Capecitabine-induced coronary artery vasospasm in a patient who previously experienced a similar episode with fluorouracil therapy

Florourasil tedavisi ile benzerini yaşamış bir hastada kapesitabine bağlı koroner arter vazospazmı

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Summary– Capecitabine is a chemotherapeutic agent used in the treatment of metastatic colon cancer and metastatic breast cancer. It is metabolized into fluorouracil (5-FU) in the liver; hence, its mechanism of action is similar to that of 5-FU. Cardiac toxicity, although rarely seen, may be of concern in some patients. Although multiple hypotheses have been proposed for the mechanism of cardiotoxicity, coronary vasospasm is the most commonly accepted one, as patients usually present with chest pain resembling acute myocardial infarction. Electrocardiography may demonstrate ST-segment elevation, and cardiac biomarkers may be elevated. Cardiotoxicity with 5-FU has been reported widely. Capecitabine has been shown to be much less cardiotoxic compared to 5-FU, with only a handful of cases reporting cardiotoxicity with capecitabine. There are no cases reporting cardiotoxicity with both 5-FU and capecitabine in the same patient. In this case report, we present a patient with adverse cardiac effect with capecitabine whose previous 5-FU therapy was stopped due to cardiotoxicity.

Özet– Kapesitabin, metastatik kolon ve meme kanseri tedavisinde kullanılan kemoterapötik bir ajandır. Karaciğerde florourasile metabolize olur, dolayısıyla da etki mekanizması florourasile benzemektedir. Nadir görülse de kardiyak toksisite bazı hastalarda önemli bir sorun olarak karşımıza çıkmaktadır. Kardiyotoksisite mekanizması ile ilgili çeşitli hipotezler öne sürülmekle birlikte koroner vazospazmı en önde gelen mekanizmalardan biridir ve böylesi hastalar akut miyokart enfarktüsüne benzer göğüs ağrısı ile gelebilirler. Elektrokardiyografide ST segment yükselmesi ve kardiyak belirteçlerde yükselme görülebilir. Florourasil ile kardiyotoksisite sık görülmektedir. Kapesitabinle kardiyotoksisite ise florourasile göre daha az görülmektedir. Aynı hastada hem florourasil hem de kapesitabinle kardiyotoksisite gelişimi bildirilmemiştir. Bu olgu sunumunda, daha önceden kardiyotoksisite gelişmesi nedeniyle florourasil tedavisi durdurulan bir hastada kapesitabinin olumsuz kardiyak etkileri sunulacaktır.

Capecitabine is an oral prodrug that is converted to its active metabolite, fluorouracil (5-FU), by thymidine phosphorylase. Its use has been approved as first-line therapy in patients with metastatic colorectal or breast cancer in cases of anthracycline/paclitaxel resistance or anthracycline toxicity. Additionally, it can be used in combination with docetaxel after failure of prior anthracycline-based chemotherapy. It has also been studied in patients with prostatic, pancreatic, renal cell, and ovarian cancer.[1] Cardiac toxicity, considered to be a consequence of myocardial ischemia induced by coronary vasospasm, has an incidence of 1.2–18% in patients receiving capecitabine treatment.[2]

Abbreviations:

5-FU *Fluorouracil*
ECG *Electrocardiogram*

We report a 61-year-old man with acute coronary syndrome associated with capecitabine use.

CASE REPORT

A 61-year-old man with metastatic colorectal carcinoma presented to the emergency department with typical angina lasting for approximately 10 hours. He had no dyspnea at rest, diaphoresis, nausea, or vomit-

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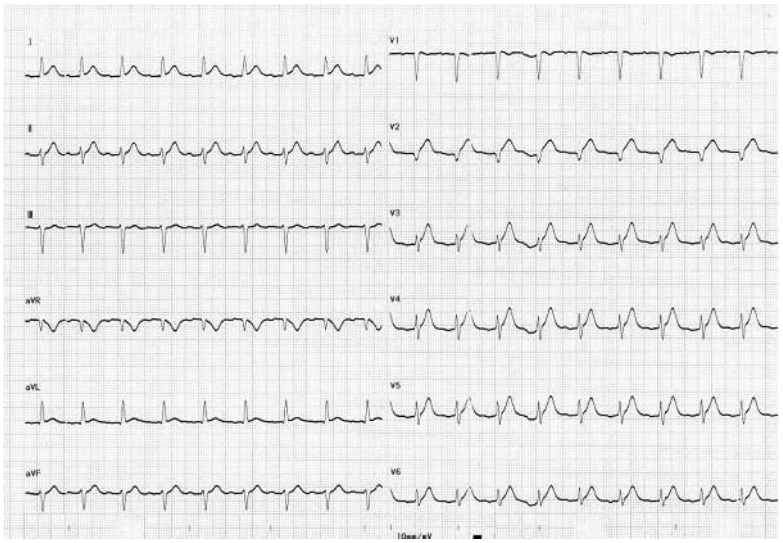

Figure 1. ECG at presentation. ST-segment elevation is seen in the anterolateral leads.

ing. At presentation, his blood pressure was 140/90 mmHg and heart rate 102 bpm. Physical examination revealed no jugular venous distention, pulmonary rales, abnormal heart sounds, or murmurs. Blood chemistry and complete blood count analyses were normal, and chest X-ray did not reveal any pathology. His cardiac biomarkers were elevated (myoglobin: 126.2 ng/ml [0–72 ng/ml]; creatine kinase myocardial B infarction: 18.29 ng/ml [0.0–5.0 ng/ml]; troponin T: 0.257 ng/ml [0–0.01 ng/ml]). An electrocardiogram (ECG) showed ST-segment elevation in leads DI and aVL (Figure 1). After intravenous chest pain resolved, the nitroglycerin ST-segment depressed to the isoelectric line (Figure 2).

Examining the patient's history, it was observed that he had received capecitabine 1900 mg/m² and oxaliplatin therapy 2 days prior as a first dose. In addition, he had experienced a similar anginal episode in May 2006 while receiving 5-FU, folinic acid, and oxaliplatin. In this previous episode, he was admitted to the emergency department because of severe chest pain in the second week of therapy. An ECG

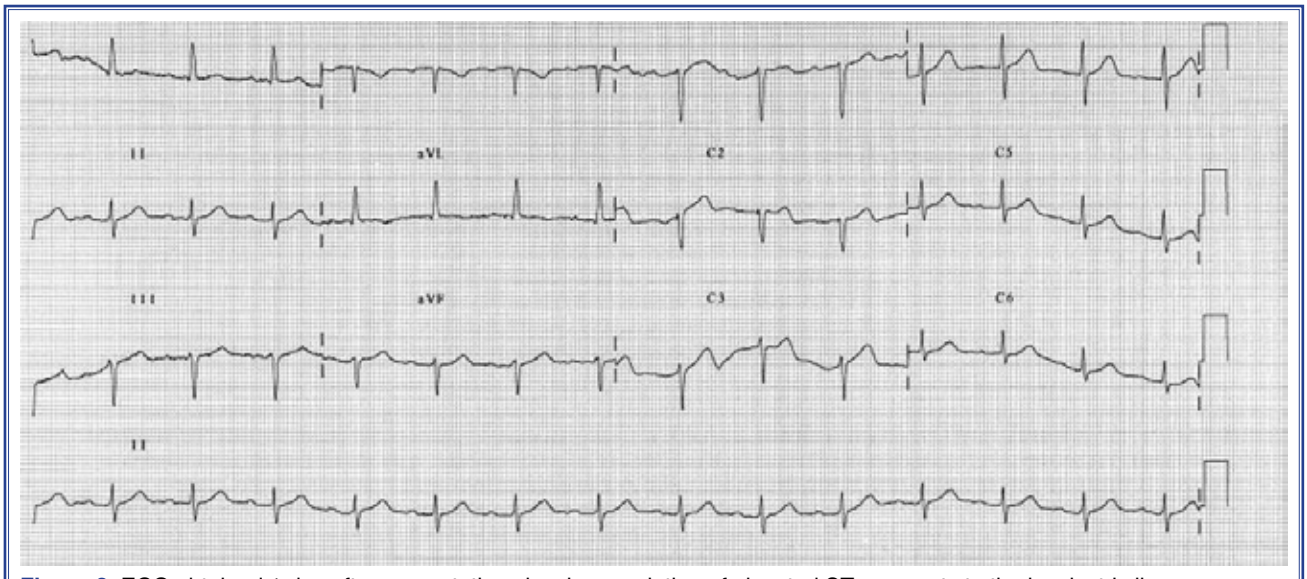

Figure 2. ECG obtained 1 day after presentation showing resolution of elevated ST segments to the isoelectric line.

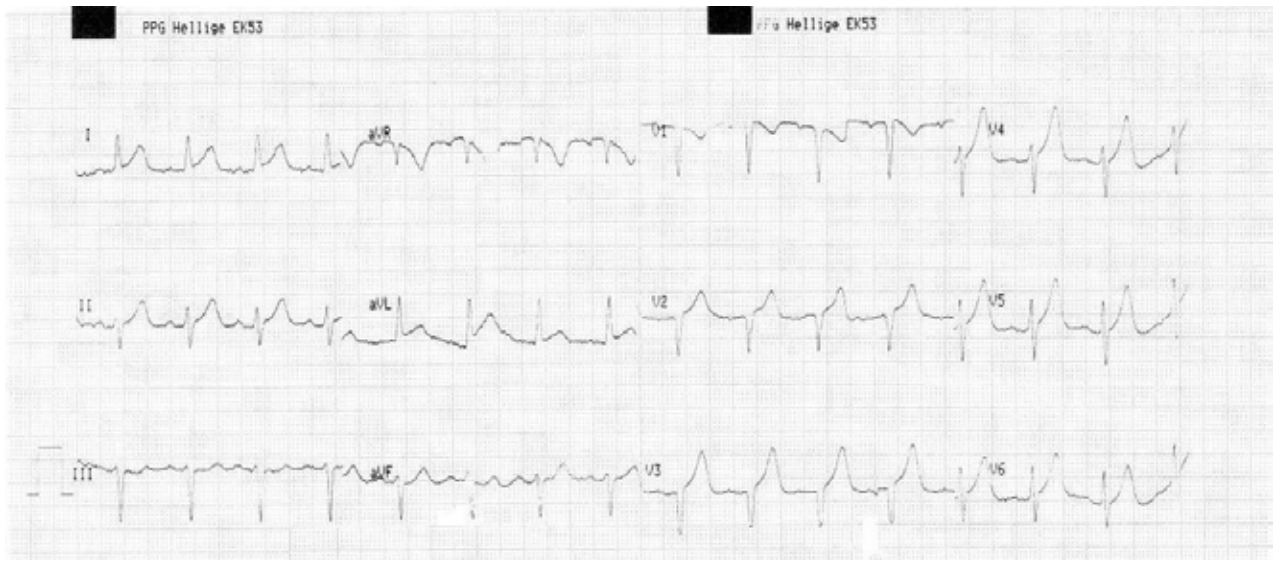

Figure 3. ECG obtained after initiation of fluorouracil therapy showing ST-segment elevation in the anterolateral leads.

taken on admission is shown in Figure 3. His chest pain was thought to be related to coronary vasospasm associated with 5-FU therapy. When 5-FU therapy was discontinued, his symptoms stopped. In order to exclude significant coronary artery disease, coronary angiogram was performed, which revealed normal coronary arteries (Videos 1, 2*). Slow-release diltiazem 90 mg qd was started.

Given the previous history of coronary vasospasm associated with 5-FU therapy, his chest pain was thought to be related to capecitabine therapy, an 5-FU analog. His capecitabine therapy was stopped. One day later, his symptoms gradually resolved, and he was discharged with slow-release diltiazem 120 mg qd and isosorbide mononitrate 40 mg bid. The patient was asymptomatic during the 4-month follow-up period.

DISCUSSION

Capecitabine is a fluoropyrimidine carbamate which is metabolized into its only active compound, 5-FU, by thymidine phosphorylase. The dosage regimens of capecitabine range between 1500–2500 mg/m²/day for 2 weeks, with either oxaliplatin or irinotecan as first-line therapy. Capecitabine is indicated as first-line treatment for patients with metastatic colon cancer when treatment with fluoropyrimidine therapy alone is preferred. Capecitabine in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

Capecitabine-induced cardiotoxicity was first reported in 2001 in a 39-year-old man with gastric cancer who was administered 2000 mg/m² daily capecitabine.[3] Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, arrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. Usual presentation is crushing chest pain resembling that of typical angina pectoris. Dyspnea, diaphoresis, and nausea usually accompany angina. ECG changes include ST-segment elevation and negative T waves.[4] Rarely, further tests are required for diagnosis, which include exercise stress test and detection of wall motion abnormalities by echocardiography.[5] In 2 phase III studies involving 603 patients, capecitabine-associated major cardiac adverse effects were seen in 3 (0.4%) patients, 2 of which were ischemic in origin, and myocarditis was diagnosed in 1 case.[6,7]

Mechanism of coronary spasm induced by fluoropyrimidines is thought to be due to an endothelium-independent, direct vasoconstrictor effect. Although the exact mechanism remains speculative, stimulation of protein kinase C activity, which is related to vascular smooth muscle tone, was suggested by animal models.[8] Other postulated mechanisms include release of endothelin-1, the most powerful vasoconstrictor, and a neural-mediated mechanism

involving the adrenergic nervous system.[5] Myocardial injury, thrombogenic effects, immune-allergic reaction, and ischemia secondary to coronary artery spasm have all been implicated in the mechanism of fluoropyrimidines-induced cardiac toxicity; however, coronary spasm is thought to be the main mechanism. Capecitabine toxicity has the same etiology as 5-FU toxicity, although capecitabine and its metabolites are minimally cytotoxic in vitro compared with 5-FU.[9] Our case is the first to show coronary vasospasm with both 5-FU and capecitabine; thus, it can be postulated that capecitabine causes coronary vasospasm by similar mechanisms as 5-FU.

Symptoms related to vasospasm can be relieved by discontinuing capecitabine and administering vasodilators such as calcium channel blockers and nitrates. Symptoms may improve simply after discontinuation of capecitabine, even in the absence of vasodilators, thus confirming that capecitabine is responsible for coronary vasospasm, making other possible causes of angina—including the presence of coronary flow-limiting stenoses—very unlikely, and showing that vasospasm is usually self-limited.[5] Vasodilators may be begun as prophylaxis in a patient being started on fluoropyrimidine; i.e., bolus administration of 5-FU may be given as co-treatment with nitrates and calcium channel blockers.[10]

Conclusion

Patients experiencing coronary vasospasm with 5-FU may be prone to coronary vasospasm with capecitabine as well. Therefore, if possible, capecitabine should be avoided in patients with a history of coronary vasospasm with 5-FU.

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****Supplementary video file associated with this article can be found in the online version of the journal.***

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Anahtar sözcükler: Kapesitabin; kardiyak toksisite; koroner vazospazm.