CLINICAL VIGNETTE

Takotsubo Cardiomyopathy in the Setting of Left Ventricular Outflow Tract Obstruction

Rahul Vasavada, MD

Case Presentation

A 99-year-old female with past medical history of end stage renal disease on hemodialysis, left internal carotid aneurysm, asymptomatic left ventricular outflow tract (LVOT) obstruction, and hypertension presented to the emergency department (ED) with new-onset chest pain associated with dizziness and nausea. She reported chest pain that radiated across her lower chest, sharp in nature, which began while she was walking in her home earlier that day. It lasted for a few hours and spontaneously resolved after coming to the ED. She denied associated dyspnea, but noted mild dizziness (without syncope) as well as nausea. She had never experienced this type of chest pain before.

Upon presentation to the ED, she was afebrile and normotensive but was bradycardic with heart rate of 41. Physical examination was significant for bradycardia with irregular rhythm, 2/6 systolic murmur at the left lower sternal border, with noted bibasilar crackles and normal work of breathing. The patient did not have significant extremity edema and neurologic exam was intact.

Electrocardiogram showed new-onset Mobitz type II second degree AV block, old left bundle branch block as well as old lateral ST depressions. Initial labs were notable for mildly increased troponin to 0.11 ng/mL, brain natriuretic peptide elevated to 1220 pg/mL, white blood cell count of 11.8 x 10^3/µL, hemoglobin with baseline anemia of 10.7 g/dL, and no acute electrolyte derangement other than chronically elevated creatinine of 4.8 mg/dL. Chest x-ray showed mild cardiomegaly with evidence of pulmonary vascular congestion and diffuse interstitial opacity, progressed from prior examination. Admission transthoracic echocardiogram showed left ventricular ejection fraction (EF) of 64%, with mild systolic anterior motion of mitral valve, moderate mitral regurgitation, and moderate diastolic dysfunction without any regional wall motion abnormalities.

She was initially given aspirin, statin, morphine and a heparin drip due to concern for acute coronary syndrome with pacer pads in place. Approximately eight hours following admission, the patient developed acute hypotension with EKG showing new-onset third degree heart block. She was transferred to the ICU and was given a peripheral dopamine vasopressor drip. She underwent transvenous pacemaker placement upon transfer to ICU, however troponin continued to increase to 17. She was taken urgently to the cardiac catheterization lab for left heart catheterization and possible intervention; however, catheterization revealed no acute blockages. Repeat echocardiogram following left heart catheterization showed apical ballooning consistent with stress-induced or Takotsubo cardiomyopathy with LVOT obstruction. This subsequently resulted in flash pulmonary edema, respiratory distress, and hypotension. She required short-term intubation and a norepinephrine drip. Repeat echocardiogram showed EF of 45% with evidence of worsening systolic anterior motion and LVOT obstruction. The patient's vasopressor was changed from norepinephrine to phenylephrine with gradual improvement of systolic anterior motion and apical dyskinesis. The patient's hospitalization was further complicated by upper GI bleeding, which resolved without endoscopic intervention, as well as healthcare associated pneumonia. By hospital day sixteen she was stable for discharge with improvement in her left ventricular systolic function. She has been free of recurrence of Takotsubo cardiomyopathy since discharge.

Discussion

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, apical ballooning syndrome, or broken heart syndrome, is a condition defined by temporary left ventricular (LV) systolic dysfunction in patients without any underlying obstructive coronary artery disease or occlusion. The condition was first described in medical literature in Japan in 1990, and the name *takotsubo* is the Japanese term for octopus trap, whose shape is similar to the characteristic LV systolic apical ballooning that is often seen.[1,2]

Takotsubo cardiomyopathy presentation is similar to acute coronary syndrome, which must first be ruled out. Patients often present with typical chest pain, shortness of breath, or syncope, and commonly have electrocardiogram abnormalities such as ST elevation as well as troponin elevation. The differential diagnosis also includes myocarditis and coronary vasospasm; however these typically present with wall motion abnormalities that differ from Takotsubo.[1-3]

The most common type of LV dyskinesis observed in Takotsubo cardiomyopathy is the classic apical ballooning variant, from which the condition derives its name. Seen in over 80% of recorded cases as well as in this case, the apical ballooning

variant involves depression of the LV mid and apical segments with hyperkinesis of the basal walls.[3] Patients can also present with atypical variants including: a mid-ventricular type with mid-ventricular hypokinesis with sparing of the apex; basal type with basal hypokinesis with sparing of the mid-ventricle and apex; focal type with hypokinesis of an isolated LV segment; or very rarely global hypokinesis. Generally the LV dyskinesis observed in Takotsubo affects a territory supplied by more than one coronary artery.

While not fully understood, the pathophysiology of Takotsubo cardiomyopathy is believed to be related to catecholamine excess as well as possible microvascular dysfunction. Studies measuring epinephrine and norepinephrine levels in humans and mouse models have found elevated catecholamine levels in those with Takotsubo cardiomyopathy.[4,5] Apical ballooning has been induced with iatrogenic administration of catecholamines and studies of myocardial tissue have demonstrated catecholamine excess in patients with Takotsubo cardiomyopathy.[4,6] These findings provide fairly compelling evidence of catecholamine surge as a cause of Takotsubo cardiomyopathy, with potential mechanisms including catecholamine-induced diffuse microvascular spasm and myocardial stunning and/or toxicity.[6,7] Other studies have found that β2 adrenoreceptors are most densely concentrated specifically in the apical myocardium. Via G-protein signaling, these receptors switch from being positively inotropic to negatively inotropic in the setting of increased epinephrine levels. This could explain the apical ballooning that is often seen in this condition.[6,7]

Classically Takotsubo cardiomyopathy is often brought on by extreme physical stressors including illness, organ failure or emotional stressors such as intense grief, shock, or anger. Hence surrogate terms have been used, including stress cardiomyopathy or broken heart syndrome. Given the likely pathophysiology, it would make sense that a potential catecholamine surge in the setting of a physical or emotional stressor could trigger Takotsubo cardiomyopathy. The International Takotsubo Registry reports only about 30% of patients did not report any preceding physical or emotional stressor prior to onset.[3,6] Our patient likely developed Takotsubo cardiomyopathy in the setting of a physical stressor of new-onset third degree heart block associated with severe hypotension, as well as iatrogenic catecholamine administration with intravenous vasopressor drugs resulting in worsening LVOT obstruction.

According to the International Registry, the condition overwhelmingly affects women of advanced age. Ninety percent of registry cases were women over the age of 50.[3] Of patients presenting with suspected biomarker-positive acute coronary syndrome, Takotsubo cardiomyopathy accounts for only one to two percent.[2] Fortunately the vast majority of patients with Takotsubo recover LV systolic function, as in our patient. Recurrence rates are low, occurring in less than ten percent of patients.[8]

This case also highlights the importance of understanding differences in treatment strategies in patients with hypertrophic cardiomyopathy and known LVOT obstruction, defined as peak LVOT gradient of ≥ 30 mmHg. Systolic anterior motion (SAM) of the mitral valve with the ventricular septum can cause obstruction of blood flow and a dynamic pressure gradient between the LV and the aorta, resulting in LVOT obstruction.[9] The degree of LVOT obstruction is dependent on preload, afterload, and inotropy. Therapies which increase preload, such as passive leg raise or intravenous fluids, increase afterload such as handgrip maneuver or alpha-1 agonist treatment, or decrease LV inotropy, such as beta blockers or nondihydropyridine calcium channel blockers can help to improve the degree of LVOT obstruction.

In this patient, vasopressor support initially with dopamine and later with norepinephrine increased contractility likely worsening SAM of the mitral valve and worsened LVOT obstruction. Worsening obstruction, in addition to the vasopressors themselves and new-onset third degree heart block may have precipitated Takotsubo cardiomyopathy. Change in the vasopressor treatment to phenylephrine improved her outflow obstruction.

Conclusion

Takotsubo cardiomyopathy is a notable yet uncommon, atypical finding in patients. While the pathophysiology of Takotsubo cardiomyopathy is not fully understood, it seems likely that this condition is related to catecholamine excess, and is often seen in patients who experience characteristic recent physical or emotional stressors. This condition is a diagnosis of exclusion, as life-threatening conditions such as acute coronary syndrome as well as coronary vasospasm or myocarditis must be considered. This case also highlights the importance of reducing inotropy, increasing preload, and/or increasing afterload when treating patients with LVOT obstruction.

REFERENCES

1. **Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS**. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med*. 2004 Dec 7;141(11):858-65. Review. PubMed PMID: 15583228.
2. **Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E**. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J*. 2006 Jul;27(13):1523-9. Epub 2006 May 23. Review. PubMed PMID: 16720686.
3. **Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M,**

Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med*. 2015 Sep 3;373(10):929-38. doi: 10.1056/NEJMoa1406761. PubMed PMID: 26332547.

4. **Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC**. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005 Feb 10;352(6):539-48. PubMed PMID: 15703419.
5. **Ueyama T**. Emotional stress-induced Tako-tsubo cardiomyopathy: animal model and molecular mechanism. *Ann N Y Acad Sci*. 2004 Jun;1018:437-44. Review. PubMed PMID: 15240400.
6. **Akashi YJ, Nef HM, Lyon AR**. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol*. 2015 Jul;12(7):387-97. doi: 10.1038/nrcardio.2015.39. Epub 2015 Apr 7. Review. PubMed PMID: 25855605.
7. **Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE**. Stress (Takotsubo) cardiomyopathy--a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med*. 2008 Jan;5(1):22-9. Review. PubMed PMID: 18094670.
8. **Kurowski V, Kaiser A, von Hof K, Killermann DP, Mayer B, Hartmann F, Schunkert H, Radke PW**. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest*. 2007 Sep;132(3):809-16. Epub 2007 Jun 15. PubMed PMID: 17573507.
9. **Liew AC, Vassiliou VS, Cooper R, Raphael CE**. Hypertrophic Cardiomyopathy-Past, Present and Future. *J Clin Med*. 2017 Dec 12;6(12). pii: E118. doi: 10.3390/jcm6120118. Review. PubMed PMID: 29231893; PubMed Central PMCID: PMC5742807.