Transformative Medicine (T-Med)

Volume 2 | Number 3 Article 3

September 2023

Diagnostic Criteria of Takotsubo Cardiomyopathy in the Clinical Setting: A Case Report

Annu R. Suresh MD
Drexel University College of Medicine

Yi-Ju Chen MD
Department of Internal Medicine, UPMC Harrisburg

Richa Neupane MD
Department of Internal Medicine, UPMC Harrisburg

Jessica Cunningham MD
Department of Internal Medicine, UPMC Harrisburg

Recommended Citation

Suresh AR, Chen Y, Neupane R, Cunningham J. Diagnostic Criteria of Takotsubo Cardiomyopathy in the Clinical Setting: A Case Report. *Transformative Medicine (T-Med)*. 2023; 2(3):56-60. doi: https://doi.org/10.54299/tmed/nfzq8029.

Diagnostic Criteria of Takotsubo Cardiomyopathy in the Clinical Setting: A Case Report

Cover Page Footnote

The authors want to express appreciation for Laurie Jo Schwing (librarian, UPMC Harrisburg, Harrisburg, Pennsylvania) for assisting the literature search and manuscript revision.

Diagnostic Criteria of Takotsubo Cardiomyopathy in the Clinical Setting: A Case Report

Annu Suresh[1], Yi-Ju Chen[2], Richa Neupane[2], Jessica Cunningham[2]

1. Drexel University College of Medicine, Philadelphia, PA
2. Internal Medicine, UPMC Harrisburg, Harrisburg, PA

Published September 2023

ABSTRACT

INTRODUCTION: Takotsubo cardiomyopathy (TTS) is a rare condition related to stress featuring apical hypokinesis. Current guidelines suggest that the exclusion of other causal factors like myocarditis is required to diagnose TTS. However, we propose that the existing diagnostic criteria for TTS, particularly, required exclusion of myocarditis, adds to the challenge of making this diagnosis in the clinical setting. Hereby, we present a case with basal hypokinesis that could have been attributed to a conjunction of reverse Takotsubo syndrome (rTTS) with viral or toxic myocarditis.

CASE PRESENTATION: A 29-year-old female complained of acute persistent chest pain, palpitations, and vomiting after smoking marijuana. She was tachycardic without hemodynamic instability or hypoxia. Electrocardiogram showed sinus tachycardia. Troponin peaked at 16.1 ng/ml. Urine drug screen was positive for amphetamines. Echocardiogram and catheterization showed left ventricular reduced ejection fraction (25-30%) with basal hypokinesia and apical hyperkinesis, suggestive of reversed Takotsubo cardiomyopathy. Cardiac magnetic resonance (CMR) also showed delayed contrast enhancement suggestive of myocarditis. Viral panel noted positive Coxsackie B titer on day 7 of hospitalization. She was treated with goal-directed medical therapy and repeat echocardiogram 6 days after showed normalized left ventricular systolic function.

DISCUSSION: Guidelines recommend the use of clinical history, inflammatory markers, and CMR to exclude infectious myocarditis before diagnosing rTTS. The clinical scenario in this case presented evidence of a catecholamine-related substance exposure known to trigger takotsubo cardiomyopathy and of an elevated Coxsackie B titer. The CMR showed features explainable by myocarditis and partially by rTTS. This case highlights the complexity of diagnosing TTS or rTTS with infective myocarditis as exclusion criteria. While imaging, history, and labs play a vital role, a lack of complete understanding about the pathophysiology of this disease as well as existing diagnostic criteria complicate the ability to make this diagnosis in the clinical setting.

KEYWORDS: Myocarditis; Takotsubo syndrome

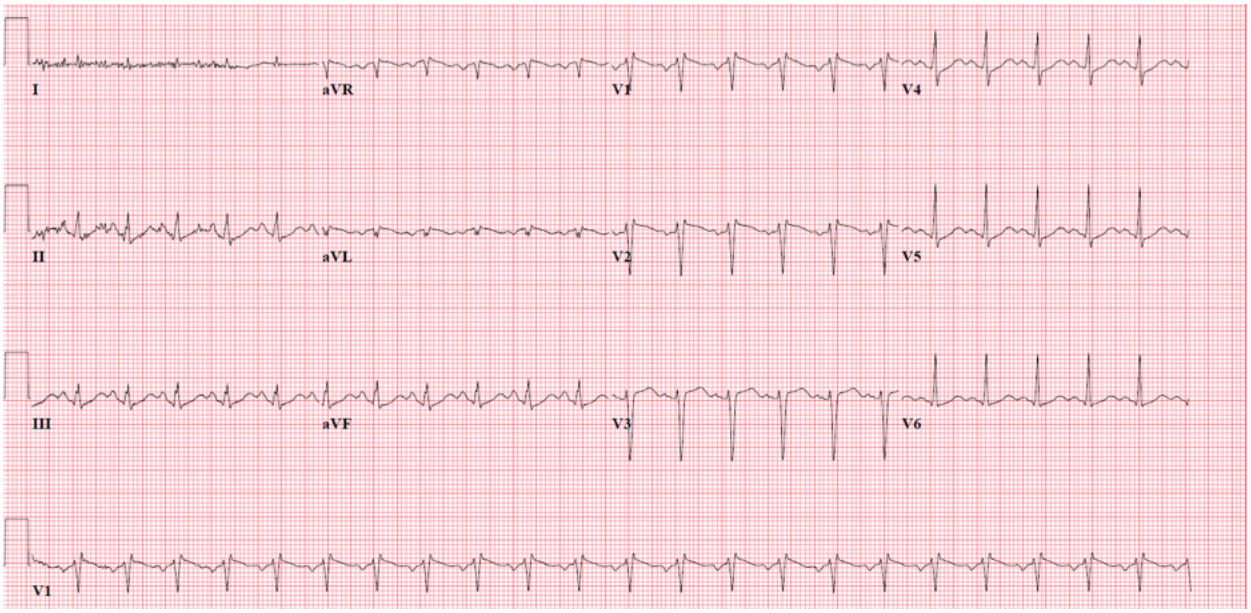
Correspondence to Annu Suresh at annsuresh@gmail.com

Disclosure Statement: The authors have no conflicts of interest to declare.

INTRODUCTION

Takotsubo syndrome, also known as takotsubo cardiomyopathy or stress-induced cardiomyopathy, is a rare condition related to physical and emotional stress that features apical hypokinesis. Reverse takotsubo syndrome is a rarer variant which is characterized by apical hyperkinesis and basal/inferior hypokinesis. Current guidelines, namely the InterTAK diagnostic criteria, Revised Mayo Clinic Criteria, and the Heart Failure Association – European Society of Cardiology Criteria, all require the exclusion of other causal factors including myocarditis to diagnose takotsubo syndrome.[1] However, the clinical approach to myocarditis is similar to takotsubo syndrome in that it involves excluding other possible diagnoses. Although tissue biopsy is required for the definitive diagnosis of myocarditis, its application is limited because of the invasiveness of the process and because management is unlikely to change significantly with a confirmed diagnosis.[2] Cardiac magnetic resonance has been recommended to identify both takotsubo syndrome and clinically suspected myocarditis,[3] with the pattern of myocardium contrast enhancement and perfusion leading to the diagnosis of either myocarditis or takotsubo syndrome by exclusion of the other. However, we propose that the existing diagnostic criteria for takotsubo syndrome, particularly the required exclusion of myocarditis contributes to the challenge of diagnosing this condition, whose pathophysiology is still poorly understood, in the clinical setting. Hereby, we present a case with basal

FIGURE 1. Patient's Electrocardiogram. Electrocardiogram showing sinus tachycardia with rSr' in V1 and V2 with J-point elevation in V1 through V3.



hypokinesis that could be attributed to reverse takotsubo syndrome or myocarditis.

CASE PRESENTATION

A 29 year old Caucasian female presented at an emergency department (ED) of a regional hospital complaining of left sided chest pain and vomiting for seven hours after she smoked marijuana at a party. She recently drove across the country over the course of four days. She described the pain as 8/10 in severity without radiation. The pain was sharp, pressure-like, and squeezing in nature with associated pleuritic pain. Additional associated symptoms included shortness of breath and palpitations. She denied alleviating factors. Her past medical history included polysubstance abuse and bipolar disorder. Family history was significant for her mother having systemic lupus erythematosus and factor V Leiden. She had a 15 pack-year smoking history, consumed alcohol daily, smoked marijuana weekly, and had a remote history of cocaine and heroin use.

In the ED, she was tachycardic with a heart rate of 144 beats per minute, respiratory rate of 22 per minute, and oxygen saturation of 100% on room air. Blood pressure was 100/66, and temperature was 97.5 °F. Physical examination showed palpable radial pulse, no tenderness on palpation of the chest, rapid heart rate without murmur or gallop appreciated, bilateral clear breath sounds on auscultation, no jugular vein distention noted, no clubbing, and no edema of lower extremities.

INVESTIGATIONS

Investigation initiated with electrocardiogram (ECG) showed sinus tachycardia (*Figure 1*) with rSr' in V1 and V2 with J-point elevation in V1 through V3. Chest radiograph revealed cephalization of bilateral pulmonary vessels. Laboratory findings showed troponin 16.1 ng/ml, leukocytosis of 19.9 k/mul, creatinine kinase 609 U/L, estimated sediment rate (ESR) 7 mm/hr, C-reactive protein (CRP) 0.83 mg/dL. Respiratory virus panel, including coronavirus 2019 polymerase chain reaction test was negative. Urine drug screen was positive for marijuana, methamphetamines, amphetamines, and methadone. Computed tomography of the chest showed no acute lung pathology or evidence of pulmonary embolism. Computed tomography of the abdomen and pelvis to investigate the sudden onset vomiting showed only mild gallbladder wall thickening but no signs of inflammation. Transthoracic echocardiogram showed preserved left ventricle (LV) function. She was given aspirin 325 mg and famotidine and was transferred to a tertiary care center for a possible cardiac procedure. On admission to the new facility, repeated troponins were 10.70 ng/mL and trended downward subsequently. Cardiac work up included repeat transthoracic echocardiogram showing rapidly reduced LV ejection fraction (EF) of 25-30%, dilated LV with normal myocardial thickness, moderate mitral and tricuspid regurgitation, mildly elevated pulmonary artery pressure, akinesis of the basal and mid inferoseptal, inferior, and inferolateral segments, and

https://scholarcommons.towerhealth.org/t-med/vol2/iss3/3
DOI: https://doi.org/10.54299/tmed/nfzq8029

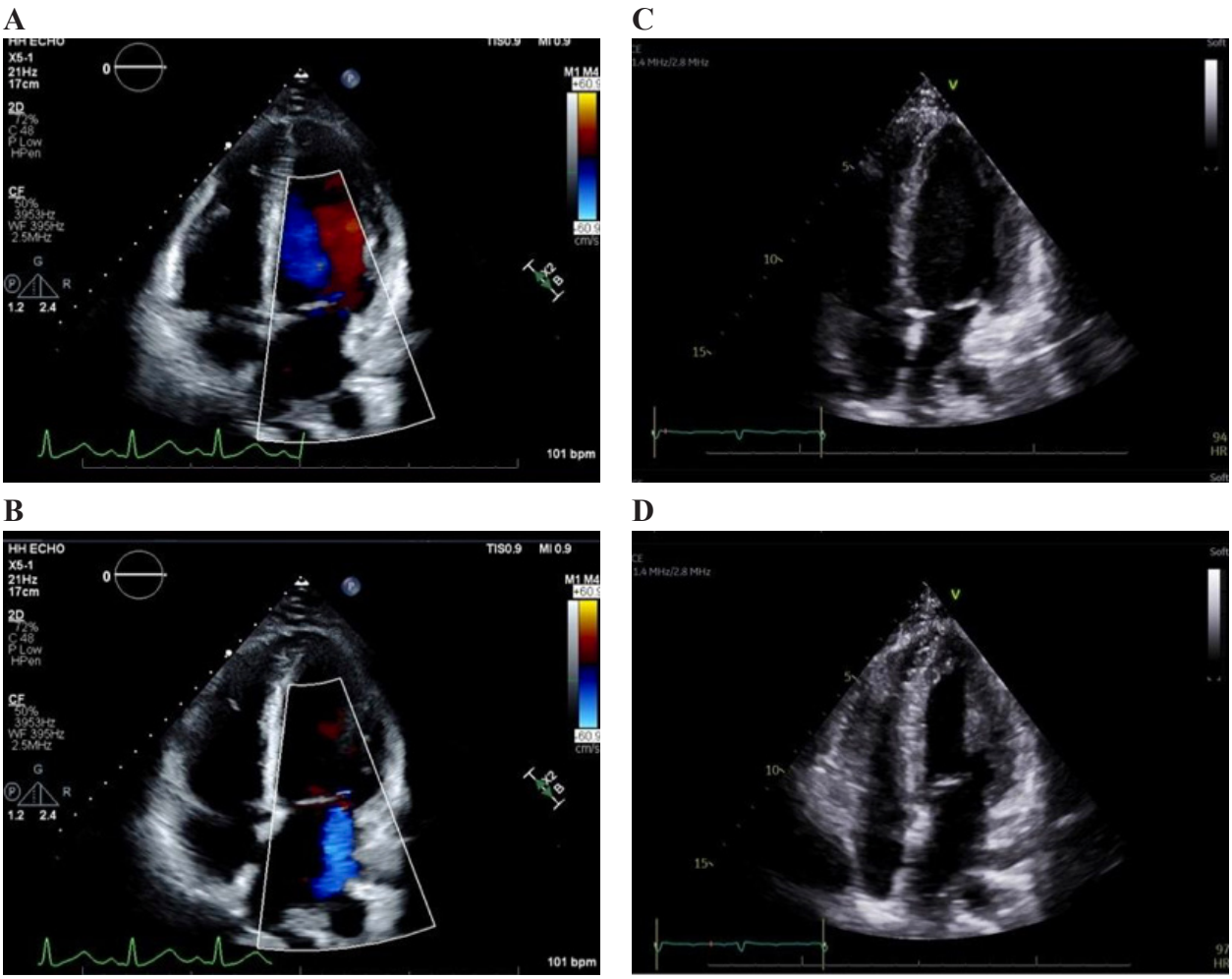


FIGURE 2. Patient's echocardiograms during admission. Echocardiogram on day 2 (a)(b) in comparison to day 8 (c)(d) of symptom onset. (a) biventricular dilation at day 2 of hospitalization. (b) biventricular systolic dysfunction with LVEF 25-30% along with moderate mitral regurgitation. (c)(d) biventricular failure improved with LVEF of 55% and diminished mitral regurgitation.

hypokinesis of mid anterolateral and apical inferior segments (*Figure 2*). Cardiac catheterization showed similar findings and ruled out coronary artery disease. Cardiac magnetic resonance with axial bright blood imaging, cine with SSFP, phase contrast flow analysis, T2 weighted black blood images with and without fat suppression, first pass perfusion at rest, and late gadolinium enhancement was performed. It showed moderately reduced LV systolic function with severely hypokinetic basal to mid LV segments and hyper-contractile apical segments and LV apex, which appeared consistent with reverse takotsubo syndrome. However, there was also evidence of delayed hyperenhancement in the mid wall involving basal anteroseptal and inferoseptal wall and apical septal wall, which is a nonischemic pattern that as a whole suggests myocarditis (*Figure 3*). Antinuclear antibody, Factor V Leiden, human immunodeficiency virus (HIV)-1 antigen and HIV-1/HIV-2 antibodies were all negative. Coxsackie B1 and B4 titers collected on Day 7 of hospitalization were 1:8, which has a low level of positivity to suggest either past or recent infection.

DIFFERENTIAL DIAGNOSIS

From the patient's initial vital signs showing sinus tachycardia with persistent left chest pain and shortness of breath, cardiac, cardiovascular, or pulmonary etiologies were considered the most relevant origin. The initial ECG ruled out arrhythmia, and the computer tomography of the chest ruled out the

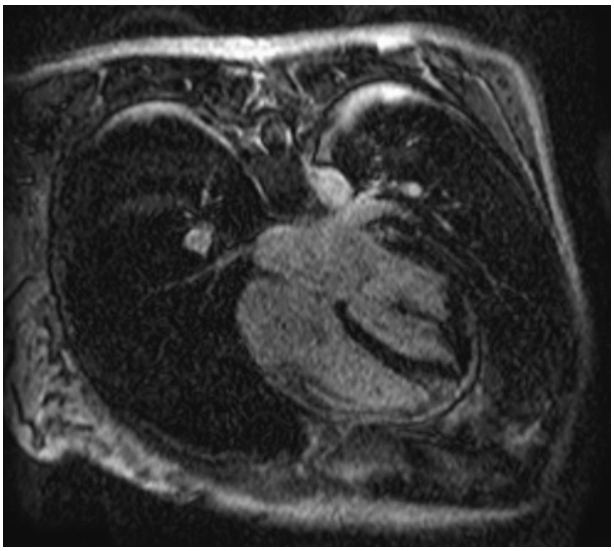


FIGURE 3. Patient's Cardiac MRI. Cardiac MRI showing the delayed enhancement in the myocardial region.

central pulmonary embolism. Coronary artery disease was finally ruled out with cardiac catheterization, and there was low suspicion for drug induced spasm of the coronary vessels, as this is less likely to present as persistent chest pain lasting several days instead of episodic pain lasting a few hours. Furthermore, both transthoracic echocardiogram and computerized tomography did not show evidence of significant pericardial or pleural pathology. Cardiac magnetic resonance showed delayed enhancement in the myocardial area. This, along with the borderline positive Coxsackie B viral titer, could suggest a possible viral myocarditis. However, flu-like symptoms were not noted, and the onset of chest pain correlated better with the substance consumption. The substance history in conjunction with the acute cardiac dysfunction could not rule out the possibility of takotsubo cardiomyopathy.

MANAGEMENT AND FOLLOW UP

The patient was prescribed naproxen for chest pain. Only low dose lisinopril and metoprolol were initiated as part of goal directed medical therapy (GDMT) for heart failure with reduced EF due to her borderline low blood pressure. The patient was discharged after symptom improvement.

Three days after discharge, she returned to the ED complaining of persistent chest tightness and a sense of shortness of breath. She reported compliance with GDMT and naproxen and denied the use of any other substances in the interim. Inflammatory markers including ESR and CRP were slightly more elevated at 12 mm/hr and 8.1 mg/dL respectively. Transthoracic echocardiogram at the second admission, six days from the prior tests, showed improved overall systolic function with LVEF of 55% and presence of hypokinesis of the inferior septal region. The severity of mitral regurgitation was also markedly diminished (*Figure 2*). The patient was discharged two days after readmission with prednisone for chest pain, continuous GDMT, and was advised to pursue another transthoracic echocardiogram in three months. She drove home safely without complication, but the remainder of her course was lost to follow up as she returned to the other side of the country.

DISCUSSION

Ultimately, we had a patient with exposure to methamphetamines immediately prior to symptom onset and positive Coxsackie B titers eight days into her symptoms. Although viral infection and autoimmune diseases are the most common causes of myocarditis in the adult population, this patient presented with no flu-like symptoms, joint pain, or myalgia. Furthermore, during our investigation, viral titers were not checked on admission leading to confusion of whether the positive Coxsackie B viral titer was evidence of prior versus present infection.

In fact, substance use, especially stimulants, was more directly linked to the onset of chest pain and dyspnea in this patient. Stress induced cardiomyopathy is commonly thought to be induced by a catecholamine surge from extreme physical or psychological stress. In a majority of cases of drug-induced takotsubo syndrome, substances with catecholamine stimulating properties are often noted.[4-6] The presence of both amphetamine use and positive viral titers adds to the complexity of diagnosis in this patient. High contenders on the differential diagnosis include stimulant induced reverse takotsubo syndrome, viral myocarditis, or even stimulant-induced myocarditis. Along with criteria regarding transient, reversible wall motion abnormalities of the left ventricle involving regions supplied by multiple arteries, early criteria from 2003 for takotsubo syndrome and reverse takotsubo syndrome excluded this diagnosis in patients with evidence of pheochromocytoma, obstructive coronary artery disease, or myocarditis on the basis that these latter diseases could also cause the transient left ventricular dysfunction.[7] Recently in 2018, the European Society of Cardiology developed new guidelines removing pheochromocytoma and coronary artery disease as exclusionary criteria, recognizing that takotsubo syndrome can co-exist

with both conditions.[8] In a letter to the editor of the International Journal of Cardiology, Hassan reviews the diagnostic criteria for takotsubo syndrome and notes that the requirement to rule out myocarditis is based on conjecture rather than on scientific evidence.[2] However, infectious myocarditis is still listed as a diagnosis that should be excluded before diagnosing takotsubo syndrome. The difficulty arises because the clinical presentation, biomarkers, and ECG changes of the two may be similar. Current literature recognizes that patients with either takotsubo syndrome or myocarditis can have similar recovery time from the reversible cardiac dysfunction,[9,10] which makes even retrospective review of recovery a poor differentiator of the two diagnoses.

Given the similarities in presentation and laboratory findings of myocarditis and takotsubo syndrome, the guidelines recommend the use of the combination of clinical symptoms, inflammatory markers, and the presence of pericardial effusions along with cardiac magnetic resonance to exclude infectious myocarditis.[2] Takotsubo syndrome is identified on cardiac magnetic resonance by the presence of edema with associated akinesis-hypokinesis in the LV wall in the apical region and sparing of the basal segments, while hypokinesis of the basal segments with apical sparing is suggestive of reverse takotsubo syndrome. In both cases, either early or delayed enhancement of gadolinium would exclude the diagnosis of takotsubo syndrome because that is suggestive of myocarditis.[11,12] However, previous studies have found that delayed gadolinium enhancement was present in a percentage of patients already diagnosed with takotsubo syndrome, ranging from 9 to 22%.[13] While cardiac MRI is a vital resource in helping to identify and diagnose takotsubo cardiomyopathy, it alone may not be enough to distinguish the two diseases.

The existing diagnostic criteria and lack of complete understanding of takotsubo syndrome are both contributors to the complexity of making this diagnosis. Particularly given that case reports included in the literature exist both about cases where takotsubo syndrome mimics myocarditis presentation and where myocarditis mimics takotsubo syndrome, it is evident that there is significant overlap between the two diseases.[14,15] As such, there may be a need to reconsider the diagnostic criteria for takotsubo syndrome and a need for further clarifying features to distinguish this condition from myocarditis if myocarditis continues to be an exclusionary criterion.

REFERENCES

1. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, et al. Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(16):1955-71. https://doi.org/10.1016/j.jacc.2018.07.072

2. Y-Hassan S. Myocarditis and takotsubo syndrome: are they mutually exclusive? Int J Cardiol. 2014;177(1):149-51. https://doi.org/10.1016/j.ijcard.2014.09.056

3. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. European Heart Journal. 2018;39(22):2047-62. https://doi.org/10.1093/eurheartj/ehy077

4. Amariles P, Cifuentes L. Drugs as Possible Triggers of Takotsubo Cardiomyopathy: A Comprehensive Literature Search - Update 2015. Curr Clin Pharmacol. 2016;11(2):95-109. https://doi.org/10.2174/1574884711666160405105841

5. Kido K, Guglin M. Drug-Induced Takotsubo Cardiomyopathy. J Cardiovasc Pharmacol Ther. 2017;22(6):552-63. https://doi.org/10.1177/1074248417708618

6. Movahed MR, Mostafizi K. Reverse or inverted left ventricular apical ballooning syndrome (reverse Takotsubo cardiomyopathy) in a young woman in the setting of amphetamine use. Echocardiography. 2008;25(4):429-32. https://doi.org/10.1177/1074248417708618

7. Gunasekara MY, Mezincescu AM, Dawson DK. An Update on Cardiac Magnetic Resonance Imaging in Takotsubo Cardiomyopathy. Curr Cardiovasc Imaging Rep. 2020;13(5):17. https://doi.org/10.1007/s12410-020-09536-0

8. Ghadri J-R, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J. 2018;39(22):2032-46. https://doi.org/10.1007/s12410-020-09536-0

9. Merlo M, Ammirati E, Gentile P, et al. Persistent left ventricular dysfunction after acute lymphocytic myocarditis: Frequency and predictors. PLoS One. 2019;14(3):e0214616. https://doi.org/10.1371/journal.pone.0214616

10. Shaikh N, Sardar M, Jacob A, et al. Possible predictive factors for recovery of left ventricular systolic function in Takotsubo cardiomyopathy. Intractable Rare Dis Res. 2018;7(2):100-5. https://doi.org/10.5582/irdr.2018.01042

11. Fernández-Pérez GC, Aguilar-Arjona JA, de la Fuente GT, et al. Takotsubo Cardiomyopathy: Assessment With Cardiac MRI. AJR Am J Roentgenol. 2010;195(2):W139-W45. https://doi.org/10.2214/AJR.09.3369

12. Friedrich MG, Marcotte F. Cardiac Magnetic Resonance Assessment of Myocarditis. Circ: Cardiovasc Imaging. 2013;6(5):833-9. https://doi.org/10.1161/CIRCIMAGING.113.000416

13. Nakamori S, Matsuoka K, Onishi K, et al. Prevalence and Signal Characteristics of Late Gadolinium Enhancement on Contrast-enhanced Magnetic Resonance Imaging in Patients with Takotsubo Cardiomyopathy. Circ. 2012;76(4):914-21. https://doi.org/10.1253/circj.CJ-11-1043

14. Taghavi S, Chenaghlou M, Mirtajaddini M, Naderi N, Amin A. Takotsubo syndrome without Major Stress Mimicking Myocarditis. Anatol J Cardiol. 2020; 23(6): 349–350. https://doi.org/10.14744/AnatolJCardiol.2020.45773

15. Sulaiman S, Rajesh GN, Vellani, H. Acute Myocarditis Morphologically Mimicking Reverse Takotsubo Cardiomyopathy. IHJ Cardiovascular Case Reports (CVCR). 2017; 1(1): 42-45. https://doi.org/10.1016/j.ihjccr.2017.04.001