# Management of patients with persistent chest pain and ST-segment elevation during 5-fluorouracil treatment: report about two cases

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*Key words:*
**Chest pain; ST-segment elevation.**

**5-Fluorouracil, a widely used drug in cancer treatment, is known to have cardiotoxic effects: chest pain with ECG changes, arrhythmias, arterial hypertension or hypotension, myocardial infarction, cardiogenic shock and sudden death have been described in the literature. Coronary artery vasospasm is the pathogenetic mechanism hypothesized in most cases, but mechanisms other than myocardial ischemia had been advocated in some patients.**

**The approach to the patient with persistent chest pain, despite therapy and persistent ST-segment elevation mimicking an acute myocardial infarction, has not been well addressed, and the appropriate diagnostic and therapeutic pathways have not yet been defined.**

**We present our experience regarding 2 patients treated with 5-fluorouracil and referred to our coronary care unit because of prolonged chest pain (in one case with clinical evidence of hemodynamic impairment) and persistent ST-segment elevation, in whom an acute myocardial infarction was suspected. One patient was treated with systemic fibrinolysis, and coronary angiography was performed 6 days later; the other was submitted to urgent coronary angiography shortly after admission. In both cases the ECG and echocardiographic abnormalities were transient and normalized within a few days, the serum markers of myocardial necrosis were persistently in the normal range and the coronary artery trees were normal.**

**The diagnostic and therapeutic approach to patients with this unusual clinical presentation is also discussed.**

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The cardiotoxic effects of 5-fluorouracil (5-FU) have been well described: effort or spontaneous chest pain with ECG modifications, myocardial infarction, systemic hypertension or hypotension, ventricular and supraventricular arrhythmias, left ventricular dysfunction and sudden death have been described in the past years[1-7].

The pathogenetic mechanism has still not been fully defined[1-11], but vasospasm is the most accepted one in patients with chest discomfort and transient ECG modifications, and the therapeutic approach in these cases is focused on the relief of the coronary artery spasm by the administration of calcium channel blockers and/or nitrates[12]. Up today the diagnostic and therapeutic pathways in patients with more severe cardiac involvement are not well defined, chiefly when persistent chest pain (unresponsive to nitrates or calcium antagonist drugs) and ST-segment elevation in multiple leads are highly suspected for the occurrence of an acute myocardial infarction or when left ventricular failure or cardiogenic shock are impending.

We report our experience regarding 2 patients admitted to our coronary care unit because of prolonged chest pain and persistent ST-segment elevation mimicking an acute myocardial infarction, in whom reperfusion therapy (pharmacological or mechanical) was planned.

A brief review of the literature about 5-FU cardiotoxicity is presented and the diagnostic and therapeutic approaches to patients with this unusual clinical presentation are also discussed.

## Description of cases

**Case 1.** A male, 61-year-old hypertensive patient whose history included previous cigarette smoking and arterial hyperten-

sion, 4 weeks following surgery for a laryngeal carcinoma, was started on a therapeutic regimen including i.v. infusion of 150 mg/die of 5-FU and 30 mg/die of cisplatinum for 4 days. On the fourth day he presented with brief and repeated episodes of chest discomfort, and the following day he became symptomatic for persistent chest pain and dyspnea; ECG showed atrial fibrillation (ventricular rate response 150 b/min) and ST-segment elevation in the precordial ($V_1$ to $V_6$) and inferior leads (Fig. 1 upper panel). Acetylsalicylic acid, i.v. nitrates, and amiodarone were started and 1 hour later the patient was admitted to our coronary care unit. At the time of admission he was pale and symptomatic for chest discomfort and dyspnea; the systolic arterial pressure was 80 mmHg and the heart rate 130 b/min (atrial fibrillation). Signs of peripheral vasoconstriction were present, without rales at chest auscultation; mild arterial oxygen desaturation and an increased central venous pressure (18 mmHg) were also found. Nitrates were stopped and the arterial pressure increased up to 95 mmHg with mild inotropic support.

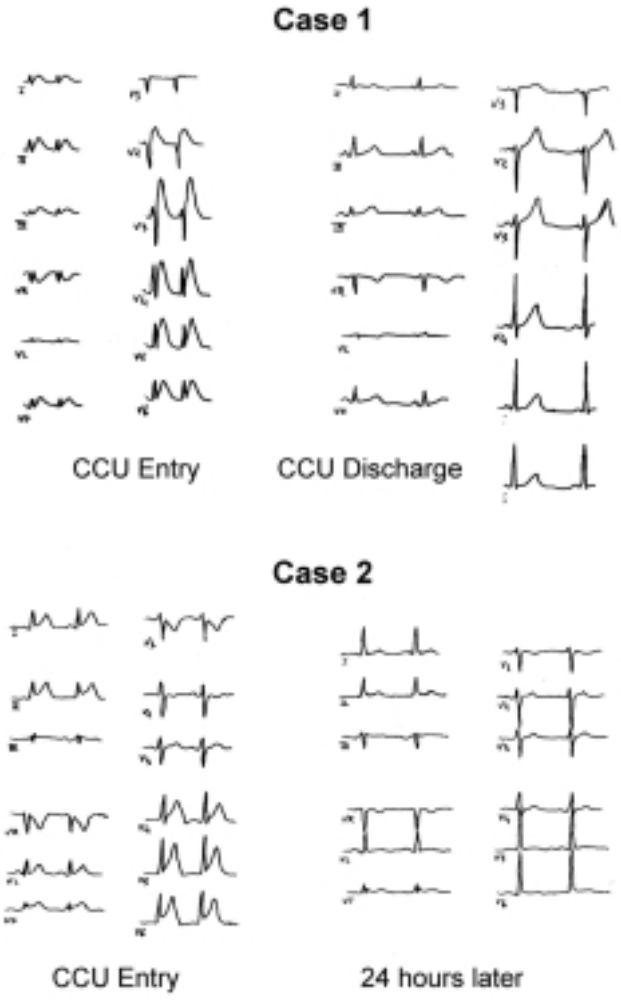


**Figure 1.** *ECGs of case 1* (upper panel) *and case 2* (lower panel). *CCU = coronary care unit.*

In view of the absence of any absolute contraindication to thrombolytic therapy, recombinant tissue-type plasminogen activator (rt-PA 100 mg) and unfractionated heparin were immediately started; echocardiography performed at admission showed normally sized left and right ventricles, akinesis of the anterior, apical and septal segments and hypokinesis of the remaining left ventricular walls and of the right ventricle; the left ventricular ejection fraction was 25%.

Following infusion of 50 mg of rt-PA, this agent was suspended because of suspected gastrointestinal bleeding, which, however, was not confirmed at urgent endoscopic evaluation.

In view of the patient's stable clinical and hemodynamic status (an increase in the systolic blood pressure up to 120 mmHg, the resolution of peripheral vasoconstriction), the relief of chest discomfort, the recovery of stable sinus rhythm at 82 b/min, and the > 50% reduction in the ST-segment elevation, it was decided to start the patient on a conservative therapeutic regimen including nitrates, captopril, furosemide and digoxin.

ECG normalized 1 day later (Fig. 1 upper panel), without no residual signs of persistent ischemia; at serial evaluation, the serum concentrations of total creatine kinase (CK) and CK-MB were within normal limits. On the fourth day, an echocardiographic examination showed only mild hypokinesis of the left ventricle, and on day 6 the patient was submitted to coronary artery angiography that showed a normal coronary artery tree (Fig. 2 upper panel) with normal coronary flow, and a normal left ventricular wall motion and ejection fraction.

**Case 2.** A female, 69-year-old patient, without risk factors for cardiovascular disease was started on 5-FU therapy (600 mg bolus for 2 days followed by a continuous i.v. infusion of 900 mg for 24 hours) 4 weeks following the resection of a colorectal carcinoma.

On the second day she presented with typical anginal chest pain and ST-segment elevation in the inferior and lateral leads at standard ECG (Fig. 1 lower panel). I.v. nitrates and acetylsalicylic acid were started in the emergency room and she was promptly admitted to our coronary care unit; owing to the persistence of symptoms and ECG modifications, and in view of the presence of inferior and postero-lateral hypokinesis with a mildly impaired left ventricular ejection fraction (45%) at echocardiographic evaluation, after the administration of 5000 IU of unfractionated heparin, she was submitted to urgent coronary angiography that showed a normal coronary artery tree (Fig. 2 lower panel) with normal epicardial flow.

Treatment with continuous i.v. infusion of verapamil and transdermal nitrates was started and maintained for 48 hours. The patient became asymptomatic within 2 hours, without signs of hemodynamic impairment. The serum markers of myocardial damage (CK-MB and troponin I) were persistently negative and

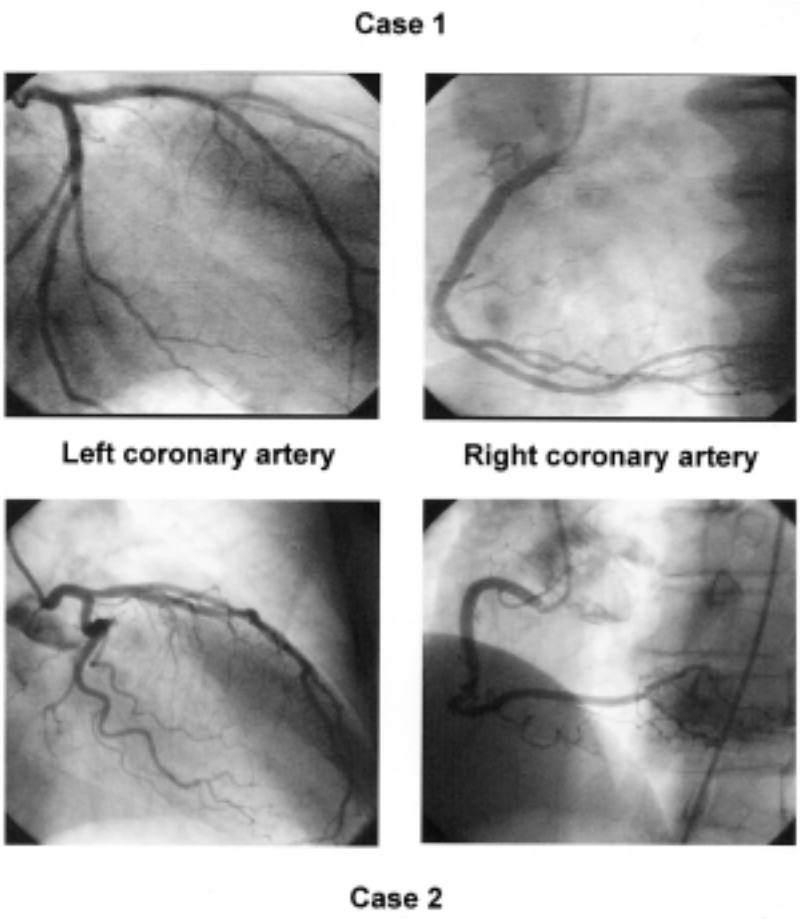


**Figure 2.** *Coronary angiography of case 1* (upper panels) *and case 2* (lower panels). *The right anterior oblique view of the left coronary artery* (lower left panel) *and the left anterior oblique view of the right coronary artery* (lower right panel) *show a normal coronary artery tree in both cases.*

echocardiography performed 1 day later showed a normal left ventricle and ejection fraction, without wall motion abnormalities. ECG showed flat/negative T waves in $V_5$-$V_6$ at 24 hours (Fig. 2 lower panel) that normalized within 2 days.

## Discussion

5-FU cardiotoxicity develops in 2-18%[3,4] of treated patients, and represents an interesting clinical challenge since it is very difficult to determine the proneness of the patient to develop this syndrome[13].

Anginal pain is the most frequent symptom and usually occurs within 24 hours of administration or, in some cases, after the discontinuation of the drug (within 2 to 5 days)[3]. Systemic hypertension or hypotension, dyspnea, ventricular and supraventricular arrhythmias, transient left ventricular dysfunction, sudden death, myocardial infarction and cardiogenic shock have been described[3-6]. In most patients the ECG and echocardiographic abnormalities are reversible[3-5,7,12] and some authors[5] consider these findings as being compatible with an ischemic stunned myocardium.

The underlying mechanism of 5-FU cardiotoxicity has still not been fully understood, but coronary vasospasm is the most accepted hypothesis[1-7] through different mechanisms able to induce coronary artery spasm or thrombus formation[8,10,11].

On the contrary, according to Sasson et al.[9], in some cases the cardiotoxic effects of 5-FU can be explained by a different pathogenetic mechanism, namely a direct myocardial damage that induces a myocarditis, accompanied by symptoms resembling cardiac ischemia with ECG modifications, and cardiac dysfunction leading to cardiogenic shock in some patients.

Coronary vasospasm could play a pivotal role in cases of spontaneous or effort-induced chest pain with transient ECG ST-segment changes: in such patients, the administration of calcium channel blocking agents and nitrates is the suggested therapy[12], but discordant results are reported about the efficacy of the prophylactic use of these drugs[10,14].

Few data regarding the incidence of significant coronary artery disease in this subgroup of patients have been published in the literature: Burger and Mannino[10] found a normal coronary artery angiography in 29 out of 38 patients (80%) with chest pain, and only

one paper[15] reported about the angiographic evidence of epicardial coronary vasospasm occurring during the treatment period.

Our experience is largely concordant with the published reports, but shows some peculiar features which have not yet been well addressed.

Our patients suffered from spontaneous and prolonged chest pain, and both showed ST-segment elevation in multiple leads at standard ECG, mimicking an extensive myocardial infarction. In the first case, we observed signs and symptoms of severe hemodynamic impairment and echocardiography showed a severely reduced left ventricular ejection fraction.

The administration of i.v. nitrates was ineffective in both cases in terms of pain reduction and ST-segment elevation resolution; the severe hemodynamic impairment in the first patient did not allow us to use calcium channel blocking drugs; on the contrary, in the second one, it was deemed safe to administer verapamil and symptoms disappeared 2 hours later.

In both cases coronary angiography showed a normal coronary artery tree; the full recovery of the left ventricular ejection fraction and the complete normalization of the ST segment confirm that these findings may be transient and reversible.

The data of our patients do not allow us to demonstrate the vasospastic origin of the symptoms: in the first case, coronary angiography was performed on the sixth day, after a half dose of fibrinolytic agent was administered, and the thrombotic origin of the symptoms cannot be completely excluded; in the second case, urgent coronary angiography failed to show epicardial arterial spasm or a slow-flow pattern of the contrast agent in the coronary artery tree. Moreover, the provocative tests of coronary vasospasm were not performed before discharge: neither the pathogenetic mechanism, nor the proneness of these patients to develop coronary vasospasm were demonstrated in our cases.

Despite the long duration of symptoms and the true ECG modifications, in both patients the serum markers of myocardial necrosis were persistently in the normal range; similar findings (but not for cardiac troponin I) were reported by de Forni et al.[3]. This feature is difficult to understand since it is well known that severe and prolonged ischemia (> 1 hour in both cases) usually leads to some degree of myocardial damage, with an increase in the serum concentration of cardiac markers and the appearance of evolutionary ECG changes in most cases.

In our opinion, a mechanism different from (or in adjunct to) coronary vasospasm should be taken into account in the patients we observed, and a kind of direct cardiotoxicity, as described by Sasson et al.[9], could be advocated.

To date, the diagnostic and therapeutic approaches to patients with more severe cardiac involvement, chiefly when long-lasting chest pain (unresponsive to nitrates or calcium antagonist drugs) and ST-segment elevation in multiple leads are highly suspicious for the occurrence of an acute myocardial infarction, or when left ventricular failure or cardiogenic shock are impending, have not yet been well defined.

On the basis of the available data and of our experience, we suggest that in patients with spontaneous chest pain and an ST-segment shift, a conservative approach should be first considered in order to evaluate the response to calcium channel blocking agents and nitrates.

We think that an invasive approach should be considered only in patients with a good oncologic prognosis, who are unresponsive to the suggested pharmacological treatment, when persistent chest pain and ST-segment elevation in multiple leads are suggestive of the presence of an extensive area of myocardium at risk (confirmed by an echocardiographic examination) or in patients presenting with or developing signs and/or symptoms of hemodynamic impairment. In these cases coronary angiography should be performed as early as possible in order to detect the presence of vasospastic or thrombotic coronary artery disease and to initiate the most appropriate therapy.

Besides, we think that in the same patients thrombolytic therapy is not an appropriate first choice treatment because of the increased risk of bleeding, the low rate of occlusive coronary artery disease[10], and the possibility of a non-ischemic origin of symptoms[9].

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