Coronary Vasospasm From 5-Fluorouracil Masquerading as Acute ST-Elevation Myocardial Infarction: A Diagnostic Conundrum

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Abstract

The antimetabolite 5-Fluorouracil (5-FU), commonly prescribed for treatment of various malignancies, has been reported to cause cardiotoxicity.[1,2] The incidence of cardiotoxicity is rare with 5-FU and angina is the most common clinical presentation. However, myocardial infarction, arrhythmias, and heart failure have also been reported.[1,3] In this report, we present the case of a 63-year-old male with stage IV colon cancer treated with 5-FU chemotherapy, presenting with chest pain and electrocardiogram changes that mimicked an acute ST-elevation myocardial infarction. This article reviews the occurrence of vasospastic angina without obstructive coronary artery disease in patients treated with 5-FU.

Case Presentation

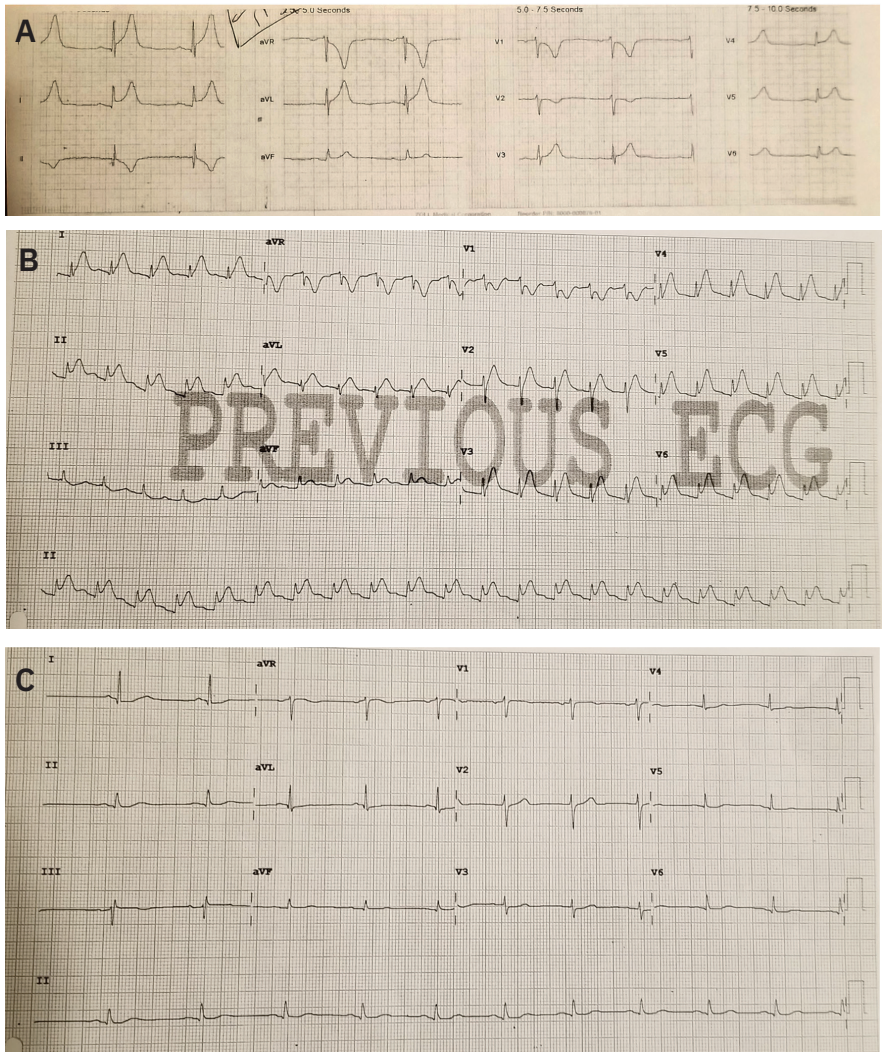
A 63-year-old male with a past medical history of hypertension, stage IV colon cancer status post colectomy 1 year prior, chronic left eye visual impairment of unclear etiology, and migraine headaches presented to the emergency department with chest pain. Two days prior, he had been started on an intravenous infusion of 5-FU as a treatment for colon cancer. He had no prior history of coronary artery disease.

The patient reported substernal chest pain radiating to his jaw that awoke him from sleep. The pain lasted 30 to 40 minutes before resolving spontaneously.

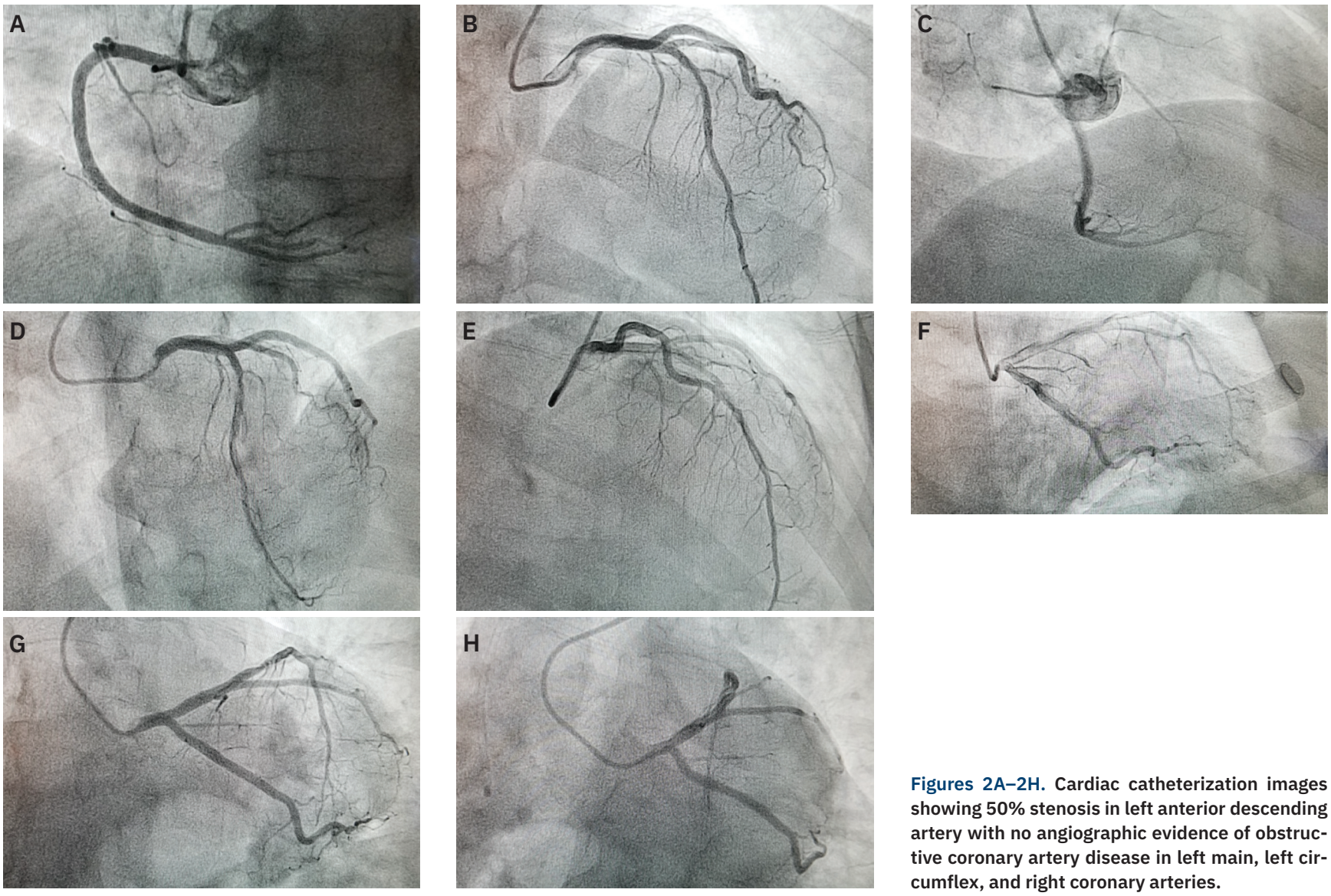
His physical exam, vital signs, cardiac biomarkers, and a chest x-ray were normal. An initial electrocardiogram (ECG) obtained by emergency medical services showed sinus rhythm with borderline ST elevation in inferior leads (Figure 1A). He received aspirin, ticagrelor, heparin bolus, and nitroglycerine sublingual, and was taken urgently to the cath lab. A coronary angiogram showed a 50% stenosis in the mid left anterior descending (LAD) artery, with no angiographic evidence of obstructive coronary artery disease in the left main, left circumflex, and right coronary arteries (Figures 2A-2H). Instantaneous wave-free ratio (iFR) of the mid LAD showed a nonobstructive stenosis. Transthoracic echocardiogram showed normal left ventricular systolic function and normal wall motion (Table 1). Thirty minutes after the procedure, he developed severe substernal chest pain radiating to his jaw. A repeat ECG showed ST elevation in inferior and anterolateral leads (Figure 1B). His physical exam and vital signs were normal. The patient was given nitroglycerine sublingual 0.4 mg and diltiazem 30 mg by mouth. Ten to 15 minutes later, his chest pain resolved and a repeat ECG showed resolution of the ST elevation (Figure 1C). He was then initiated on diltiazem 30 mg by mouth every 4 hours and isosorbide mononitrate 30 mg once a day with inpatient monitoring. The 5-FU chemotherapy was discontinued. He did not report any further anginal episodes.

Table 1. Laboratory evaluation.

Lab test	Result	Laboratory reference range
Troponin T (serial measurements)	<0.030	<0.030 negative
Serum sodium	139 mEq/L	134-144 mEq/L
Serum potassium	3.4 mEq/L	3.6-5.6 mEq/L
Serum creatinine	1.01 mg/dL	0.5-1.5 mg/dL
Creatine kinase	31 U/L	24-204 U/L
Serum calcium	8.8 mg/dL	8.3-10.0 mg/dL
Erythrocyte sedimentation rate	4 mm/hr	2-10 mm/hr
White cell count	8.4 X 1000/uL	3.9-11.0 X 1000/uL
Hemoglobin	13.3 g/dL	12.5-17.0 g/dL
Platelet count	264 X 1000/uL	150-450 X 1000/uL
C-Reactive protein	3.70 mg/L	0.0-4.9 mg/L
Urine drug screen	negative	negative



Figures 1A–C. **(A) Initial ECG showing sinus rhythm with borderline ST elevation in inferior leads. (B) Repeat ECG showed ST elevation in inferior and anterolateral leads. (C) Resolution of the ST elevation.**



Figures 2A–2H. Cardiac catheterization images showing 50% stenosis in left anterior descending artery with no angiographic evidence of obstructive coronary artery disease in left main, left circumflex, and right coronary arteries.

On the second day of his hospitalization, the patient developed headaches and vivid visual patterns. Magnetic resonance imaging of his brain showed multiple foci of restricted diffusion in bilateral supratentorial subcortical white matter, with the largest in the left anterior corpus callosum, measuring up to 6 mm. Neurology consultation was obtained and the findings were suggestive of cerebral vasospasm, resulting in small infarcts. Neurology recommended a calcium channel blocker for the duration of his 5-FU chemotherapy. The patient continued to report seeing vivid faces and geometric patterns with a cartoony quality for 48 hours before the symptoms finally resolved. He was discharged home on amlodipine, isosorbide mononitrate, and aspirin. He had no recurrence in his symptoms. His 5-FU was permanently discontinued.

Discussion

We describe a rare case of 5-FU induced cardiotoxicity presenting as an acute ST-elevation myocardial infarction, later confirmed to be vasospastic angina.

The exact mechanism by which 5-FU may lead to coronary artery vasospasm and possible widespread vasospasm is not well understood.[2,4] Diagnosis of 5-FU induced coronary vasospasm can be challenging and coronary artery disease must be ruled out in these patients.[3,5]

5-FU induced coronary vasospasm is commonly described during the first cycle of the therapy. The most common clinical manifestation is angina. The diagnosis is clinical and based on clinical presentation, cardiac biomarkers, ECG changes, echocardiographic cardiac function changes, and coronary angiography.[4-6] Ideally, 5-FU should be immediately discontinued in those patients thought to have cardiotoxicity from its administration. Angina and ischemic-appearing ECG changes usually resolve after cessation of 5-FU, suggestive of complete reversibility of the cardiotoxicity.[4,5,7] The reintroduction of 5-FU may be associated with a high recurrence rate of vasospastic episodes. However, for patients in whom no alternative chemotherapy regimens are feasible, such as in our case, the role of medical management with prophylactic medications may need to be considered.[6-8]

There are limited data in the literature regarding the reintroduction of 5-FU. If reintroduction is sought, then aggressive medical management with calcium channel blockers (CCB), long-acting nitrates, and aspirin are required before 5-FU chemotherapy can be reintroduced, and 5-FU may need to be immediately discontinued if further signs of cardiotoxicity are evident.[6,8,9]

Rechallenging in patients who are thought to have 5-FU associated coronary vasospasm is controversial, with high recurrence rates noted in a literature review. Currently, rechallenging with 5-FU is not recommended in general, due to a high risk for the recurrence of vasospasm, although it may be successful in certain cases.[8,10,12] Rechallenge may be reasonable in selected patients when other therapeutic alternatives are exhausted and the potential 5-FU treatment benefits significantly outweigh the risks.[10,13]

When rechallenge with 5-FU is considered, the administration of nitrates and CCB as prophylactic agents against coronary vasospasm recurrence has been reported to be successful in some cases.[7,9,10] The 5-FU rechallenge strategies may include reducing the dose, along with use of nitrates and CCB as prophylactic agents, and telemetry monitoring with reintroduction of 5-FU therapy.[8,10,11] It is unclear if the use of prophylactic agents with the reintroduction of 5-FU is safe in individuals with reduced left ventricular systolic function incurred after experiencing coronary vasospasm.[9-11]

Current data suggest that it is acceptable to administer low-dose aspirin, CCB such as diltiazem, and a long-acting nitrate such as isosorbide dinitrate up-titrated to the highest dose tolerated at least several hours prior to rechallenging with 5-FU.[7,9,13] Careful clinical and telemetry monitoring along with cardiology consultation would be advisable when rechallenge is attempted. If any cardiovascular signs or symptoms recur, 5-FU must be immediately discontinued.[7,9,12,13]

There are currently no randomized trials assessing the safety and efficacy of rechallenge approach to 5-FU with prophylactic medications. It is important to recognize 5-FU associated coronary vasospasm, because continued administration of 5-FU may be potentially deleterious.[11,13,14] However, early cessation of effective 5-FU comprised chemotherapy may compromise adequate treatment of cancers. There are not enough data available currently to identify patients at high risk for 5-FU associated coronary vasospasm.[13-15]

More research is required to evaluate the safety and efficacy of rechallenging with 5-FU, along with prophylactic agents for individuals with known 5-FU associated coronary vasospasm.[12,14,15] ■

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