# Capecitabine-induced cardiotoxicity mimicking myocardial infarction

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**Capecitabine, a fluoropyrimidine derivative, is an orally administered drug that delivers 5-fluorouracil (5-FU) selectively to the tumour. The drug has demonstrated activity in metastatic colorectal cancer. We describe a male patient receiving capecitabine therapy with typical chest pain and electrocardiographic changes consistent with ST-segment elevation myocardial infarction. Capecitabine-induced cardiotoxicity may develop in patients who have had a previous episode of 5-FU-induced cardiotoxicity. Capecitabine-induced cardiotoxicity is a rare condition that may lead to diagnostic and therapeutic dilemmas. (*Neth Heart J* 2009;17:277-80.)**

Keywords: capecitabine, myocardial infarction, cardiotoxicity

Fluoropyrimidine chemotherapy has been a standard therapy in a range of solid tumours for many years. The cardiovascular side effects of fluoropyrimidines have been extensively reported.[1] Capecitabine, a precursor of 5-FU, is an oral fluoropyrimidine cytotoxic agent developed with the aim of providing a more effective and less toxic alternate to 5-FU. Capecitabine has significantly less serious toxic effects than 5-FU when used alone or in combination with other cytotoxic agents[2] and cardiotoxicity is an uncommon adverse effect.

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In this paper, we report a male patient without evidence of cardiovascular symptoms and risk factors for cardiovascular disease, who developed cardiac ischaemia with severe angina after oral administration of capecitabine.

## Case report

A 34-year-old man was referred to the Department of Cardiology, Uludag University School of Medicine (Turkey), for assessment of chest pain at resting state. He underwent low anterior resection because of stage III adenocarcinoma of the rectum (T4N2M0) one month ago. After the operation, adjuvant chemotherapy consisting of infusional 5-FU, folinic acid and oxaliplatin (FOLFOX4) was started. During the first cycle of chemotherapy, the patient developed typical angina pectoris at rest which lasted for ten minutes. The pain reappeared, and therapy was discontinued because the electrocardiogram (ECG) showed ischaemic changes. The cardiac enzymes were within normal limits. Then the chemotherapy was changed to capecitabine (2000 mg/m$^2$) plus oxaliplatin. On the fifth day of initiation of capecitabine therapy (8000 mg/m$^2$), the patient had another episode of severe chest pain that lasted for one hour and radiated to the left arm. The patient had no coronary risk factors, such as a family history of cardiovascular disease, diabetes mellitus, hypertension, smoking or hyperuricaemia. He was 183 cm in height and 88 kg in weight. On physical examination, he was in a stable condition, with a blood pressure of 100/70 mmHg and a regular pulse of 90 beats/min. The lungs were clear and heart sounds were normal on auscultation. On admission, the ECG showed sinus rhythm with 2 mm ST-segment elevation in leads II2, III3, aVF and hyperacute T wave changes in leads V3 to V6 (figure 1). The capecitabine treatment was stopped. The pain resolved after treatment with a 25 mg intravenous bolus of diltiazem, but the ECG findings persisted. The ECG abnormalities normalised rapidly (figure 2) after initiation of intravenous nitroglycerin infusion started after admission to the coronary care unit. Echocardiographic examination did not show any significant abnormalities. Serial serum cardiac enzymes and serum troponin T levels were within normal limits. Blood lipid analysis showed a total

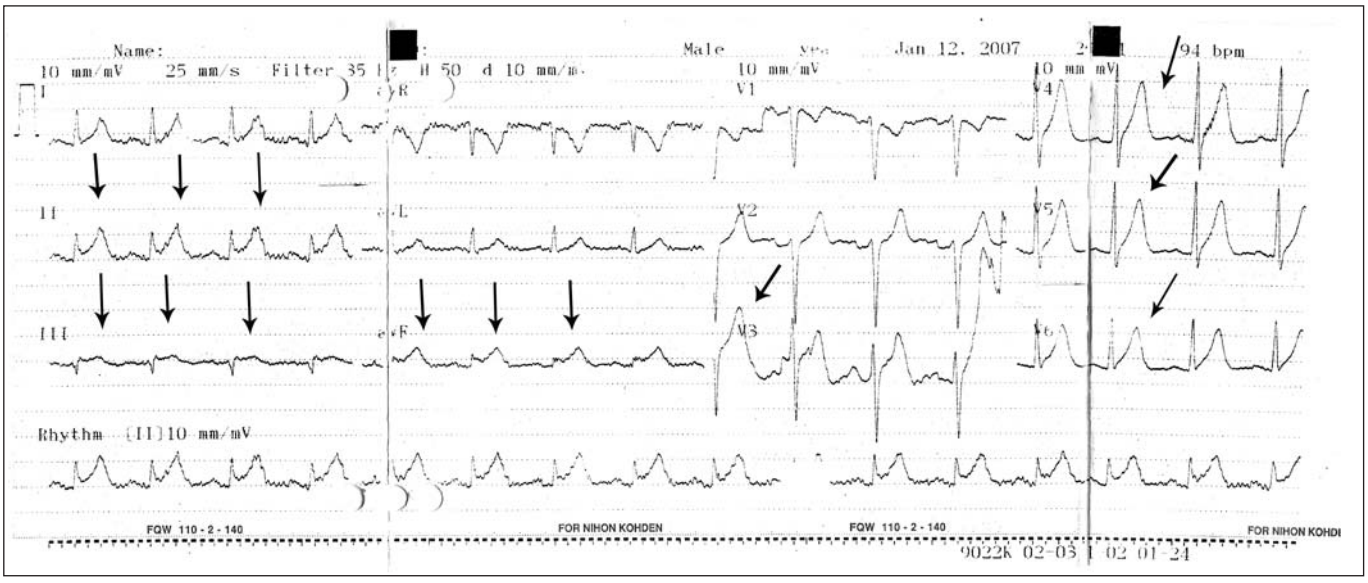


*Figure 1. The electrocardiogram on admission, showing sinus rhythm with ST-segment elevation in leads II2, III3, aVF and hyperacute T wave changes in leads V3 to V6.*

cholesterol of 194 mg/dl, triglycerides of 77 mg/dl, high-density lipoprotein cholesterol of 51 mg/dl and low-density cholesterol of 127 mg/dl. Possible reasons for this chest pain, such as pericarditis, hyperventilation and alkalosis, were excluded. Coronary angiography was also performed to determine the cause of the chest pain. We confirmed that both the left and the right coronary arteries were normal. A coronary spasm secondary to capecitabine was suspected. He was prescribed isosorbide mononitrate 40 mg/day and diltiazem 90 mg/day. Three days later, chemotherapy was continued with oxaliplatin. No recurrences of the

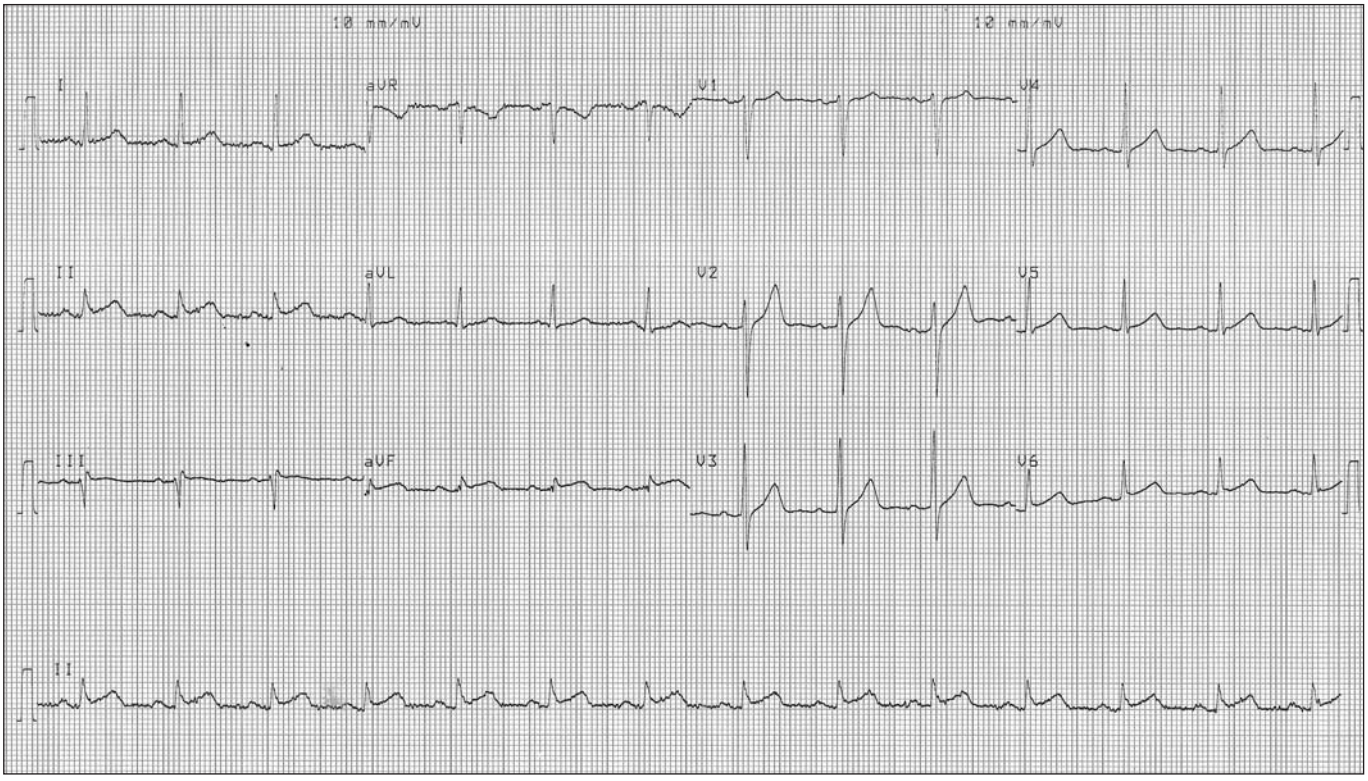


*Figure 2. The ECG after the pain had resolved.*

chest pain and/or ECG abnormalities were observed during the therapy. Applying Naranjo's adverse drug reaction probability scale, a causality assessment was made, which categorised this reaction as probable with a score of 8.[3]

## Discussion

In this paper, we have presented a case of capecitabine-induced cardiotoxicity which showed clinical findings consistent with acute myocardial infarction. A resolving pain and normalisation of ECG changes with calcium channel blocker and nitrate therapy and normal coronary arteries suggest that this incident was due to coronary spasm caused by capecitabine therapy.

Although rare, cardiotoxicity may occur during therapy with several cytotoxic agents. The spectrum of cardiotoxicity with chemotherapeutic agents includes hypertension, Q-T interval prolongation, acute cardiomyopathy, and bradyarrhythmias. The anthracyclines, such as doxorubicin and epirubicin, are the best known chemotherapeutic agents that cause cardiotoxicity. A cumulative dose of anthracyclines seems to be the most important factor in the development of this serious complication. The incidence of sympthomatic heart failure is approximately 7.5% in patients receiving a cumulative doxorubicin dose of 550 mg/m$^2$.[4] Patient-related factors including advanced age, prior thoracic irradiation, concomitant use of other chemotherapeutics and underlying heart disease may also increase the cardiotoxicity. Other cytotoxic drugs that have been reported to lead to cardiotoxicity include 5-fluorouracil (5-FU), capecitabine, mitoxantrone, cisplatin, taxoids and newer drugs such as the monoclonal antibody trastuzumab. 5-FU-induced cardiotoxicity usually occurs during continuous intravenous infusion, and estimates of its incidence vary from 1 to 5% to as much as 18%.[5] Cisplatin is a platina substance and used in the treatment of many tumours (paediatric brain tumours, osteosarcoma, ovarian cancer and head and neck cancer). Cardiotoxicity is a relatively uncommon complication of cisplatin chemotherapy.[4] The taxoids paclitaxel and docetaxel are important agents in the treatment of a variety of tumours that have been associated with cardiotoxicity. Data from various studies including thousands of patients receiving paclitaxel suggest that the incidence of cardiac side effects is between 14 and 29%.[6,7] Trastuzumab is a monoclonal antibody directed against the HER2 receptor protein on breast cancer cells and it is used alone or in combination with other chemotherapeutic agents. When receiving trastuzumab as a single therapy, 7% of the women developed heart failure.[5] Cyclophosphamide can also cause an acute coronary syndrome during administration, but seldom causes permanent damage to the heart. The incidence of myocarditis caused by a high dose of cyclophosphamide (>150 mg/kg) is estimated to be 7 to 25% in adults.[4] Cardiotoxicity has been incidentically associated with several other cytotoxic drugs such as melphalan, fludarabine, mitomycin, busulfan, mechlorethamine and dacarbazine.[5]

Capecitabine is the pro-drug of 5-FU. It is an oral chemotherapeutic agent widely used in the treatment of colorectal, breast, gastric and pancreatic cancer, both as a single agent and as a component of combination chemotherapy.[8] Capecitabine-induced cardiotoxicity has been reported infrequently.[9-12] Our patient previously developed chest pain during treatment with a continuous infusion of 5-FU and then capecitabine was chosen because of the ease of administration. We thought that low systemic peak levels of 5-FU would decrease the risk of cardiotoxic effects but four days after the initiation of capecitabine therapy, he developed continuous, severe chest pain. Frickhofen et al.[12] reported a patient experiencing chest pain and ST-segment elevation during capecitabine treatment who previously developed similar symptoms during treatment with continuous infusion of 5-FU. Published case reports indicate that symptoms may occur within two to three days after the initiation of capecitabine therapy.[13] The patient experienced chest pain after 96 hours following the initiation of capecitabine therapy; we did not observe any increment of the enzymatic index of cardiac damage in our patient, although there were severe signs of ischaemia on ECG. Delayed cardiotoxicity may occur due to cumulative dose effect of 5-FU or its metabolites after administration of capecitabine.

The possibility of oesophageal spasm, pericarditis, or a gastrointestinal or neuromuscular aetiology was ruled out on the basis of the clinical course. We could not identify the predisposing factors such as previous chest radiation, history of cardiovascular disease, and concurrent treatment with other cardiotoxic agents in our patient. Reviewing the literature, cardiotoxicity is completely reversible with cessation of capecitabine therapy.[10] In our case, no recurrence was observed after cessation of the capecitabine therapy. The precise pathophysiological mechanisms of capecitabine-induced cardiotoxicity are unknown. The patient's chest pain and ST-segment elevation both disappeared immediately after the infusion of diltiazem and nitroglycerin. Considering the young age of the patient and absence of coronary risk factors, we presumed that the coronary artery spasm was the possible mechanism for cardiotoxicity in accordance with literature reports, based mainly on the findings of clinical and electrocardiographic evidence of reversible ischaemic heart disease in the absence of coronary atherosclerosis on angiography. We assumed that 5-FU or its metabolites were responsible for cardiotoxicity after capecitabine administration. Coronary artery vasospasm, direct toxicity to the myocardium, thrombogenic effects and autoimmune phenomena have been proposed.[14,15] Vasospasm is a reasonable mechanism, since it would explain reports of the efficacy of vasodilating drugs given prophylactically to patients who experienced a previous episode of chest pain during 5-FU treatment.[15]

## Conclusions

In summary, capecitabine-induced cardiotoxicity is a rare but potentially fatal complication. We consider that careful clinical evaluation, such as frequent ECG controls, should be performed in patients treated with capecitabine. A history of cardiotoxicity associated with 5-FU should be considered as a risk factor for similar cardiotoxicity after administration of capecitabine. ■

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