Case Report

5-Fluorouracil–Induced Tako-Tsubo–Like Syndrome

Cécile Basselin, P.D., Thierry Fontanges, M.D., Jacques Descotes, M.D., Ph.D., Philippe Chevalier, M.D., Ph.D., Bernard Bui-Xuan, M.D., Ph.D., Gwennaelle Feinard, P.D., and Quadiri Timour, Ph.D.

Tako-Tsubo cardiomyopathy (also known as apical ballooning syndrome) is a relatively new clinical entity characterized by reversible left ventricular dysfunction. Its clinical presentation and electrocardiographic findings are similar to acute myocardial infarction but without significant coronary artery disease. Cardiotoxicity is a major complication of various anticancer drugs; however, only a few cases of Tako-Tsubo cardiomyopathy associated with anticancer drugs, including 5-fluorouracil, have been reported. We describe a 48-year-old man who developed acute coronary syndrome, thought to be similar to Tako-Tsubo syndrome, after receiving a chemotherapy regimen consisting of 5-fluorouracil, oxaliplatin, and calcium folinate (FOLFOX protocol) for colic adenocarcinoma. Approximately 24 hours after receiving his first cycle of chemotherapy, the patient, who did not have a history of cardiovascular disease, developed chest pain, with abnormal electrocardiographic results and a mildly increased troponin T level. Coronary angiography did not show any significant coronary lesions. Echocardiography revealed marked left ventricular dysfunction (left ventricular ejection fraction [LVEF] 15%) with severe hypokinesia in all apical and median segments. The patient was stabilized with the introduction of an intraaortic balloon pump and pressor therapy. One month later, myocardial magnetic resonance imaging confirmed total recovery of left ventricular systolic function. Thus, the second chemotherapy cycle was administered at half the dose-intensity, along with ramipril and diltiazem. The chemotherapy regimen was well tolerated. Two weeks later, at the end of the third chemotherapy cycle, administered using the full-dose regimen, the patient experienced cardiac arrest, necessitating cardiopulmonary resuscitation. After transfer to the cardiology intensive care unit, acute heart failure recurred (LVEF 35%). Normal recovery of left ventricular function occurred a few days later. Chemotherapy was discontinued, and treatment with bisoprolol was started. Four months later, the patient remained completely asymptomatic of any cardiac manifestations. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 8) between the patient's development of acute coronary Tako-Tsubo–like syndrome and 5-fluorouracil. Clinicians should be aware of this potential adverse effect when monitoring patients receiving chemotherapy with 5-fluorouracil.

Key Words: 5-fluorouracil, Tako-Tsubo syndrome, cardiomyopathy, chemotherapy-induced cardiotoxicity.

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Cardiotoxicity is a major complication of various anticancer drugs, including 5-fluorouracil[1, 2] and the 5-fluorouracil prodrug capecitabine.[3] 5-Fluorouracil–associated cardiac complications are

estimated to occur in 1.5–18% of patients worldwide.[4] Clinical manifestations are polymorphic and include rhythm disturbances, cardiac failure leading to cardiogenic shock and death, and signs of myocardial ischemia with anginal chest pain and electrocardiographic abnormalities.[5] Cardiac enzyme levels may be elevated, but coronary angiography results are normal. These cardiac manifestations appear consistent with those of Tako-Tsubo syndrome.

Tako-Tsubo syndrome is a clinical entity described for the first time in Japan in the early 1990s.[6] This is a cardiomyopathy that clinically mimics an acute coronary syndrome with no significant associated coronary lesions. It is defined as a contractile dysfunction of the left ventricular apex characterized by reversible akinesia of the apical segments. This condition is also called apical ballooning or broken heart syndrome. Postmenopausal women are primarily affected, typically after physical or emotional stress.

A few cases of Tako-Tsubo syndrome have been reported in Japan and more recently in Caucasian populations from Western Europe and North America.[7–9] This rare syndrome may account for 1–2% of patients hospitalized for suspected myocardial infarction.[10, 11] To our knowledge, only a few cases of Tako-Tsubo syndrome have been described in patients treated with anticancer drugs such as 5-fluorouracil.[11–14] We describe a patient who developed acute coronary Tako-Tsubo–like syndrome in a patient treated with a chemotherapeutic regimen containing 5-fluorouracil.

Case Report

A 48-year-old man (weight 71 kg, height 5′10″) with colic adenocarcinoma underwent colectomy followed by adjunct chemotherapy on an outpatient basis. His first cycle of chemotherapy was with the FOLFOX protocol, consisting of a bolus dose of 5-fluorouracil 400 mg/m² (750 mg) followed by a slow infusion of 5-fluorouracil 2400 mg/m² (4510 mg) over 46 hours, oxaliplatin 85 mg/m² (160 mg), and calcium folinate 200 mg/m² (375 mg). The patient had no history of cardiovascular disease, and his only cardiovascular risk factor was occasional smoking.

Approximately 24 hours after completing his first cycle of chemotherapy, the patient came to the emergency department with complaints of chest pain at rest, which radiated toward both arms, as well as diarrhea and vomiting. On arrival, his blood pressure (127/85 mm Hg) and heart rate (87 beats/min) were stable, and no signs of cardiac failure were noted. An electrocardiogram showed normal sinus rhythm with depressed apicolateral ST-segment and T-wave inversion. Laboratory results showed a peak troponin T level of 0.5 ng/ml (normal < 0.1 ng/ml). Due to the patient's clinical signs, electrocardiographic abnormalities, and laboratory results, an emergency coronarography was performed. Angiographically healthy coronary arteries with a predominating right network were observed, and a negative methylergometrin test ruled out a coronary spasm. Echocardiography showed marked left ventricular dysfunction with severe hypokinesia in all apical and median segments, with only the basal wall being normokinetic. Left ventricular ejection fraction (LVEF) was measured at 15% with a markedly reduced cardiac output index (estimate 1.3 L/min/m²). The rest of the examination showed no remarkable findings, in particular the lack of valvulopathy, nondilated and normokinetic right cavities, and a fully dry pericardium.

The patient was treated in the intensive care unit where he rapidly improved after introduction of an intraaortic balloon pump and administration of dobutamine. The next day, clear improvement of his left ventricular dysfunction was noted on echocardiography, with an LVEF of 30%. On hospital day 3, the intraaortic pump was removed, and dobutamine was discontinued. On hospital day 5, left ventricular function had fully normalized. In addition, myocardial biopsy results were normal, and myocarditis was not suspected. Treatment with ramipril 10 mg/day and bisoprolol 5 mg/day was started for the patient's cardiac failure and rhythm disturbances.

The patient was discharged and agreed to continue with his chemotherapy. Ramipril therapy was continued, but his β-blocker (bisoprolol) was switched to a calcium channel blocker (diltiazem 240 mg/day). One month later, myocardial

From the Centre Antipoison, Centre de Pharmacovigilance (Drs. Basselin, Descotes, and Timour), and the Département de Cardiologie (Dr. Chevalier), Hospices Civils de Lyon, France; the Service de Gastroentérologie (Dr. Fontanges) and Service Pharmaceutique (Dr. Feinard), Centre Hospitalier Pierre Oudot, Bourgoin-Jallieu, France; and INSERM ERI 22: Agression Vasculaire, Réponse Tissulaire, Université Claude Bernard, Lyon, France (Drs. Bui-Xuan and Timour).

For reprints, visit http://www.atypon-link.com/PPI/loi/phco. For questions or comments, contact Dr. Quadiri Timour, INSERM ERI 22, Laboratoire de Pharmacologie Médicale, 8 avenue Rockefeller 69373, Lyon, cedex 08, France.

magnetic resonance imaging (MRI) confirmed full recovery of his left ventricular systolic function, with mild dilation of telediastolic and telesystolic ventricle volumes.

Thirty-eight days after the start of his first chemotherapy cycle, the second cycle of the FOLFOX protocol was administered using half the initial doses. The protocol was well tolerated from a clinical and cardiologic viewpoint, and laboratory results were within normal limits. Ramipril therapy was continued; diltiazem was discontinued. Fourteen days later, a third cycle, using the full-dose regimen, was started. On the second day of the cycle, the patient complained of chest pain radiating to the upper limbs; however, electrocardiogram results remained unchanged, and his troponin T level was normal. Thus, the third cycle was continued. However, a few hours after the end of the 5-fluorouracil infusion, the patient developed convulsive status epilepticus. He underwent cardiovascular resuscitation for cardiac arrest with small-mesh ventricular tachycardia for nearly 25 minutes, including seven external electrical shocks and epinephrine administration to restore hemodynamic stability. A computed tomography scan of the patient's brain was normal, and the patient was transferred to the cardiology intensive care unit.

No signs of cardiac failure were found on clinical examination. Flattened or negative T waves were noted on all electrocardiogram leads. The patient's troponin T level was mildly increased at 0.5 ng/ml. Transthoracic echocardiography showed an abnormal left ventricle with diffuse hypokinesia, an LVEF of 35%, and low cardiac output indexes. After several days of telemetry, transthoracic echocardiography showed nearly normal recovery of left ventricular function, with an LVEF of 62%. No postischemia fibrosis was found on cardiac MRI, but intramyocardial fibrosis was localized. No rhythm disturbances recurred during the rest of the patient's hospital stay. His cancer chemotherapy was discontinued; treatment with ramipril was continued, and bisoprolol 3.75 mg/day was started.

Four months later, a liver metastasis was discovered, which led to a new chemotherapy regimen (irinotecan and bevacizumab) along with close cardiologic monitoring. Cardiac MRI performed before the chemotherapy regimen was begun showed conserved systolic function. No recurrence of the patient's cardiac manifestations was subsequently noted.

Discussion

This report describes a patient with no history of cardiovascular disease who experienced myocardial ischemia associated with marked left ventricular dysfunction (LVEF 15%, cardiac output index 1.3 L/min/m^2). Cardiac failure seemingly developed after coronary alterations occurred after the first cycle of chemotherapy and recurred after the third cycle. On both occasions, the doses of 5-fluorouracil, oxaliplatin, and calcium folinate (FOLFOX protocol) were identical.

Among the anticancer drugs used in the FOLFOX protocol, 5-fluorouracil is well known to induce cardiotoxicity even in patients with a previously healthy heart.[15] In contrast, to our knowledge, no direct cardiotoxicity from oxaliplatin use has been reported. Potentiation of 5-fluorouracil cardiotoxicity by oxaliplatin[11] or calcium folinate[16] infusions, however, is possible.

Our patient had many features that are consistent with a diagnosis of Tako-Tsubo syndrome. Manifestations of the syndrome include acute chest pain typically developing after stress, abnormalities of T waves, a moderate increase in plasma troponin T level, and left ventricular dysfunction without coronary lesions.[8] Major diagnostic criteria proposed in 2003 include transient balloonization of the left ventricle apex and abnormalities of the ST segment and T waves, which leads to suspicion of myocardial infarction.[17] Minor criteria are chest pain, moderately increased cardiac enzyme levels, and physical or emotional stress as a trigger.[17] Other possible triggering stimuli include acute pathologic conditions, surgery, intracranial adverse events (hemorrhage, trauma, or ischemic stroke), and exaggerated production of endogenous catecholamines or administration of catecholaminergic agents.[7] In our patient, the lack of coronarographic abnormalities of the coronary arteries and the echocardiographic pattern with more diffuse myocardial involvement than typically described suggest a Tako-Tsubo–like syndrome.

To assess causality in our patient's case, the Naranjo adverse drug reaction probability scale[18] was used. It indicated a probable relationship (score of 8) between the patient's development of Tako-Tsubo–like syndrome and 5-fluorouracil.

Two case reports of Tako-Tsubo syndrome induced by 5-fluorouracil have been published.[11, 12] In both, the onset of the syndrome was several weeks after exposure to 5-fluorouracil; our

patient's case was different, with an onset of only 24 hours after the end of the 5-fluorouracil infusion. Clear differences in the chemotherapy dosage regimen may explain this discrepancy. In one patient, clinical manifestations first developed after the patient received 5-fluorouracil 375 mg/m² 10 times,[11] and in the other patient, 5-fluorouracil 750 mg 6 times,[12] compared with a total cumulative dose of 5260 mg (750-mg bolus plus 4510-mg infusion) in our patient. The shorter time to onset in our patient may be explained by the high dose of the infusion. However, a high 5-fluorouracil dose is not included as part of the criteria for diagnosis of Tako-Tsubo syndrome, defined as myocardial stunning resulting from intense emotional stress.[19, 20] The underlying mechanism is thought to be linked to an abrupt increase in blood catecholamine levels induced by acute stress and/or by abnormal coronary vasomotricity that would induce acute toxicity to myocytes.[19–21] However, our patient revealed that he had not experienced any potential stressful trigger events other than chemotherapy. Thus, we suggest that our patient developed 5-fluorouracil–induced Tako-Tsubo–like syndrome, rather than the actual Tako-Tsubo syndrome.

Conclusion

5-Fluorouracil as part of a chemotherapy regimen may be the factor that contributed to the Tako-Tsubo (or Tako-Tsubo–like) syndrome in our patient. If so, this suggests a new etiology for this recently described cardiac syndrome. Tako-Tsubo cardiomyopathy is a rare adverse effect of 5-fluorouracil and should be differentiated from acute coronary syndrome in patients with angiographically healthy coronary arteries. The reporting of additional cases will be instrumental in better understanding the pathophysiology and frequency of this syndrome.

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