Takotsubo Cardiomyopathy and LV Outflow Tract Obstruction after Initiation of Novel Oral Chemotherapy

KARUPPIAH ARUNACHALAM, MD; SUBRAMANIAN GNANAGURUPARAN, MD; JOHN PAULOWSKI, MD, FACC

ABSTRACT

BACKGROUND: Japanese authors first reported a reversible cardiomyopathy due to emotional stress known as Takotsubo cardiomyopathy or stress-induced cardiomyopathy or apical ballooning syndrome. In this case report, we describe Takotsubo cardiomyopathy associated with use of a chemotherapy drug, Regorafenib (Stivarga).

CASE HISTORY: A 72-year-old female with history of metastatic colon cancer, with liver metastasis status post-resection and a recent diagnosis of primary non-small cell lung cancer on chemotherapy presented with shortness of breath exacerbated on exertion for 3 days. Patient was treated with Regorafenib for 10 days. EKG done showed 2mm ST elevation in V2-V4 leads and troponin was elevated to 6.8 ng/ml. The patient was taken for emergency cardiac catheterization which revealed normal coronaries but left ventriculogram showed low ejection fraction of 30% with apical akinesis and basal hyperkinesis with typical Takotsubo pattern.

DISCUSSION: Regorafenib is a multi-kinase inhibitor, approved by the FDA for metastatic colon carcinoma, hepatic carcinoma and advanced gastrointestinal stromal tumors. The stress of cancer diagnosis and chemotherapeutic agents can cause significant cardiac mortality including Takotsubo cardiomyopathy. Cardiogenic shock and thromboembolic complications are an important cause of mortality.

CONCLUSION: This is a rare presentation of Takotsubo cardiomyopathy associated with use of Regorafenib along with dynamic LVOT obstruction and systolic anterior motion of the mitral valve.

KEYWORDS:
Takotsubo cardiomyopathy, Regorafenib, systolic anterior motion of mitral valve

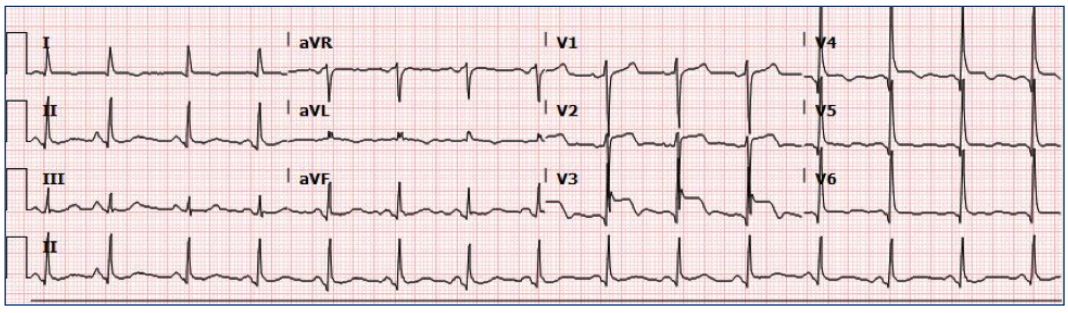
INTRODUCTION

Japanese authors first described Takotsubo cardiomyopathy secondary to emotional stress and it was first reported in 1990 by Sato et al as a reversible cardiomyopathy with a Takotsubo-like pattern.[1] The appearance of the left ventricle (LV) during systole resembles a Japanese octopus fishing pot called Tako-Tsubo. Other names for Takotsubo cardiomyopathy include stress-induced cardiomyopathy and transient apical systolic ballooning syndrome. Apart from emotional stress, new drugs, intracranial process and surgical procedures are also known to cause Takotsubo cardiomyopathy. In this case report, we describe a patient with Takotsubo cardiomyopathy and LV outflow tract obstruction related to the novel chemotherapeutic agent, Regorafenib (Stivarga).

CASE REPORT

A 72-year-old female with a history of metastatic colon cancer and liver metastasis, treated with surgical resection and a recent diagnosis of primary non-small cell lung cancer on chemotherapy presented with shortness of breath on exertion for 3 days. The patient had been started on the new oral chemotherapy drug, Regorafenib 10 days prior to presentation. She stopped the drug one day prior to hospitalization and presented to the emergency department with progressively worse shortness of breath. She had no past history of smoking or myocardial infarction. On presentation, the patient was tachypneic with a respiratory rate of 26/min and a blood pressure of 140/80 mm hg. Auscultation revealed a systolic ejection systolic murmur in the left parasternal area and bibasilar crackles. The patient's EKG showed 2 mm ST elevation in leads V2-V4. [**Figure 1**]

Figure 1. EKG showing ST elevation in V2-V4.



Laboratory data was remarkable for anelevated white cell count of 12500 cells/cu.mm and a troponin I of 6.8 ng/ml. The patient underwent emergency cardiac catheterization which revealed normal coronary arteries and a left ventriculogram with apical akinesis, basal hyperkinesis and a depressed ejection fraction of 30%. [**Figure 2**]

A transthoracic echocardiogram demonstrated reduced left ventricle systolic function of 30–35%, basal hyperkinesis and a dynamic left ventricle outflow tract (LVOT) obstruction with peak gradient of more than 100 mm Hg due to basal hyperkinesis and systolic anterior motion (SAM) of mitral valve. [**Figures 3–5** and **Video 1**]

Figure 2. Left ventriculogram depicting the classical apical ballooning with basal contraction suggestive of Takotsubo pattern.

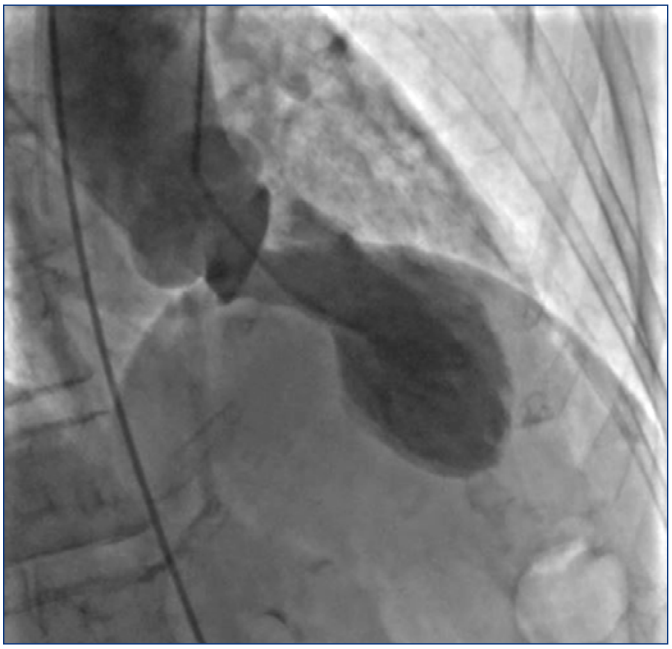


Figure 3. Color doppler image of the apical 5 chamber view showing flow acceleration (yellow arrow) near left ventricle outflow tract region when anterior mitral valve leaflet moves towards the septum during the systole.

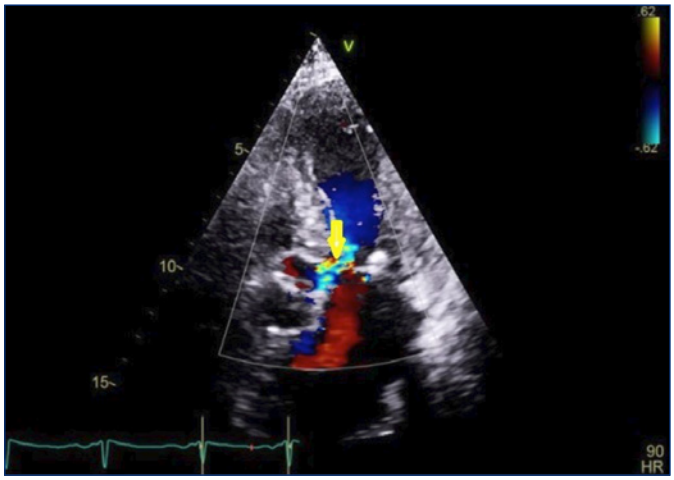


Figure 4. Magnified image demonstrating systolic anterior motion of mitral (SAM) valve. (yellow arrow)

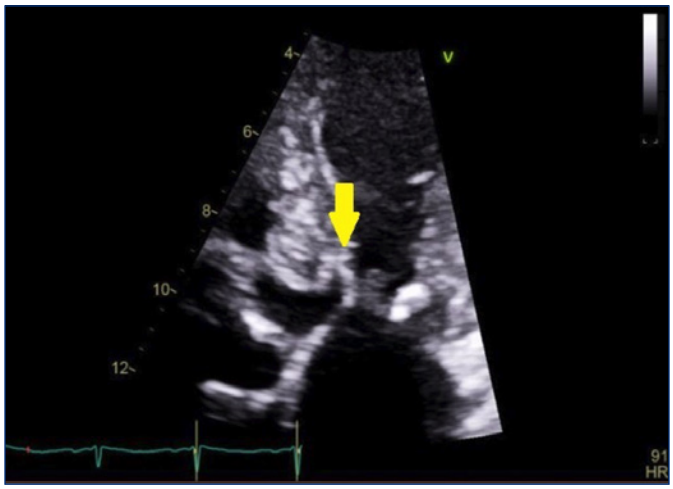


Figure 5A. Pulse wave doppler depicting the significantly increased velocity and gradient across LVOT. Double density noted is contamination from mitral regurgitation.

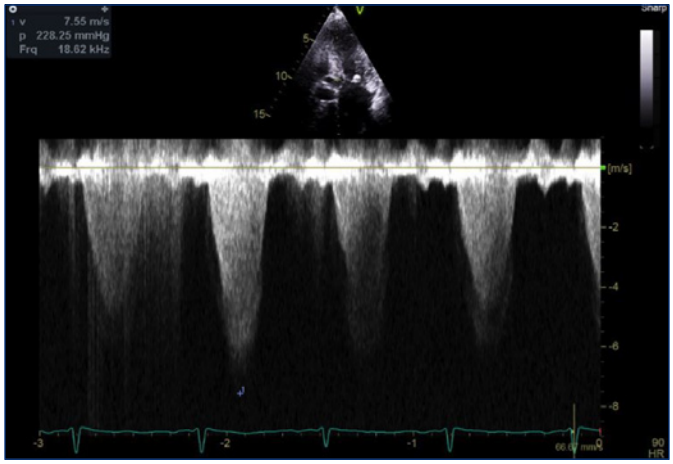
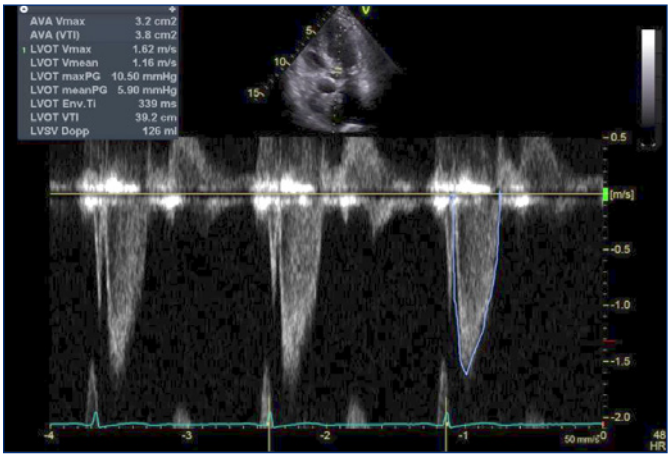
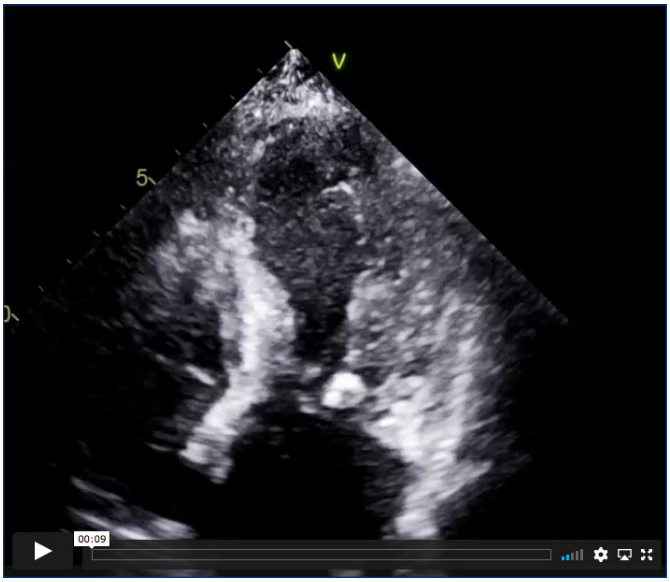


Figure 5B. Pulse wave doppler image demonstrating normal LVOT velocity and gradient 6 weeks after discharge from hospital.



Video 1. 2D Echocardiographic video of apical 4 chamber view demonstrating anterior mitral valve leaflet impinging on the septum during systole, hyperkinetic base of left ventricle with akinetic apical segment. [CLICK TO VIEW VIDEO]



The patient developed hypotension and atrial fibrillation and was treated initially with fluid resuscitation and IV amiodarone infusion. LVOT obstruction and hypotension resolved clinically within 24 hours and blood pressure remained stable for the next 48 hours. Guideline-directed medical therapy was initiated with metoprolol succinate and losartan. After recovery, the patient was discharged to a skilled nursing facility; complete recovery of left ventricle ejection fraction to 60–65% was noted 6 weeks later. There was no evidence of dynamic LV outflow tract obstruction on repeat echocardiogram.

DISCUSSION

Approximately 1–2% of acute myocardial infarctions are due to Takotsubo cardiomyopathy.[2] Takotsubo cardiomyopathy is more common in post-menopausal women from age 62 to 75 years and women accounted for 82% to 100% of patients. Most studies documented ST elevation myocardial infarction in 90% of the patients. Left ventricle function often normalizes in 1 to 3 months. Catecholamines are felt to be an important component of the pathophysiology behind the development of Takotsubo cardiomyopathy. Microvascular ischemia and multivessel epicardial spasm have also been hypothesized as part of the pathogenesis.[3]

Common complications reported are hypotension, atrial and ventricular arrhythmias. Cardiogenic shock, LV free wall rupture, ventricular septal defect and LV mural thrombus can occur rarely. Cardiogenic shock and thromboembolic complications are important causes of mortality.[4] LVOT obstruction due to SAM of the mitral valve is also one of the complications which may occur with Takotsubo cardiomyopathy.

This is the first case of Takotsubo cardiomyopathy reported with Regorafenib, a drug which is a multi-kinase inhibitor approved by the FDA for metastatic colon carcinoma, hepatic carcinoma and advanced gastro intestinal stromal tumors. Literature review showed that side effects like hypertension and hemorrhage are the most common adverse events associated with Regorafenib.[5] The stress associated with a cancer diagnosis and novel chemotherapeutic agents can cause significant adverse cardiac events.[6] Similar to this case report, Takotsubo cardiomyopathy with SAM of the mitral valve and severe LVOT obstruction was reported in a patient with melanoma treated with the immunomodulator drug ipilimumab.[7] Interestingly, our patient also had dynamic LVOT obstruction due to basal hyperkinesis and SAM of the mitral valve which is a known complication associated with Takotsubo cardiomyopathy. LVOT obstruction is reported to occur in 25% of patients. Apart from coronary angiography, with left ventriculography and transthoracic echocardiography, cardiac MRI may also be useful to differentiate Takotsubo cardiomyopathy from acute myocardial infarction or myocarditis. Cardiac MRI typically shows absence of delayed gadolinium hyperenhancement.[8]

During the acute phase, management is mainly symptomatic with supportive therapy. Stress- induced cardiomyopathy is usually well tolerated and complete recovery is expected within a few days to months. Intra-aortic balloon pump counterpulsation, cardiopulmonary circulatory support and continuous veno-venous hemofiltration are very rarely required for hemodynamically unstable patients. There is no consensus regarding long-term management of TCM, although it is reasonable to treat patients with β-blockers and ACE inhibitors during the ventricular recovery period. There is no data to support the continuous use of these drugs for the prevention of TCM recurrence or improvement in long-term survival. After LV function normalizes, physicians may consider discontinuation of these drugs. Anti-arrhythmic medications are not indicated for arrhythmia prevention.[9,10]

CONCLUSION

It is important to recognize and manage Takotsubo cardiomyopathy and its complications in a prompt fashion. This case report is unique in that Takotsubo cardiomyopathy occurred after initiating the chemotherapeutic drug Regorafenib and was associated with basal hyperkinesis and SAM leading to LVOT obstruction and hypotension. Though no causal association can be proven, physicians should be cautioned to recognize stress-induced cardiomyopathy during chemotherapy.

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Conflict of Interest

None

Disclosures

None

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