Delayed Coronary Vasospasm in a Patient with Metastatic Gastric Cancer Receiving FOLFOX Therapy

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A 40-year-old man with stage IV gastric adenocarcinoma was found to have coronary artery vasospasm in the setting of recent 5-fluorouracil administration.

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Coronary artery vasospasm is a rare but well-known adverse effect of 5-fluorouracil (5-FU) that can be life threatening if unrecognized. Patients typically present with anginal chest pain and ST elevations on electrocardiogram (ECG) without atherosclerotic disease on coronary angiography. This phenomenon typically occurs during or shortly after infusion and resolves within hours to days after cessation of 5-FU.

In this report, we present an unusual case of coronary artery vasospasm that intermittently recurred for 25 days following 5-FU treatment in a 40-year-old male with stage IV gastric adenocarcinoma. We also review the literature on typical presentation and risk factors for 5-FU-induced coronary vasospasm, findings on coronary angiography, and management options.

5-FU is an IV administered antimetabolite chemotherapy commonly used to treat solid tumors, including gastrointestinal, pancreatic, breast, and head and neck tumors. 5-FU inhibits thymidylate synthase, which reduces levels of thymidine, a key pyrimidine nucleoside required for DNA replication within tumor cells.[1] For several decades, 5-FU has remained one of the first-line drugs for colorectal cancer because it may be curative. It is the third most commonly used chemotherapy in the world and is included on the World Health Organization's list of essential medicines.[2]

Cardiotoxicity occurs in 1.2 to 18% of patients who receive 5-FU therapy.[3] Although there is variability in presentation for acute cardiotoxicity from 5-FU, including sudden death, angina pectoris, myocardial infarction, and ventricular arrhythmias, the mechanism most commonly implicated is coronary artery vasospasm.[3] The direct observation of active coronary artery vasospasm during left heart catheterization is rare due its transient nature; however, several case studies have managed to demonstrate this.[4,5] The pathophysiology of 5-FU-induced cardiotoxicity is unknown, but adverse effects on cardiac microvasculature, myocyte metabolism, platelet aggregation, and coronary vasoconstriction have all been proposed.[3,6]

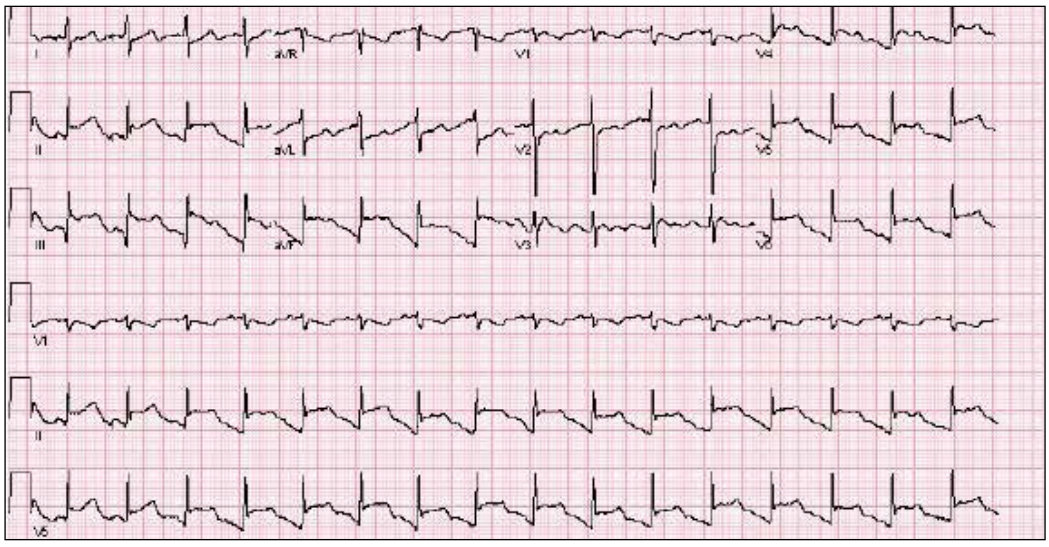
In the current case, we present a patient with stage IV gastric adenocarcinoma who complained of chest pain during hospitalization and was found to have coronary artery vasospasm in the setting of recent 5-FU administration. Following coronary angiography that showed a lack of atherosclerotic disease, the patient continued to experience episodes of chest pain with ST elevations on ECG that recurred despite cessation of 5-FU and repeated administration of vasodilatory medications.

CASE PRESENTATION

A male aged 40 years was admitted to the hospital for abdominal pain, with initial imaging concerning for partial small bowel obstruction. His history included recently diagnosed stage IV gastric adenocarcinoma complicated by peritoneal carcinomatosis status post initiation of infusional FOLFOX-4 (5-FU, leucovorin, and oxaliplatin) 11 days prior. The patient was treated for small bowel obstruction. However, several days after admission, he developed nonpleuritic, substernal chest pain unrelated to exertion and unrelieved by rest. The patient reported no known risk factors, family history, or personal history of coronary artery disease. Baseline echocardiography and ECG performed several months prior showed normal left ventricular function without ischemic findings.

Physical examination at the time of chest pain revealed a heart rate of 140 beats/min. The remainder of his vital signs were within normal range. There were no murmurs, rubs, gallops, or additional heart sounds heard on

FIGURE 1 Electrocardiogram Obtained During Patient's Initial Chest Pain Episode



ST elevations can be seen in leads II, III, aVF, V4, V5, and V6, and reciprocal depressions in leads I and aVL.

cardiac auscultation. Chest pain was not reproducible to palpation or positional in nature. An ECG demonstrated dynamic inferolateral ST elevations with reciprocal changes in leads I and aVL (Figure 1). A bedside echocardiogram showed hypokinesis of the septal wall. Troponin-I returned below the detectable level.

The patient was taken for emergent coronary catheterization, which demonstrated patent epicardial coronary arteries without atherosclerosis, a left ventricular ejection fraction of 60%, and a right dominant heart (Figures 2 and 3). Ventriculogram showed normal wall motion. Repeat troponin-I several hours after catheterization was again below detectable levels.

Given the patient's acute onset of chest pain and inferolateral ST elevations seen on ECG, the working diagnosis prior to coronary catherization was acute coronary syndrome. The differential diagnosis included other causes of life-threatening chest pain, including pulmonary embolism, pneumonia, aortic dissection, myopericarditis, pericardial effusion, cardiac tamponade, or coronary artery vasospasm. Computed tomography (CT) angiography of the chest was not consistent with pulmonary embolism or other acute cardiopulmonary process. Based on findings from coronary angiography and recent exposure to 5-FU, as well as resolution followed by recurrence of chest pain and ECG changes over weeks, the most likely diagnosis after coronary catheterization was coronary artery vasospasm.

Treatment

Following catheterization, the patient returned to the medical intensive care unit, where he continued to report intermittent episodes of chest pain with ST elevations. In the following days, he was started on isosorbide mononitrate 150 mg daily and amlodipine 10 mg daily. Although these vasodilatory agents reduced the frequency of his chest pain episodes, intermittent chest pain associated with ST elevations on ECG continued even with maximal doses of isosorbide mononitrate and amlodipine. Administration of sublingual nitroglycerin during chest pain episodes effectively relieved his chest pain. Given the severity and frequency of the patient's chest pain, the oncology consult team recommended foregoing further chemotherapeutic treatment with 5-FU.

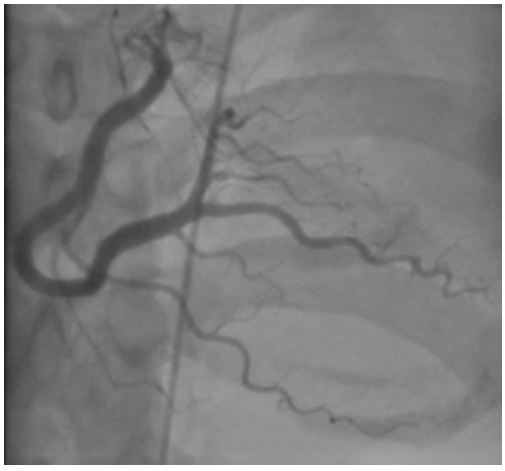
Outcome

Despite holding 5-FU throughout the patient's hospitalization and treating the patient with antianginal mediations, frequent chest pain episodes associated with ST elevations continued to recur until 25 days after his last treatment with 5-FU (Figure 4). The patient eventually expired during this hospital stay due to cancer-related complications.

DISCUSSION

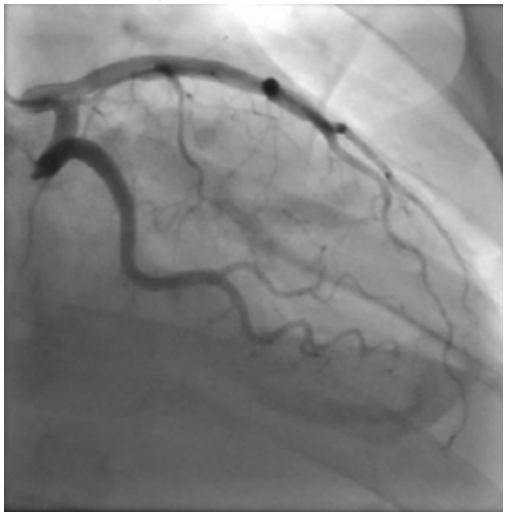
Coronary artery vasospasm is a well-known complication of 5-FU that can be life threatening if unrecognized.[6-8] As seen in our case, patients

FIGURE 2 Left Coronary Artery System



Patent left anterior descending and left circumflex arteries.

FIGURE 3 Right Coronary Artery System



Patent right coronary artery, posterior descending artery, and posterolateral extension.

typically present with anginal chest pain relieved with nitrates and ST elevations on ECG in the absence of occlusive macrovascular disease on coronary angiography.

A unique aspect of 5-FU is its variability in dose and frequency of administration across chemotherapeutic regimens. Particularly, 5-FU can be administered in daily intravenous bolus doses or as a continuous infusion for a protracted length of time. The spectrum of toxicity from 5-FU differs depending on the dose and frequency of administration. Bolus administration of 5-FU, for example, is thought to be associated with a higher rate of myelosuppression, while infusional administration of 5-FU is thought to be associated with a higher rate of cardiotoxicity and a higher tumor response rate.[9]

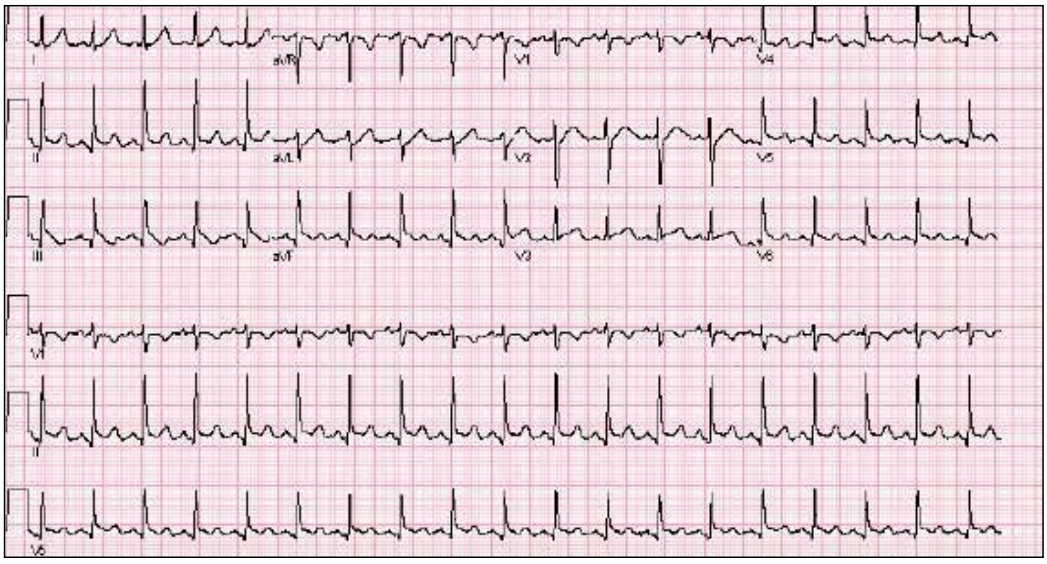
Most cases of coronary vasospasm occur either during infusion of 5-FU or within hours to days after completion. The median time of presentation for 5-FU-induced coronary artery vasospasm is about 12 hours postinfusion, while the most delayed presentation reported in the literature is 72 hours postinfusion.[6,8] Delayed presentation of vasospasm may result from the release of potent vasoactive metabolites of 5-FU that accumulate over time; therefore, infusional administration may accentuate this effect.[6,9] Remarkably, our patient's chest pain episodes persisted for 25 days despite treatment with anti-anginal medications, highlighting the extent to which infusional 5-FU can produce a delay in adverse cardiotoxic effects and the importance of ongoing clinical vigilance after 5-FU exposure.

Vasospasm alone does not completely explain the spectrum of cardiac toxicity attributed to 5-FU administration. As in our case, coronary angiography during symptomatic episodes often fails to demonstrate coronary vasospasm.[8] Additionally, ergonovine, an alkaloid agent used to assess coronary vasomotor function, failed to induce coronary vasospasm in some patients with suspected 5-FU-induced cardiac toxicity.[10] The lack of vasospasm in some patients with 5-FU-induced cardiac toxicity suggests multiple independent effects of 5-FU on cardiac tissue that are poorly understood.

In the absence of obvious macrovascular effects, there also may be a deleterious effect of 5-FU on the coronary microvasculature that may result in coronary artery vasospasm. Though coronary microvasculature cannot be directly visualized, observation of slowed coronary blood velocity indicates a reduction in microvascular flow.[8] Thus, the failure to observe epicardial coronary vasospasm in our patient does not preclude a vasospastic pathology.

The heterogeneous presentation of coronary artery vasospasm demands consideration of other disease processes such as atherosclerotic coronary artery disease, pericarditis, myopericarditis, primary arrythmias, and stress-induced cardiomyopathy, all of which have been described in association with 5-FU administration.[8] A 12-lead ECG should be performed during a suspected attack. An ECG will typically demonstrate ST elevations corresponding to spasm of the

FIGURE 4 Electrocardiogram Obtained During Chest Pain Episode 25 days After Last Administration of 5-Flurouracil



ST elevations in leads II, III, aVF, V4, V5, and V6, and reciprocal depressions in lead aVL demonstrated.

involved vessel. Reciprocal ST depressions in the contralateral leads also may be seen. ECG may be useful in the acute setting to identify regional wall motion abnormalities or to rule out pericardial effusion as a cause. Cardiac biomarkers such as troponin-I, -C, and creatine kinase typically are less useful because they are often normal, even in known coronary artery vasospasm.[11]

Coronary angiography during an episode may show a localized region of vasospasm in an epicardial artery. Diffuse multivessel vasospasm does occur, and the location of vasospasm may change, but these events are rare. Under normal circumstances, provocative testing involving angiography with administration of acetylcholine, ergot agents, or hyperventilation can be performed. However, this type of investigation should be limited to specialized centers and should not be performed in the acute phase of the disease.[12]

Treatment of suspected coronary vasospasm in patients receiving 5-FU involves stopping the infusion and administering calcium channel blockers or oral nitrates to relieve anginal symptoms.[13] 5-FU-induced coronary artery vasospasm has a 90% rate of recurrence with subsequent infusions.[8] If possible, alternate chemotherapy regimens should be considered once coronary artery vasospasm has been identified.[14,15] If further 5-FU use is required, or if benefits are deemed to outweigh risks, infusions should be given in an inpatient setting with continuous cardiac monitoring.[16]

Calcium channel blockers and oral nitrates have been found to produce benefit in patients in acute settings; however, there is little evidence to attest to their effectiveness as prophylactic agents in those receiving 5-FU. Some reports demonstrate episodes where both calcium channel blockers and oral nitrates failed to prevent subsequent vasospasms.[17] Although this was the case for our patient, short-acting sublingual nitroglycerin seemed to be effective in reducing the frequency of anginal symptoms.

Long-term outcomes have not been well investigated for patients with 5-FU-induced coronary vasospasm. However, many case reports show improvements in left ventricular function between 8 and 15 days after discontinuation of 5-FU.[7,10] Although this would be a valuable topic for further research, the rarity of this phenomenon creates limitations.

CONCLUSIONS

5-FU is a first-line chemotherapy for gastrointestinal cancers that is generally well tolerated but may be associated with potentially life-threatening cardiotoxic effects, of which coronary artery vasospasm is the most common. Coronary artery vasospasm presents with anginal chest pain and ST elevations on

ECG that can be indistinguishable from acute coronary syndrome. Diagnosis requires cardiac catheterization, which will reveal patent coronary arteries. Infusional administration of 5-FU may be more likely to produce late cardiotoxic effects and a longer period of persistent symptoms, necessitating close monitoring for days or even weeks from last administration of 5-FU. Coronary artery vasospasm should be treated with anti-anginal medications, though varying degrees of effectiveness can be seen; clinicians should remain vigilant for recurrent episodes of chest pain despite treatment.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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