ST Elevation Myocardial Infarction Due to Left Main Coronary Artery Thrombus and Vasospasm Associated with 5-Fluorouracil: Case Report

5-Florourasil ile İlişkili Ana Koroner Arterde Trombüs ve Vazospazm Sonucu Gelişen ST Elevasyonlu Miyokard İnfarktüsü

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ABSTRACT Cardiotoxicity is one of the rare side effects of 5-fluorouracil. The pathogenesis of 5-fluorouracil cardiotoxicity is not clear. Coronary vasospasm is the most suggested hypothesis. Previous reports was mentioned only one mechanism that contribute to ST elevation myocardial infarction after 5-fluorouracil infusion. In our knownledge there was no data that involve multiple mechanisms in the occurrence of myocardial infarction. A thrombus and vasospasm were seen concominantly distal segment of left main coronary artery that causes 70% stenosis on coronary angiography. Firstly an operation was thougt for revascularization. The chest pain of patient was released and ST resolution was observed on anterior derivations after intensive medication. While the preparations for operation was continuing, chest pain was totally disappeared. The thrombus in the left main coronary artery disappeared and vasospasm resolved on control angiography. According to our information such life-threatening left main coronary artery thrombus and vasospasm concomitantly was not seen before related to administration of 5-fluorouracil.

Key Words: Fluorouracil; coronary vasospasm; thrombosis

ÖZET Kardiyotoksisite 5-florourasilin nadir görülen yan etkilerinden biridir. 5-florourasil ile ilişkili kardiyotoksisitenin patogenezi tam net değildir. En sık öne sürülen hipotez vazospazmdır. Önceki yayınlarda 5 florourasile bağlı ST elevasyonlu miyokard infarktüsünün oluşmasında sadece bir mekanizmanın rol oynadığı ileri sürülmüştür. 5 florourasile bağlı miyokard infarktüsünün oluşmasında birden çok mekanizmanın eş zamanlı rol oynadığı ile ilgili bilgilerimiz bulunmamaktadır. Bizim vakamızda 67 yaşında erkek hastanın koroner anjiyografisinde ana koroner arterde %70 darlığa neden olan trombüs ve vazospazm tespit edildi. Aorto-koroner baypas operasyonu kararı verildi. Operasyona hazırlık aşamasında yoğun medikal tedavi sonrası hastanın göğüs ağrısı azaldı ve anterior derivasyonlardaki ST elevasyonları geriledi. Yapılan kontrol anjiyografide ana koroner arterdeki trombüsün ve vazospazmın kaybolduğu tespit edildi. Bildiğimiz kadarıyla daha önceden 5- florourasil sonrası ana koroner arterde yaşamı tehdit eden trombüs ve vazospazm birlikteliği gözlenmemiştir. Bu sebeple bu vakayı sunmayı uygun gördük.

Anahtar Kelimeler: Florourasil; koroner vazospazmı; tromboz

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5-Fluorouracil (5-FU) has been used in the chemotherapeutic treatment of gastrointestinal malignancies for many years. Cardiotoxicity is a rare adverse effect of 5-FU with a reported incidence of 1,2% to 18%. The pathogenesis of 5-FU cardiotoxicity is not clear and coronary vasospasm is the most suggested hypothesis.[1-4] However, several mechanisms have also been described that cause cardiotoxicity such as endothelial damage, throm-

bogenic effects, direct myocardial toxicity. 5-FU may lead to the development of thrombosis by inducing endothelial damage in patients with coronary artery disease.[5]

CASE REPORT

A 67 year-old man had recently been admitted to the general surgery clinic with vomiting and weight loss. Gastric cancer (T2N1M0) had been diagnosed after gastroscopy and biopsy evaluation. A subtotally gastrectomy + omentectomy + D2 lymph node dissection had been performed 20 days before admission. Additionally, 5-fluorouracil and folinic acid chemoterapy had been decided to administer after the operation**.** A severe chest pain started after 20 hours administration of 750 mg/day 5-FU and 30 mg/day folinic acid. Electrocardiography showed ST elevation in the anterior leads (V1-V6) and resiprocal ST depressions in the inferior leads (II,III,avF). Acute myocardial infarction (MI) was diagnosed. 300 mg of acetyl salicylic acid and 600 mg of clopidogrel were given orally. He was immediately taken to the catheter laboratory. Both thrombus and vasospasm were seen concomitantly in the distal segment of left main coronary artery (LMCA) that cause 70% of luminal stenosis on coronary angiography (Figure 1, Video 1). First, operation (aorto-coronary by-pass surgery) was considered for the revascularization. He was taken to Coronary care unit (CCU) and administered 200 μg/min of nitroglycerin, 0.1 μg/kg/min of tirofiban and 25 mg of diltiazem, intravenously. While the patient was preparing for the operation, chest pain totally disappeared 2 hours after admission. Therefore control coronary anjiography was performed 4 hours after patients received CCU. The thrombus

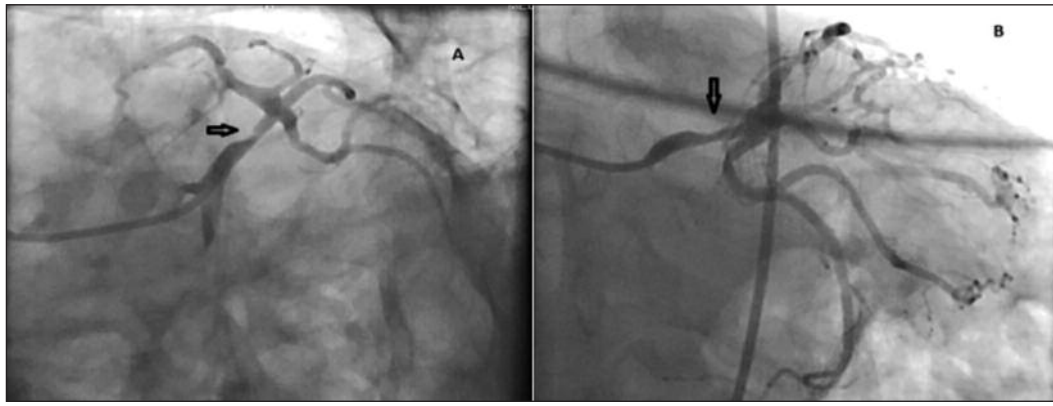

FIGURE 1: Coronary angiogram showed coronary thrombosis and vasospasm (see arrows), concomitantly in the left main coronary artery.

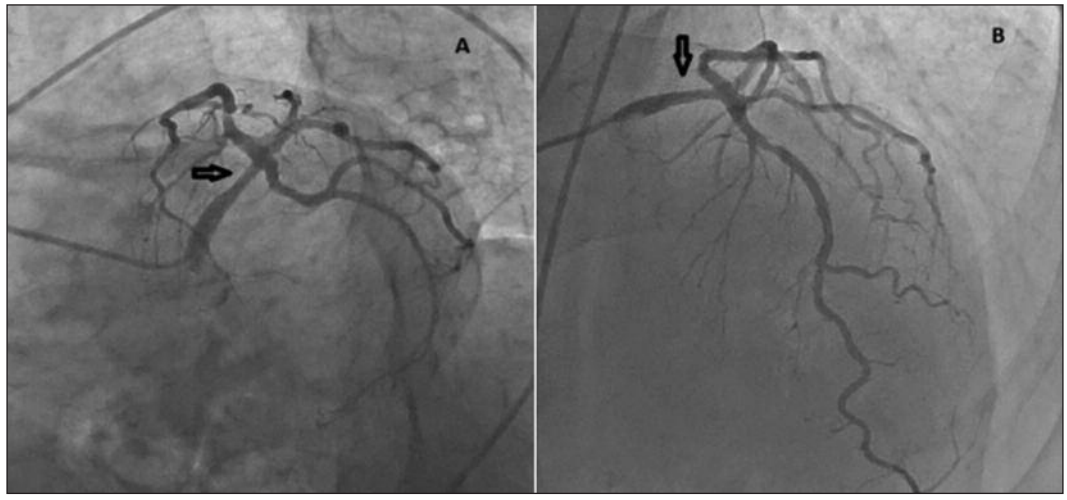

FIGURE 2: Control angiography after medication showed an atheromatous plaque without significant stenosis in the left main coronary artery..

in the LMCA was absent and the vasospasm was resolved. An atheromatous plaque occuring 40% stenosis was observed on coronary angiography after loss of thrombus and vasospasm (Figure 2, Video 2). Therefore the preparations for the surgery was stopped. IV 0.1 μg/kg/min of tirofiban was continued for 24 hours, nitroglycerin with decreased doses for 18 hours. After intravenous therapy, medication was continued with antiaggregants, nitrates, calcium canal blokers per oral. The patient follow-up continued in CCU for 7 days.

DISCUSSION

The precise etiology and pathophysiology of 5-FU cardiotoxicity are still controversial. Numerous mechanisms have been proposed such as vasospasm, endothelial injury, thrombogenic effects, direct myocardial toxicity, autoimmune-mediated injury of the myocardium and accumulation of metabolites.[6] Significant coronary vasospasm causing myocardial ischemia is the most common suspected mechanism of this clinical entity.[2,9] Both animal and human studies indicate a dose dependent vasospasm that terminates with cessation of drug administration.[3] Other studies note the efficacy of vasodilator therapy, including nitrates and calcium channel blockers, in resolving chest pain and dynamic ECG changes in the setting of 5-FU administration.[7,8] Endothelial dysfunction and thrombus formation, have also been shown to contribute as potential mechanisms of the cardiotoxic effects of 5-FU administration. Several animal studies revealed the direct effects of 5-FU on vascular endothelial cells and showed direct endothelial injury and platelet and fibrin accumulation with increased thrombus formation on both gross examination and electron microscopic evaluation.[6-8] Kuzel et al. demonstrated an increase in the quantity of fibrinopeptide A and a decrease in the amount of protein C activity in the presence of 5-FU, which together make a blood vessel more susceptible to thrombus formation.[9] Prophylactic calcium channel blockers or nitrates should be administered to patients with coronary artery diseases (CAD) during 5-FU administration, to prevent vasospasm.[1,2] Another case report revealed an acute myocardial infarction after capecitabine treatment caused by coronary thrombosis rather than spasm.[10]

In our case acute ST elevation myocardial infarction (STEMI) may be primarily considered due to vasospasm. However, both thrombosis and vasospasm were observed in the same segment of LMCA on coronary angiography. Second coronary angiography had done due to significant ST resolution on ECG. On control coronary angiography, a 40% atherosclerotic plaque was detected and there was no thrombus and/or vasospasm. To our knowledge, such life-threatening left main coronary artery thrombus and vasospasm concomitantly, were not seen before related to administration of 5-FU. Previous reports were usually emphasized vasospasm alone, as the only mechanism that contributes to the occurrence of STEMI after 5-FU infusion. STMI due to thrombus was very rare after 5-FU infusion. In our case both vasospasm and thrombus formation was observed. Besides on second coronary angiography revealed atherosclerotic plaque after destruction of thrombus and relieving vasospasm. Although our patient did not have a history of CAD, a large atheromatous plaque was found on coronary angiography after destruction of thrombus and vasospasm. This finding supports as mentioned some reports 5-FU is seen more common with a history of CAD.

Both platelets and thrombin play an essential role in the pathophysiological mechanism of Acute coronary syndrome (ACS). Although aspirin and clopidogrel have been used as therapeutic mainstays for ACS, the activation of platelets is not always inhibited by aspirin or clopidogrel. The final common pathway to the coronary thrombosis underlying ACS involves the aggregation of platelets mediated by the binding of soluble fibrinogen to the platelet receptor glycoprotein (GP) IIb-IIIa.[11] Tirofiban has a rapid onset and short duration of action after proper IV administration. There is possibly a favorable effect of the glycoprotein IIb/IIIa antagonist for the treatment of intracoronary thrombosis. These properties seem to prevent not only thrombus formation, but also to promote (at

higher drug concentration) lysis of fresh thrombus.[12]

The PRISM-PLUS study suggests that the combination of tirofiban plus heparin reduces the isovolumic contraction time (ICT) burden of the culprit lesions, improves the perfusion grade, and decreases the severity of the obstruction in patients with ACS.[13] There is no certain algorithm available for the therapeutic options of ICT. The conventional approach to coronary thrombosis is either an interventional procedure or bypass surgery. Different medical approaches have been suggested.[10-13] It is believed anticoagulant and antiplatelet medications contribute to clot dissolution. Therefore tirofiban was given intravenously while the patient was preparing for the operation. The contribution of GP IIb/IIIa inhibitor therapy to clot dissolution remains unclear. However, we believe that tirofiban had a beneficial effect on coronary clot dissolution in our case.

This case supports the vasospastic and thrombogenic hypothesis of 5-FU cardiac toxicity and all patients should have a careful evaluation for cardiovascular risk factors as well as any subclinical coronary artery disease which may be aggravated by 5-FU infusion. We consider that patients under 5-FU treatment should be referred for emergent, coronary angiogram if they experience acute coronary events, as coronary vasospasm is not always the culpable mechanism and intensive medical treatment with tirofiban, nitrates and calcium channel blocker should be administered before final decision. Physicians should be aware of this potentially lethal side effect and should start the appropriate treatment when 5-FU cardiotoxicity develops.

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