Diagnosis and management of a patient with 5 FU-induced ST elevation and nonsustained VT as a late presentation of cardiotoxicity and successful rechallenge of 5-FU

Lalitha C Medepalli (✉ lalitha.medepalli@gmail.com)
a. ¹ Department of Cardiology, Northside Hospital Cardiovascular Institute, NHHI, Chair, Cardio-Oncology task force chair, Northside Hospital, Atlanta, GA, USA  https://orcid.org/0000-0002-5661-3020

Tariq S. Mahmood
Department of Oncology, Atlanta Cancer care, affiliated with Northside Hospital Cancer Institute, Atlanta, GA, USA

Henry Liberman
Department of Interventional Cardiology, Northside Hospital Cardiovascular Institute, Northside Hospital, Atlanta, GA, USA

Anita M. Medepalli
Mercer University School of Medicine, Macon, GA, USA  https://orcid.org/0000-0002-9772-2143

Thomas W. Bagwell
Mercer University School of Medicine, Macon, GA, USA  https://orcid.org/0000-0002-2814-7640

Case Report

Keywords: 5-FU, colorectal cancer, chest discomfort, ST elevation, rechallenge of 5-FU, vasodilator therapy

Posted Date: August 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1961432/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

5-FU is an antimetabolite drug that is used to treat cancer. It is usually administered to decelerate and prohibit cancer cell proliferation. It acts by inhibiting the enzyme thymidylate synthase by blocking the thymidine formation required for DNA synthesis [1]. The most common clinical manifestation of 5-FU cardiotoxicity is chest pain related to coronary vasospasm [2]. An increase in endothelin-1, a vasoconstrictor, and a decrease in prostacyclin, a vasodilator, is thought to be the cause of endothelial dysfunction, which typically results in coronary vasospasm [3]. Cardiotoxicity induced by 5-FU carries a high risk of morbidity and mortality if it is left untreated [3]. Patients experiencing cardiotoxicity induced by 5-FU present with signs and symptoms of acute coronary syndromes with elevated cardiac biomarkers (troponin), and their ECGs often reveal ST segment differences. There can be two distinct clinical presentations, early or late presentation of cardiotoxicity. Usually, with early toxicity, troponin elevation may be evident. However, in late presentation of cardiotoxicity symptoms, troponin elevation and/or ECG changes may be undetectable. Our case has a unique presentation of 5-FU toxicity in a patient developing ST elevation and nonsustained ventricular tachycardia as a late presentation of cardiotoxicity. Despite the malignant presentation of this vasospasm with continuous infusion 5-FU administration (modified FOLFOX6), our patient was successfully treated and rechallenged with complete bolus 5-FU (FLOX) neoadjuvant chemotherapy. Chakrabarti, S. et al performed a retrospective review of approximately ten patients to explore the safety of substituting FLOX (bolus 5-FU, oxaliplatin, leucovorin) for FOLFOX (infusional 5-FU, oxaliplatin, leucovorin) and CAPOX (capecitabine, oxaliplatin) in patients who had 5-FU-induced coronary vasospasm. Out of the 10 patients, 8 patients had chest pain as the presenting complaint within 48 hours after beginning the 5-FU infusion. In 9 out of the 10 patients, coronary vasospasm occurred during the first cycle of therapy. All of the patients made a full recovery after the discontinuation of infusion of 5-FU or capecitabine. Subsequently, all patients received FLOX from 7 days to 18 months after the event, with 7 patients treated within 4 weeks of the event. FLOX did not cause any cardiovascular adverse events in any of the 10 patients [4].

Because our patient manifested malignant ST elevation and ventricular tachycardia during the late presentation coronary spasm with 5-FU, the cardio-oncology multidisciplinary team administered a vasodilator pre- and posttreatment regimen. This regimen was described previously in the literature for late presentation of 5-FU cardiotoxicity [5].

Case Presentation And Discussion

A patient in his late 30s with no known significant past medical history or risk factors for cardiac disease was admitted to our hospital with chest pain. The patient was diagnosed with rectal cancer (Fig. 1) in late August of 2021. He then received 5 sessions of XRT and started chemotherapy. He had completed the 1st cycle of continuous infusion 5-FU delivered by his CADD pump. Approximately 18 hours into his scheduled 2nd cycle continuous infusion 5-FU, the patient started experiencing mid sternal non-radiating chest pressure with an elevated heart rate and generalized weakness while he walked his dog. His chest pain was described by him as “minimal” whenever the patient walked his dog during the 1st infusion
The pain was normally alleviated when he took two oral tablets of calcium carbonate (Tums) since he had a history of acid reflux. However, during the second cycle, the Tums failed to alleviate his discomfort. He later walked up the stairs of his home and stated that the pain had reoccurred. He reported that the pain would last 20 to 30 minutes at each occurrence. He began to develop worsening chest pain even with less exertion. He contacted our on-call oncology service at our institution, who advised him that it could be reflux or coronary artery spasm and recommended that he be evaluated in the emergency room. He continued to have bouts of sternal chest discomfort that occurred even during the transfer from wheelchair to bed or ambulation from bed to bathroom. The patient denied experiencing associated diaphoresis, dizziness, or nausea symptoms and reported not having done any heavy lifting recently. He denied any prior cardiac evaluation, including a stress test. After the patient was admitted and was in the emergency department, the pain recurred again. At the time, the patient had been receiving his second cycle of 5-FU CADD pump as a treatment for his rectal cancer. Lestuzzi et al., in a prospective study, evaluated the prevalence of exercise-induced myocardial ischemia in patients undergoing in-hospital long-lasting continuous infusion of 5-FU. The results showed a 10.3% global incidence of ischemia, as manifested by ECG changes, corresponding to previous observations reporting mostly ST-segment elevation; less frequently, ST segment depression, negative T waves, nonspecific ST-T changes, QT interval prolongation, and arrhythmias [6]. Thus, due to the patient experiencing continued chest pain, the 5-FU pump infusion was discontinued on October 22nd at approximately 6:30 AM since it has been known to have adverse reactions resulting in coronary spasms, angina, and myocardial infarction.

The CT chest angiogram did not reveal a pulmonary embolism. His admitted ECG (Fig. 2) showed a sinus rhythm with a mild nonspecific inferolateral ST T abnormality. No significant ST elevation or depression was noted. His initial troponin level was recorded to be 1.0 ng/ml, which subsequently decreased to 0.5 ng/ml in the next 24 hours with no recurrence of chest pain or arrhythmia on the telemetry monitor during the next 24 hours. The patient had no known cardiovascular risk factors and denied having any family history of early cardiovascular disease. To evaluate the etiology of his chest pain, 26 hours after the 5FU pump was discontinued, the patient underwent an exercise treadmill stress test under the supervision of the cardiology team. Approximately 7–9 minutes into the exercise on the standard Bruce protocol, the patient started developing recurrence of chest pain with frequent PVCs and inferior ST elevation (Fig. 3). The stress test was terminated, and the ECG revealed inferolateral ST elevation in the immediate recovery period with frequent PVCs, nonsustained ventricular tachycardia, and idio-ventricular rhythm. SL NTG was administered with the resolution of the inferolateral ST elevation (Fig. 4). The patient was taken for emergent cardiac catheterization, which revealed normal coronary arteries angiographically.

After discussing the plan of care with the patient’s primary oncologist, the patient was admitted for the 3rd cycle of 5-FU via bolus infusion (FLOX regimen) to the observation unit to reduce the tumor burden before his scheduled colorectal surgery. The patient was pretreated with Nifedipine ER 30 mg 5 hours before, isosorbide mononitrate 3 hours before, and Cardizem 30 mg 1 hour before the planned administration of the 5-FU bolus. During bolus administration, the cardio-oncologist and the oncological pharmacist were at the bedside as the patient was monitored on continuous telemetry monitoring. A plan
was established to immediately discontinue the 5-FU 12-minute bolus dose and to administer SL NTG if chest pain recurs. The patient completed the scheduled 5-FU bolus administration without any complications or chest pain recurrence. Twelve hours later, the patient was discharged to his home. The patient was also re-administered Nifedipine XL 30 mg the evening before and the morning after the 5-FU bolus administration. The patient successfully completed his planned neoadjuvant therapy as an outpatient without any recurrence of chest pain or repeat cardiac complications. This was accomplished via the 3-drug pre- and posttreatment vasodilator regimen and 5-FU bolus administration (FLOX regimen).

**Conclusion**

1. Today, the survival of patients with advanced stages of colorectal cancer has improved. 5-FU is indicated for the treatment of patients with adenocarcinoma of the colon and rectum, adenocarcinoma of the breast, gastric adenocarcinoma, and pancreatic adenocarcinoma. New therapeutics, such as monoclonal antibodies targeting HER-2, including trastuzumab and pertuzumab, are also recommended (7).

2. Although 5-FU was approved by the FDA in 1962 (over 50 years ago) for the treatment of colorectal cancer, 5-FU is still utilized to treat patients with advanced stages of cancer and serves as the backbone therapy for colorectal cancer treatment.

3. It is critical to provide education about potential cardiac manifestations before treatment initiation and to identify early, at-risk patients for cardiac complications.

4. This case report emphasizes the importance of increased awareness, vigilant monitoring, and a multidisciplinary CO team's involvement with high-risk cardiac patients receiving 5-FU-based chemotherapy.

5. If the patient is experiencing symptoms of malignant cardiac toxicity while undergoing 5-FU chemotherapy treatment, 3-drug vasodilator therapy should be considered for administration prior to and after bolus 5-FU treatment during ongoing chemotherapy.

**Abbreviations**

5-FU: 5-fluorouracil; VT: ventricular tachycardia; DNA: deoxyribonucleic acid; ECG: electrocardiogram; XRT: radiotherapy treatment; CADD: computerized ambulatory delivery device, CT: computerized tomography; PVC: Premature ventricular contraction; SL: sublingual; NTG: Nitroglycerine; cm: centimeters; bpm: beats per minute; HER-2: human epidermal growth factor receptor 2; FDA: Food and drug administration; CO: Cardio-Oncology.

**Declarations**

**Contributions:**

1. Dr. Lalitha C Medepalli: Cardio-Oncologist on the case involved in the patient care, preparing, coordinating, and editing the manuscript
2. Dr.: Tariq S. Mahmood, Oncologist on the case, involved in the patient care

3. Dr.: Interventional cardiologist on the case, involved in the patient care

4. Anita M Medepalli: Medical student editing and preparing the manuscript

5. Thomas W. Bagwell: Medical student editing and preparing the manuscript

Disclosures: All authors have no conflicts of interest relevant to the topic in discussion.

Consent for publication: Dr. Lalitha C Medepalli, the Cardio-Oncologist on the case, received consent from the patient. Also, N/A – Patient`s name or identity was never disclosed.

References


Figures
Figure 1

An ulcerated nonobstructing large mass was found 10 cm proximal to the anus. The mass was partially circumferential (involving one-half of the lumen circumference). Biopsies were taken with cold forceps for histology, and the area was tattooed with an injection of 3 mL of Spot (carbon black). The biopsies proved that the patient had rectal cancer.
Figure 2

Baseline admit 12-lead ECG
Figure 3

Peak stress 12-lead ECG

Figure 4

12-lead ECG 3 minutes into recovery 4/10 chest tightness HR 79 bpm, inferolateral ST elevation with pvc