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CASE REPORT

5-Fluorouracil-related Cardiotoxicity with Coronary Vasospasms

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Abstract

FOLFIRINOX has been commonly utilized to treat patients with pancreatic cancer; however, it can manifest with rare, significant adverse effects. In particular, 5-FU has been associated with cardiotoxic effects, including but not limited to ischemic events, myocarditis, cardiac arrhythmias, cardiac death, heart failure, as well as coronary vasospasm. Two common thought processes regarding the mechanism of cardiotoxicity with 5-FU include exacerbation of ischemia secondary to coronary vasospasm and direct cell injury to the myocardium. Management of cardiotoxic adverse effects includes discontinuing 5-FU therapy if the patient can tolerate an alternative regimen or initiating prophylactic anti-anginal treatments with very close monitoring of the patient while they receive 5-FU therapy. Here, we describe a case of a 77-year-old patient with stage III pancreatic cancer who developed coronary vasospasm after initiation of combination therapy including 5-FU. Additional studies to gain further understanding of 5-FU cardiotoxicity are warranted, especially considering the common use of this medication with regards to pancreatic cancer patients. Further research of this topic may benefit patient care, prevent cardiovascular events, and determine which patients may benefit from prophylactic therapy while receiving 5-FU.

Keywords: Pancreatic carcinoma, Fluorouracil (5-FU) toxicity, 5-FU cardiotoxicity, Coronary vasospasm, Cardiotoxicity, Myocardial ischemia

1. Introduction

Fluorouracil with Irinotecan, Leucovorin, and Oxaliplatin (FOLFIRINOX) is one of the most common chemotherapy regimens utilized in patients with pancreatic carcinoma; however, it can be associated with significant side effects. 5-fluorouracil (5-FU) is the third most commonly used chemotherapy agent in treating solid tumors across the globe.[1] After anthracyclines, 5-FU is the second most common medication associated with cardiac toxicities such as coronary vasospasms and myocardial ischemia.[1] In this case report, we discuss a patient with stage III pancreatic carcinoma who was recently initiated on a combination regimen of chemotherapy including fluorouracil, who developed coronary vasospasm secondary to his treatment regimen. This is a rare side effect of 5-fluorouracil that may benefit from further research and studies.

2. Case report

This is a 77-year-old gentleman with a past medical history significant for coronary artery disease status post coronary artery bypass grafting and percutaneous intervention with a drug-eluting stent, as well as recently diagnosed stage III pancreatic cancer who presented to the Emergency Department (ED) with a chief complaint of moderate non-radiating retrosternal chest pain with associated nausea and diaphoresis with onset 1 h prior to presentation. The patient received sublingual nitroglycerin twice in the ambulance in route to the hospital which provided relief of symptoms, as well as a loading dose of aspirin.

As for the patient's Oncologic history, the patient underwent computed tomography (CT) of the abdomen and pelvis approximately 1 month prior to presentation, significant for heterogeneous mostly hypoenhancing mass in the pancreatic head/body

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measuring 4.8 × 3.6 × 3 cm with encasement and partial occlusion of superior mesenteric vein and with encasement of the distal aspect of the superior mesenteric artery. The patient then underwent upper endoscopic ultrasound (EUS) which displayed irregular heterogeneous mass in the pancreatic head measuring 50 × 35 mm with poorly defined borders. Biopsies revealed pathology that was consistent with poorly differentiated adenocarcinoma. The patient underwent chemo port placement. The plan was to initiate neoadjuvant leucovorin calcium, fluorouracil (5-FU), irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) treatment. During cycle 1, on day 3 of the treatment, 1 h prior to disconnecting the 5-FU pump, the patient developed retrosternal, non-radiating, pressure-like chest pain. Vitals were remarkable for mild hypertension with a blood pressure of 149/87 mmHg and a heart rate of 87 beats per minute.

In the ED, electrocardiogram (EKG) was significant for ST-segment elevation in the inferior leads, and a code STEMI was activated [Fig. 1]. Troponin levels were unremarkable. Moments later the patient's chest pain resolved. A repeat EKG [Fig. 2] demonstrated resolution of the ST-elevations and the STEMI code was canceled. The patient was admitted to the cardiac critical care unit for further management. Transthoracic echo was significant for left ventricular ejection fraction of 40–45% as well as apical septal, apical anterior, and mid anteroseptal walls displaying hypokinesis and a basal inferoseptal wall displaying akinesis.

Upon further discussion with Cardiology, the patient was considered to be experiencing coronary vasospasm, which can be a rare manifestation following treatment with 5-FU. The patient endorsed the resolution of his symptoms, cardiac catheterization was deferred with a clear inciting event of his chest pain, and the patient was discharged home with close outpatient follow-up, and a prescription for sublingual nitroglycerin as needed for chest pain. Ultimately, the patient's treatment with 5-FU was discontinued by the Oncology team, with consideration for transition to alternative regimens such as Gemcitabine and Abraxane.

3. Discussion

Fluoropyrimidines, such as 5-fluorouracil (5-FU) and capecitabine are the mainstay chemotherapy regimens for a wide variety of gastrointestinal tract adenocarcinomas.[1] Despite the proven therapeutic efficacy, 5-FU carries several drug-related toxicities. After anthracyclines, 5-FU is the second most common medication associated with cardiotoxicity, including coronary vasospasms, myocardial ischemia, myocarditis, arrhythmias, heart failure, and even sudden cardiac death.[1] A study conducted by Rezkalla et al. reported ischemic changes with ST-segment deviation and QT-prolongation in almost 68% of the patients receiving 5-FU infusion.[2] Other studies have reported asymptomatic diagnostic ECG changes in roughly 88% of patients during the infusion, and while still, other studies have reported about 7% of patients to have elevations in troponin levels.[1] Patients receiving treatment with 5-FU most commonly present with atypical chest pain, on exertion or rest, and found to have acute coronary syndromes including myocardial infarction.[2] The cardiotoxicity from 5-FU is evaluated via electrocardiogram (ECG) changes with ST-segment elevations, troponin elevations, echocardiographic changes, and cardiac events like myocardial infarction (MI), coronary angiography with coronary stenosis.

It has been noted that Fluoropyrimidine-related cardiotoxicity most commonly tends to occur during the first cycle of its administration and that the median time to the onset of symptoms is approximately 12 h following infusion initiation.[1] Cardiotoxicity may occur anytime during the infusion or even 1–2 days after the infusion. Patient symptoms and ECG changes may resolve quickly with prompt drug discontinuation or may last a few days.

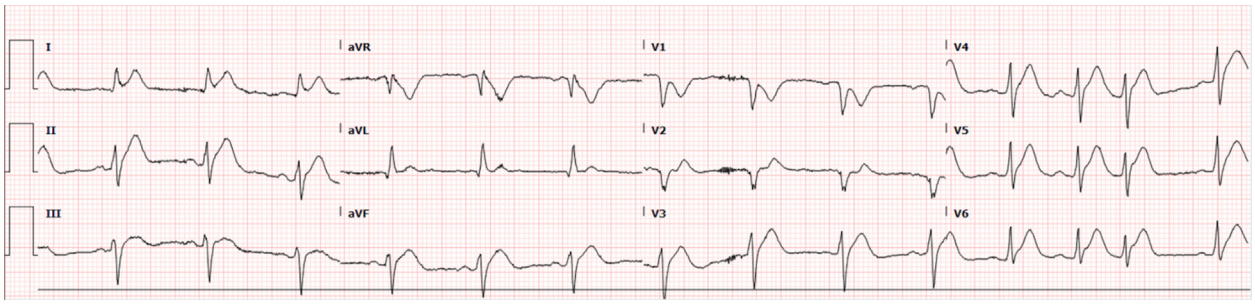

Fig. 1. Electrocardiogram demonstrating ST elevation in the inferior leads.

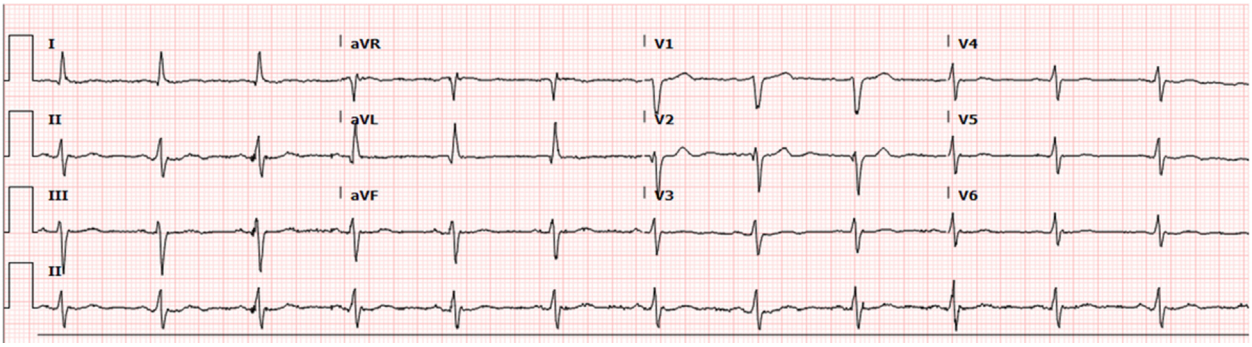

Fig. 2. Repeat Electrocardiogram demonstrating resolution of ST elevations in the inferior leads.

3.1. Mechanisms of cardiotoxicity

The two most common potential mechanisms likely responsible for 5-FU-related cardiotoxicity are myocardial ischemia and direct myocardial cell injury.[1] In terms of myocardial ischemia, coronary vasospasms appear to be the main reason. It is hypothesized that coronary vasospasm may be related to an endothelial dysfunction signifying the typical reaction to injury of the vessels during an insult. Normally acetylcholine induces vasodilation and release of nitric oxide from endothelial cells which allow for muscle relaxation and vessel dilation; however, when there is damage to endothelial cells, this process is interrupted, and any release of acetylcholine instead leads to vasoconstriction.[1,3] These changes can be noted via ECG alterations along with coronary vasospasms provoked with the 5-FU challenge.[1,3] At times, we may only see ECG changes without directly observing coronary vasospasm on angiography.

Another mechanism proposed is the direct myocardial endothelial cell injury by 5-FU through hypoxic cell injury and oxidative stress; however, these have been largely documented in animal model studies.[1,3] Further clinical studies in human subjects are needed to better understand the mechanisms involved in 5-FU-induced cardiotoxicity.

3.2. Risk factors for cardiotoxicity

It is also important to evaluate risk factors for cardiotoxicity in patients taking fluoropyrimidines as to date there is no consensus as to what these risk factors are.[1,4] There are observational studies that point to pre-existing cardiovascular and renal disease (defined as creatinine clearance less than 30 ml min-1) as possible risk factors for cardiotoxicity.[1] Studies have shown that underlying ischemic heart disease or MI or structural heart disease may be associated with cardiotoxicity in the setting of 5-FU infusion.[5] Interestingly, most cases of cardiotoxicity occur in patients who do not have pre-existing heart disease. Instead, the risk factors for developing cardiovascular diseases, such as hypertension, hyperlipidemia, and history of smoking may be more predictive of cardiotoxicity than a history of pre-existing heart disease itself.[1,4,5] Our patient had pre-existing coronary artery disease and hypertension along with hyperlipidemia that potentially led to cardiotoxicity in the setting of 5-FU infusion.

The schedule of administration of 5-FU also has been known to influence the risk of developing cardiotoxicity, with infusion regimens being linked with a greater risk than with bolus regimens 1). With infusion regimens of 5 or more days, the incidence of toxicity ranges between 2% and 18%. For patients receiving a short-term infusion with FOLFOX regimen for gastrointestinal tract cancers, the incidence of cardiotoxicity was 8.5%, compared to bolus regimens it was 3%, pointing to the net duration of treatment that may be associated with toxicity. Capecitabine is an orally available 5-FU prodrug that is metabolized in tissues and has similar pharmacokinetics to giving continuous infusion of 5-FU, and its incidence of cardiotoxicity is comparable at 3%–9% to that of a short-term infusion regimen. Unfortunately, thus far, the relationship between the dose administered of 5-FU and cardiac toxicity has not been demonstrated, and similarly circulating serum levels of 5-FU in patients with reported cardiotoxicity after 5-FU infusion has not been significantly different than those patients without cardiotoxicity.[1]

3.3. Management of cardiotoxicity

The cardiotoxic effects of 5-FU are potentially fatal. There is no definitive test that can demonstrate

5-FU causes cardiotoxicity directly and thus clinical judgment is required. Typically, the most important clue may be the temporal association between the development of symptoms of cardiotoxicity and administration of 5-FU. It is vital to discontinue chemotherapy immediately as the first step, and thereafter provide prompt symptomatic treatment with antianginal medications like nitrates or calcium channel blockers.[1,2] This approach has been reported to alleviate symptoms in almost 69% of the affected patients.[1] Other effective treatment methods have been to use alternative non-FU drugs that may be difficult to do in gastrointestinal cancers where 5-FU is an integral part of the regimen. But some good options do exist in patients with metastatic disease such as in colorectal cancer with irinotecan alone or irinotecan plus oxaliplatin, cetuximab.[1]

Currently, there are no alternative FU drugs that are available for use in the USA. However, there are alternative treatment modalities for patients with limited disease who may undergo locally directed therapy who cannot qualify for alternative chemotherapy. These include surgery, radiofrequency ablation, radioembolization, or transarterial chemoembolization.[1,2] Ultimately, management of patients exhibiting cardiotoxicity focuses on establishing whether 5-FU can in fact be the underlying cause and making every effort to identify and treat the other coexisting coronary artery disease while exploring acceptable alternative treatments or additional 5-FU is required. If additional 5-FU treatment is needed, clinicians ought to be cautious in its use and consider prophylactic antianginal therapies with a low threshold to discontinue 5-FU therapy.

4. Conclusion

5-FU-related cardiotoxicity is poorly understood and not well reported even though it is a common clinical entity. Given the frequency of use of 5-FU as a chemotherapeutic regimen, it is imperative to pay special consideration to the potential morbidity and mortality linked with using it. It is important to recognize that patients with preexisting cardiac disease receiving a continuous versus bolus regimen of 5-FU may be at a higher risk of cardiotoxicity. A good history and physical, and evaluation of cardiac risk factors or coronary artery disease that may be exacerbated using 5-FU, prior to chemotherapy, is paramount. The etiology of cardiotoxicity in the setting of 5-FU is likely multifactorial including coronary vasospasm and direct myocardial injury. It may help to pre-treat our patients with nitrates or calcium channel blockers, albeit the most effective to-date strategy has been treatment cessation or dose reduction of 5-FU.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Conflict of interest

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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