Coronary insufficiency and 5-fluorouracil therapy

A case report, review, and suggestion regarding mechanism

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This report discusses the clinical and stress electrocardiographic findings in a patient with angina pectoris during courses of cancer chemotherapy with 5-fluorouracil. Similar cases from the literature are reviewed. Coronary artery spasm may be an explanation for the phenomenon.

Index terms: Angina pectoris • Chemotherapy, complications • Fluorouracil
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Cancer chemotherapy can affect the cardiovascular system in a wide variety of ways, from direct myocardial injury to indirect stresses such as pulmonary vascular changes. A rare difficulty is the inducement of a syndrome suggesting acute myocardial ischemia. The following case illustrates this complication and suggests a possible mechanism.

Case report

A 51-year-old man with well-differentiated adenocarcinoma of the bowel, which was metastatic to regional lymph nodes and liver, was treated with sigmoid resection and started on a chemotherapy program of 800 mg of 5-fluorouracil, intravenously, for five consecutive days each month. He began to note a regular and consistent effort-related chest pressure sensation starting in the mid-chest and radiating to the arms, throat, and jaw. This occurred late on the fifth day of infusion and persisted for 36–48 hours. However, neither this sensation nor rest pain nor prolonged pain occurred at other times during the month. After this occurred over three treatment periods, the patient brought it to the attention of his physicians. He had undergone cardiac catheterization four years earlier for evaluation of similar pain that occurred only at rest. At the time of catheterization marked spasm of the right and left anterior descending arteries was described by the attending angiographer but this finding was not documented on the cineangiogram. Review of that study showed a significant occlusion of the proximal anterior descending artery of 80%. There was a 60% proximal occlusion in the right coronary artery, which resolved with subsequent injections. The possibility of catheter-induced spasm was raised by the reviewing angiographer. A 30% circumflex lesion was also present. Isosorbide dinitrate (Isordil), 10 mg four times per day, was given with resolution of distress and was continued on a regular basis. Physical examination of the vascular system was unremarkable. The electrocardiogram (ECG) was normal. Exercise testing was performed once during a time free of chemotherapy and once on the fifth day of a chemotherapy course. During the first test he exercised 8 minutes and achieved 9 mets of physical output and a pulse of 100% of target. No pain or ECG changes occurred (*Fig. 1*). There were rare unifocal premature ventricular contractions. The second test was 7.5 minutes and again 9 mets. The pulse reached was 98% of target. At maximal effort ST-segment depression in V_1 was noted and in the early postexercise period progressive ST-segment elevation in leads I–III, aVF, and V_4–V_6 developed (*Fig. 2*) associated with typical pain. No arrhythmia occurred. Pain and ST-segment elevation resolved over 10 to 11 minutes. Exercise testing in conjunction with thallium-201 scintigraphy produced similar ECG changes and occurrence of pain. Thallium images were negative for regional perfusion defects. The chemotherapy schedule was modified to be given weekly with the same total dose per month and on this program the pain syndrome resolved and he returned to his baseline state of moderate asymptomatic activity.

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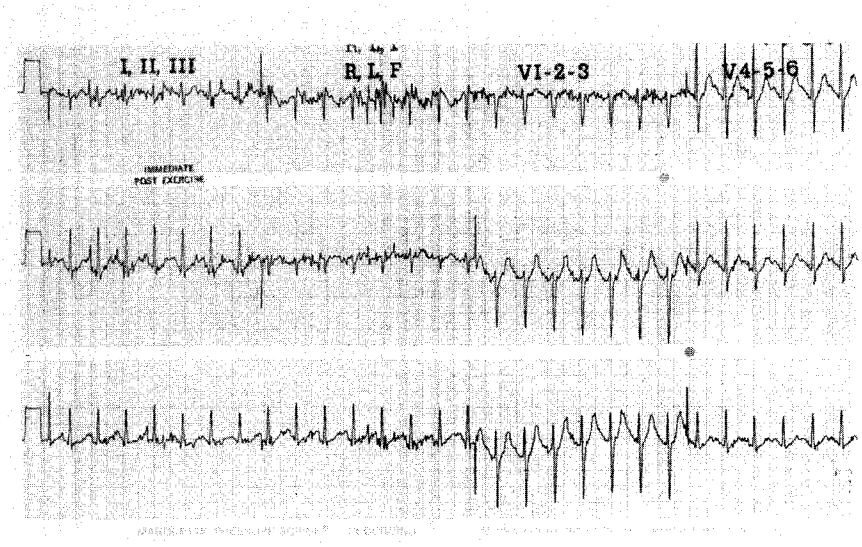

Figure 1. Maximal-effort ECG obtained in the period free of 5-fluorouracil exposure. No pain or other significant symptoms were present. The ST-segment and T-wave responses to exercise are normal.

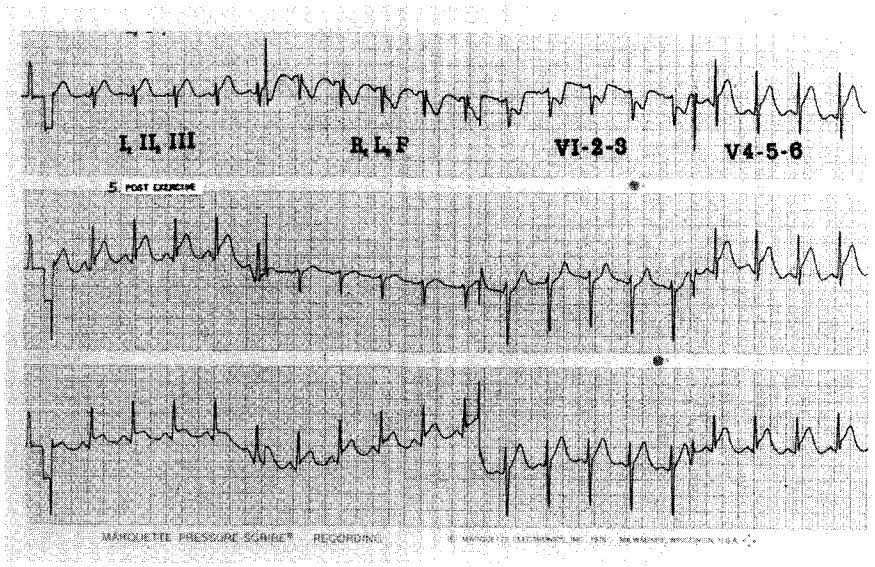

Figure 2. Five-minute recovery period ECG obtained after maximal stress on the fifth day of a course of 5-fluorouracil. Typical angina pectoris was present at maximal intensity at this time. Marked ST-segment elevation in lateral precordial and inferior leads is seen.

Discussion

This patient clearly had an anginal/ischemic syndrome precipitated by a chemotherapeutic agent. This is an uncommon but recognized occurrence and the pattern of his symptoms is similar to that described by others. Pottage et al[1] described 4 of 140 patients treated with bolus, intravenous 5-fluorouracil infusion. They developed typical cardiac ischemic pain 3–18 hours after an intravenous dose. This recurred with subsequent doses in 3 patients. All had pain after the second or third exposure to the drug. In the 3 with ECG changes, the pain was associated with acute T-wave changes and in one, anterior ST-segment elevation that cleared in four days. Roth et al[2] described a 48-year-old man who on three occasions (the last a controlled challenge) developed typical angina pectoris and pain associated with inferolateral T-wave inversion. The pain syndrome developed in this patient several hours after the second dose on the first two occasions.

Soukop et al[3] described 2 patients with a similar pattern of "severe central chest pain," "several," and "seven" hours after receiving their sixth and second respective intravenous bolus doses of 5-fluorouracil, 15 mg/kg. One patient developed acute anterolateral myocardial infarction and died in cardiogenic shock; the other showed transient ST depression with negative enzyme changes. He had a similar reaction to a lesser dose on retreatment. Stevenson et al[4] described a 33-year-old man who experienced neuromuscular quality pain after his second dose of 5-fluorouracil (15 mg/kg); after the fifth dose, he complained of chest tightness associated with tachycardia and ST-segment elevation in lead II and T-wave inversion in leads I, II, V_4–V_6. Acute pulmonary edema immediately followed. There were slight elevations of the creatine phosphokinase and serum glutamic oxaloacetic transaminase. A second course was associated with mild pain quickly responsive to nitroglycerin. Finally, Dent and McColl[5] described 3 patients with anginal pain associated with 5-fluorouracil therapy. One, a man with known coronary artery disease, had typical pain and ST-segment elevation following several courses of chemotherapy. No pain occurred between therapy sessions and he died suddenly after the fourth dose of the 16th course. The other 2 patients had typical anginal pain, which responded to nitroglycerin after the first dose of intravenous 5-fluorouracil; one had transient T-wave changes, and one had recurrent pain on subsequent doses.

In the present case and in those reviewed, a pattern is evident. The pain syndrome tends to follow infusion by several hours (7 of 7 were stated) and usually develops after the second or later doses (9 of 12). When noted, all had transient ECG abnormalities associated with normal or trivial enzyme changes with only one definite transmural infarction and one episode of sudden death.

Effort-related ST-segment elevation as seen in the present patient can be seen with fixed severe coronary artery disease,[6] left ventricular aneurysm or extensive scar,[7] and coronary artery spasm.[8–10] This man had definite coronary artery disease and at the time of catheterization was considered to show spasm of the right coronary artery and the anterior descending branch of the left coronary artery. Pharmacologic agents can induce coronary spasm. The most notable example is ergonovine maleate, the infusion of which is now an established means of provoking the process.[11] Alcohol[12] and histamine[13] precipitate spasm and variant angina pectoris in some patients.

The regularly recurrent quality of the pain and the reproducible abnormalities of stress ECG associated with pain in this patient in temporal relationship to 5-fluorouracil exposure suggests that a dynamic abnormality, such as a spasm, was responsible. The findings in the patients reviewed would suggest that such a process was active in at least some and perhaps in all of them. This patient had significant coronary artery disease noted at earlier catheterization. This had been clinically silent and remained so except during drug exposure. If spasm was responsible, the mechanism is unclear and any suggestion would only be speculation as the cause of spasm, whether direct or the result of an indirect or uncovered mediator, is itself unknown. Whatever the cause, there is clearly a subset of patients who will on exposure to the drug manifest coronary insufficiency at some point after the onset of therapy. Modifying dosage appears to help in some instances as well as the administration of nitrates, either as maintenance therapy or acutely as sublingual nitroglycerin. Calcium antagonists would also seem to be an appropriate treatment if these two measures fail to control symptoms, and alternative means of treating the tumor are thought to be less optimal.

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