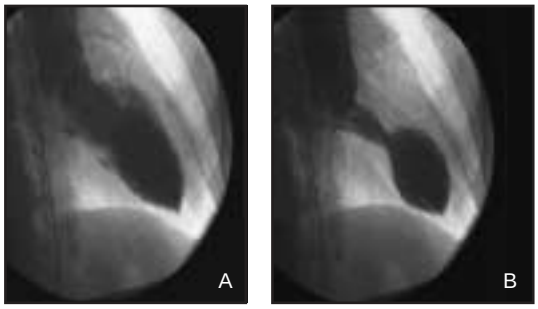


Figure 5. *Left ventriculography showed mid and distal* **(A)** *segments akinesis with basal hyperkinesis* **(B)**.

β-blocker, an angiotensin-converting enzyme (ACE) inhibitor, and a statin. One month later her mitral valve murmur disappeared on physical examination and repeat echocardiography demonstrated normal left ventricular function with no wall motion abnormality. Ejection fraction was estimated at this time at 60% with complete resolution of the mitral regurgitation. Her clinical course therefore suggested tako-tsubo syndrome as the most probable diagnosis.

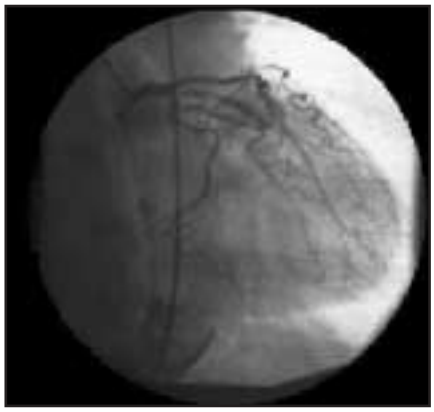
Discussion

Tako-tsubo cardiomyopathy is a syndrome characterized by a transient left ventricular apical wall motion abnormality, with compensatory hyperkinesis of the basal walls, generating ballooning of the apex, in the absence of coronary artery disease.[1,2] It was first described in Japan by Dote and colleagues,[1] who named the syndrome after a Japanese fishing pot with a round bottom and narrow neck used for trapping octopus, called "tako-tsubo." Several case series have been described in Japan and a few in the United States.

The syndrome is mostly observed in women over the age of 60 years. In most cases some physical (including cerebrovascular accidents) or mental stresses precede the onset of symptoms. The syndrome mimics ST-segment elevation acute myocardial infarction, as many patients present with chest pain or dyspnea with ischemic electrocardiographic changes and modestly elevated cardiac biomarker levels.[2]

Tako-tsubo syndrome mimics ST-segment elevation acute myocardial infarction, as many patients present with chest pain or dyspnea with ischemic electrocardiographic changes and modestly elevated cardiac biomarker levels.

Figure 4. *Angiography showing left anterior descending artery and left circumflex artery with minimal disease.*



The time course of ECG changes in this syndrome is similar to acute myocardial infarction, so there is still no way to make the distinction on presentation.[3] The most common ECG change is ST-segment elevation in the precordial leads, especially in leads V3 and V4[2] that returns to normal within 3 days.[3] Less frequently, ST-segment depression, pathologic Q wave formation, T wave inversion that is usually deep,[2,4] and a longer QT interval are found as compared with the ECG findings seen in acute MI patients.[3]

Most of the case series report a minimal and rapid increase in biomarker levels that does not appear to follow the same slow rise and fall in levels seen with acute myocardial infarction. The most frequently affected biomarker is troponin. Two case series that evaluated troponin levels reported a 100% incidence of troponin release.[5,6]

Patients with this syndrome characteristically have abnormal left ventricular ejection function on presentation that is reversible over a period of days to weeks, with normal coronary arteries.

Possible Mechanisms of Pathogenesis

The pathogenesis of this disorder is not well understood as yet. Several mechanisms have been proposed. Ito and associates[7] studied the elevation

of the ST-segment before and after administration of nicorandil, suggesting that coronary microvascular spasm is one of the causative mechanisms. However, this cannot explain persistent ST-segment elevation at the time of coronary angiography in patients who have no identifiable epicardial spasm or stenosis.[8]

There are reports describing coronary angiography, 2-dimensional echocardiography, and 99mTc-tetrofosmin myocardial SPECT pattern with tako-tsubo cardiomyopathy.[7,9] Those reports demonstrated a perfusion defect and wall motion abnormality despite normal coronaries in the acute phase, suggesting a probable microcirculation dysfunction. The defect improves in the course of the recovery. Subsequently, some reports have described microvascular spasm explaining an abnormal coronary flow in the absence of obstructive disease.[8]

Moreover, patients with tako-tsubo syndrome display a pronounced abnormality in apical myocardial fatty acid metabolism that is more severe than apical perfusion abnormalities. Thus, neurogenically mediated stunned myocardium may be one of the mechanisms explaining the pathophysiology of this syndrome.[10]

High plasma levels of norepinephrine can cause ST-elevation and regional wall motion abnormality, as it has been shown in the neurogenic stunned myocardium during acute cerebrovascular accidents[11] and in catecholamine cardiomyopathy during the endocrine crisis of pheochromocytoma.[12] Patients presenting with this syndrome appear to have abnormalities of cardiac sympathetic innervation with evidence of sympathetic hyperactivity at the cardiac apex.[2,13] Discrepancy of the sympathetic innervation between the apical and basal regions may be a cause of the characteristic left ventricular apical akinesis.[14]

It has been noted as well that this phenomenon has several characteristics similar to the left ventricular wall motion abnormality and dynamic ST-segment elevation seen in patients with subarachnoid hemorrhage or with brain death.[11,15,16] Another consideration is whether genetics has any role, as the syndrome was reported in 2 sisters.[17]

A recent study by Wittstein and coworkers demonstrated a supraphysiologic plasma level of catecholamines and stress-related peptide in patients presenting with stress-related reversible myocardial dysfunction.[18] Endomyocardial biopsy from 5 patients revealed evidence of elevated catecholamine. Among these patients, 4 of 5 had mononuclear inflammatory infiltrates, but the fifth patient had extensive contraction-band necrosis, which is a form of myocyte injury secondary to high levels of catecholamine described histologically in patients with pheochromocytoma and subarachnoid hemorrhage.[11,12]

Several researchers demonstrated no evidence of myocarditis on endomyocardial biopsy in the acute phase of tako-tsubo syndrome.[13,19,20]

Prognosis and Management

Although the overall prognosis for tako-tsubo syndrome is usually favorable, several complications have been reported, including cardiogenic shock, left heart failure, pulmonary edema, sinus bradycardia, paroxysmal atrial fibrillation, atrioventricular block, ventricular tachycardia, ventricular fibrillation,[2] left ventricular mural thrombus formation,[21] and left ventricular rupture.[22] An intraventricular pressure gradient and midventricular obstruction can occur as a result of an akinetic apex with hyperdynamic basal segments, which is believed to play a role in

Main Points

- Tako-tsubo cardiomyopathy is a syndrome characterized by a transient left ventricular apical wall motion abnormality, with compensatory hyperkinesis of the basal walls, generating ballooning of the apex, in the absence of coronary artery disease.
- The time course of electrocardiography changes in this syndrome is similar to acute myocardial infarction, so there is currently no way to make the distinction on presentation.
- Most of the case series report a minimal and rapid increase in biomarker levels that does not appear to follow the same slow rise and fall in levels seen with acute myocardial infarction.
- Prognosis is generally favorable, and the condition reversible over a period of days to weeks. After the confirmatory arteriography, supportive medical management includes β-blockers, ACE inhibitors, aspirin, and diuretics, as well as short-term anticoagulants.
- Little is known about the pathophysiology of the syndrome, or the prominent predilection toward the syndrome of women over 60 years of age.

apical balloon formation.[2] This can be accompanied by mitral regurgitation secondary to systolic anterior motion of the mitral valve leaflets and chordal apparatus, as noticed in our case.[8]

After the confirmatory arteriography, supportive medical management should be given with β-blockers, ACE inhibitors, aspirin, and diuretics. Short-term anticoagulation should be considered, particularly in patients with severe left ventricular dysfunction, in order to prevent left ventricular mural thrombus formation.[8,21] Nondihydropyridine calcium-channel blockers, such as diltiazem and verapamil, could be considered in patients with documented epicardial coronary vasospasm. Administration of phenylephrine with resultant afterload increase might alleviate the intraventricular gradient. Similarly, β-blockers could reduce the dynamic intraventricular obstruction by increasing ventricular diastolic filling time and left ventricular end-diastolic volume.[8]

Conclusion

In summary, our patient represents a typical case of tako-tsubo cardiomyopathy after a cerebrovascular accident. Coronary angiography did not suggest an epicardial cause of the transient left ventricular dysfunction. Although several series have been reported recently, little is known about the pathophysiology of the syndrome, and the question yet to be answered is the one of prominent predilection toward the syndrome in women of advanced age. ■

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