Capecitabine-induced vasospasm: a case report

Fayez El Shaer[1,2*], Ismail R Raslan[1], Waleed Al Habeeb[1], Mostafa Alshimiri[1], Hanan Albaker[1], Khalid AlHabib[1]

European Journal of Medical Case Reports
Volume 2(1):33-37

https://doi.org/10.24911/ejmcr/1/36
Discover Publishing Group

ABSTRACT

Background: Coronary heart disease with acute coronary syndrome (ACS; type II myocardial infarction) may be an iatrogenic and a reversible cause with complete recovery after cessation of the accused agent.

Case Presentation: We present the case of a 52-year-old male patient who had received adjuvant chemotherapy consisting of capecitabine, 3 mg orally once per day, after resection of moderately differentiated invasive adenocarcinoma in the transverse colon. Three days (3 doses) after the initiation of chemotherapy, the patient reported typical anginal chest pain and an electrocardiogram (ECG) indicated ST-segment elevation. A repeated ECG in the catheterization laboratory showed normal results. Echocardiography showed that left ventricular systolic function was moderately to severely reduced. Coronary angiography revealed normal coronary arteries.

Conclusion: Capecitabine should be used with caution, as patients receiving this medication might present with symptoms suggestive of ACS that might not always originate from epicardial coronary artery disease. There is always a possibility of vasospasm when a patient is receiving Capecitabine.

Keywords: Vasospasm, chemotherapy, capecitabine, case-report.

Received: 4 October 2017 **Accepted:** 24 October 2017

Type of Article: CASE REPORT

Funding: None

Declaration of conflicting interests: None

Corresponding Author: Fayez El Shaer
*King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
Email: elshaerfayez@yahoo.com
Full list of author information is available at the end of the article.

Background

Capecitabine is known to cause acute chest pain syndrome. There have been eight previous case reports describing cardiotoxic complications associated with the use of capecitabine. There have been four cases similar to our presentation reported in the literature, and our case marks the fifth (Table 1). Capecitabine becomes activated after *in vivo* conversion to 5-fluorouracil (5-FU; fluorouracil), which is converted in turn to two active metabolites, 5-fluoro-2′-deoxyuridine monophosphate and 5-fluorouridine 5′-triphosphate (FUTP). Cytotoxic effects are produced by two different mechanisms. First, thymidylate formation is inhibited; this precursor is essential for DNA synthesis, and its deficiency inhibits cell division. Second, nuclear transcriptional enzymes can incorporate FUTP instead of uridine triphosphate during ribonucleic acid (RNA) synthesis, resulting in a metabolic error that interferes with RNA processing and protein synthesis.

Case Presentation

A 52-year-old man underwent hemicolectomy for colon cancer in the transverse colon. Biopsy revealed moderately differentiated invasive adenocarcinoma. As part of his preoperative assessment, our team performed echocardiography and the results were normal for his age.

Adjuvant chemotherapy (capecitabine 3 g po once daily) was initiated three days prior to the patient's presentation. The patient arrived at our emergency department with continuous chest pain that began at early morning and was partially controlled with self-administered analgesia until presentation 12 hours later when the pain was no longer bearable. The pain was central, debilitating, radiated to both shoulders and graded as 7 out of 10.

The patient had no history of heart disease and on examination was hemodynamically stable with a normal clinical exam aside from sinus tachycardia. His laboratory results were normal with a progressive minor rise in troponin and creatine kinase.

The patient had no history suggestive of cardiac decompensation and was hemodynamically stable. His laboratory results were unremarkable apart from his Hb level, 10.5 g/dl. Serial troponin levels (<0.01, 0.07, 0.110, 0.16, 0.090, and 0.030) were marginally elevated.

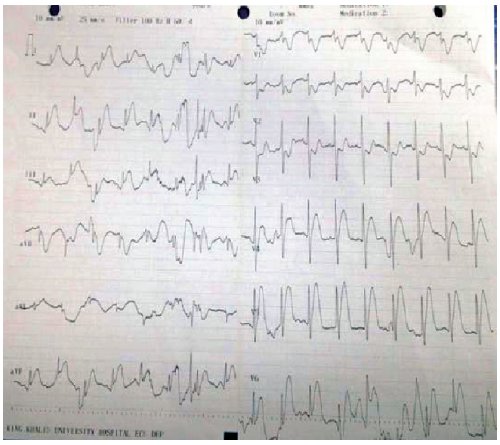
The patient's electrocardiogram (ECG) showed sinus tachycardia with ST-segment elevation in leads 1, 2, 3, AvF, AvL, V4, V5, and V6 with reciprocal changes in V1, V2, and V3 (Figure 1(a) and (b)). A ST-elevation myocardial infarction code was activated, acute coronary syndrome (ACS) protocol including nitro-glycerine infusion was initiated and the patient was sent to the catheterization laboratory. However, on further questioning, the patient stated that pain had suddenly completely stopped. Repeated ECG within one hour of the initial ECG showed normal findings (Figure 1(c)).

Cardiac catheterization was therefore aborted, an ACS protocol was continued and the patient was shifted to the coronary care unit (CCU).

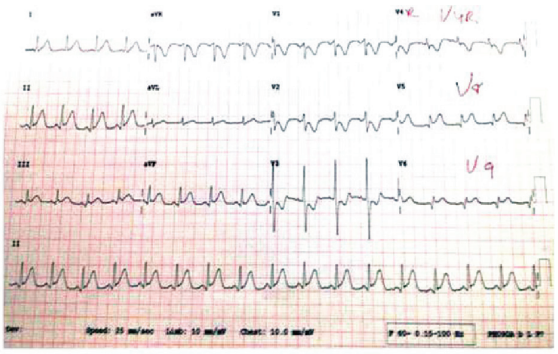
Echocardiography was performed the next morning that showed contrast clearly in comparison to the previous echocardiography findings prior to the initiation of the patient's chemotherapy. Echocardiography findings showed global hypokinesia with regional wall motion abnormality and moderate to severely reduced left ventricular (LV) systolic function, mildly reduced right ventricular systolic function, with a transmitral spectral Doppler flow pattern, suggesting impaired LV relaxation

Table 1. Capecitabine-related events in the literature.

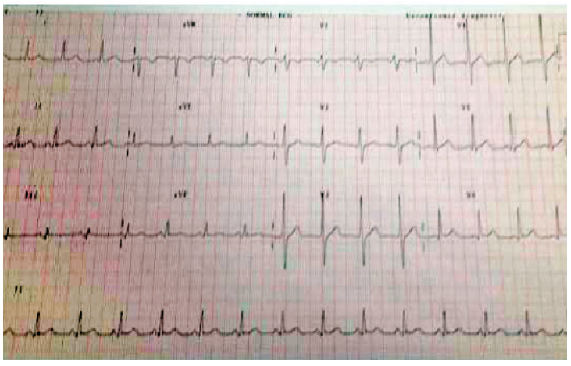
REASON TO GIVE CAPECITABINE	AGE AND GENDER	DOSE AND DURATION	REPORTED EFFECT	REFERENCE
Metastatic breast carcinoma after total mastectomy due to invasive ductal carcinoma.	47/Female	Capecitabine for 3 months	Acute inferior MI	Güvenç et al. [1]
Recently diagnosed colorectal cancer before surgery.	52/Female	Capecitabine and doxorubicin 3,000 mg/day for 3 days	Coronary artery Vasospasm	Tsiamis et al. [2]
Metastatic colorectal cancer	28/Male	Fifth course of capecitabine	Ventricular fibrillation	Kounis [3]
Metastatic colorectal cancer	61/Male	Capecitabine (Xeloda®) 1,500 mg twice a day had been started just one day earlier	Coronary artery vasospasm	Camaro et al. [4]
Colorectal carcinoma with an isolated liver metastasis a month before his admission	63/Male	2.5 g twice a day for 3 days	Coronary artery Vasospasm	Scott et al. [5]
Metastatic cancer of the sigmoid colon	43/Female	5 days	Coronary artery Vasospasm	Papadopoulos et al. [6]



(a)



(b)



(c)

Figure 1: ***(a)*** *Acute inferoposterior MI.* ***(b)*** *Resolution of ST segment elevation.* ***(c)*** *Normal electrocardiogram (60 min later).*

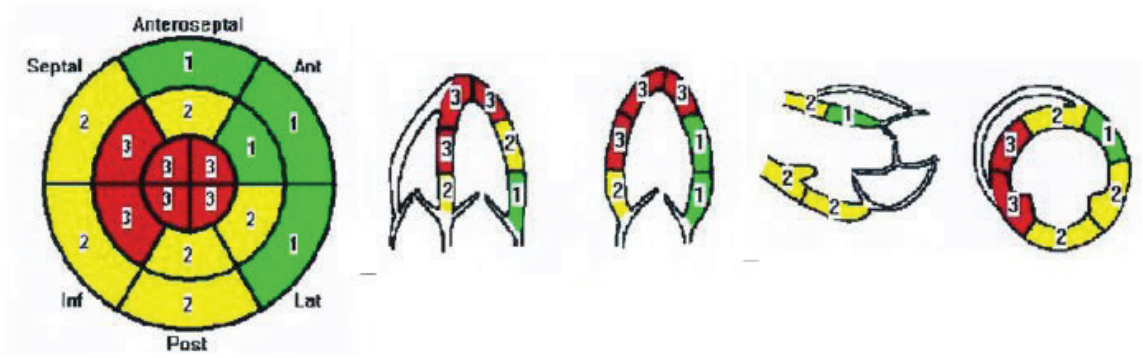


Figure 2: *Wall motion abnormalities by echocardiography (inferior and inferoseptal, inferolateral and apical wall hypokinesia).*

and a mild mitral regurgitation with a mildly dilated left atrium (Figure 2).

Based on the wall motion abnormality, LV systolic dysfunction, and elevated troponin levels, it was decided to perform cardiac catheterization again.

The patient underwent left heart catheterization via the right-trans-radial approach, the coronary angiogram revealed normal coronaries (Figure 3(a)–(d)).

The repeated echocardiography after catheterization still had no improvement. The oncology team and the clinical pharmacologist reviewed the patient's report and recommended discontinuing chemotherapy based on previous accounts of capecitabine-induced cardiac events. The patient was discharged and prescribed aspirin 100 mg, Plavix 75 mg, and lisinopril 2.5 mg, all orally once daily. He returned for a follow-up 2 months later and underwent repeat echocardiography that was completely normal.

Discussion

5-Fluorauracil (FU) is used widely in various chemotherapy regimens and is the second most common cause of chemotherapy-related cardiotoxicity, after anthracyclines [7,8]. In a review of the literature, the risk of cardiac toxicity with 5-FU was between 1.6% and 2.3%; concurrent radiation therapy was a predisposing factor [7]. The risk appears higher with infusion (both long-term and short-term schedules) as opposed to bolus

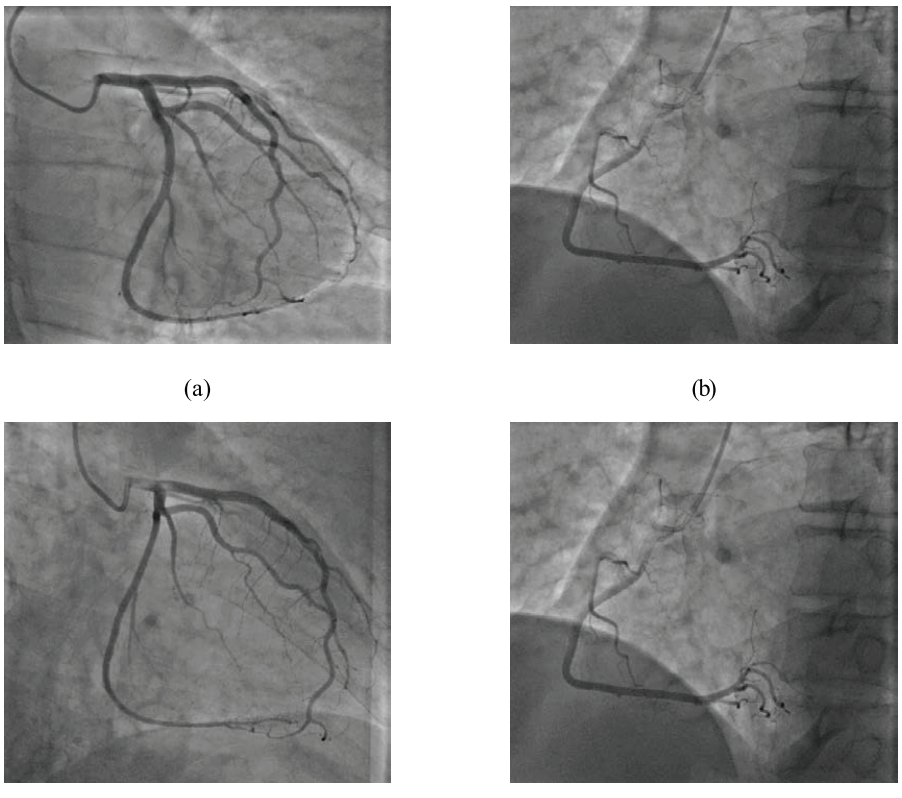


Figure 3: ***(a)*** *Normal coronary angiography.* ***(b)*** *Normal coronary angiography.* ***(c)*** *Normal coronary angiography.* ***(d)*** *Normal coronary angiography.*

regimens [9]. The presence of coronary artery disease increases the likelihood of cardiotoxicity; however, most cases of cardiotoxicity occur in patients without heart disease, and pre-existing cardiac disease is not predictive of cardiotoxicity [10]. Capecitabine administration has been associated with various allergic reactions [3], including acneiform skin rash, lichenoid photosensitive eruption, exudative non-healing scalp, skin reactions, pyogenic granuloma, subacute cutaneous systemic lupus erythematosus, exudative hyponychial dermatitis, and hand–foot syndrome. As in the present case, the majority of patients presented transient ST elevation, unobstructed coronaries, and resolved symptoms after drug cessation. One case of myocardial infarction and subsequent death has been described [1]. The overall risk of symptomatic cardiotoxicity with capecitabine appears to be slightly lower than with 5-FU-based regimes. Pre-existing cardiac and renal diseases are reported risk factors for cardiotoxicity [11]. Capecitabine is enzymatically metabolized in the liver to 5-FU, which in turn plays a major role in inhibiting DNA and RNA syntheses in tumor cells by blocking the synthesis of precursor nucleotides [12]. In contrast to the direct myocardial toxicity of anthracyclines, capecitabine and its active metabolite 5-FU are thought to exert their cardiac effects by causing reversible coronary spasms [2].

A retrospective analysis of the incidence and severity of capecitabine-related cardiotoxicity in different regimens in the treatment of metastatic colorectal cancer in three randomized phase 3 studies used the data of cardiac events reported in the CAIRO, CAIRO2, and CAIRO3 studies of the Dutch Colorectal Cancer Group and analyzed the incidence and severity of cardiac events in the different treatment regimens of the trials which all included the use of capecitabine. The following events were included: chest pain, newly diagnosed cardiac ischemia/infarction, atrial fibrillation, other arrhythmias and heart failure, all graded according to National Cancer Institute Common Toxicity Criteria. A total of 1,973 patients were included, who received a total of 2,461 capecitabine-based lines of treatment. Overall, 5.9% of patients (n = 117) experienced at least one cardiac event, and 2.3% (n = 46) experienced at least one grade ≥3 event. Three patients had two cardiac events. The most frequently observed cardiac event was ischemia/infarction (2.9%, n = 57), followed by arrhythmias (2.0%, n = 40, including atrial fibrillation in 10 patients), chest pain (0.8%, n = 16), and heart failure (0.4%, n = 7). The highest incidence of cardiac events was observed in patients treated with capecitabine in combination with oxaliplatin and bevacizumab (12%, n = 43). This analysis concluded that capecitabine-related cardiotoxicity in 5.9% of patients, and severe cardiotoxicity in 2.3% of patients. Combination treatment with capecitabine, oxaliplatin, and bevacizumab was associated with the highest risk of cardiotoxicity [13].

Conclusion

With the increasing use of capecitabine, it is important that its potential cardiac side effects are more widely appreciated. This knowledge will reduce unnecessary interventions such as thrombolytics or percutaneous coronary intervention and their associated risks. On the other hand, emergency interventions may still be required since some cases are not due to vasospasm, as in a previously reported case of myocardial infarction and subsequent death. One should exercise caution before prescribing capecitabine to patients at high risk for coronary atherosclerosis. Treatment should be discontinued if coronary symptoms develop and re- administration is generally not recommended for those with cardiac symptoms.

Acknowledgement

We thank ER, Cath. Lab., CCU, and oncology teams for their great support throughout the management of this patient. The deanship of scientific research at King Saud University, Riyadh, Saudi Arabia (Research grant number: RG-1436-013).

List of Abbreviations

ACS	Acute Coronary Syndrome
CCU	Coronary Care Unit
ECG	Electrocardiogram
ER	Emergency
FU	fluorouracil
FUTP	5-fluorouridine 5’-triphosphate
LV	Left Ventricle
RNA	Ribonucleic Acid

Consent for publication

Informed consent was obtained from the patient to publish this case report.

Ethical approval

Not applicable

Author details

Fayez El Shaer[1,2], Ismail R Raslan[1], Waleed Al Habeeb[1], Mostafa Alshimiri[1], Hanan Albaker[1], Khalid AlHabib[1]

1. King Fahad Cardiac Center, Department of Cardiac Sciences, College of Medicine, King Saud University, Riyadh, Saudi Arabia
2. National Heart Institute, Cairo, Egypt

References

1. Güvenç TS, Celiker E, Ozcan KS, Ilhan E, Eren M. Acute myocardial infarction after capecitabine treatment: not always vasospasm is responsible. Chin Med J 2012; 125:3349–51.
2. Tsiamis E, Synetos A, Stefanadis C. Capecitabine may induce coronary artery vasospasm. Hellenic J Cardiol 2012; 53:320–3.
3. Kounis NG, Tsigkas GG, Almpanis G, Mazarakis A. Kounis syndrome is likely culprit of coronary vasospasm induced by capecitabine. J Oncol Pharm Pract 2012; 18:316–8. https://doi:10.1177/1078155211423118

4. Camaro C, Danse PW, Bosker HA. Acute chest pain in a patient treated with capecitabine. Neth Heart J 2009; 17:288–91. https://doi:10.1007/BF03086268
5. Scott PA, Ferchow L, Hobson A, Curzen NP. Coronary spasm induced by capecitabine mimicks ST elevation myocardial infarction. Emerg Med J 2008; 25:699–700. https://doi:10.1136/emj.2008.060574
6. Papadopoulos CA, Wilson H. Capecitabine-associated coronary vasospasm: a case report. Emerg Med J 2008; 25:307–9. https://doi:10.1136/emj.2007.055681
7. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994; 28:374–8. https://doi:10.1177/106002809402800314
8. Akhtar SS, Salim KP, Bano ZA. Symptomatic cardiotoxicity with high-dose 5-fluorouracil infusion: a prospective study. Oncology 1993; 50:441–4. https://doi:10.1159/000227226
9. de Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 1992; 10:1795–801.
10. Lestuzzi C, Viel E, Picano E, Meneguzzo N. Coronary vasospasm as a cause of effort-related myocardial ischemia during low-dose chronic continuous infusion of 5-fluorouracil. Am J Med 2001; 111:316–8. https://doi:10.1016/S0002-9343(01)00808-7
11. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf 2009; 8:191–202. https://doi:10.1517/14740330902733961
12. Golias C, Dimitriadis G, Dimitriadis D, Graidis C, Dimitrelos I, Tsiakou A, et al. Acute presentation of vasospastic angina induced by oral capecitabine: a case report. J Med Case Rep 2014; 8:18. https://doi:10.1186/1752- 1947-8-18
13. Kwakman JJM, Simkens LHJ, Mol L, Kok WEM, Koopman M, Punt CJA. Incidence of capecitabine-related cardiotoxicity in different treatment schedules of metastatic colorectal cancer: a retrospective analysis of the CAIRO studies of the Dutch Colorectal Cancer Group. Eur J Cancer 2017; 76:93–9. https://doi:10.1016/j. ejca.2017.02.009

Summary of the case

Patient (gender, age)	1	Male, 52 years
Final Diagnosis	2	Invasive adenocarcinoma in the transverse colon
Symptoms	3	Chemotherapy patient reported angina pain
Medications	4	Capecitabine, aspirin, plavix, lisinopril
Clinical Procedure	5	ECG was done twice, echocariography and angiography
Specialty	6	Cardiology, oncology