A Case of 5-Fluorouracil Cardiotoxicity Simulating Acute Myocardial Infarction

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5-Fluorouracil (5-FU) is widely used in the treatment of various solid tumors. However, 5-FU cardiotoxicity is being reported with increasing frequency. The main symptom of cardiotoxicity is chest pain at rest with ischemic electrocardiographic changes. Up until now, the underlying mechanism has been suspected to be coronary artery spasm. However, this chest pain associated with 5-FU has several characteristics that are incompatible with coronary artery spasm: eg, inefficacy of calcium-channel blocker and a slow increase in cardiac enzyme levels. We experienced a case of 5-FU-induced cardiotoxicity which showed clinical findings consistent with acute myocardial infarction. Based on the clinical findings, coronary angiography, and left ventricular angiography in a prolonged attack, we concluded that the cardiotoxicity in this case was not due to ischemia caused by coronary artery spasm. (Jpn Circ J 1995; 59: 303—307)

5-Fluorouracil (5-FU) is widely used in the treatment of various solid tumors. However, 5-FU cardiotoxicity is being reported with increasing frequency. The incidence of 5-FU cardiotoxicity was 1.6% in a retrospective study of 1083 patients! The cardiotoxicity due to 5-FU is manifested in the form of chest pain, electrocardiographic changes, and arrhythmia? Many investigators have suggested that coronary artery spasm may cause this chest pain3.4 However, chest pain associated with 5-FU has several characteristics that are incompatible with coronary artery spasm. For example, the duration of the attack is prolonged and calcium-channel blockers are ineffective in treating 5-FU cardiotoxicity.

We experienced a case of 5-FU-induced cardiotoxicity that showed clinical findings compatible with acute myocardial infarction. Based on these clinical findings, coronary angiography, and left ventricular angiography in a prolonged attack, we concluded that the cardiotoxicity in this case was not due to ischemia caused by coronary artery spasm.

CASE REPORT

A 73-year-old woman underwent an operation for left breast carcinoma in September 1992. There was no history of cigarette smoking, diabetes mellitus, or heart, lung or renal disease. She received 5-FU therapy (300 mg/day per os) for 31 days. About 7 h after administration of a dosage of 100 mg, she experienced severe chest pain, and was brought to our hospital 30 min after the attack. Upon physical examination, her heart rate was 70 beats/min, her blood pressure was 170/90, and III sound was audible. Electrocardiograms (ECG) showed marked

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ST segment elevations in all leads except III and aVR (Fig. 1, left panel). Anterior to inferior left ventricular wall motion was akinetic on two-dimensional echocardiography. Administration of sublingual nitroglycerin and intravenous isosorbide dinitrate did not reduce her chest pain or ST segment elevation. We initially suspected acute myocardial infarction based on these clinical data. One hour after the onset, cardiac catheterization was performed. The mean pulmonary wedge pressure was 19 mmHg with a cardiac index of 2.2 L/min/m². Coronary angiography (CAG) revealed almost normal coronary arteries (Fig. 2). Left ventricular angiography (LVG) showed significant akinesis from the anterior wall to the inferior wall and the an ejection fraction was of 46.0%. The akinetic area was incompatible with the distribution of the major coronary arteries (Fig. 3 upper panels). Despite near normalcy and patency on CAG, ST segments on the ECG continued to increase for several hours, and she still complained of chest pain 4 h after the attack. Maximum creatine kinase (CK) was 480 IU/L and its peak time was prolonged to 18 h after the onset of attack. Two days later, she experienced chest pain again 2 h after taking 5-FU 100 mg despite the administration of diltiazem 120 mg/day. We discontinued the administration of 5-FU and no attack was observed thereafter. One month later, we attempted to provoke coronary spasm by hyperventilation, but this trial produced negative results, even under calcium antagonist- and nitrite-free conditions. The following day, cardiac catheterization was performed again. The mean pulmonary wedge pressure was 4 mmHg with a cardiac index of 2.6 L/min/m². LVG showed significant improvement in the area of asynergy area,
and the ejection fraction was improved to 75.0% (Fig. 3, lower panels). Once again, coronary angiography was normal. We tried to provoke coronary spasm by intracoronary infusion of acetylcholine (ACh), before and 2 h after the intravenous infusion of 5-FU 750 mg. All tests were performed with the patient’s informed consent. Two hours after the infusion of 5-FU, we observed vasoconstriction in the left and right coronary arteries upon intracoronary infusion of ACh, and the patient complained of chest pain with slight ST segment elevation (Fig. 4). Intracoronary infusion of isosorbide dinitrate (10 mg) had little effect. Her chest pain and the change in the ECG lasted about 15 min, even though coronary artery flow was observed in both left and right CAG. The following day, we orally administered 5-FU at a dosage of 100 mg, again with her informed consent. Eight hours later, a spontaneous attack of chest pain with ST segment elevation in all of the leads except III and aVR appeared. This attack disappeared 20 min after the administration of sublingual nitroglycerin (0.6 mg).

DISCUSSION

This patient showed 5-FU-induced cardiotoxicity with clinical findings that were compatible with acute myocardial infarction. Up until now, 5-FU-induced cardiotoxicity has been thought to be caused by coronary artery spasm. We examined whether coronary artery spasm was the cause of 5-FU-induced cardiotoxicity in this case. During the first prolonged attack, CAG demonstrated patent and almost normal major coronary arteries with no delay in coronary flow, and LVG showed diffuse akinetic anterior to inferior wall motion. The delay in the peak CK time, sustained chest pain and ST-T change on ECG after recanalization can not be explained by assuming that coronary angiography was recanalized at the emergent coronary angiography. Based on these findings, we believe that the 5-FU-induced cardiotoxicity in this case was not caused by myocardial ischemia due to coro-
Fig.4. The right coronary artery angiogram in the left anterior oblique projection, and the left coronary angiogram in the right anterior oblique projection. Representative ECG leads (III, V₃) are displayed. Acetylcholine was first injected into the right coronary artery.
(A) Before intravenous infusion of 5-Fluorouracil. After intracoronary infusion of acetylcholine 50 μg, the right coronary artery showed no stenosis.
(B) Two hours after intravenous infusion of 5-Fluorouracil 750 mg. After intracoronary infusion of acetylcholine 50 μg, the right coronary artery showed vasoconstriction and the ST segment was slightly elevated in lead III during severe chest pain. Even though the coronary artery was patent and there was no delay in flow, her chest pain lasted for another 18 min.
(C) After intravenous infusion of isosorbide dinitrate. The right coronary artery was normal by coronary angiography.
(D) Before intravenous infusion of 5-Fluorouracil. After intracoronary infusion of acetylcholine 100 μg, the left coronary artery showed only slight vasoconstriction.
(E) Two hours after intravenous infusion of 5-Fluorouracil 750 mg. After intracoronary infusion of acetylcholine 30 μg, the left coronary artery showed vasoconstriction, the ST segment was slightly elevated in precordial leads, and the patient felt severe chest pain. Although the coronary artery was patent and there was no delay in flow, we injected isosorbide dinitrate 10 mg into the intracoronary artery. However, her chest pain continued for another 17 min.
(F) After intravenous infusion of isosorbide dinitrate. The left coronary artery was normal by coronary angiography.

Matsubara et al demonstrated that myocardial blood flow remained constant during ischemic ST-T changes observed after administration of 5-FU in guinea pigs, and demonstrated decreased stores of adenosine triphosphate and creatine phosphate and accumulation of citrate. Robben et al reviewed 134 cases of 5-FU-induced cardiotoxicity and reported that prophylaxis with calcium-channel blocker is difficult and that few patients with left ventricular dysfunction had cardiac enzyme changes. They concluded that 5-FU-induced cardiotoxicity is an elusive cardiomyopathy that may have a metabolic pathway in common with ischemic heart disease. We showed here that 5-FU could not produce typical vasospasm of major coronary arteries, despite the conclusions of other previous reports. We also demonstrated that 5-FU may sensitize major coronary arteries to vasospastic stimuli such as ACh. However, the possibility that it also produces myocardial ischemia due to vasoconstriction of coronary resistance vessels can not be completely excluded. The present results support the hypothesis that the mechanism of this cardiotoxicity is not myocardial ische-

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mia due to major coronary artery spasm, but is rather a disorder of the myocardocytes themselves.

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