A Case of Takotsubo Cardiomyopathy During 5-Fluorouracil Treatment for Rectal Adenocarcinoma

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Abstract

A case of acute heart failure due to Takotsubo cardiomyopathy induced by 5-fluorouracil is described. Acute heart failure developed during the administration of 5-fluorouracil (5-FU) and levofofolinate calcium in a 62-year-old woman who had underwent a Miles operation for rectal adenocarcinoma. Electrocardiography upon admission showed slight ST elevation in leads V1-3, and follow-up electrocardiography on the third hospital day revealed QT interval prolongation and giant negative T waves in leads II, III, aVF, and V1-6. Echocardiography and myocardial scintigraphy showed left ventricular apical ballooning in the acute phase of heart failure, but left ventricular contraction was normal during the recovery phase. Coronary angiography demonstrated normal coronary arteries, and multi-vessel coronary artery vasospasms including microcirculation disorders could be provoked by intracoronary acetylcholine infusion during, but not before, the intravenous administration of levofolinate calcium and 5-FU. The cause of heart failure in this patient, Takotsubo cardiomyopathy induced by multivessel coronary vasospasm including microcirculation disorders only during 5-FU administration, is notable. (J Nippon Med Sch 2009; 76: 27–33)

Key words: acute heart failure, takotsubo cardiomyopathy, coronary vasospasm, microcirculation disorders, 5-fluorouracil

Introduction

Although 5-fluorouracil (5-FU) is one of the most frequently used drugs for treating malignant diseases, it is associated with several adverse cardiac effects, such as chest pain and ST-T segment changes on electrocardiography (ECG)1–3. Such cardiac adverse effects might be related to vasospasms of the coronary arteries4–6. However, although severe heart failure sometimes develops in patients treated with 5-FU, whether vasospasm is the cause remains unknown. We describe a patient with rectal adenocarcinoma whom severe heart failure developed during treatment with 5-FU. We also discuss the mechanism of the heart failure in

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this patient.

**Case Report**

A 62-year-old woman underwent a Miles operation for rectal adenocarcinoma in February 2003. Her only coronary risk factor was smoking. **Figure 1** shows the clinical course. Starting on March 11, 2003, she had received weekly intravenous 5-FU (750 mg) and levofolinate calcium (375 mg) for 6 consecutive weeks. Four weeks after the start of chemotherapy (April 2, 2003), intermittent shortness of breath and slight chest pain developed. On April 18, she was admitted to the intensive care unit with chest pain and severe dyspnea. Severe acute heart failure was diagnosed at that time. Upon admission, the patient showed a disturbance of consciousness (Glasgow Coma Scale, 12), and vital signs were as follows: blood pressure, 204/120 mm Hg; heart rate, 110/minute and regular; and respiratory rate, 30/minute. Peripheral edema and cervical vein dilation were evident, and moist rales were audible in both lungs. Anemia, jaundice or other abnormalities were absent. Chest X-ray films showed pulmonary congestion (**Fig. 2**), and ECG showed mild ST segment elevation in leads V1-3 (**Fig. 3a**). Blood chemistry analysis revealed increased concentrations of serum troponin T (0.82 ng/mL), creatine kinase (359 IU/L), and creatine kinase MB (13 IU/L). The white blood cell count was 7,580/µL, and levels of C-reactive protein, serum creatinine, and serum brain-type natriuretic peptide were 0.51 mg/dL, 4.09 mg/dL, and 1,256.8 pg/mL, respectively. Echocardiography demonstrated extensive left ventricular apical akinesis (**Fig. 4a**).
Fig. 3  ECG on admission (a) and on hospital day 3 (b)
Giant negative t waves with QT prolongation developed on hospital day 3.

Fig. 4  Left ventricular apical akinesis. ECG upon admission (a); myocardial scintigraphy (technetium-99m tetrofosmin quantitative gated) on hospital day 2 (b). Left ventricular apical akinesis was extensive.

Myocardial scintigraphy (technetium-99m tetrofosmin quantitative gated scintigraphy) performed on hospital day 2 also revealed extensive apical akinesis (Fig. 4 b). Follow-up ECG on hospital day 3 revealed QT interval prolongation and giant negative T waves in leads II, III, aVF, and V1-6 (Fig. 3b). Left ventricular function evaluated with echocardiography gradually improved with treatment. The left ventricular ejection fraction was 28% on admission, 45% on April 21, and 67% on April 28. The heart failure improved immediately after the administration of low-dose diuretics (furosemide, 10 mg/day) and a vasodilator (nitroglycerin, 0.2 μg/kg/minute). We suspected that the heart failure was caused by
Fig. 5 Coronary angiography

Normal coronary arteries at baseline (a), vasodilatory actions after intracoronary acetylcholine infusion (b), and multiple coronary vasospasms after intracoronary acetylcholine infusion during administration of 5-FU and levofolinate (c).

Takotsubo cardiomyopathy. After the heart failure was compensated for and the serum concentration of 5-FU was sufficiently reduced, we performed cardiac catheterization on June 4. Coronary angiography demonstrated normal coronary arteries (Fig. 5a), and left ventriculography showed normal contraction (Fig. 6). Coronary vasospasm could not be provoked, but the coronary arteries were dilated with intracoronary infusions of acetylcholine (Fig. 5b). The doses of acetylcholine were 50 μg to the right coronary artery (RCA) and 100 μg to the left coronary artery (LCA). In contrast, 15 minutes after the intravenous administration of levofolinate calcium (drip infusion for 2 hours) and 5-FU (bolus infusion of 750 mg), the intracoronary infusion of acetylcholine provoked multivessel coronary artery vasospasms with coronary artery flow disturbances (20 μg to RCA and 50 μg to the LCA) (Fig. 5c). The flow disturbances were evaluated by corrected Thrombolysis In Myocardial Infarction (TIMI) frame counts. There were flow disturbances in all 3 coronary arteries. Corrected TIMI frame counts were 31 cineframes in the RCA, 49 in the LAD, and 60 in the left circumflex artery (LCX). Chest pain similar to that before admission occurred during vasospasms and was accompanied by T wave changes on ECG. The symptom and the changes on ECG disappeared after coronary vasospasms were resolved with intracoronary infusions of nitroglycerin (100 μg). The results of ECG before and after intracoronary infusion of acetylcholine are shown in Figure 7. Pseudonormalizations of T wave in II, III, and aVF leads appeared after intracoronary infusion of acetylcholine to the RCA (Fig. 7b) and in V3-6 leads after infusion to the LCA (Fig. 7c). An oral calcium antagonist (nifedipine, 40 mg) was started, and the administration of 5-FU and levofolinate calcium was stopped. Thereafter, the symptoms of both myocardial ischemia and heart failure resolved.

Discussion

Myocardial Ischemia and 5-FU

The underlying mechanism of 5-FU cardiotoxicity remains obscure. Carpenter first described the adverse cardiac effects of 5-FU in 1972. Thereafter, some reports described 5-FU cardiotoxicity including myocardial ischemia. Dent et al. described angina pectoris caused by 5-FU. Burger et al. and Lestuzzi et al. concluded angina pectoris arising as a complication of 5-FU was due to coronary vasospasm. Although the coronary arteries were normal in patients with angina pectoris after 5-FU administration, only a few reports revealed vasospasms on coronary angiography. In 1991, Luwaert et al. identified coronary vasospasm before and during 5-FU administration. Our patient is notable because intracoronary acetylcholine infusion
induced normal vasodilating action before 5-FU administration but induced significant vasospasm in several coronary arteries after 5-FU administration. We believe that coronary vasospasm can be induced by intracoronary infusion of acetylcholine in patients with damaged endothelium and in patients with normal endothelium.

The mechanism of vasospasm remains unclear, although myocardial ischemia as an adverse cardiac effect of 5-FU could be explained by coronary vasospasm. Mosseri et al. reported that the mechanism of vasospasm in patients receiving 5-FU involves activation of protein kinase C. They reported that a protein kinase C inhibitor could prevent 5-FU-induced vasoconstriction in animal models. Sudhoff et al. found that the mechanism also involves an increase in the plasma concentration of big endothelin. They showed that the plasma level of big endothelin tended to be higher in patients receiving intravenous 5-FU than in patients
receiving other types of chemotherapy.

**Congestive Heart Failure and 5-FU**

Another adverse effect of 5-FU is congestive heart failure\(^{11}\). We postulate that the mechanism of congestive heart failure in the present patient was Takotsubo cardiomyopathy. Emotional or physical stress has been implicated in Takotsubo cardiomyopathy\(^{12,13}\), but 5-FU, thus far, has not. Although Labianca et al. described acute myocardial infarctions during 5-FU administration\(^{9}\), severe myocardial infarction with heart failure has not been reported. David et al. reported on one patient with nonischemic heart failure during 5-FU administration but did not describe the cause of the heart failure in detail\(^{16}\). Tsibiribi et al. found in an animal model that apoptosis of myocardial and endothelial cells could result in inflammatory lesions mimicking toxic myocarditis\(^{8}\). However, whether this mechanism causes congestive heart failure remains unknown.

In the present case, intracoronary infusion of acetylcholine provoked coronary artery spasms after the administration of 5-FU. In this case, the LAD was not dominant, and the coronary artery spasms occurred in multiple coronary arteries, including the LAD, LCX, and RCA (Fig. 3c). We believe that global left ventricular dysfunction developed because multivessel coronary artery spasms, including coronary microcirculation disorders\(^{17-19}\), occurred during the use of 5-FU. Corrected TIMI frame counts were 31 cineframes in the RCA, 49 in the LAD, and 60 in the LCX. There is a possibility that these frame counts indicate coronary microcirculation disturbance. Bybee et al. reported that patients with Takotsubo cardiomyopathy had abnormal TIMI frame counts (>30 cineframes) in coronary arteries\(^{27}\). The guidelines of the Japanese Circulation Society exclude transient left ventricular dysfunction caused by coronary vasospasm from the diagnosis of Takotsubo cardiomyopathy\(^{20}\), but there have been many reports of Takotsubo cardiomyopathy caused by coronary vasospasm, and many cases without excluding the presence of coronary vasospasm\(^{21,22}\) have been reported. In the present case, intracoronary acetylcholine infusion induced normal coronary artery dilation; therefore, the diagnosis of Takotsubo cardiomyopathy should be accurate. Furthermore, only in special circumstances, such as during the administration of 5-FU, could multiple coronary vasospasms and microcirculation disturbances be provoked. We postulate that multiple coronary vasospasms and microcirculation disorders in our patient during 5-FU administration were followed by the onset of Takotsubo cardiomyopathy and congestive heart failure.

**References**


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