

Case Report

Capecitabine May Induce Coronary Artery Vasospasm

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Capecitabine is a new oral chemotherapeutic agent that is considered highly specific for sensitive tumor cells. We present the case of a patient who, after treatment with capecitabine for colorectal cancer, presented to our hospital with angina pectoris and electrocardiographic changes indicative of myocardial ischemia. The absence of epicardial coronary stenosis on the coronary angiogram ruled out atherosclerotic coronary disease as the cause of ischemia. The occurrence of coronary spasm, although not evident during coronary angiography, seems to be a possible explanation of the patient's symptoms.

Capecitabine is a new oral chemotherapeutic agent that is considered highly specific for sensitive tumor cells. It is a fluoropyrimidine, which after oral administration is metabolized into 5-fluorouracil (5-FU) by thymidine phosphorylase. This enzyme is preferentially expressed by tumor cells; therefore, capecitabine is considered to exert a selective antitumoral action.¹ While cardiac events associated with the use of 5-FU are a well known side effect, capecitabine-induced cardiotoxicity has been only rarely reported. We report a case of acute coronary syndrome, possibly due to coronary vasospasm following oral capecitabine administration.

Case presentation

A 52-year-old female, with no history of cardiovascular disease and with no predisposing factors for coronary artery disease, was admitted to our hospital for chest pain at rest, with radiation to the left arm accompanied by sweating. The patient had been treated with capecitabine (3000 mg/day) for the previous three days due to recently diagnosed colorectal cancer. She was scheduled for surgical excision of the

tumor and she had started intravenous chemotherapy with doxorubicin 3 days before admission. She described three episodes of chest pain with a time interval of three hours between the attacks. Each episode had a duration of 10 minutes and resolved spontaneously. Physical examination on admission revealed no pathological findings, while her blood pressure was 120/80 mmHg. The electrocardiogram (ECG) on admission showed sinus rhythm with 1 mm depression of the ST-T segment in leads I, aVL, and negative T waves in leads III, V₁₋₃ (Figure 1). The chest X-ray was normal, while cardiac enzymes were negative. Echocardiography showed hypokinesia of the anterior wall of the left ventricle, with mild aortic regurgitation. The patient was treated with intravenous nitroglycerin, clopidogrel, aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and heparin, and remained free of symptoms. Coronary angiography performed on the next day revealed normal coronary arteries with normal left ventricular ejection fraction (Figure 2). One day before discharge, the patient underwent a second cardiac ultrasound, which showed a normal ejection fraction. The patient

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Figure 1. The patient's electrocardiogram on admission.

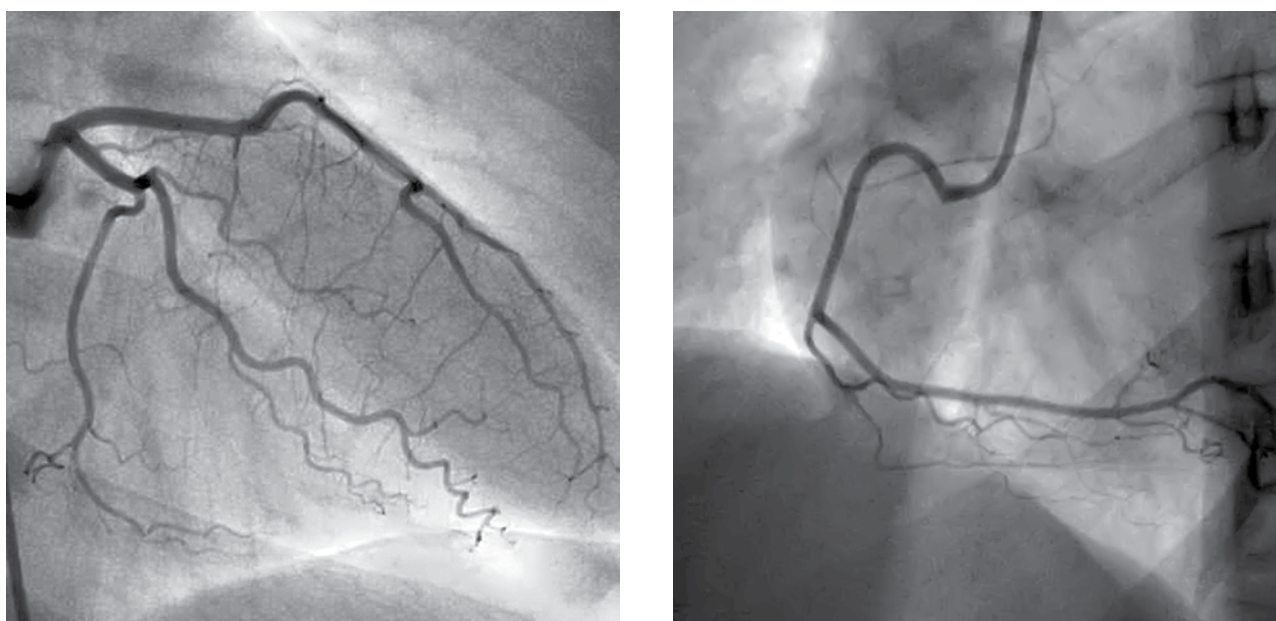


Figure 2. Coronary angiography showing coronary arteries with no significant stenosis.

was discharged with calcium blockers and oral nitroglycerin as the only medication.

Discussion

Cardiotoxicity is a recognized side effect of 5-FU, a related fluorinated pyrimidine antagonist. The clinical manifestations of the side effects may vary, from cardiogenic shock and death to angina pectoris, myocardial infarction or arrhythmias.^{2,3} Prospective clinical trials have demonstrated that 2% to 10% of patients exposed to 5-FU developed cardiovascular complications;^{4,5} this chiefly applies to patients with known coronary artery disease and previous radiotherapy.⁶ The possible mechanism involves 5-FU-related endothelial activation with release of endothelin-1.^{7,8} Capecitabine is an effective alternative to intravenous 5-FU in the adjuvant treatment of colon cancer.⁹ The action of a series of enzymes such as thymidine phosphorylase, which has higher concentrations in tumor cells, converts capecitabine to the active 5-FU, providing a favorable ratio for toxicity, radiosensitization and specificity for the tumor cells.¹⁰

A randomized phase II study with capecitabine performed in 109 colorectal cancer patients reported 5 cases (4.5%) of probable cardiac toxicity, including 4 patients with chest pain,¹¹ while Walko et al, in a review of 758 breast and colorectal cancer patients, reported that 6% of patients experienced chest pain after treatment with capecitabine at a dose of 2500 mg/m² per day in 2 divided doses for 14 days followed by 1 week rest.¹² Furthermore, in two phase III studies, involving 603 patients, the drug was reported to be associated with 2 episodes of myocardial ischemic syndrome and one of myocarditis.^{13,14} In all these cases there was no coronary angiography to exclude the possibility of coronary artery disease. Apart from coronary artery vasospasm, other mechanisms that have been proposed for causing cardiac ischemia due to 5-FU or its metabolites are direct toxicity to the myocardium,¹⁵ thrombogenic effects¹⁶ and autoimmune phenomena.¹⁷

In our case, the patient presented with resting angina pectoris, accompanied by electrocardiographic changes indicative of myocardial ischemia and an abnormal echocardiogram. The absence of epicardial coronary stenosis on coronary angiography ruled out atherosclerotic coronary disease as the cause of ischemia. Small vessel thrombosis is a possibility that cannot be excluded by coronary angiography, while since 1990, when it was first proposed, no data have

been found to support the hypothesis of autoimmunity. The possibility of direct damage to the myocardial cells or the blood vessels of the heart by 5-FU or 5-FU metabolites can be excluded, given that left ventriculography was normal. In the case of direct toxicity, the presence of diffuse ischemia suggestive of a transient cardiomyopathic process without myocardial necrosis would have been evident.^{18,19}

The occurrence of coronary spasm, although not evident during coronary angiography, seems to be a possible explanation of the patient's symptoms. According to the literature, 6 more case reports came to this conclusion in patients with similar clinical history and symptoms.^{6,10,20-23} In all of these cases the patients presented with angina and the ECG showed ST-T segment elevation, indicative of the coronary spasm. The typical pattern of ST-T segment elevation on the ECG depends on the presence of the symptoms at the time of the examination. Our patient's symptoms had diminished before the ECG was recorded. Our case shows that capecitabine may be responsible for vasospastic angina in patients with cancer who are treated with capecitabine, even if the echocardiogram is abnormal and the ECG is not typical for coronary spasm. This clinical observation should remind physicians about the potential coronary toxicity of capecitabine.

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