5-Fluorouracil-Induced Chest Pain and ST-Segment Elevation

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Abstract: 5-Fluorouracil (5-FU) is a chemotherapeutic agent commonly used to treat various malignancies. Cardiotoxicity is a rare adverse effect in patients being treated with 5-FU, but it can be severe and even fatal. The mechanism of myocardial ischemia caused by 5-FU is not known but several hypotheses exist, of which coronary vasospasm is the most widely accepted. Importantly, patients with preexisting coronary artery disease have been shown to be at increased risk of developing myocardial ischemia secondary to 5-FU. We present a case of 5-FU-induced chest pain and ST segment elevation in a patient with pre-existing coronary artery disease. The aim of this article is to provide a brief review of the available literature surrounding the topic of 5-FU cardiotoxicity and to heighten the readers’ awareness of the potential adverse cardiac effects of this agent.

Background
5-fluorouracil (5-FU) is a synthetic pyrimidine antimetabolite used to treat various malignancies, most commonly in breast and gastrointestinal cancers. Cardiac toxicity is a rare, but potentially serious adverse effect, and results in a spectrum of complications ranging from angina to myocardial infarction to sudden death. One large study including 910 patients treated with 5-FU found that the incidence of serious cardiotoxicity (defined as acute ST elevation or ventricular arrhythmias) was 0.55% (1). We present a case of 5-FU-induced cardiotoxicity which simulated an acute ST elevation myocardial infarction.

Case Report
A 40-year old black male with a history of HIV, hypertension, end-stage renal disease, and anal cancer with no history of cardiac disease presented after experiencing the sudden onset of substernal “squeezing” chest pain radiating to his neck and left arm and associated with nausea and diaphoresis. The patient had been diagnosed with squamous cell carcinoma of the anus one week prior and was receiving his third day of continuous intravenous 5-fluorouracil infusion. He was resting at the time the chest pain commenced and the pain persisted for approximately 30 minutes until he received 0.4 mg of sublingual nitroglycerin en route to the hospital. When he initially arrived at the emergency department, his blood pressure was 160/110, he reported no chest pain and his electrocardiogram was unremarkable (Fig. 1). However, while lying on the gurney, he again developed severe substernal chest pain which occurred approximately 1.5 hours after the first episode. A repeat electrocardiogram at that time showed diffuse ST elevations (Fig. 2). The patient was given 0.4 mg sublingual nitroglycerin which again completely relieved the pain. Aspirin 325 mg was given, nitroglycerin paste was applied, a heparin bolus was administered and a drip was started. The patient was then transferred to our facility and the 5-FU infusion was discontinued.

Upon arrival to our hospital, the patient continued to be free of chest pain and the electrocardiogram showed resolution of the ST elevations. However, given the recent chest pain and ECG changes, the patient was taken immediately for coronary angiography which showed 50% stenoses in the mid left anterior descending and left circumflex arteries but no occlusion or filling defects to suggest thrombus. Transthoracic echocardiogram revealed mild global left ventricular hypokinesis with an estimated
Discussion
This case demonstrates an example of cardiotoxicity caused by 5-fluorouracil. The mechanism of such adverse cardiac effects has not been proven, although many proposed mechanisms have been described in the literature. One such mechanism is thrombus formation. Kuzel et al. have demonstrated an increase in fibrinopeptide A in the blood during 5-FU infusion, which suggests that there may be an increased tendency towards thrombus formation in these patients. The same group has demonstrated a mild decrease in Protein C activity during 5-FU infusion [2]. Other studies have suggested a direct toxic effect of 5-FU on the coronary endothelium.

The most widely accepted hypothesis for 5-FU cardiotoxicity is that of coronary artery spasm. This hypothesis is supported in several studies, one of which is by Wacker et al. including 102 consecutive patients receiving 5-FU [3]. Nineteen patients had angina pectoris and ECG changes. Of these 19 patients, 6 underwent coronary angiography for severe symptoms. All 6 patients had non-obstructive coronary artery disease, suggesting vasospasm as the cause of their symptoms. There have also been in vitro studies which support the concept of 5-FU coronary vasospasm. Mosseri et al. demonstrated that 5-FU induces vasospasm in isolated rabbit aorta preparations [4]. Porta et al. have shown that endothelin-1 levels are increased in some patients with 5-FU induced cardiotoxicity, however, it is unclear whether endothelin-1 release is the cause or the result of vasospasm [5].

Cardiotoxicity caused by 5-FU is more common in patients with existing coronary artery disease which supports the hypothesis of increased vascular tone and vasospasm as an underlying cause. The syndrome most frequently occurs in patients receiving continuous infusion of the drug [1]. Furthermore, studies have shown that 5-FU induced cardiotoxicity is dose-dependent. In 1995, Weidmann et al. demonstrated that severe cardiac effects are more likely to occur when more than a cumulative 7 grams of 5-FU is administered [8]. However, in a more recent study by Tsibiribiri et al. 16 patients out of a total of 1,350 patients treated with various doses of 5-FU developed electrocardiographic and/or clinical manifestations of cardiotoxicity. Half of these patients had received less than 7 grams of 5-FU [9]. Therefore, although patients receiving high doses of the drug are at increased risk for cardiotoxicity, there remains a similar incidence of cardiotoxicity with “modern” dosing regimens.

It is important to note that the risk of recurrence after repeated exposure to 5-FU is between 82 and 100% [6]. Although one study by Dongiovanni et al. suggested that it may be safe to readminister 5-FU after an episode of cardiotoxicity if the patient’s angina is responsive to nitroglycerin, we would suggest that patients not be re-challenged [7]. Our patient’s pain and EKG changes were responsive to nitroglycerin, however, he did have evidence of myocardial depression on echocardiogram despite the brevity of his symptoms. While this patient’s depressed ejection fraction might have been pre-existing due to his other comorbidities, he is at higher risk for recurrence of cardiac toxicity related to 5-fluorouracil. The patient’s anti-retroviral therapy might also have put him at increased risk for this complication as.
there could have been some interaction between these drugs and the 5-fluorouracile which might have altered the pharmacokinetics of the chemotherapeutic agent.

**Note**
None of the authors have conflicts of interest to declare.

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