CLINICAL VIGNETTE

An Unusual Case of Takotsubo Cardiomyopathy

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Case Report

A 66-year-old male with presented to the Emergency Department after transiently losing consciousness that morning. He reported becoming lightheaded and then losing consciousness immediately upon standing after having a bowel movement. He woke up on the bathroom floor but did not remember how long he was unconscious for. He denied any chest pain, palpitations, or prior syncopal episodes. His past medical history includes recurrent falls, alcohol abuse, and hypertension. He lived alone with occasional visits from family members. He reported drinking two glasses of cognac a day, but family later stated he drank more than reported.

On arrival to the Emergency Department (ED), vital signs were significant for a blood pressure of 98/68 mm Hg and a heart rate of 155 beats per minute. Physical exam revealed a disheveled male with waxing and waning mental status. He had mild tenderness upon palpation of the bilateral thighs. The remainder of his physical exam was unremarkable. Labs were notable for serum creatinine of 1.44 mg/dL (baseline was 0.7 mg/dL), high sensitivity troponin of 59 ng/L which peaked at 100 ng/L six hours after presentation, AST of 209 U/L, ALT of 50 U/L, and serum lactate of 3.7 mmol/L. His CBC and TSH were unremarkable. Electrocardiogram (EKG) demonstrated a tachycardia of 150 beats/minute, appeared regular in rhythm, without significant ST segment or T wave changes. It was difficult to discern P waves and thus the physicians were unable to distinguish between sinus tachycardia and supraventricular tachycardia.

The patient was admitted to Cardiology for evaluation of possible cardiogenic syncope given his initial tachycardia and EKG findings. His tachycardia improved to a heart rate of 100 beats per minute after administration of 2 liters of isotonic fluids. Based on this clinical response, the Cardiology team felt his initial EKG consistent with sinus tachycardia. Transthoracic echocardiogram revealed a left ventricular ejection fraction (LVEF) of 55-60% with no other significant abnormalities (see Figure 1A). He was transferred to a general medicine team on hospital day 2.

On the day of transfer to general medicine, the patient developed a fever to 101.0ºF. While his mentation had significantly improved by this time, he complained of worsening bilateral anterior thigh pain. Rhabdomyolysis was considered given his fever, proximal muscle pain, acute kidney injury, predominant AST elevation compared to ALT, unknown period of down time, and corroboration with patient's family that he drank significantly more than was initially reported. Creatinine kinase level returned elevated at 13,900 U/L. He was given continuous isotonic fluids and his creatinine kinase level trended down to <5,000 U/L within two days. He also defervesced and his acute kidney injury and bilateral anterior thigh pain both resolved.

On hospital day 4, the patient's tachycardia worsened to 120 beats per minute in the absence of any new symptoms. EKG revealed sinus tachycardia with new deep T wave inversions in leads V1-V6. Bedside point-of-care ultrasound exam demonstrated significantly decreased left ventricular systolic function. Repeat high-sensitivity troponin level was elevated at 1,848 ng/L. Cardiology recommended transfer to the CCU for possible urgent cardiac catheterization. Stat transthoracic echocardiogram demonstrated an LVEF of 25-30%, and significant apical ballooning consistent with Takotsubo cardiomyopathy (see Figure 1B).

Plans for an urgent cardiac catheterization were canceled after blood cultures were positive for vancomycin-resistant *Enterococcus faecium* (*E. faecium*) in one out of four bottles. Infectious Diseases recommended treating the patient with intravenous linezolid. Repeat blood cultures grew *E. faecium*, in four out of four bottles. Transesophageal echocardiogram revealed a nonmobile echodensity on the mitral valve. It was unclear whether this finding represented a true bacterial vegetation. However, due to the patient's prior fevers and high-grade bacteremia, he was treated with a four-week course of intravenous daptomycin for presumed endovascular infection. Repeat blood cultures demonstrated clearance of the *E. faecium* and the patient remained fever-free for the remainder of his hospitalization. Myocardial perfusion imaging with a Regadenoson stress test was obtained due to his high-grade bacteremia, and did not show signs of reversible ischemia that could explain his newly reduced LVEF. A repeat transthoracic echocardiogram showed significant improvement in apical ballooning and LVEF to 45-50% (see Figure 1C). Given the absence of any ischemic defect and the rapid improvement in echocardiogram findings, the diagnosis of Takotsubo cardiomyopathy was established.

Discussion

Takotsubo cardiomyopathy is often referred to as "stress cardiomyopathy" or "broken heart syndrome". It is characterized by transient systolic dysfunction of the left ventricle in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture.[1] The typical form affects up to 80% of patients, with mid and apical segments of the left ventricle become hypokinetic, with hyperkinesis of the basal walls causing a systolic apical ballooning of the left ventricle.[2] In the remaining 20% of patients, midventricular ballooning occurs. In either form, the regional wall motion abnormality generally extends beyond a territory that can be explained by a single coronary artery branch lesion. This syndrome was first described in Japan in 1990 by Dr. Hikaru Sato, who noted that the apical ballooning resembled a "takotsubo" which translates to "octopus trap" in Japanese, in reference to the shape of traditional Japanese octopus pot traps.[3] This condition gained further recognition in Japan following the significant increase of confirmed diagnoses immediately following large earthquakes in 1995 (Hanshin-Awaji) and 2004 (Niigata Chuetsu).[4]

The pathogenesis of Takotsubo cardiomyopathy is unclear, though emotional or physical stress is known to be an inciting factor in the majority of cases. Among the 1,759 patients in the International Takotsubo Registry, 36% of cases are associated with a physical stressor (e.g. acute medical illness), 28% with an emotional stressor, 8% with both types.[5] Its association with emotional stressors such as death of a loved one and relationship conflicts led to the coinage "broken heart syndrome". While the pathogenesis of this condition is not well understood, its association with physical and emotional stressors suggest that this syndrome may be caused by catecholamine excess, leading to microvascular spasm and resulting in myocardial stunning.[6] This condition affects predominantly older women, with the 90% occurring in post-menopausal women with a mean age of 66 years.[5] The explanation for the marked gender and age predilection in this condition remains unclear.

The clinical manifestations of Takotsubo cardiomyopathy are similar to those of acute coronary syndrome, with the most common symptoms being chest pain (76%) and dyspnea (47%).[5] Our patient's presenting complaint of syncope is relatively less common, with a reported incidence of 8%. The data from the International Takotsubo Registry demonstrated a substantial risk of severe hemodynamic compromise with approximately 10% of patients developing signs and symptoms of cardiogenic shock. Electrocardiographic abnormalities are common, with ST segment elevation in 44% of patients and ST depression in 8% of patients. Our patient's EKG demonstrated new T-wave inversions which are less common findings. Laboratory abnormalities in Takotsubo cardiomyopathy are nonspecific, but the majority of patients in the International Takotsubo Registry had elevated serum troponin levels with the median initial troponin 7.7 times the upper limit of normal, while creatine kinase levels are generally normal to mildly elevated. Elevated brain natriuretic peptide levels are frequently present. The mean left ventricular ejection fraction on echocardiography at time of presentation is 29%.[7] There are many different diagnostic criteria for Takotsubo cardiomyopathy. In the United States, the Mayo Clinic diagnostic criteria[8] are most widely used, with all four criteria required to establish the diagnosis: 1) transient left ventricular systolic dysfunction, 2) absence of obstructive coronary disease or angiographic evidence of plaque rupture, 3) new electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion), 4) absence of pheochromocytoma or myocarditis. Echocardiography is used to identify left ventricular systolic dysfunction, and coronary angiography will typically demonstrate normal coronary vessels or mild to moderate coronary atherosclerosis.[9]

Takotsubo cardiomyopathy is usually a transient disorder, with a significant majority of patients recovering left ventricular systolic function within one to four weeks.[7] Conservative treatment and resolution of the initial stressor will usually result in resolution. Management of heart failure symptoms generally follow standard guidelines for inpatient management of acute heart failure exacerbation, including supplemental oxygen as needed, diuretics to treat volume overload, and vasodilator therapy if needed to decrease left ventricular afterload. A beta blocker and an angiotensin converting enzyme (ACE) inhibitor (or angiotensin II receptor blocker) may be initiated once the patient is hemodynamically stable, in accordance with standard treatment for heart failure with reduced ejection fraction. The optimal duration of these therapies are unknown given the transient nature of this condition. Observational studies have shown mixed data regarding survival benefit at one year with continuation of beta blocker and ACE inhibitor/angiotensin II receptor blocker. However, expert consensus reports that at a minimum, patients should continue treatment until recovery of systolic function. [5,10] Overall, the prognosis of Takotsubo cardiomyopathy is excellent with up to 95% of patients making a full recovery.[11] Among the 10% of patients that develop cardiogenic shock, in-hospital mortality is lower compared with shock due to acute myocardial infarction (15% versus 37%), while total in-hospital mortality is approximately 5%.[11,12] Interestingly, patients who develop this condition due to physical stressors have higher mortality compared to patients with emotional stressors.[5] Patients with Takotsubo cardiomyopathy, have recurrence rates of about 5%. 6 years from initial diagnosis.[13]

In our patient, male gender would be considered unusual based on the female-predominant distribution of this disorder, while his age of 66 years is the exact mean age for this disorder. Additionally, he did not display the commonly expected symptoms of chest pain and/or dyspnea at the time of presentation, making the diagnosis particularly challenging to establish. We hypothesize that the trigger for his case of Takotsubo cardiomyopathy was likely a physical stressor either secondary to rhabdomyolysis, bacteremia, or both. While our patient did not undergo cardiac catheterization to definitively exclude obstructive coronary artery disease, he still met three

of the four criteria in the Revised Mayo Clinic diagnostic criteria for establishing a diagnosis of Takotsubo cardiomyopathy. Diagnostic testing for pheochromocytoma and myocarditis was not pursued in our patient's case to secure the fourth criterion. Yet, his negative myocardial perfusion test and rapid improvement of apical ballooning and left ventricular ejection fraction on serial echocardiograms were highly suggestive of Takotsubo cardiomyopathy.

Conclusion

Takotsubo cardiomyopathy is a rare clinical entity that often mimics acute coronary syndrome. While patients with Takotsubo cardiomyopathy often achieve a complete recovery, there is still a significant risk of in-hospital morbidity and mortality associated with this condition. Given its preponderance for affecting post-menopausal females, clinicians should have a low threshold to obtain initial diagnostic workup especially in those who have experienced a recent physical or emotional stressor.

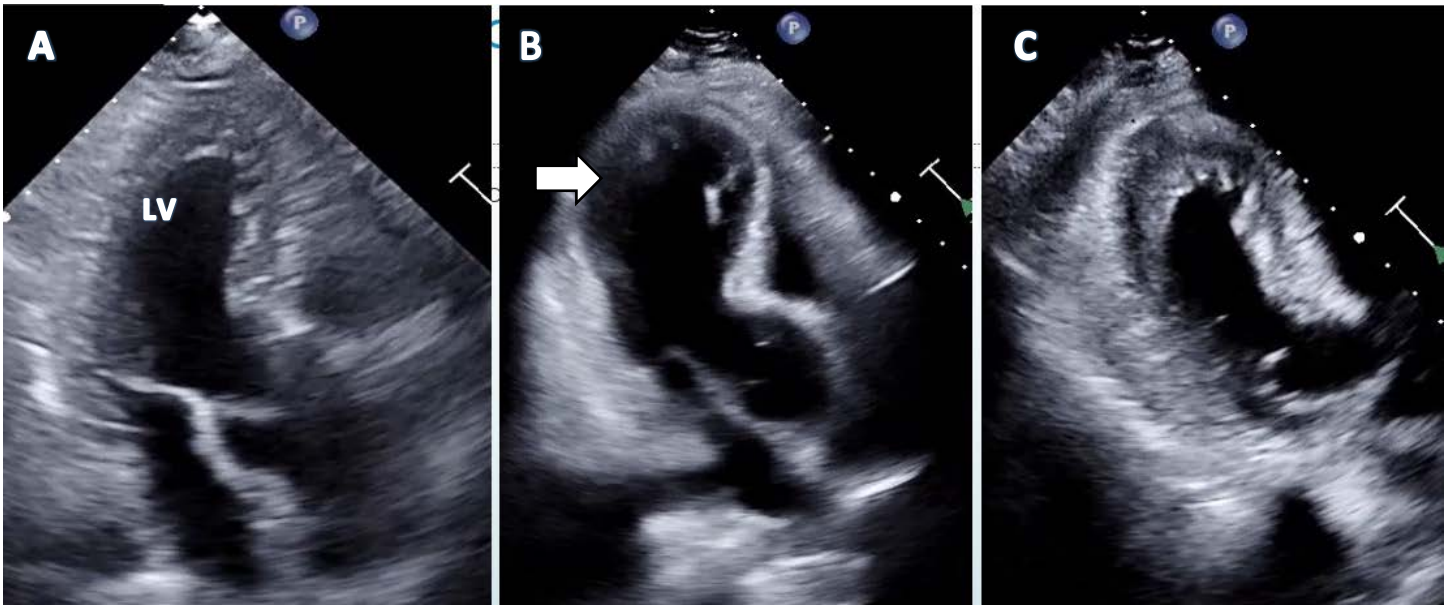

Figure 1. Comparison of serial transthoracic echocardiogram apical long-axis views for the patient in this case report, where Figure 1A is taken on day 1 of hospitalization, prior to the patient developing Takotsubo cardiomyopathy. The left ventricle is denoted by "LV". Figure 1B is taken on day 4 of hospitalization which is when this patient is presumed to have developed Takotsubo cardiomyopathy; note the marked apical ballooning of the left ventricular cavity (white arrow). Figure 1C is taken on day 8 of hospitalization; note the significant improvement in apical ballooning of the left ventricular cavity compared to Figure 1B. Each figure's image is taken at a similar phase during the cardiac cycle at the beginning of systole.

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