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Successful infusional 5-fluorouracil administration in a patient with vasospastic angina

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Abstract

A 48-year-old female with metastatic colon adenocarcinoma and history of pre-existing coronary vasospasm with ventricular tachycardia (VT) successfully tolerated *de novo* 5-fluorouracil (5-FU) chemotherapy infusions with prophylactic administration and optimization of anti-spasm medications. 5-FU has been reported to produce severe cardiotoxic side effects, including coronary vasospasm, ventricular arrhythmias, and sudden cardiac death, and is not typically reported in individuals with pre-existing coronary vasospasm.

Keywords

Cardio-oncology; 5-Fluorouracil; Variant angina; Coronary vasospasm

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

Our case report is unique in a number of ways. First, to the best of our knowledge, this is the only case report detailing the management of 5-FU administration in a patient diagnosed with coronary vasospasm prior to initiation of 5-FU. Second, this report highlights the successful use of a range of methods (oral, intravenous, and patch) of nitroglycerin delivery. These are important, especially in the outpatient setting as oral administration of nitroglycerin may be difficult in patients with colectomy and resultant poor absorption of oral medications. Lastly, this report highlights the role of additional monitoring such as a 14-day or implantable loop recorder in patients who are suspected to have arrhythmias secondary to vasospasm.

2. Case presentation

A 48-year-old female with a past medical history of hypertension, dyslipidemia, Raynaud's disease, and nicotine use underwent hemicolectomy fort an enhancing soft tissue density initially suspected as complicated diverticulitis of the descending colon. During surgery, she developed sinus bradycardia, ST depressions, and T-wave inversions, followed by non-sustained VT. Immediately post-operatively, the patient experienced chest and left shoulder pain with diaphoresis, associated with ST elevation in the inferior leads, ST depression in the lateral leads, and high-grade atrioventricular block (Fig. 1), followed by several episodes of sustained VT lasting for as long as 50 s (Fig. 2). She also then reported substernal chest pain at rest with spontaneous resolution (which she had thought to be heartburn) on multiple occasions prior to surgery.

On postoperative day 1, a transthoracic echocardiogram showed an ejection fraction of 64% with no regional wall motion abnormalities. On postoperative day 2, coronary angiography demonstrated no evidence of obstructive coronary artery disease (Fig. 3). Given that the symptoms and ECG findings were self-resolving, along with the risk of excessive bleeding with angiography and PCI in the immediate postoperative setting, catheterization was deferred to postoperative day 2. The troponin levels have been negative. Her symptoms and ECG findings, along with the absence of angiographically demonstrable obstructive coronary artery disease were highly suggestive of coronary artery vasospasm [1,2]. Her symptoms and ECG findings subsided on antianginal medications that included amlodipine, isosorbide mononitrate, and metoprolol tartrate which further supported the diagnosis.

Oncologic workup revealed colonic adenocarcinoma, with liver metastasis. 4 cycles of systemic chemotherapy, followed by resection of the liver metastases, then another 8 cycles of systemic chemotherapy were planned, with curative intent [3]. She was evaluated in cardio-oncology prior to planned infusional 5-FU therapy. Initially, an alternative chemotherapy regimen consisting of bolus 5-FU (FLOX5-FU and oxaliplatin) was discussed [4]. However, in view of paucity of data regarding the efficacy of the FLOX regimen in potentially curable oligometastatic colon cancer and given known increased gastrointestinal side effects of 5-FU bolus [5], modified FOLFIRINOX (folinic acid, infusional 5-FU, irinotecan, and oxaliplatin) was initiated, after an extensive risk *versus* benefit discussion with the patient and her multidisciplinary care team.

For the first cycle of chemotherapy, the patient was admitted to intensive care unit with continuous electrocardiographic monitoring. Cycle 1 of FOLFIRINOX was administered as follows: irinotecan (165 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), and then slow infusion of 5-FU (1600 mg/m^2) over two 24-h infusions. Nitroglycerin infusion (10 μg/min) was started prior to initiation of chemotherapy and continued until the first 24 h of 5-FU infusion was completed; oral amlodipine was continued. The patient tolerated the 5-FU infusion well without development of chest pain or ECG abnormalities. For the second 24-hour infusion of 5-FU, the nitroglycerin infusion was replaced with oral isosorbide mononitrate, which the patient successfully tolerated.

The second cycle of FOLFIRINOX was successfully administered in the outpatient setting. She developed diarrhea and noted passing of whole isosorbide mononitrate pills in her stool. This coincided with recurrence of substernal chest pain similar to prior episodes, prompting an emergency room visit, with unremarkable troponin and ECG. Sublingual nitroglycerin alleviated her symptoms. Before her discharge from the ER, the dose of isosorbide mononitrate was increased, and sublingual nitroglycerin was prescribed for breakthrough pain. A 14-day external ambulatory memory loop recorder event monitor was placed to record any associated arrhythmias.

The third and fourth cycles of FOLFIRINOX were also successfully administered in the outpatient setting. The memory loop recorder captured 2 episodes of non-sustained VT without ST elevation, associated with chest pain promptly relieved by sublingual nitroglycerin. Implantable cardioverter-defibrillator implantation was considered and deferred, and an implantable loop recorder was placed. Nitroglycerin patches (0.2 mg/h) were initiated and up-titrated, with breakthrough chest pain relieved by sublingual nitroglycerin, in the setting of malabsorption of oral isosorbide mononitrate.

3. Discussion

Cardiotoxicity from 5-FU may include coronary vasospasm, cardiac arrhythmias, and SCD, with anginal chest pain as the most common presentation, with an incidence of up to 18% [4]. While prior data suggested that the risk of cardiotoxicity is higher in patients with pre-existing cardiac disease such as coronary vasospasm, coronary artery disease, or cardiomyopathy [6,7]; a more recent analysis reveals that patients with vasospasm may actually be less likely to have prior cardiovascular disease or risk factors or be on cardiac medications [8]. Our patient had pre-existing coronary vasospasm, hypertension, and dyslipidemia, without ischemic heart disease.

Mechanisms of cardiotoxicity induced by 5-FU include coronary vasospasm, direct myocardial injury, vascular endothelial dysfunction, and impaired oxygen delivery [6]. The primary mechanism is coronary vasospasm leading to an acute ischemic event. The direct toxic effect of 5-FU on vascular endothelial cells results in endothelial damage and subsequent platelet and fibrin accumulation as well [6]. 5-FU also converts the usual biconcave shape of erythrocyte membranes to an echinocyte shape, which diminishes the erythrocyte's ability to deliver and transport oxygen, resulting in myocardial ischemia and injury [6].

In colorectal cancer treatment, 5-FU infusion is preferred over bolus in the adjuvant and metastatic settings in part due to tolerability [5,9]. In adjuvant treatment of resected colon cancer, infusion and bolus share similar disease-free survival and overall survival. However, side effects including neutropenia, diarrhea, and mucositis are significantly reduced with infusion compared to bolus and thus are the preferred route of administration [5]. In metastatic colorectal cancer, 5-FU infusion has shown a significantly improved response rate, and fewer toxicities compared to bolus dosing [9].

To the best of our knowledge, this is the first case report documenting successful *de novo* 5-FU administration in a patient with pre-existing coronary artery vasospasm. Recent literature has suggested strategies to manage fluoropyrimidine-induced chest pain in patients without pre-existing coronary vasospastic disease, but there are no established guidelines for managing 5-FU-induced cardiac complications in patients with pre-existing coronary vasospastic disease [4]. For prophylaxis of coronary vasospasm induced by 5-FU infusion in these high-risk patients, we propose starting nitroglycerin (10 μg/min) prior to chemotherapy infusion while inpatient followed by oral isosorbide mononitrate (and nitroglycerin patches if necessary), with sublingual nitroglycerin available for breakthrough, to vasodilate the coronary vessels during chemotherapy treatment. For the management of vasospastic episodes in between or after 5-FU treatments, appropriate titration of oral isosorbide mononitrate and nitroglycerin patches is warranted. In a recent study, 115 patients with vasospasm induced by 5-FU were studied; 5-FU rechallenge after pretreatment with calcium channel blockers (CCB) and/or nitrates was safe and allowed continued 5-FU therapy [10]. Of note, 78 of the 115 patients received oral long-acting CCB or nitrate therapy in this study and 34 patients had to stop 5-FU therapy. In our report, we use prophylactic and empiric IV nitroglycerin in a patient with baseline/pre-existing idiopathic and recurrent 5-FU-induced coronary vasospasm and high risk for ventricular arrythmias. The successful use of our approach may be crucial for some patients in a similar circumstance, as chemotherapy options are limited in these situations and an inability to use 5-FU may result in higher mortality [8,10].

For treating cardiotoxicity, vasodilation with non-dihydropyridine calcium channel blockers and nitrates has been effective in relieving chest pain and ECG changes from coronary vasospasms induced by 5-FU, aborting symptoms in up to 70% of patients [6]. In the past, it was recommended that 5-FU should be immediately discontinued upon clinical symptoms or ECG changes, with avoidance of subsequent rechallenge – which has an 82–100% risk of recurrence and a mortality of 13% [6]. However, more recent data and associated recommendations suggest that rechallenge can be considered with appropriate monitoring and pre-treatment with nitrates and calcium-channel blockers [10–12].

Life-threatening ventricular arrhythmias and SCD are rare complications of coronary artery vasospasm. It has been suggested that patients with coronary artery vasospasm and life-threatening ventricular arrhythmias may benefit from ICD placement for secondary prevention of SCD [13]. Our patient did not receive an ICD for secondary prevention of SCD, due to an absence of hemodynamically unstable sustained VT or a history of cardiac arrest due to ventricular fibrillation, given that her VT was situational in the

perioperative setting and therefore considered to be from a reversible cause. Her coronary artery vasospasm continues to be managed with medications.

A key limitation to our report was that we did not utilize a provocative challenge test to confirm the diagnosis of coronary vasospasm. While this testing would provide definitive evidence, it is not without risk, and while routine in some practices, is recommended particularly when clinical criteria and non-invasive assessment fail to confirm the diagnosis [14,15]. Our patient had symptoms and ECG changes suggestive of vasospasm, without any evidence of epicardial coronary artery disease on invasive angiography. Additionally, her symptoms were relieved by medications targeting coronary vasospasm. Given that her clinically diagnosed vasospasm was associated with VT, the risk *versus* benefit balance was considered in favor of treating the vasospasm without additional provocation testing to potentially elicit further VT. Echocardiographic, clinical, and laboratory findings were not otherwise suggestive of idiopathic myocarditis, and a cardiac MRI or further cardiovascular testing was not obtained. Clinical diagnosis of 5-FU vasospasm is consistent with prior literature, including a recent large retrospective analysis from Massachusetts General Hospital, where the authors described coronary vasospasm induced by 5-FU as the occurrence of new typical resting chest pain *with or without* ECG or biomarker changes [8]. Despite this limitation, this is the first case report documenting successful *de novo* 5-FU administration in a patient with pre-existing coronary artery vasospasm and therefore adds to scant prior literature and guidance on this subject.

4. Conclusions

5-FU is well known to cause severe cardiotoxic side effects, often presenting as chest pain related to coronary vasospasm with a high risk of fatal cardiac complications. For patients with pre-existing coronary vasospasm, optimization of oral anti-spasmic medication and early preemptive treatment with nitroglycerin infusion, as well as prompt cessation of 5-FU when indicated, may be critical.

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Abbreviations:

ECG	electrocardiogram
5-FU	5-fluorouracil
SCD	sudden cardiac death
VT	ventricular tachycardia

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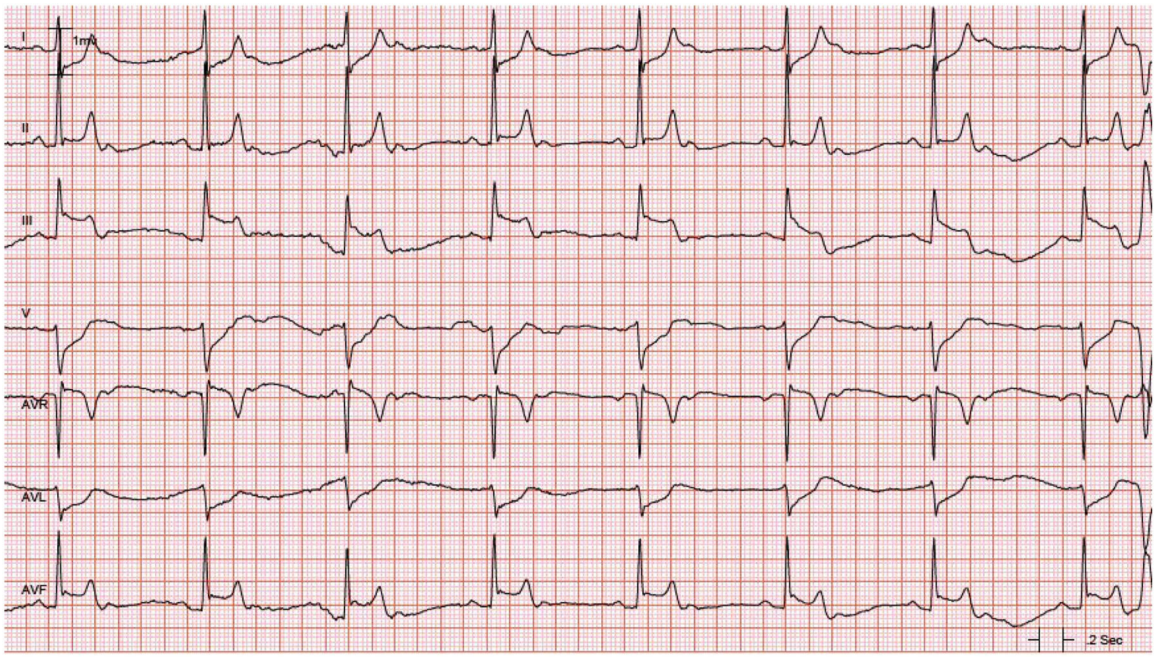

Fig. 1.

Rhythm strip post-operation with ST changes.

Sinus bradycardia, ST elevation in inferior leads (III, aVF), ST depression in lateral leads (I, aVL), and a high-grade atrioventricular block.

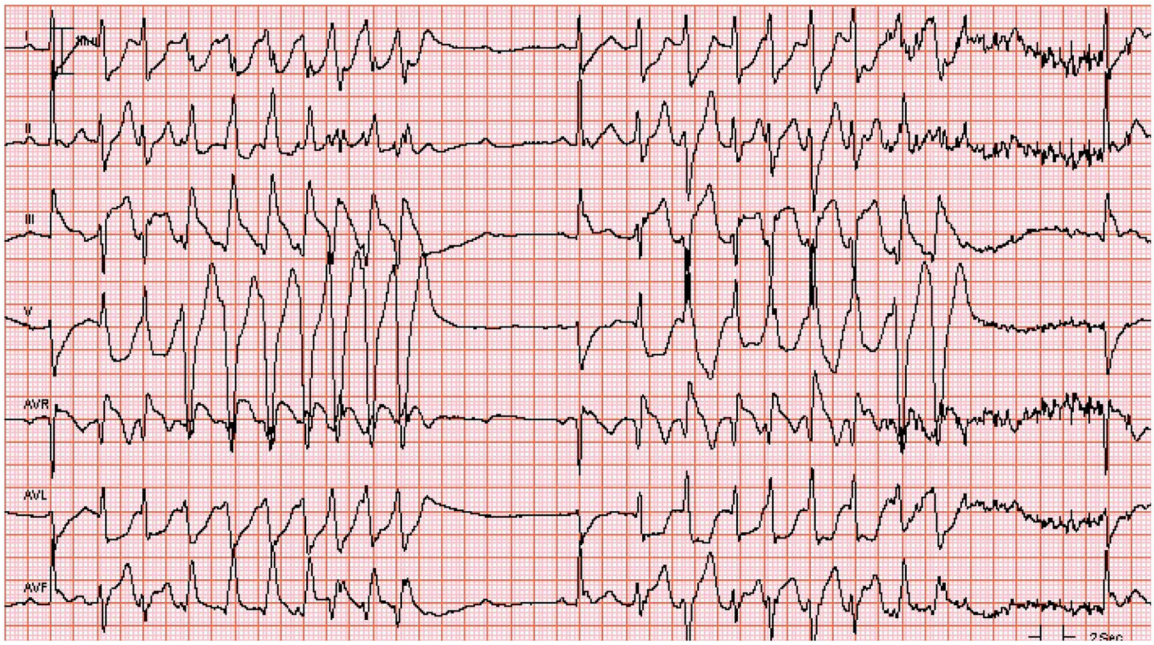

Fig. 2.

Rhythm strip post-operation with sustained VT.

Sustained polymorphic VT that continues for a total of 50 s.

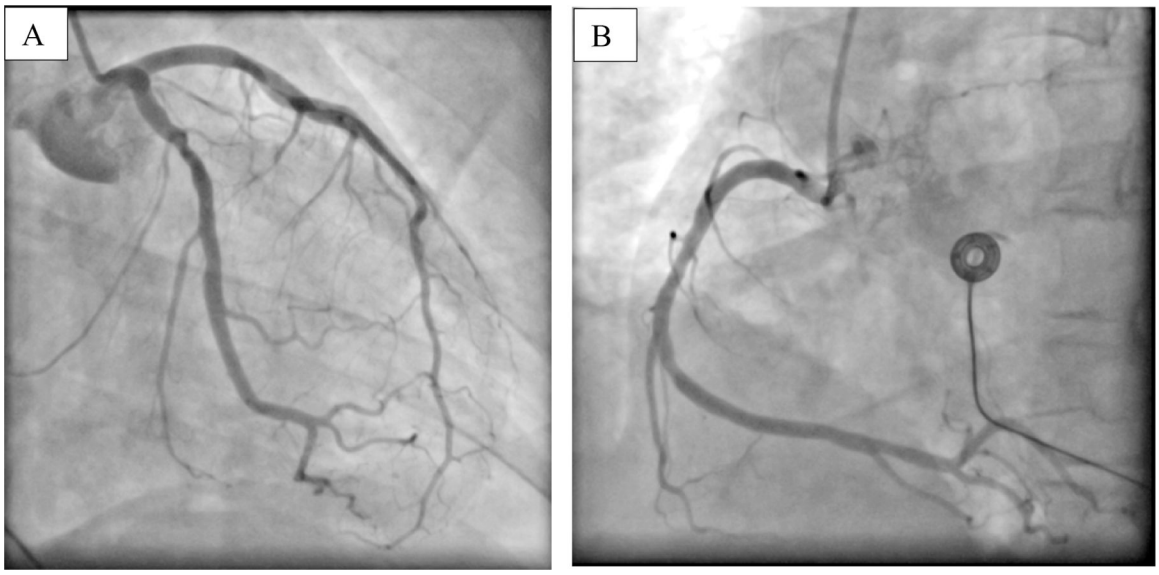

Fig. 3.

No obstructive epicardial coronary disease.

Left heart catheterization showing absence of obstructive epicardial coronary artery in the left coronary artery (A) and right coronary artery (B), respectively, viewed in multiple projections.