Cardio-oncology: Capecitabine Can Sometimes be Heatbreaking Capecitabine-Induced Takotsubo Cardiomyopathy Case Report and Literature Review

Ramy Abdelmaseih, MD[a,b,*], Anamarys Blanco, MD[a,b], Randa Abdelmasih, MD[a,b], Krutika Desai, MD[a,b], Joshua Pothen, MD[a,b], Jay Patel, DO[a,b], and Rama Balaraman, MD[a,b]

From the [a] University of Central Florida College of Medicine, Graduate Medical Education, Orlando, FL and [b] HCA/Ocala Health, Ocala Regional Medical Center, Department of Internal Medicine, Ocala, FL.

Abstract: Capecitabine has been more recognized for its cardiotoxicity with an incidence that varies widely. It demonstrates its toxicity in the forms of acute coronary syndrome, arrhythmias and, to a lesser extent, cardiomyopathy. There are several proposed theories including coronary vasospasm, endothelial injury, and oxidative stress. We present a case of capecitabine-induced cardiomyopathy in a patient with pancreatic cancer and mild coronary artery disease, and shed light on other cardio-toxic agents, their proposed mechanism of cardiotoxicity, and on cardiomyopathy in general. (Curr Probl Cardiol 2021;46:100854.)

Introduction

Capecitabine is an orally-administered chemotherapeutic agent with antineoplastic activity used in the treatment of certain metastatic breast and colorectal cancers. Also, in combination with Gemcitabine for pancreatic cancers. It is a prodrug that is enzymatically

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.
Curr Probl Cardiol 2021;46:100854
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2021.100854

converted in the tumor cells to 5-Fluorouracil leading to DNA synthesis inhibition and slow tumor tissue growth. Capecitabine has relatively low cardiotoxicity compared to other Fluropyrimidines due to its preferential targeted delivery of 5-Fluorouracil to tumor tissue. Although rare, Capecitabine adverse effects include: angina-like chest pain, coronary artery vasospasm, arrhythmias and sudden cardiac death.[1] We report a rare case of Takotsubo cardiomyopathy (TCM) within 72 hours of Capecitabine therapy induction.

Case Presentation

A 66-year-old female with medical history of mild coronary artery disease, emphysema, hypertension, and pancreatic cancer presented to the hospital with worsening dyspnea, chest tightness, and diaphoresis. She denied any fever, chills, urinary or gastrointestinal symptoms. She had a recent echocardiogram 1 month ago consistent with left ventricular ejection fraction (LVEF) of 55% without regional wall motion abnormalities. She was recently started on Capecitabine as part of her pancreatic cancer regimen and received only one dose about 3 days ago. On presentation, patient was tachycardic with HR 140 bpm, otherwise vitally stable. She was in mild respiratory distress with bibasilar crackles and 1+ lower extremity edema. Laboratory workup showed: Troponin 0.042 > 0.62, B-Natruiretic Peptide 34400 pg/mL. Chest x-ray (CXR) and computed tomography (CT) chest scan with pulmonary embolism protocol showed pulmonary venous congestion with small pleural effusion. Electrocardiogram showed sinus tachycardia, right axis deviation with hyperacute T waves. Cardiac catheterization showed mild angiographic coronary artery disease. She continued to complain of chest tightness with rising troponins of 2.16 ng/mL which raised concern for Capecitabine-induced TCM versus coronary vasospasms. Echocardiogram showed LVEF of 25% with hypokinesis of anteroseptal myocardium. She was diagnosed with Capecitabine-induced TCM. Capecitabine was discontinued and heart failure therapy was started. Echocardiogram 1 week later showed normalized LVEF with complete resolution of regional wall motion abnormalities (Figs 1–4).

Discussion

TCM, also known as stress cardiomyopathy, is a reversible clinical syndrome that often mimics acute coronary syndrome or presents as acute heart failure with sudden onset deterioration in left ventricle segmental function in response to emotional, physical or medical stress. The exact

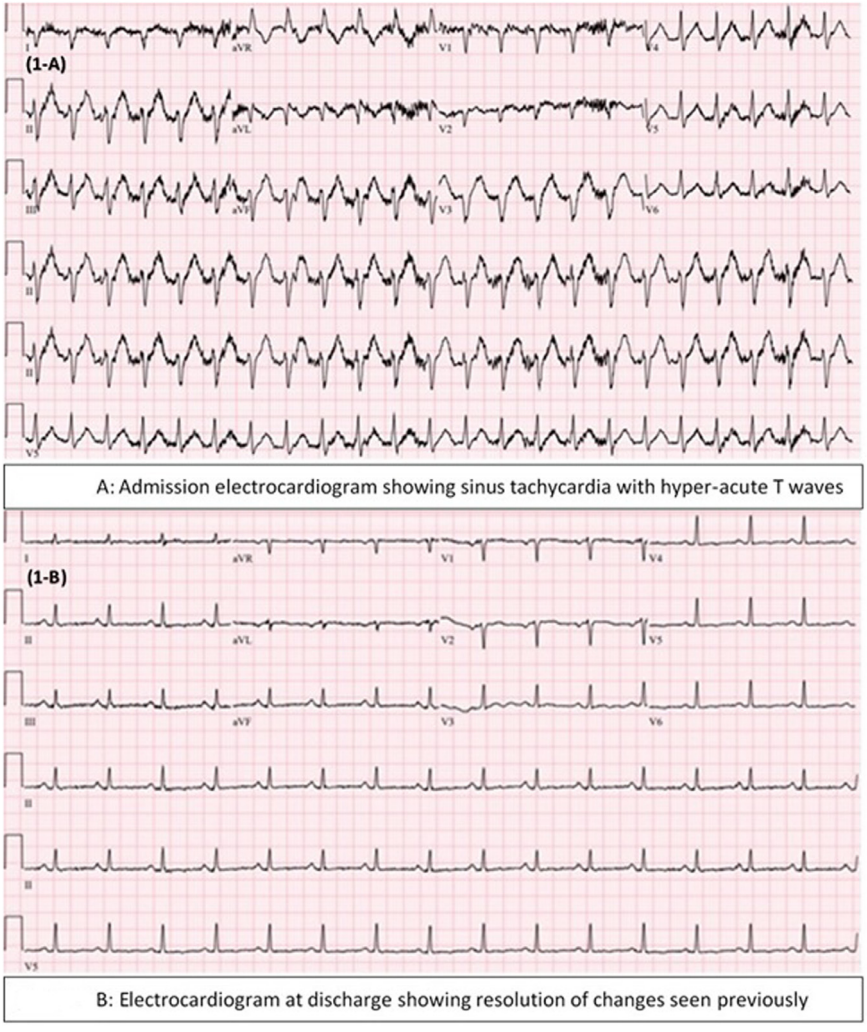

FIG 1. (A, B) Electrocardiogram at discharge showing resolution of changes seen previously.

pathophysiology of this syndrome is not well understood, but most commonly proposed mechanisms are: catecholamine excess with subsequent stunning of the myocardium, coronary artery vasospasm, and underlying microvascular dysfunction.[2]

The The InterTAK (International Takotsubo) registry study that evaluated 1604 TCM patients showed that 16.6% of patients had cancers.[3] Similarly, another study of 24,701 TCM patients that evaluated demographic and co-morbid predictors of TCM reported that 14.4% of patients had cancers.[4] The potential triggers of TCM in cancer patients include:

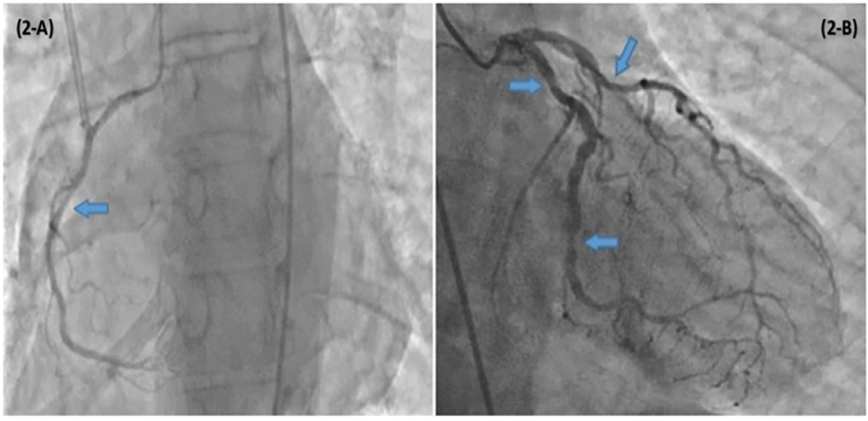

FIG 2. (A, B) Coronary angiogram showing RCA, LCX and LAD mind nonobstrucutive CAD.

the emotional burden of cancer diagnosis, chronic inflammation tied to cancer, physical stress of cancer surgery and chemo-radiation, and cardiotoxicity of chemotherapeutic agents.

Several chemo-therapeutic agents have been implicated to be associated with TCM, most commonly 5-Fluorouracil. Others include: Capecitabine, Combretastatin, Rituximan, vascular endothelial growth factors inhibitors and Taxols. TCM associated with Capecitabine is very rare, and reported only in a handful of cases,[5-12] most of them suffered from this syndrome within 72 hours of drug initiation. All patients had electrocardiogram changes, elevated cardiac enzymes, normal coronary angiography, and a complete recovery of LVEF in 4-6 weeks of drug discontinuation.

The pathogenesis of Capecitabine-induced TCM is largely unknown. Coronary artery vasospasm is the most commonly accepted hypothesis through direct toxic effect on coronary vasculature. However, other explanation such as direct toxic effect on myocytes, thrombogenesis, and autoimmune etiologies have also been proposed.[13]

Here, we present a rare case of Capecitabine-induced TCM that manifested as an acute ischemic event in a patient with mild coronary artery disease within 72 hours of drug initiation. Workup included cardiac catheterization and coronary angiogram that showed nonobstructive coronary artery disease. Echocardiogram showed LVEF 25% with hypokinesis of anteroseptal myocardium. The drug was stopped and heart failure therapy was initiated. A follow-up echocardiogram after 1 week showed normalized LVEF with complete resolution of regional wall motion abnormalities. A multidisciplinary team including a cardiologist and medical oncologist created a new treatment plan for the patient with regular follow-ups.

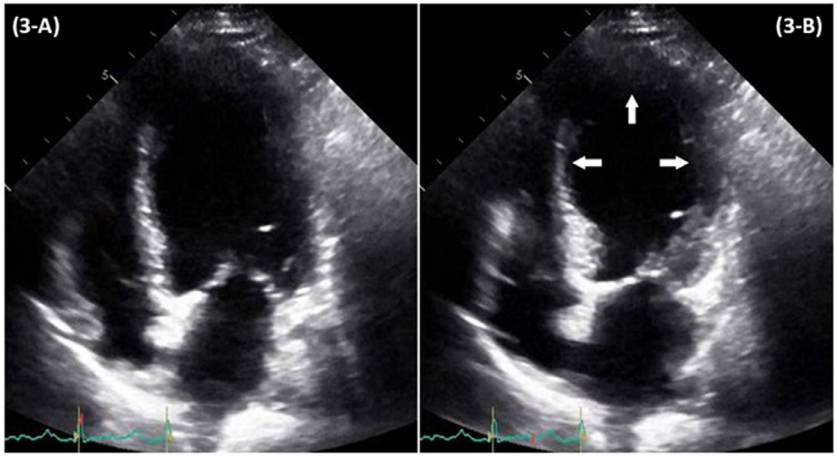

FIG 3. (A,B) 2-D echocardiogram showing apical ballooning (TCM).

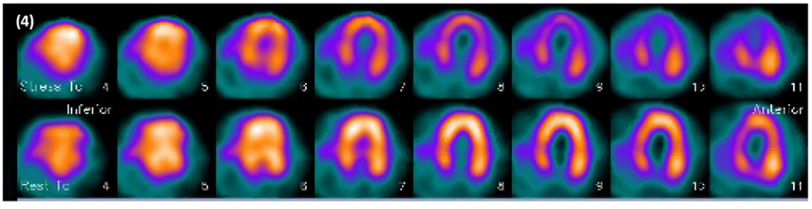

FIG 4. Nuclear medicine stress test revealing anterior wall reversible ischemia.

In the near future, the incidence of cardiovascular toxicities of such agents are expected to increase worldwide, mostly because of their more convenient oral route and less toxic profile compared to their parent drug 5-Fluorouracil which is administered as an intravenous infusion. Physician should be aware of potential cardiovascular toxic effects of such drugs, and consider medication adverse event as a source of cardiac pain.

Conclusion

TCM is a challenging clinical entity that requires a high index of suspicion. It is a very rare, but potentially devastating complication of chemo-therapeutic agents. Whether Capecitabine is the offender agent, or just a bystander, it is very critical to stop it and initiate heart failure therapy. A multidisciplinary approach through a team of cardiologist and medical oncologist is very crucial to improve the prognosis and to create new treatment plan for the patient.

REFRENCES

1. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol* 2006;58(4):487–93. https://doi.org/10.1007/s00280-005-0178-1.
2. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352(6):539–48. https://doi.org/10.1056/NEJMoa043046.
3. Cammann VL, Sarcon A, Ding KJ, et al. Clinical features and outcomes of patients with malignancy and Takotsubo syndrome: observations from the International Takotsubo Registry. *J Am Heart Assoc* 2019;8(15):e010881. https://doi.org/10.1161/JAHA.118.010881.
4. El-Sayed AM, Brinjikji W, Salka S. Demographic and co-morbid predictors of stress (takotsubo) cardiomyopathy. *Am J Cardiol* 2012;110(9):1368–72. https://doi.org/10.1016/j.amjcard.2012.06.041.
5. Powers Anna, Michelle Joanne, Gomez D, Okwuosa Tochukwu. Capecitabine-induced Takotsubo cardiomyopathy with classic apical ballooning. *J Am Coll Cardiol* 2020;75(11 Supplement 1):3279.
6. Bhardwaj PV, Chaubey VK, Islam AM. Capecitabine-induced Takotsubo cardiomyopathy: a case report. *Perm J* 2019;23:18–245. https://doi.org/10.7812/TPP/18.245.
7. Sabharwal S, Sharma A, Manek G, Grover P. A case of capecitabine-induced takotsubo cardiomyopathy. *Chest* 2018;54(4 suppl):107A. https://doi.org/10.1016/j.chest.2018.08.092.
8. Sakamoto T, Endo A, Ito S, Okada T, Watanabe N, Tanabe K. Capecitabine induced Takotsubo cardiomyopathy. *J Cardiac Fail* 2016;Vol. 22. No. 9S September.
9. Qasem A, Bin Abdulhak AA, Aly A, Moormeier J. Capecitabine-induced takotsubo cardiomyopathy: a case report and literature review. *Am J Ther* 2016;23(5):e1188–92. https://doi.org/10.1097/mjt.0000000000000134.
10. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. *Intern Med J* 2010;40(4):303–7.
11. Y-Hassan S, Tornvall P, Törnerud M, syndrome Henareh LCapecitabine caused cardiogenic shock through induction of global takotsubo. *Cardiovasc Revasc Med* 2013;14(1):57–61. https://doi.org/10.1016/j.carrev.2012.10.001.
12. Ang C, Kornbluth M, Thirlwell MP, Rajan RD. Capecitabine-induced cardiotoxicity: case report and review of the literature. *Curr Oncol* 2010;17(1):59–63. https://doi.org/10.3747/co.v17i1.437.
13. Yeh ETH, Bickford CL. Cardiovascular complications of Cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53(24):2231–47.