Introduction

The drug 5-fluorouracil (5-FU) is a pyrimidine antagonist used for chemotherapy. Cardiotoxicity is a rare side effect of this compound (1). We present two cases of 5-FU cardiotoxicity, because every cardiologist has to be aware of the possible clinical presentations and its management as it can be life threatening.

Case Report

The first case is a 40-year-old female patient with adenocarcinoma of the cecum who was started on continuous intravenous (i.v.) 5-FU (425 mg/m²/day) and folinic acid (25 mg/m²/day) infusion. The patient had no history of heart disease. On the third day of 1st cycle, she developed chest pain. The electrocardiogram (ECG) showed ST segment elevation in leads II, III, aVF, V5 and V6 (Fig. 1a). The angina and ECG changes disappeared after sublingual nitrate administration (Fig. 1b).

She continued to experience angina despite discontinuation of 5-FU, so she was admitted to the coronary care unit (CCU). She was heparinized with a 5000 U i.v. bolus followed by 1000 U/hr infusion and was started on a 5 mg/min nitroglycerine infusion, with the rate gradually increased to 100 mg/min. She continued to have anginal attacks of decreasing frequency and severity till day 4 of the i.v. heparin and nitrate therapy. Her serum levels of creatine kinase (CPK) and CPK-MB, and troponin-I remained within normal limits. Echocardiography was normal at all times.

A coronary angiography was performed. The coronary arteries were normal (Fig. 2a). The fractional flow reserve (FFR, defined as the ratio of the mean pressure distal to a coronary stenosis to the mean aortic pressure during maximal hyperemia, indicates significant stenosis if <0.75) was measured to rule out any significant stenosis. FFR of the left anterior descending (LAD) and circumflex (Cx) arteries were measured. The FFR for the LAD artery was 1.02 (102/100), and this remained unchanged after an intracoronary injection of adenosine. The FFR of the Cx artery was 1.01 (102/101). Hyperventilation-induced respiratory alkalosis did not cause vasospasm in the coronary arteries. However, the cold pressor test, performed by placing the patient’s left arm in ice-cold water, resulted in 30-40% narrowing of the Cx artery (Fig. 2b).

The patient’s chemotherapy regime was changed. She was discharged on oral diltiazem 90 mg/day. She remained free of any cardiac symptoms in follow-up.

Our second case is a 63-year-old man who had coronary artery disease. He had adenocarcinoma of the duodenum and was started i.v. 5-FU (425 mg/m²/day) and folinic acid (25 mg/m²/day). On the 3rd day of the regimen shortly after the continuous infusion of 5-FU, the patient developed chest pain with ST segment elevation in leads II, III, aVF, V4, V5 and V6 (Fig. 3A). He was admitted to CCU and i.v. nitroglycerine and diltiazem infusion was started. The ST segment changes (Fig. 3B) and

**Figure 1. A) ST segment elevation in leads DII, DIII, V5 and V6 during an anginal attack of Case 1 B) Complete resolution of ECG changes after resolution of the pain in Case 1**

ECG - electrocardiogram
Vasospasm was not observed with hyperventilation-induced respiratory alkalosis or the cold pressor test.

He was discharged on oral nitrate and diltiazem. He received a different chemotherapy regimen with no 5-FU.

Discussion

Cases of mild precordial pain with ST segment and/or T-wave changes, myocardial infarction, left ventricular failure, cardiogenic shock, ventricular and supraventricular arrhythmias, and sudden cardiac death have been reported (2-6) in >20% of patients receiving 5-FU. The underlying pathophysiological mechanism remains unclear. Coronary vasospasm may play a role in the pathogenesis. More than 60% of patients respond to conventional antianginal therapy (7).

Discontinuation of 5-FU infusion and immediate administration of sublingual nitrate is the life saving first line of therapy in the treatment of cardiovascular complications of 5-FU. As the symptoms may continue even after cessation of 5-FU administration, the patients should be followed for at least 72 hours in coronary care units. Patients with known CAD are more at risk, therefore should be followed more closely with a high level of alertness. The chemotherapy regimen of these patients should be changed. Patients should be evaluated for cardiovascular risk factors and managed accordingly in the follow-up.

References