VENTRICULAR SEPTAL PERFORATION: A RARE BUT LIFE-THREATENING COMPLICATION ASSOCIATED WITH TAKOTSUBO SYNDROME

Masaki Tsuji¹, Toshiaki Isogai¹, Yuta Okabe¹, Yoshihiro Nishimura¹, Shingo Itagaki², Kazuaki Enatsu³, Motoyuki Hisagi¹, Takahiro Nonaka³, Mikio Ninomiya³, Toshiya Otsuka¹, Hiroyuki Tanaka¹ and Tamotsu Tejima¹

Abstract:
A 71-year-old woman was admitted with dyspnea. An electrocardiogram revealed ST-segment elevation, and echocardiography showed akinesis in the left ventricular apex with hyperkinesis of the base. Coronary angiography revealed no stenosis, and left ventriculography indicated ballooning of the left ventricular apex and apical ventricular septal perforation. We diagnosed the patient with Takotsubo syndrome complicated by ventricular septal perforation, which was surgically repaired. Although ventricular septal perforation is recognized as a life-threatening complication after acute myocardial infarction, it can also occur after Takotsubo syndrome. The early recognition and management of this condition can help prevent morbidity and mortality.

Key words: Takotsubo syndrome, ventricular septal perforation, heart failure, cardiac magnetic resonance, patch closure

(Intern Med Advance Publication) (DOI: 10.2169/internalmedicine.0014-17)

Introduction

Takotsubo syndrome (TTS), previously known as Takotsubo cardiomyopathy, presents as transient left ventricular dysfunction that mimics acute myocardial infarction (AMI) in the absence of any significant coronary artery disease (1). The left ventricular systolic dysfunction generally improves within several weeks and eventually shows complete resolution in most cases of TTS (1-3). Various serious complications have been reported during the acute phase of TTS (1, 4).

Ventricular septal perforation (VSP) is a major complication after AMI. The mortality rate associated with this condition is extremely high, ranging from 45% to 80% (5-8). We herein report a rare case of TTS complicated by VSP that was successfully repaired with patch closure.

Case Report

A 71-year-old woman presented to our emergency department with dyspnea. She had a history of thyroid excision and spinal fusion due to follicular thyroid cancer, which had metastasized to the lungs, cranial bones, and vertebrae. She experienced a recurrence of spinal metastasis and required acetaminophen, loxoprofen, and morphine for pain relief. On admission, her pulse was 118 beats per minute, her blood pressure was 121/86 mmHg, her respiratory rate was 28 breaths per minute, and her oxygen saturation level was 96%. Cardiac auscultation revealed no significant heart murmurs. Her 12-lead electrocardiogram (ECG) findings demonstrated ST-segment elevation in leads I, aVL, and V2-5 without any reciprocal ST-segment depression (Fig. 1). A chest X-ray showed a cardiothoracic ratio of 71%, and pulmonary congestion and an infiltrative shadow were identified. Transthoracic echocardiography demonstrated apical akinesis with basal hyperkinesis. Laboratory analyses revealed the
The time-course of 12-lead electrocardiography. On the day of admission, significant ST-segment elevation was seen in leads I, aVL, and V2-5. On days 2 and 4, persistent ST-segment elevation was seen in leads V2-5. On day 15, a deeply inverted T-wave was seen in leads V1-6, and QT interval prolongation was confirmed. T-wave inversion was seen in leads V1-6 at the 6-month follow-up and in leads V1-5 at 1 year.

The patient was subsequently admitted to the intensive care unit. Non-invasive positive pressure ventilation was applied, and intravenous nitroglycerin, furosemide, heparin, and piperacillin tazobactam were administered. However, her condition failed to improve. ECG showed persistent ST-segment elevation in leads V2-5 on hospital days 2 and 4 (Fig. 1). On hospital day 9, the patient presented worsening dyspnea and the onset of a harsh, loud, holosystolic murmur. Repeated echocardiography detected a ventricular septal defect near the apex, showing a left-to-right shunt (Fig. 2). On day 10, cardiac catheterization was performed. Coronary angiography showed normal arteries. Left ventriculography revealed abnormal wall motion with apical akinesis and basal hyperkinesis accompanied by shunt flow to the right ventricle (Fig. 3). The pulmonary to systemic flow ratio was 2.95. We concluded that VSP had developed and performed intra-aortic balloon pumping for hemodynamic support. On day 15, ECG showed deeply inverted T-waves in leads V1-6 and QT interval prolongation (Fig. 1).

After stabilizing her hemodynamics, we performed elective surgery on hospital day 16. Extracorporeal circulation was established with blood withdrawal via the superior vena cava and inferior vena cava and supply from the ascending aorta. Under cardiac arrest, we incised the apex and found an area of perforation measuring 10×10 mm in the posterior wall near the apex (Fig. 4). The VSP was closed with a Gore-Tex™ patch. A pathological examination of the trabeculae carneae of the left ventricle revealed the loss of myocardial cells and myocardial fibrosis with lymphocyte and macrophage infiltration (Fig. 5).

The postoperative course was uneventful. On day 50, we performed cardiac magnetic resonance (CMR) imaging and
Discussion

TTS is a clinical condition in which patients present reversible left ventricular dysfunction, which was first described in Japan in 1990 (9). The underlying pathophysiology remains unknown (1, 10-13). In most cases, the left ventricular dysfunction in TTS resolves almost completely within several weeks to months after onset (14). However, the prognosis of TTS is not as favorable as previously thought (15-17). The cardiac complications of TTS, which occur in up to 50% of patients, include cardiogenic shock, arrhythmia, intraventricular pressure gradient, right ventricular dysfunction, and left ventricular thrombus (17-20). VSP has also been reported as a rare complication of TTS (20-23).

A systematic review of 12 TTS cases with cardiac rupture by Kumar et al. suggested that the risk factors for cardiac rupture complicating TTS were female sex, Asian ethnicity, late gadolinium enhancement (LGE) imaging of the septal and posterior wall of the apex (Fig. 6). The patient was discharged from our tertiary care center to a rehabilitation facility on day 63. One year after her discharge, follow-up electrocardiography showed T-wave inversion in leads V1-5 (Fig. 1), and follow-up echocardiography showed residual mild hypokinesis of the apex.

Figure 3. The right anterior oblique view of the left ventriculography showed apical ballooning with the filling of the right ventricle through the ventricular septal perforation. (A) Systolic phase. (B) Diastolic phase. (C) A schematic illustration. LV: left ventricle, RV: right ventricle

Figure 4. An intraoperative image showing ventricular septal perforation (white arrow). LV: left ventricle, RV: right ventricle

Figure 5. Pathology findings (Hematoxylin and Eosin staining) showing the loss of myocardial cells and myocardial fibrosis with infiltration by lymphocytes and macrophages (yellow arrow)

Figure 6. Cardiac magnetic resonance imaging with gadolinium enhancement showed delayed enhancement in the posterior wall of the apex in the axial view (yellow arrow).
older age, higher blood pressure, higher left ventricular ejection fraction, and persistent ST-segment elevation (24). Although the definition of persistent ST-segment elevation was unclear in the systematic review, a previous study reported that the ST-segment elevation generally returned to normal within 3 days in patients with TTS (25). Our patient was an Asian woman, and ECG showed ST-segment elevation until day 8. Thus, our patient was considered to have several risk factors for cardiac rupture as a complication of TTS.

Regarding VSP complicating AMI, a previous study reported that the short-term mortality was lower in patients who underwent surgical repair at $\geq$8 days after presentation in comparison to those who underwent repair within 7 days after presentation (18.4% vs. 54.1%, respectively) (26). The improved outcome of delayed surgery was associated with the stabilization of the infarcted cardiac tissues (27). However, the optimal timing for repair surgery in cases of VSP complicating TTS remains unclear. We consider emergency surgical repair for VSP to be mandatory in hemodynamically unstable patients. On the other hand, in hemodynamically stable patients with TTS, elective surgery for VSP may be preferable because the left ventricular dysfunction often improves daily in TTS and the cardiac tissues at the site of VSP can be expected to stabilize in a manner similar to AMI. We were able to stabilize our patient’s hemodynamics by performing intra-aortic balloon pumping and thus opted to delay surgery for VSP.

CMR imaging allows for the assessment of regional wall motion abnormalities, ventricular thrombosis, and pericardial effusion while LGE can reveal small, focal myocardial abnormalities and can be useful in diagnosing various cardiac diseases (28). Although LGE was not initially thought to be a feature of TTS, recent studies have reported LGE during the acute phase in 10-40% of TTS patients (2, 29). The intensity of LGE in TTS is frequently lower than that in AMI (30). A previous report revealed that both ECG and wall motion abnormalities persisted for longer in patients who demonstrated low-intensity LGE on their initial CMR study (3). We hypothesize that the LGE observed in our case may have been associated with the residual apical hypokinesis and T-wave inversion that were observed at the one year follow-up examination.

Experimental findings have revealed the histological changes in TTS. Contraction-band necrosis is commonly found in TTS, especially in the acute phase (31, 32). Five studies in which myocardial biopsies were performed in a subset of patients reported interstitial fibrosis and mild cell infiltration as well as focal myocardial depletion and contraction-band necrosis (10-12, 33, 34). The pathological findings in our case differed from the dense polymorphonuclear infiltrates and necrosis that are typically observed in AMI.

We cannot totally exclude the possibility of AMI with spontaneous recanalization. However, the coronary angiography revealed no significant stenosis, the left ventricular wall motion abnormalities extended beyond the distribution of any single coronary artery, and neither creatine kinase nor creatine kinase myocardial band elevation were observed. We therefore diagnosed the patient with TTS complicated by VSP.

**Conclusion**

VSP is a rare but life-threatening complication that may occur in the acute phase of TTS. Patients with this condition should be carefully monitored for mechanical complications. Early recognition and management can help prevent morbidity and mortality.

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

**References**

1. Tsuchitashiki K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol 38: 11-18, 2001.
2. Kawai S, Suzuki H, Yamaguchi H, Tanaka K, Sawada H, Aizawa T, et al. Ampulla cardiomyopathy (“Tako-tsubo” cardiomyopathy)—reversible left ventricular dysfunction: with ST-segment elevation. Jpn Circ J 64: 156-159, 2000.
3. Kurisu S, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J 143: 448-455, 2002.
4. Sakai K, Ochiai H, Katayama N, Nakamura K, Arakata K, Kido T, et al. A serious clinical course of a very elderly patient with takotsubo cardiomyopathy. Heart Vessels 20: 77-81, 2005.
5. Crenshaw BS, Granger CB, Bimbaum Y, Pieper KS, Morris DC, Kleiman NS, et al. Risk factors, angiographic patterns, and outcomes in patients with ventricular septal defect complicating acute myocardial infarction. Circulation 101: 27-32, 2000.
6. French JK, Hellkamp AS, Armstrong PW, Cohen E, Kleiman NS, O’Connor CM, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol 105: 59-63, 2010.
7. Lopez-Sendon J, Gurfinkel EP, Lopez de Sa E, Agnelli G, Gore JM, Steg PG, et al. Factors related to heart rupture in acute coronary syndrome in the Global Registry of Acute Coronary Events. Eur Heart J 31: 1449-1456, 2010.
8. Moreyra AE, Huang MS, Wilson AC, Deng Y, Cosgrove NM, Kostis JB. Trends in incidence and mortality rates of ventricular septal rupture during acute myocardial infarction. Am J Cardiol 106: 1095-1100, 2010.
9. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessels spasms. In: Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Kodama K, Haze K, Hon M, Eds. Kagakuyouronsha, Tokyo, Japan, 1990: 56-64.
10. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 352: 539-548, 2005.
11. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo Cardiomyopathy: a new form of acute, reversible heart failure. Circulation 118: 2754-2762, 2008.
12. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 155: 408-417, 2008.
13. Sadamatsu K, Tashiro H, Maehira N, Yamamoto K. Coronary microvascular abnormality in the reversible systolic dysfunction observed after noncardiac disease. Jpn Circ J 64: 789-792, 2000.

14. Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 111: 472-479, 2005.

15. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 373: 929-938, 2015.

16. Isogai T, Yasunaga H, Matsu H, Tanaka H, Ueda T, Horiguchi H, et al. Out-of-hospital versus in-hospital Takotsubo cardiomyopathy: analysis of 3719 patients in the Diagnosis Procedure Combination database in Japan. Int J Cardiol 176: 413-417, 2014.

17. Redfors B, Vedad R, Angeras O, Ramunddal T, Petursson P, Haraldsson I, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction-A report from the SWEDHEART registry. Int J Cardiol 185: 282-289, 2015.

18. Citro R, Rigo F, D’Andrea A, Ciampi Q, Parodi G, Provenza G, et al. Echocardiographic correlates of acute heart failure, cardiogenic shock, and in-hospital mortality in tako-tsubo cardiomyopathy. JACC Cardiovasc Imaging 7: 119-129, 2014.

19. Schneider B, Athanasiadis A, Schwab J, Pistorner W, Gottwald U, Schoeller R, et al. Complications in the clinical course of takotsubo cardiomyopathy. Int J Cardiol 176: 199-205, 2014.

20. Nakamura S, et al. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. Circ J 68: 77-81, 2004.

21. Arnaoutakis GJ, Zhao Y, George TJ, Scinti CM, McCarthy PM, Conte JV. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society for Thoracic Surgeons National Database. Ann Thorac Surg 94: 436-444, 2012.

22. Jones BM, Kapadia SR, Smedira NG, Robich M, Tuzcu EM, Menon V, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. Eur Heart J 35: 2060-2068, 2014.

23. Kim DH, Choi SI, Chang HJ, Choi DJ, Lim C, Park JH. Delayed hyperenhancement by contrast-enhanced magnetic resonance imaging: Clinical application for various cardiac diseases. J Comput Assist Tomogr 30: 226-232, 2006.

24. Han Y, Kondo M, Matsuoka R, Araki M, Dohya K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. J Am Coll Cardiol 38: 11-18, 2003.

25. Naruse Y, Sato A, Kasahara K, Makino K, Sano M, Takeuchi Y, et al. The clinical impact of late gadolinium enhancement in Takotsubo cardiomyopathy: serial analysis of cardiovascular magnetic resonance images. J Cardiovasc Magn Reson 13: 67, 2011.

26. Nef HM, Möllmann H, Akashi YJ, Hamm CW. Mechanisms of stress (Takotsubo) cardiomyopathy. Nat Rev Cardiol 7: 187-193, 2010.

27. Rolf A, Nef HM, Möllmann H, Troisdal C, Voss S, Canradi G, et al. Immunohistological basis of the late gadolinium enhancement phenomenon in tako-tsubo cardiomyopathy. Eur Heart J 30: 1635-1642, 2009.

28. Athanasiadis A, Vogelsberg H, Hauer B, Meinhardt G, Hill S, Sechtem U. Transient left ventricular dysfunction with apical ballooning (tako-tsubo cardiomyopathy) in Germany. Clin Res Cardiol 95: 321-328, 2006.

29. Desmet WJ, Adrijaeenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. Heart 89: 1027-1031, 2003.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).