Acute severe coronary spasm associated with initial first dose of 5-fluorouracil chemotherapy

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Key words:
Cardiotoxicity; Vasospasm.

Among the various pathophysiologic mechanisms proposed to explain the 5-fluorouracil cardiotoxicity, coronary vasospasm, occurring most frequently after the completion of the second or third dose of the cycle, has gained wide acceptance. We describe what to our knowledge is the first observation of typical Prinzmetal variant angina occurring very early after having started a 5-fluorouracil infusion administered as a chemotherapy regimen to a 66-year-old man with an adenocarcinoma of the right colon.

(Ital Heart J 2003; 4 (8): 568-570)

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Received February 21, 2003; revision received May 29, 2003; accepted June 12, 2003.

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Fluorouracil (5-FU) was introduced in the late 1950s as an antiproliferative compound for the treatment of various solid malignancies, namely adenocarcinomas of the breast and gastrointestinal tract and squamous cell carcinomas of the head and neck[1]. The spectrum of 5-FU side effects includes cardiotoxicity which has been reported with an increasing frequency since the first description in 1969 as a side effect of the administration of multiple chemotherapy regimen and later even following the administration of the drug alone[2,3]. The most common clinical presentation of 5-FU-induced cardiotoxicity is angina with ECG changes and a typical response to nitroglycerin[3-5]. Less frequent presentations include cardiac arrhythmias, the sudden death syndrome, cardiomyopathy with or without congestive heart failure and myocardial infarction[6-10].

We report what to our knowledge is the first observation of 5-FU cardiotoxicity manifesting as angina with ST-segment elevation very shortly following the initiation of a chemotherapy infusion regimen including only 5-FU.

Case report

A 66-year-old male patient with no significant medical history, no allergies or coronary risk factors and never evaluated for suspected coronary artery disease, was referred to the oncologic hospital-day service in November 2002 with a pT3pN1M0 right colon adenocarcinoma resected 1 month before. On preliminary physical examination he showed no signs of pulmonary or cardiac dysfunction nor any other organic disease. Given the otherwise excellent health status, the patient was scheduled for adjuvant chemotherapy including 5-FU alone (500 mg/m^2 administered once weekly for 6 months). Based on the planned regimen, the patient received the first 850 mg 5-FU dose administered as a 100 ml short infusion. After the first few milliliters of infusion he started to complain of chest pain, diaphoresis, nausea, and pruritis. At this point, the 5-FU infusion was immediately stopped. The patient appeared acutely ill and physical examination revealed severe bradycardia and hypotension (70/50 mmHg), a sweaty skin and localized urticaria. The ECG showed sinus bradycardia and marked ST-segment elevation on the infero-lateral leads without any pathological Q waves (Fig. 1). The prompt administration of intravenous fluid and minidoses of dopamine led to the resolution of the clinical and ECG picture in about half an hour (Fig. 1). Within 1 hour the patient was transferred to a tertiary hospital where he underwent urgent coronary angiography that revealed the presence of normal coronary arteries (Fig. 2). All laboratory parameters remained normal and there was no release of myocardial specific enzymes (creatine phosphokinase, creatine kinase-MB, troponin T).

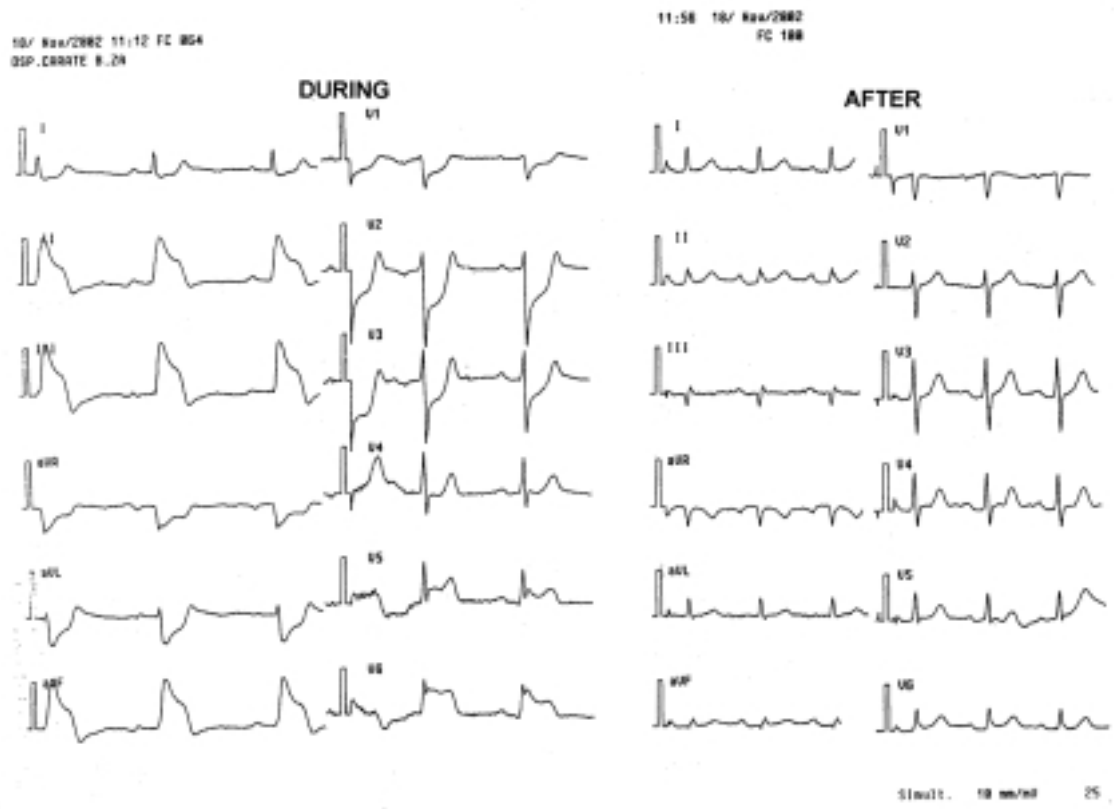

Figure 1. *Standard 12-lead ECG recorded during the 5-fluorouracil infusion* (left) *and showing marked ST-segment elevation in the infero-lateral leads. A normal ECG pattern was restored once the infusion was stopped* (right).

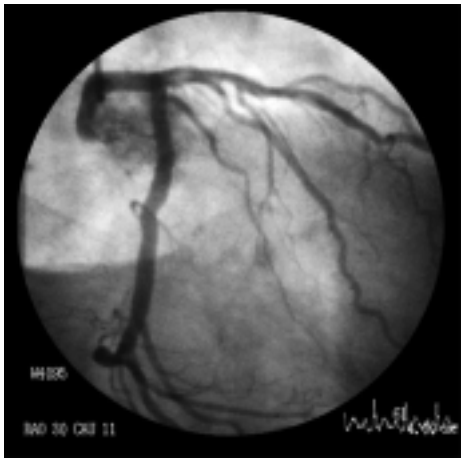

Figure 2. *Left coronary angiogram in the right anterior oblique 30° and caudal 11° view, taken within 1 hour of symptom onset and showing a normal dominant left coronary artery.*

Discussion

To our knowledge, this is the first case report in the literature in which symptoms and ECG signs of severe cardiac ischemia have manifested after only a few milliliters of 5-FU administered as an intravenous short infusion. In the majority of reports adverse cardiac events usually occurred within hours to a few days of the completion of the second or third dose of a cycle[1]. Although in some cases the toxic manifestations have been attributed to the first dose, to date no description has reported ischemic cardiac events after such a small dose of drug administered.

The estimated incidence of 5-FU cardiac toxicity varies from as low as 1.6% up to 68%, depending both on differences in the size and design of different studies as well as on the criteria employed for the diagnosis of cardiac toxicity[1,11]. A known history of coronary artery disease and prior or concomitant radiation therapy appear to be the strongest predictors of drug-induced cardiotoxicity[7,12,13]. However, the relationship between the therapeutic regimen (continuous infusion rather than bolus administration), the concomitant use of different chemotherapeutic agents and cardiac toxicity is still uncertain[13].

The actual pathophysiologic mechanism of 5-FU-related cardiotoxicity remains still unclear. Among the postulated theories the hypothesis that 5-FU induces electromechanical uncoupling secondary to a direct cytotoxic effect at the level of the myocardial cell membrane ion channels, mitochondria and nuclei has recently gained support[13]. However, the above and other proposed mechanisms (an autoimmune response against the cardiac myocytes with which the 5-FU metabolites form antigenic complexes, myocarditis), may not explain the clinical manifestation of typical angina concomitant to ECG changes often indicative of

regional ischemia. Such a clinical presentation associated with the prompt response to nitrates, and the finding of transient silent ischemia at continuous ECG monitoring are globally regarded as evidence supporting the hypothesis of a drug-mediated regional myocardial hypoperfusion[1,4-6,13]. On the other hand, the left ventricular dysfunction, which largely improves following the discontinuation of chemotherapy, has suggested the possibility of a stunned myocardium secondary to a widespread reversible drug-induced coronary ischemia[8,9].

Although coronary artery disease has been implicated as a risk factor for 5-FU cardiotoxicity, stress testing, coronary angiography and autopsy data indicate that the classic atherosclerotic plaque formation and rupture is not always involved[4]. Single or multivessel coronary spasm has been suggested as the main mechanism of the regional or global reduction in myocardial perfusion on the basis of the typical clinical and ECG presentation of transient cardiac ischemia without significant coronary stenosis[9,14,15]. While neither a direct action on the coronary smooth muscle by 5-FU nor definite biochemical mediators have until now been demonstrated[7], some clinical and experimental data suggest the intriguing hypothesis that coronary vasospasm could be triggered by a 5-FU-associated endothelial cell damage which in turn leads to the production of vasospasm, inducing compound either directly (endothelin-1) or secondary to thrombus formation[15-18].

The case we present, on the basis of the chest pain associated with the transient ST-segment elevation and normal coronary arteries at angiography, may be diagnosed as typical Prinzmetal variant angina, the mechanism of which has been universally accepted as being coronary spasm[19]. The sudden onset of the clinical presentation after only a few milliliters of 5-FU infusion, never reported before to our knowledge, may be explained, in our opinion, as an anaphylactic-like reaction to the drug.

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