

Cyclophosphamide-induced Cardiotoxicity with a Prolonged Clinical Course Diagnosed on an Endomyocardial Biopsy

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Abstract

A 31-year-old woman with primary mediastinal large B-cell lymphoma refractory to conventional chemotherapy was treated with high-dose chemotherapy containing cyclophosphamide (CY). Subsequently, she was treated with auto peripheral blood stem cell transplantation. Although a complete remission was obtained, heart failure developed two months later. Echocardiography showed an impaired systolic function with pericardial effusion. A biopsy of the endomyocardial region from the left ventricle demonstrated spotty myocardial hemorrhage and myocardial fibrosis with disruption and aggregation of mitochondrial cristae. Based on these findings, CY-induced cardiotoxicity was diagnosed. The patient was treated with conventional therapy for heart failure, which required approximately one year to improve her condition.

Key words: chemotherapy, cardiotoxicity, heart failure

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Introduction

Cyclophosphamide (CY) is a potent alkylating agent that is widely used in anticancer treatments and preparative regimens for blood stem cell transplantation. However, CY can cause a variety of adverse effects, including fatal cardiotoxicity, in high-dose regimens (1). It has been reported that CY-induced cardiotoxicity can occur soon after the administration of CY and is potentially reversible; however, few patients with fatal and progressive heart failure die within a few weeks (2). We herein report a case of CY-induced cardiotoxicity with systemic endothelial damage that gradually developed following the administration of high-dose CY and caused a prolonged clinical course that required conventional therapy for heart failure.

Case Report

A 31-year-old woman consulted a physician regarding pain around her back and lower jaw. Chest computed tomography (CT) showed a large mediastinal mass lesion (Fig. 1A, B). A series of careful examinations, including histopathology, was conducted, and the patient was diagnosed with primary mediastinal large B-cell lymphoma. Chemotherapy was initiated with two courses of rituximab (375 mg/m²), CY (0.75 g/m²), doxorubicin (50 mg/m²), vincristine (total, 2 mg) and prednisolone (R-CHOP therapy). The effects of the R-CHOP therapy were judged to be insufficient. Therefore, auto peripheral blood transplantation was planned. The patient was treated with one course of ifosfamide (1,500 mg/m²), carboplatin (300 mg/m²), etoposide (100 mg/m²) and dexamethasone (DeVIC therapy). Subse-

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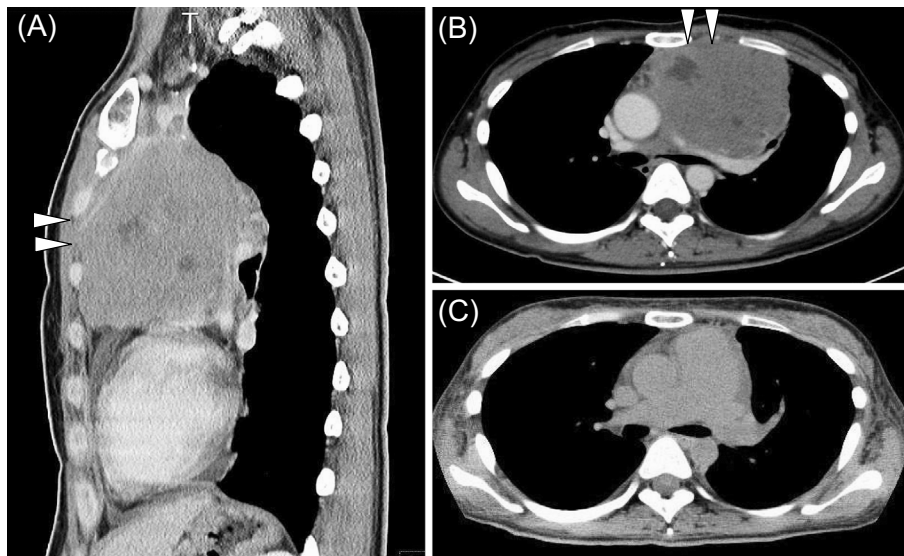


Figure 1. Contrast material-enhanced CT angiography before the administration of chemotherapy showing a large mass lesion in the anterior mediastinum (arrowheads) on sagittal (A) and horizontal (B) sections. Plain CT showing no recurrence of the mediastinal mass lesion (C) on admission for heart failure.

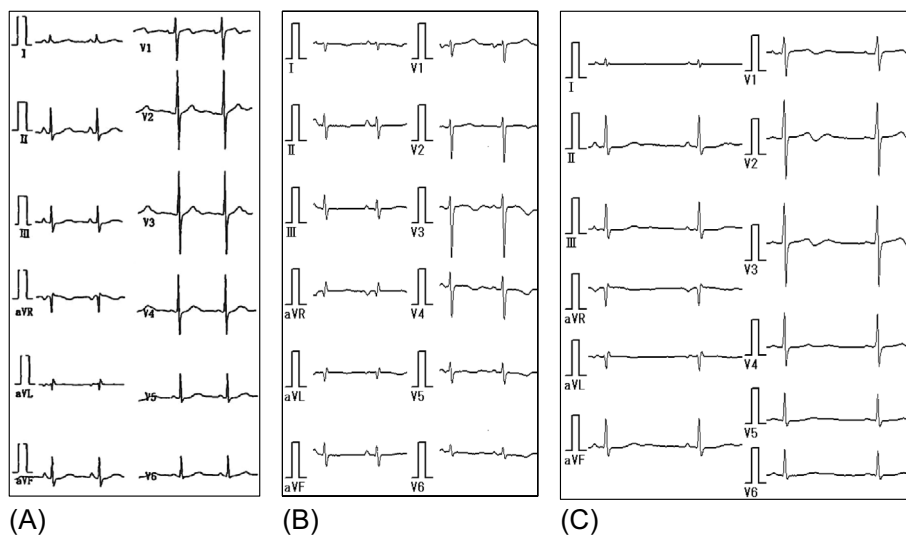


Figure 2. Electrocardiograms. (A) An electrocardiogram showing normal findings before the pre-chemotherapy autologous peripheral blood stem cell transplantation. (B) An electrocardiogram obtained on admission showing sinus tachycardia, low voltage in all limb leads, right axis deviation and inversion of T waves in leads I, aVL and V3-6. (C) An electrocardiogram obtained six months after hospital discharge showing that the low voltage in all limb leads and sinus tachycardia had improved.

quently, two courses of CY (1.2 g/m^2), etoposide (100 mg/m^2), cytarabine (2 g/m^2) and prednisolone (CHASE therapy) were administered, and peripheral blood stem cell harvest was performed. Following the administration of these treatments, a significant decrease in the size of the mediastinal mass was observed.

At that time, the results of electrocardiography (ECG) were normal (Fig. 2A), and echocardiography (UCG) showed a normal systolic function in the left ventricle (LV) without ventricular dilatation (end-diastolic diameter, 48 mm; end-systolic diameter, 33 mm; LV ejection fraction

(LVEF), 57%). The patient therefore received high-dose chemotherapy comprising ranimustine (250 mg/m^2) for two days, then carboplatin (300 mg/m^2), etoposide (20 mg/kg) and CY (1.8 g/m^2) for two days, followed by peripheral blood stem cell transplantation. The total doses of CY and doxorubicin administered were 10.4 g (254 mg/kg or 7.6 g/m^2) and 100 mg/m^2 , respectively. After completing the chemotherapy, the patient gradually developed general fatigue and exertional dyspnea and was referred to our hospital two months later.

On admission, the patient was normotensive with tachy-

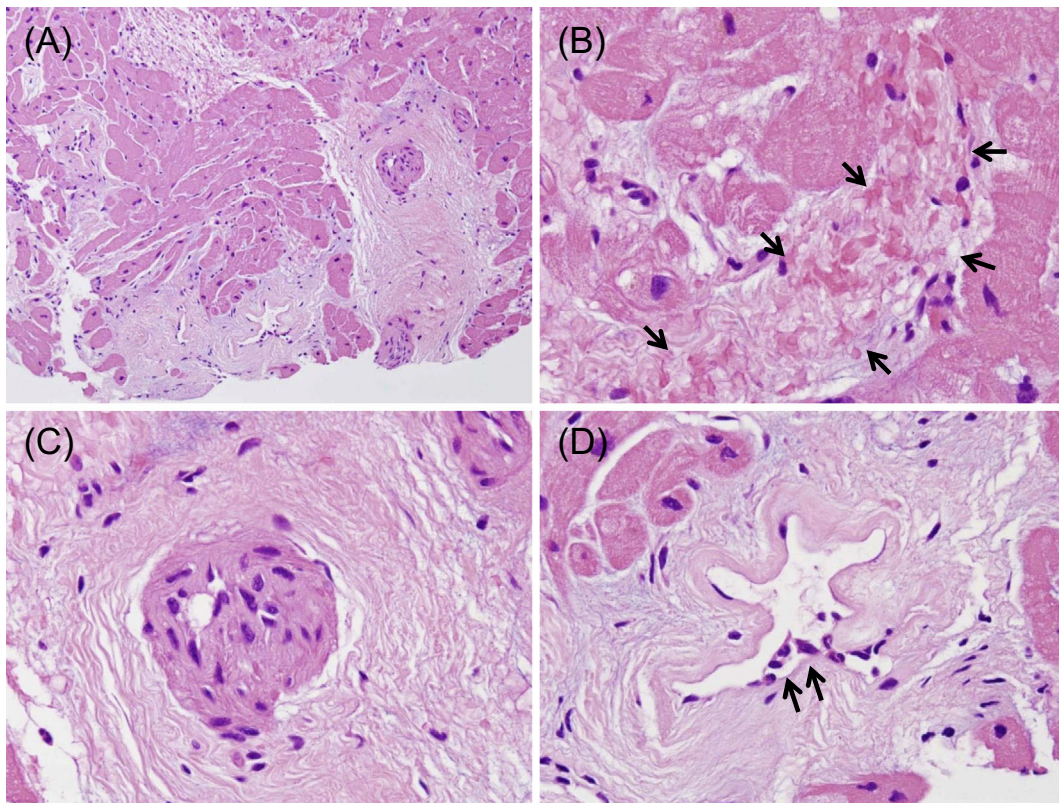


Figure 3. Representative histological findings of the endomyocardial biopsy samples. (A) Myocyte disarrangement and replacement interstitial fibrosis. (B) Spotty hemorrhage in the interstitium. (C) Wall thickness and obstruction of the intramural small artery. (D) Dislodgement of vascular endothelial cells with neutrophil attachment. Hematoxylin and Eosin staining; original magnification: A, $\times 40$; B-D, $\times 200$.

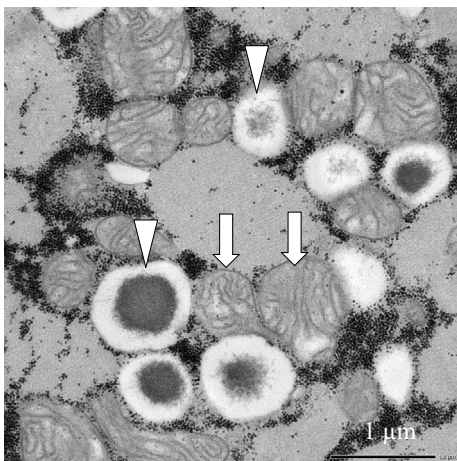


Figure 4. Electron micrographs of the lesions in the left ventricular myocardium showing disruption and aggregation of mitochondrial cristae (arrowheads) and normal mitochondria (arrows).

cardia (blood pressure, 106/69 mmHg; heart rate, 109 beats/min; body temperature, 36.6°C). A physical examination revealed a gallop rhythm without heart murmurs or inspiratory crackles on chest auscultation. Mild pretibial edema was evident. Chest radiography showed mild pulmonary congestion and cardiomegaly. ECG demonstrated sinus tachycardia, low voltages in all limb leads, right axis deviation and inversion

of T waves in leads I, aVL and V3-6 (Fig. 2B). Chest CT did not suggest any recurrence of the mediastinal mass lesion (Fig. 1C). UCG showed a diffusely impaired systolic and diastolic function of the LV with moderate pericardial effusion and mild LV wall hypertrophy with a normal LV diameter (thickness of the interventricular septum (IVS), 10 mm; thickness of the LV posterior wall (LVPW), 11 mm; end-diastolic diameter, 34 mm; end-systolic diameter, 26 mm; E-wave/A-wave (E/A) ratio, 0.5; deceleration time, 153 msec; LVEF, 47%). The laboratory data on admission were as follows: serum aspartate aminotransferase concentration, 114 IU/L (normal, 13-33 IU/L); serum alanine aminotransferase concentration, 122 IU/L (normal, 8-42 IU/L); total bilirubin, 0.7 mg/dL (normal, 0.3-1.5 mg/dL); blood urea nitrogen concentration, 42 mg/dL (normal, 8-22 mg/dL); the serum creatine level, 1.41 mg/dL (normal, 0.4-1.1 mg/dL); the C-reactive protein level, 0.53 mg/dL (normal, 0.0-0.17 mg/dL); and the N-terminal pro-brain natriuretic peptide (NT-proBNP) level, 11,970 pg/mL (normal, <131 pg/mL). The serum levels of creatine kinase (CK) and the CK-MB isoform were normal and had not been elevated during the patient's hospitalization. The troponin T level was slightly elevated at 0.05 ng/mL (normal <0.012 ng/mL). Pericardiocentesis was performed under echocardiographic guidance, and 170 mL of yellowish serosanguineous pericardial effusion was drained. An examination of the fluid revealed no

invasion of malignant cells, and no bacteria or tuberculosis mycobacteria were cultured. The patient was therefore diagnosed with heart failure. Cardiac catheterization and an endomyocardial biopsy of the LV was performed to investigate the cause of the heart failure three days after admission. Swan-Ganz catheterization showed mild pulmonary hypertension with increased pulmonary vascular resistance and a normal pulmonary capillary wedge pressure and LV end-diastolic pressure under treatment with carperitide and furosemide (mean pulmonary artery pressure, 26 mmHg; mean pulmonary capillary wedge pressure, 3 mmHg; LV pressure 104/0/8 mmHg; cardiac output, 3.90 L/min; cardiac index, 2.78 L/min/m²; pulmonary vascular resistance, 430 dyne/s/cm⁵ (normal range, \leq 250 dyne/s/cm⁵); systemic vascular resistance, 1,825 dyne/s/cm⁵ (normal, 800-1,200 dyne/s/cm⁵)). Coronary angiography revealed a normal coronary arteriogram, and left ventriculography demonstrated diffuse LV systolic dysfunction with a LVEF of 52%. A histological examination of the myocardium under light microscopy demonstrated replacement interstitial fibrosis with spotty hemorrhage, degeneration of cardiac muscle fibers, wall thickening with obstruction of the small arteries and dislodgement of vascular endothelial cells (Fig. 3). An examination performed under electron microscopy revealed disruption and aggregation of mitochondrial cristae with high-density material in the mitochondria (Fig. 4). Antiviral antibody examinations for Coxsackie A and B virus, enterovirus, enteric cytopathogenic human orphan virus, parainfluenza and adenoviruses performed on admission and three weeks later both yielded negative results. Moreover, negative results were obtained for antinuclear antibodies and double-stranded DNA antibodies. The patient was therefore diagnosed with CY-induced cardiotoxicity.

We initially began to treat the patient with an intravenous infusion of furosemide (20 mg/day) and continuous intravenous infusion of carperitide (0.0125 γ), then added 1.25 mg/day of carvedilol, 12.5 mg of losartan, 12.5 mg/day of spironolactone and 20 mg/day of furosemide as the initial doses. The doses of carvedilol, losartan, spironolactone and furosemide were gradually increased and finally maintained at 5 mg, 25 mg/day, 25 mg/day and 40 mg/day, respectively. The patient's exertional dyspnea and general fatigue gradually improved, and she was discharged able to walk two months after admission, although slight pericardial effusion and pulmonary hypertension remained and the serum level of NT-proBNP was still high (2,528 pg/mL). Six months later, the pericardial effusion disappeared and the serum level of NT-proBNP normalized (119 pg/mL). ECG showed an improvement in low voltage in all limb leads and sinus tachycardia (Fig. 2C). UCG demonstrated amelioration of the systolic function, mild LV hypertrophy and diastolic function as follows: LVEF, 64%; IVS thickness, 7 mm; LVPW thickness, 7 mm; E/A ratio, 2.1; and deceleration time, 218 msec. Two years after the treatment of malignant lymphoma, the patient remains in complete remission and has exhibited no deterioration of heart failure.

Discussion

Generally, several factors contribute to the development of cardiotoxicity in patients receiving chemotherapy, i.e., the dose of the drug administered during each session, the cumulative dose, the delivery schedule, the combination of drugs administered and the administration interval. Although CY is relatively well tolerated at low doses, high-dose regimens are associated with adverse effects (1). The risk of cardiotoxicity with CY appears to be dose-related (>150 mg/kg or 1.55 g/m²/day) (3, 4), and the total dose of an individual course is the best predictor of acute cardiotoxicity (5). A recent case report described the induction of fulminant fatal congestive heart failure following the administration of CY at 1.5 g/m² for two days (6). In the present case, the dosage of CY used as pretransplant preparation was 1.8 g/m²/day (60 mg/kg) for two days, and the total dose of CY was 254 mg/kg. The dose of CY in the present case was thus sufficient to induce cardiomyopathy.

CY has been reported to cause various types of cardiac damage, including arrhythmias, acute fulminant heart failure and hemorrhagic myopericarditis, thus leading to pericardial effusion, cardiac tamponade and even death (1, 7, 8). A previous report suggested that the mechanisms underlying the cardiotoxicity associated with high-dose CY treatment result from endothelial toxicity due to the transudation of toxic metabolites, with subsequent damage to the myocardium, interstitial hemorrhage and edema (2). CY can also cause ischemic damage due to the development of intracapillary microemboli or coronary vasospasm (9). The histological findings of CY-induced cardiotoxicity are as follows: multiple areas of myocardial hemorrhage; extravasation of blood; interstitial edema; and multifocal myocardial necrosis with fibrin microthrombi (1). In other reports of myocardial damage induced by CY in animal models, the loss of myofibrils and damage to mitochondrial cristae were observed under electron microscopy (10). Most of these histological findings were seen in the biopsied myocardium in the present case.

The clinical manifestations of CY-induced cardiotoxicity vary. Heart failure has been reported to be associated with CY therapy in 7-28% of patients (3, 4, 11). Acute symptoms usually occur within three weeks, last for a few weeks and, in some patients, resolve without late consequences (1, 2, 8). However, approximately 11% of those who receive high-dose CY develop fatal cardiomyopathy (12). In the present case, symptoms of heart failure gradually appeared approximately two months after the administration of CY, and the patient took approximately one year to recover with conventional pharmacotherapy for heart failure, including angiotensin-receptor blockers and beta-blockers. Therefore, the present case differs from acute and severe CY-induced cardiotoxicity. Moreover, mild pulmonary hypertension was observed even after the pulmonary wedge pressure normalized. Elevation of systemic and pul-

monary vascular resistance and worsening of the renal and liver functions were also observed in this case. These various clinical manifestations are thought to be associated with systemic endothelial damage induced by high-dose CY, which may have caused the prolonged clinical course of CY-induced cardiotoxicity. In turn, the prolonged clinical course may have reflected the manifestations of transplantation-associated thrombotic microangiopathy (TA-TMA) (13). Although liver dysfunction was observed in this case, the total bilirubin level was normal, and clinical manifestations such as jaundice, hypochondralgia, ascites and hepatomegaly were not observed. Therefore, hepatic veno-occlusive disease (VOD) following blood stem cell transplantation was not diagnosed in this case.

Previous studies have demonstrated an increased risk of complications among elderly patients and those exposed to anthracycline and/or mitoxantrone therapy or mediastinal irradiation (7, 8, 14). The present patient was not elderly and did not undergo mediastinal irradiation. Although the total doses of doxorubicin and ifosfamide were lower than the reported cardiotoxic doses (anthracycline >550 mg/m², ifosfamide >12.5 g/m²), these agents can potentiate CY-induced cardiotoxicity (7, 15). Moreover, cytarabine may also have contributed to the condition of this patient because this drug is associated with pericarditis and arrhythmia, especially when used in combination with CY (2). The magnitude of these mechanisms vary in different patients, provoking different degrees of severity of cardiotoxicity, in addition to other factors, including aging and risk factors for cardiovascular disease, which can complicate the clinical manifestations in patients undergoing CY therapy.

In conclusion, we observed prolonged CY-induced cardiotoxicity with heart failure occurring relatively late after the administration of CY. Systemic endothelial damage can prolong the clinical course of heart failure caused by CY-induced cardiotoxicity.

The authors state that they have no Conflict of Interest (COI).

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