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Coronary Vasospasm Secondary to 5-Fluorouracil and Its Management: Case Report

5-Flourouras ile Bağlı Koroner Vazospazm ve Yönetimi: Vaka Sunumu

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Abstract

Although rare, 5-fluorouracil (5-FU) may lead to cardiotoxicity that presents with angina, elevated cardiac enzymes and electrocardiogram (ECG) changes. Coronary vasospasm related to 5-FU is a rare clinical entity in oncological practice and may be seen during both bolus and protracted infusional administration. This toxicity is generally reversible and responds well to conventional anti-angina treatment following discontinuation of infusion. We propose that parenteral diltiazem is an effective and safe approach for the treatment of coronary vasospasm secondary to 5-FU infusion. We present clinical findings and management of a case in which coronary vasospasm occurred during the infusion of the 5-FU component of FOLFIRI-bevacizumab chemotherapy (CT) regimen given for treatment of metastatic rectal cancer.

Key Words: 5-fluorouracil, Coronary vasospasm, Diltiazem

Özet

Az görülmesine rağmen; 5-Flourourasil, (5-FU) EKG değişiklikleri, kardiyak enzim yüksekliği ve anjina ile kendini gösteren kardiyotoksisiteye yol açabilmektedir. 5-FU ile ilişkili koroner vazospazm onkoloji pratiğinde nadir bir klinik durumdur ve hem bolus hem de intravenöz infüzyon tedavisi esnasında karşılaşılabilir. Bu toksisite genellikle geri dönüşümlüdür ve infüzyonun durdurulması sonrası uygulanan anti-anjinal tedaviye iyi yanıt vermektedir. Bizce, panrenteral diltiazem, infüzyonel 5-FU'ya bağlı koroner vazospazmın tedavisinde etkili ve güvenli bir yaklaşımdır. Yazımızda, metastatik rektum kanseri tanısıyla FOLFIRI-Bevasizumab kemoterapi rejiminin bir bileşeni olarak verilen 5-FU infüzyonu sırasında koroner vazospazm geçiren bir vakanın klinik bulguları ve yönetimi sunulmaktadır.

Anahtar Kelimeler: 5-flourourasil, Diltiazem, Koroner vazospazm

Introduction

Colorectal cancer ranks as the third most common malignancy in both men and women and is the second leading cause of cancer-related mortality [1]. 5-fluorouracil (5-FU), a member of the fluoropyrimidine family, is an essential component of systemic treatment of colorectal cancer in a primary or adjuvant setting. 5-FU is an antimetabolite that acts during the S phase of the cell cycle. Its active metabolite, 5-fluorodeoxyuridylate (5-FdUMP), inhibits thymidylate synthase and leads to cell death by preventing DNA synthesis [2]. The toxicity of 5-FU may cause various symptoms, including nausea, vomiting, diarrhea, stomatitis, alopecia and leucopenia, depending on different chemotherapy (CT) regimens and schedules of administration. The most prominent dose-limiting manifestations include myelosuppression, diarrhea and hand-foot syndrome. Although it is rare, 5-FU may also lead to cardiotoxicity that presents with angina, elevated cardiac enzymes and electrocardiogram (ECG) changes [3, 4].

We present clinical findings and management of a case in which coronary vasospasm occurred during the infusion of the 5-FU component of FOLFIRI-Bevacizumab CT regimen given for treatment of metastatic rectal cancer.

Case Report

A 53-year-old female patient was referred to our clinic with a histopathologically proven diagnosis of poorly differentiated rectal adenocarcinoma and liver metastasis. Staging work-up revealed no other sites of metastasis. Systemic CT using the FOLFIRI-Bevacizumab regimen was planned, and the first course of CT was delivered in June 2009 after pretreatment car-

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diological evaluation showed no risk. The regimen consists of 5-FU 400 mg/m^2 i.v. bolus, 5-FU 600 mg/m^2 protracted infusion over 22 hours, Leucovorin (LV) 200 mg/m^2, Irinotecan 180 mg/m^2 and Bevacizumab 5 mg/kg. There was no significant toxicity noted until the fifth course. At the time of fifth cycle, inpatient laboratory studies done prior to KT were within normal range, with a Hb value of 12.6 mg/dl, Hct of 36%, platelet count of 294.000/mm^3, WBC of 5.770/mm^3, blood urea of 8 mg/dl and serum creatinine level of 0.5 mg/dl. However, on the first day of the fifth cycle, the patient complained of chest pain during the third hour of 5-FU infusion, which was discontinued immediately. Physical examination showed a heart rate of 67 beats per minute and a blood pressure of 110/70 mm/Hg, with no cardiac murmurs. Cardiac marker tests revealed a myoglobin value of 6 ng/mL, CK-MB level of 0.2 ng/mL and troponin-I level of 0.02 ng/mL. Infusion of diltiazem was started after ST segment depression (Figure 1), which was noted in the V2 and V6 derivation. Within 2 hours, chest pain and ST depression resolved (Figure 2) and infusion of 5-FU was re-started at a slower rate. There were no such symptoms noted during the last course of CT. Response evaluation revealed a significant regression in metastatic lesions in the liver. The patient is still alive and has had no major medical problems for 9 months.

Discussion

Colorectal cancer ranks as the third most common malignancy in both men and women and is the second leading cause of cancer-related mortality [1]. Cancer of the rectum, the fifth most common cancer in adults, is less frequent than colon cancer, accounting for 5% of malignant tumors. Approximately 15-25% of patients present metastases at diagnosis, and 45-50% of patients develop metastases at various intervals in their clinical history. The most frequent sites of metastases are the liver and lungs [5].

In stage IV rectal cancer, chemotherapy has been used for palliation, with 5-FU-based treatment, including 5-FU plus LV, considered to be standard in both Europe and the US. Infusional 5-FU/LV is now considered to be the best choice. However, combination treatment with 5-FU plus irinotecan was shown to be superior to single agent therapy in terms of disease control and overall survival [6]. 5-FU/LV infusion plus irinotecan has been shown to be much better tolerated and more effective than bolus regimens [5]. Moreover, a phase III trial testing the addition of bevacizumab to irinotecan plus 5-FU/LV CT reported a significant advantage of 4.7 months in median survival (p<.001) [7]. In light of these data, we administered combination CT consisting of infusional 5-FU/LV with irinotecan and bevacizumab (FOLFIRI-bevacizumab) to a patient with a diagnosis of carcinoma of the rectum with unresectable liver metastasis.

5-FU is a member of the antimetabolite family and acts during the S phase of the cell cycle. The active metabolite, 5-FdUMP, inhibits thymidylate synthase, thus preventing DNA synthesis, which would lead to imbalanced cell growth and ultimately cell death. 5-FU is also converted to 5-fluorouridine monophosphate (5-FUMP) and can be incorporated into and interfere with RNA processing and function [2].

The toxicity of 5-FU, which induces symptoms including nausea, vomiting, diarrhea, stomatitis, alopecia and leucopenia, differs depending on its schedule of administration. Dose-limiting manifestations of bolus 5-FU are diarrhea and myelosuppression, while hand- foot syndrome and stomatitis are dose-limiting with prolonged infusion. In rare cases, infu-

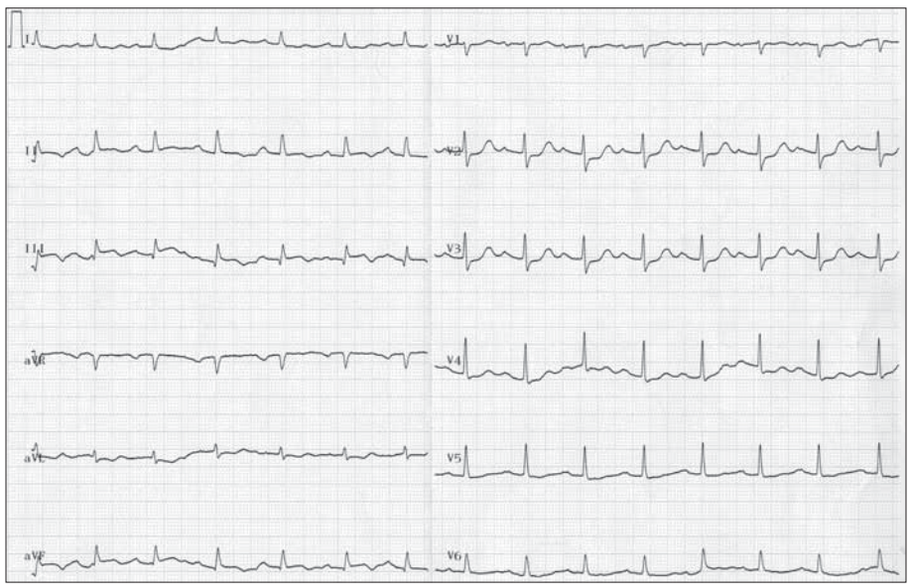

Figure 1. *ST segment depression in V2-V6 derivations.*

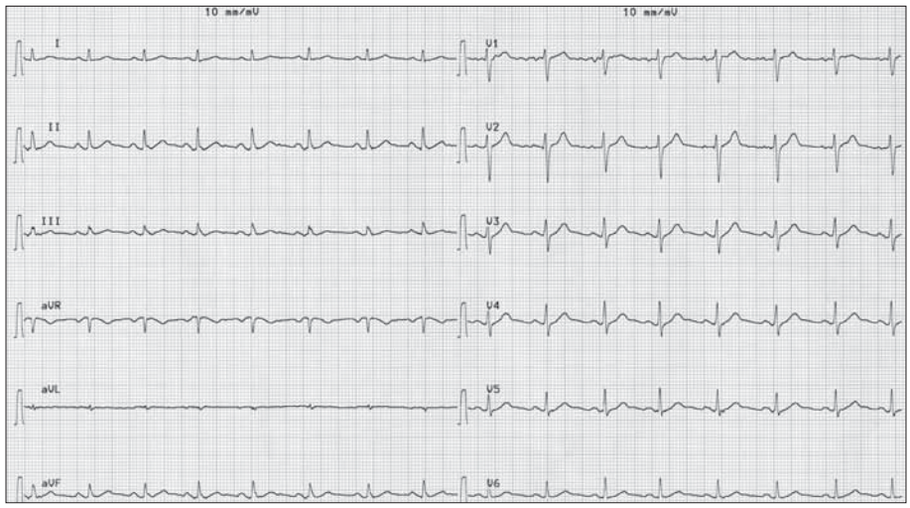

Figure 2. *Normalization of ST segment depression.*

sional 5-FU may lead to cardiotoxicity that presents with angina, elevated cardiac enzymes and electrocardiogram (ECG) changes at various dose levels [3, 4]. Cardiotoxicity has been reported to occur with 5-FU administered either as a single agent or in combination with other chemotherapy agents [4].

Clinical expression of cardiotoxicity related to 5-FU was first identified by Dent and McColl [7]. The incidence of 5-FU cardiotoxicity ranged from 1.6% to 8.5% in subsequent reports [3, 4]. Coronary vasospasm secondary to 5-FU is one of the rare, but life-threatening, forms of cardiotoxicity, which should be kept in mind throughout delivery of CT. The underlying mechanism of coronary vasospasm is likely the result of endothelial dysfunction caused by 5-FU and its active metabolites. Endothelial dysfunction is thought to be due to an increase in the release of endothelin-1, a vasoconstrictor, and a decrease in the release of prostacyclin, a vasodilatator [8, 9]. Coronary vasospasm has been diagnosed in these patients using coronary angiography. Symptoms include precordial pain and dyspnea that usually starts within a few hours of infusion, accompanied by ECG changes [9]. Our patient complained of chest pain during the third hour of infusion of 5-FU, and ST segment depression was shown in the ECG (Figure 1).

Parenteral nitrates and parenteral or oral calcium channel blockers are used for the treatment of coronary vasospasm. No interaction between 5-FU and these drugs has been documented [10]. We preferred parenteral diltiazem, a calcium channel blocker, for our patient following discontinuation of infusion. Rapid symptom relief and normalization of depression of ST segment (Figure 2) was seen after administration of diltiazem.

In conclusion, coronary vasospasm related to 5-FU is a rare but life-threatening clinical entity in oncological practice and may be seen during both bolus and protracted infusional administration of CT. This toxicity is generally reversible, and responds well to conventional anti-angina treatment following discontinuation of infusion. We propose that parenteral diltiazem is an effective and safe approach for the treatment of coronary vasospasm secondary to infusional 5-FU.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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