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ORIGINAL ARTICLE

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Failure of oral nitrate and calcium channel blocker therapy to prevent 5-fluorouracil-related myocardial ischemia: a case report

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Abstract *Background*: Myocardial ischemia induced by 5-fluorouracil (5-FU) is a relatively rare, but potentially serious, occurrence. Some case reports have indicated that recurrent ischemia may be prevented if 5-FU is resumed after pretreatment with antianginal therapy. *Methods*: A 54-year old woman was diagnosed with stage IIA squamous cell carcinoma of the anus. Treatment with concurrent radiation and chemotherapy (mitomycin-C and 5-FU) was initiated with curative intent. *Results*: The patient had no evidence of underlying coronary artery disease based on history, physical examination or ECG. Approximately 48 h after initiation of 5-FU infusion the patient developed anginal pain associated with ECG changes compatible with ischemia. After resolution of ischemia and ruling out of myocardial infarction, coronary arteriography demonstrated normal coronary arteries. In an attempt to prevent myocardial ischemia, calcium channel blocker and nitrate therapy was started, but anginal pain with ECG change recurred when 5-FU was resumed. This necessitated selection of an alternative chemotherapy regimen. *Conclusions*: Even in the presence of normal coronary arteries, antianginal therapy may not preclude the occurrence of potentially serious 5-FU induced myocardial ischemia. For patients who experience 5-FU-induced myocardial ischemia, development of alternative chemotherapy regimens should be considered.

Key words 5-Fluorouracil · Cardiac · Ischemia · Anal carcinoma

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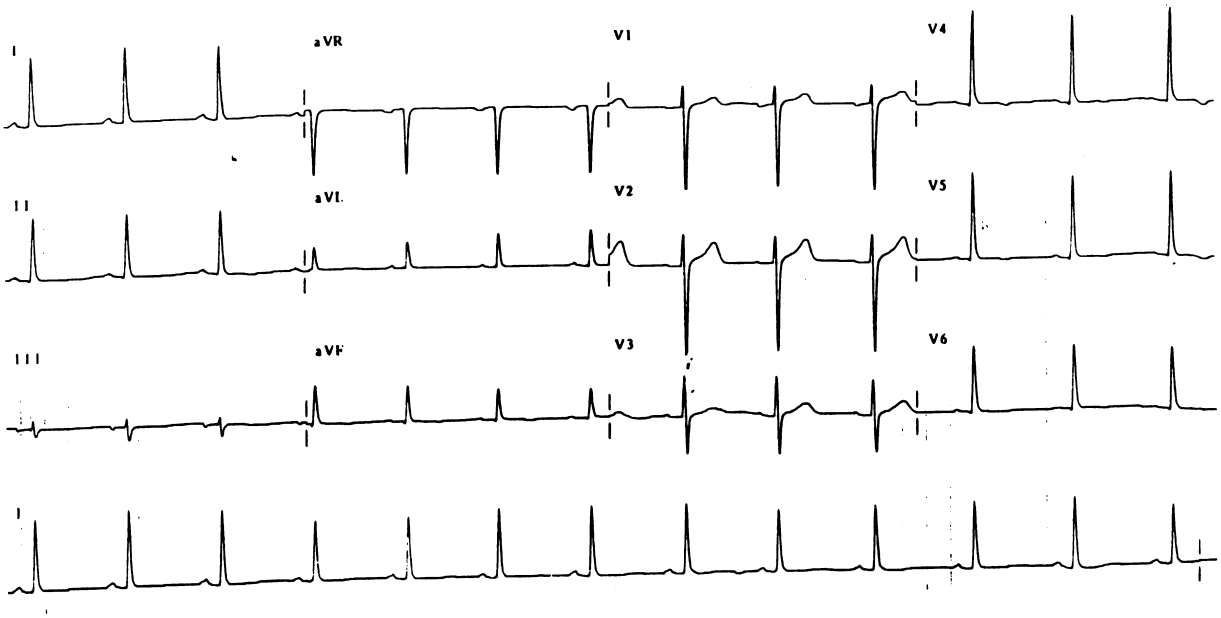
Introduction

5-Fluorouracil (5-FU) has found increasing application in a variety of cancers. 5-FU is an integral part of curative regiments for colorectal cancer in the adjuvant setting, or, when given concurrently with radiation, as primary therapy for other gastrointestinal cancers (e.g. anal or esophageal carcinoma). For this reason, guidelines for management of 5-FU toxicities are needed. Myocardial ischemia is an uncommon, but potentially very serious, side effect of 5-FU [5]. We here present an extensively documented case of 5-FU-related myocardial ischemia in a patient without underlying coronary disease which recurred despite pretreatment with calcium channel blockers and nitrates.

Case report

The patient was a 54-year-old white woman diagnosed with stage IIA squamous cell carcinoma of the anus (T2 N0 M0, poorly differentiated) after she herself palpated the lesion. She had no significant past medical history including specifically no history of chest pains, hypertension, diabetes, or alcohol use. She had a 15 pack-year smoking history but had not smoked in 16 years. She was admitted to Boston Medical Center for the first cycle of concomitant radiation therapy and chemotherapy containing mitomycin-C (10 mg/m^2 given by intravenous (IV) bolus) and 5-FU (1000 mg/m^2 per day given by continuous infusion over 5 days). Prior to beginning chemotherapy the patient's ECG showed nonspecific T-wave flattening in frontal and lateral leads and voltage compatible with left ventricular hypertrophy (see Fig. 1). After approximately 48 h of 5-FU infusion the patient developed severe substernal chest pain when she stood up to go to the bathroom. The pain radiated to her throat but was not accompanied by nausea or vomiting, diaphoresis, palpitations, or dizziness. It lasted about 20 min and was relieved with one sublingual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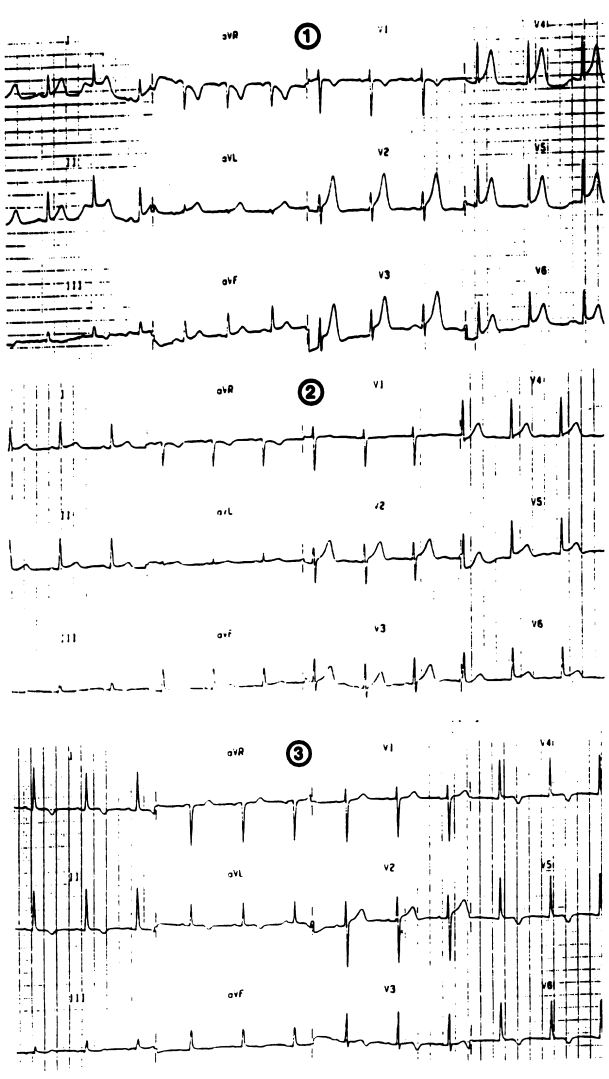
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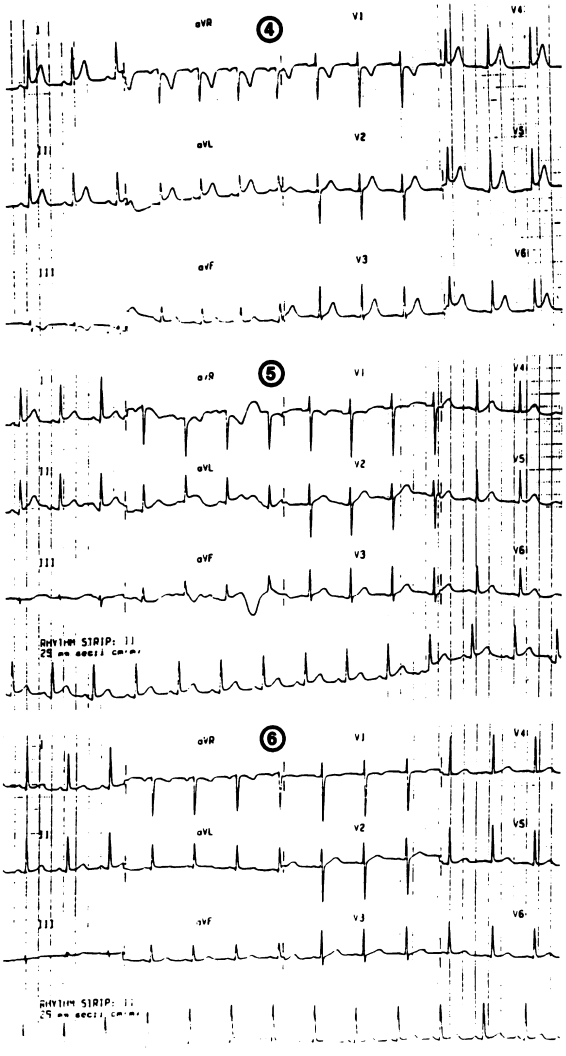
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Fig. 1 ECGs prior to during and after resolution of chest pain. The baseline ECG taken on the day of admission is shown at the top of the figure. *Panel 1* shows the ECG obtained during the first episode of chest pain that occurred approximately 48 h after initiation of chemotherapy. Note peaked T waves in leads V2–V6, I and II, and ST elevation in leads V2 and V3. *Panel 2* shows the ECG taken 7 min later after administration of nitroglycerin. Note that T waves and ST segment changes are resolving. *Panel 3* shows the ECG taken 20 min later (after resolution of chest pain) in which T wave inversions are present in leads I, II aVL and V3-6. *Panel 4* shows the ECG changes that occurred during the second episode of chest pain (approximately 2 h after the first episode; described as 7/10 in intensity). Note ST elevations in leads I, II, aVL, V4, and V5 as well as T-wave inversion in V1. *Panel 5* shows partial resolution of these changes 8 min later (after three sublingual nitroglycerin tablets; pain described as 1/10 in intensity). Finally, *Panel 6* shows complete resolution of ECG changes several hours later after discontinuation of 5-FU and institution of intensive antianginal therapy

nitroglycerin tablet. The ECG changes observed during and after this episode are shown in Fig. 1 (panels 1–3). A chest radiograph was normal. 5-FU was not discontinued at this time. A second episode of similar pain occurred about 2 h later while the patient was in the bathroom. In this instance the pain was relieved only after three sublingual nitroglycerin tablets were given and was described as similar to "a ton of bricks" on the patient's chest and reported as 10 on a scale of 1 to 10. ECGs taken during and after this episode of chest pain are shown in Fig. 1, panels 4–6.

After the second episode of chest pain 5-FU was discontinued and the patient was started on IV heparin, IV nitroglycerin, enteric-coated aspirin, and oxygen. The patient was transferred to the coronary care unit (CCU) with the diagnosis of unstable angina pectoris. Amlodipine 5 mg daily, isosorbide dinitrate 20 mg three times daily and metoprolol 25 mg twice daily were begun. An echocardiogram done in the CCU showed normal valves and ejection fraction. Myocardial infarction was ruled out based on resoulution of ECG changes (Fig. 1, panel 6) and normal cardiac enzymes. Cardiac catheterization showed normal coronary arteries. There was no recurrence of chest pain after discontinuation of IV nitroglycerin, metoprolol and heparin and reinstitution of radiation therapy.

Resumption of 5-FU therapy was discussed at length with the patient. Since 5-FU is integral to curative treatment regiments for anal cancer, it was decided to resume 5-FU while monitoring the patient in the CCU on high doses of calcium channel blocker and nitrate (amlodipine 10 mg daily and isosorbide dinitrate 40 mg three times daily). 5-FU was resumed 2 days after it had been discontinued. Approximately 42 h after resumption of 5-FU, chest pain recurred associated with ECG changes similar to those shown in Fig 1, panel 2. The pain began when the patient was getting up to use the commode, was of equal sverity to prior episodes and associated with dyspnea. 5-FU was discontinued permanently. Pain relief was initially achieved after 30 min with sublingual nitroglycerin (five tablets) and nifedipine (10 mg) and 2 mg IV morphine sulfate. However, after this recurrent twinges of pain occurred and IV nitroglycerin was resumed which fully relieved the chest pain. There was no recurrence of chest pain after this and ECG findings again reverted to normal. No sustained arrhythmias or evidence of congestive hear failure were noted during the patient's hospital course.

The patient continued to receive her radiation therapy as an outpatient. She did not develop severe diarrhea, stomatitis or other chemotherapy-related toxicities after discharge. Cisplatin (20 mg/m^2 per day for 5 days) and mitomycin (10 mg/m^2) were given for her second chemotherapy cycle without evidence of myocardial ischemia. At the end of her radiation therapy a near complete tumor regression was noted on rectal examination and 12 months later no recurrent chest pains were reported and complete tumor regression was noted.

Discussion

Concurrent chemotherapy and radiation have the ability to give long-term remission in the majority of localized anal cancers without need for surgery. The two major chemotherapy regimens used in this setting include 5-FU and mitomycin-C (as used initially in our patient) [11] and 5-FU with cisplatin [3, 4]. A recent trial has confirmed that the regimen of 5-FU and mitomycin-C is superior to 5-FU alone [4]. A large randomized trial has confirmed that for patients with anal cancer greater than 4 cm, disease-free survival is improved by the use of chemotherapy concurrent with radiation as compared to radiation alone [1]. 5-FU was included as part of chemotherapy regimens for anal carcinoma in all of these studies and must be considered an essential ingredient in the standard management of this cancer at present. The incidence of 5-FU-related cardiotoxicity has been reported at 0.55% and 1.6% in two large series [5, 8]. Of 35 patients with anal cancer treated using a regimen of cisplatin and 5-FU (750 mg/m^2 per day for 4 days) one case of cardiotoxicity was noted [3]. The type of cardiotoxicity was not specified, although it was noted that a second cycle of chemotherapy was given under strict cardiac monitoring without further sign of toxicity.

The incidence and severity of 5-FU-induced cardiotoxicity may be higher in patients with preexisting coronary artery disease [8, 18], although many cases have been reported in patients without a history of cardiac diseases [18]. The incidence may also be higher when 5-FU is used as part of combined chemotherapy regimens [6], although this is not agreed upon by all authors [16]. 5-FU-induced cardiac events occurring during 5-FU infusional therapy have their onset most commonly after several days therapy [5] (similar to our case). Cardiac events occur with bolus 5-FU therapy as well [5, 16]. The outcome of 5-FU-induced ischemia can be reversible angina (as in our case), arrhythmia, myocardial infarction, cardiac failure or death [5, 9, 16]. Angina occurring

after completion of 5-FU treatment has also been reported [16].

The potential for occurrence of cardiac events in patients being treated at home with infusional 5-FU therapy is of concern. Some of the home regimens (e.g. for concurrent chemoradiotherapy of rectal cancer) involve the use of lower doses of 5-FU. It is possible (although not yet clearly established) that such regimens have a lower incidence of cardiac toxicity. In a series involving 328 patients receiving 5-FU at 225 mg/m^2 per day for more than 30 days, no cardiac toxicity was reported [12]. In any case, patients and home infusion teams involved in home therapy with 5-FU should be aware of the potential for cardiotoxicity and be prepared to discontinue the infusion if significant symptoms occur.

One hypothesis is that 5-FU-induced myocardial ischemia results from coronary spasm [5, 7]. This hypothesis is supported by recent in vitro data showing that 5-FU can directly induce vasoconstriction in freshly isolated rabbit aorta preparations [10]. This in vitro effect is abolished by nitroglycerin. There have been some reports indicating that recurrent 5-FU-induced ischemia can be prevented by treatment with calcium-channel blockers or nitrates [2, 7, 13], although these agents have not been uniformly successful [14, 16, 18]. One explanation of the failure of these agents to prevent recurrence is that 5-FU may cause cardiotoxicity through mechanisms other than, or in addition to, vasoconstriction. For instance, 5-FU has been associated with left ventricular dysfunction [16] and ventricular arrhythmias [15] in the absence of myocardial infarction or chest pain. A direct toxic effect of 5-FU on cardiac myocytes has been proposed as a possible alternative explanation for cardiotoxicity [16].

Given the prompt response of our patient to nitroglycerin, the documented absence of coronary disease, and the importance of 5-FU in achieving cure of her cancer, we decided to resume 5-FU while monitoring the patient in the CCU under the usual treatment with high doses of a calcium-channel blocker and nitrates. Unfortunately, myocardial ischemia of similar (or greater) severity recurred after a similar period of 5-FU treatment. Fortunately, the ischemia was again reversible. If underlying coronary disease had been present more serious sequelae might have resulted. Her subsequent course did not suggest increased severity of other 5-FU-related toxicities which indicates that altered metabolism of 5-FU (e.g. as in dihydropyrimidine dehydrogenase deficiency) was probably not involved.

This case illustrates that pretreatment with relatively high doses of a calcium channel blocker and nitrates cannot be relied upon to prevent recurrent 5-FU-induced myocardial ischemia in a susceptible patient, even in the absence of demonstrable coronary disease. Also, the initial responsiveness of the patient's 5-FU-induced chest pain to sublingual nitrates did not predict a protective effect for long-acting nitrates. Failure of this approach might have been because the doses were not sufficiently high. Also, we cannot rule out that the use of different calcium-channel blocker or nitrate formulations might have been more effective. Alternatively, as suggested by Robben et al. [16] and Sasson et al. [17], mechanisms other than vasospasm per se may be involved in 5-FU-mediated cardiotoxicity.

The appropriate management of patients who experience cardiac ischemia during 5-FU therapy remains unclear. Even in cases where no underlying coronary disease exists, and in which rapid response to antianginal therapy occurs, initiation of relatively high doses of oral calcium channel blocker and long-acting nitrates will not necessarily prevent recurrence of 5-FU-induced myocardial ischemia. We conclude that the risk of resuming 5-FU in a susceptible patient must be weighed against the risk of choosing an alternative and perhaps less effective chemotherapy approach. It is uncertain if maximal anti-ischemic therapy, including other calcium channel blockers, beta blockers, and possibly IV nitroglycerin might prove more reliable in preventing these troublesome and potentially dangerous events. The need for equally effective alternative chemotherapy regimens for patients who develop 5-FU-induced myocardial ischemia is obvious.

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