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Cyclophosphamide 연관 중증 심부전을 동반한 Cardiomyopathy 환자에서 치료 후 회복된 증례

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A Case of Successfully Treated Severe Heart Failure due to Cyclophosphamide Induced Cardiomyopathy

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Cyclophosphamide-induced cardiotoxicity is an uncommon complication especially in patients who have never undergone mediastinal irradiation or cardiotoxic chemotherapy and do not have underlying cardiac diseases. Here, we describe the case of a 19-year-old female with chronic myeloid leukemia. She was previously treated with oral tyrosine kinase inhibitors and developed cardiomyopathy after receiving infusion of 60 mg/kg intravenous cyclophosphamide for two days with a conditioning regimen for allogenic hematopoietic stem cell transplantation. Severe thickening of the left ventricle and reduced ejection fraction without triggering agents were characteristic for cyclophosphamide-induced cardiomyopathy. Her NT-pro BNP and troponin T concentrations surged to >70,000 pg/mL (0=130 pg/mL) and 2,031 pg/mL (0-14 pg/mL), respectively, during the course of the therapy and multiple organ failure seemed imminent evidenced by unresponsive decline in blood pressure. However, with close monitoring and persistent conservative management which consisted of intravenous hydration, continuous hemodialysis, and mechanical ventilation, her condition recovered.

Key Words: Cyclophosphamide, Cardiomyopathy, Chemotherapy

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Introduction

Cardiac dysfunction related to chemotherapy has become an important cause of morbidity and mortality in patients [1]. Common cardiovascular complications include left ventricular dysfunction, myocardial ischemia, hypertension, thromboembolism, QT prolongation, and bradycardia [2]. Since many of these adverse effects significantly impact patient's outcome, they have been an enormous concern for both cardiologists and oncologists.

Cyclophosphamide is a nitrogen mustard alkylating agent with potent antineoplastic, immunosuppressive, and immunomodulatory properties. Despite its use in cancer therapy and pretransplant stem cell conditioning regimens, the toxicity profile using distinctive dosing regimens has not been clarified [3-5]. Herein, we report the case of cyclophosphamide-induced cardiotoxicity occurring without an

underlying heart disease or a history of previous radiation or cardiotoxin use. In addition, we introduce the manifestations, laboratory findings, and echocardiography of the patient and suggest the screening markers for the early detection and treatment approach for heart failure due to cyclophosphamide.

Case Report

A 19-year-old woman with chronic myelocytic leukemia was admitted to our hospital for sibling hematopoietic stem-cell transplantation on January 8th, 2018. In February 2016, she was diagnosed as having chronic myelocytic leukemia revealing a *BCR/ABL1* gene rearrangement (b2a2 type) with a triple translocation, 46,XX,t(3;9;22)(p21;q34;q11.2), on bone marrow. Results were negative for the *JAK2* V617F mutation. The patient started taking imatinib mesylate (Gleevec) but was switched to dasatinib (Sprycel) after a year because of the non-reactive BCR/ABL1 quantitation in whole blood. However, Spyrcel caused her severe skin problems, such as multiple erythematous papules on the forehead, and she underwent a dermatologic consult. Due to an unsatisfactory treatment response and adverse effects of tyrosine kinase inhibitors, the medical faculty searched for a suitable hematopoietic stem cell transplantation donor and found her brother suitable despite one locus mismatch of DRB1.

At the time of admission, the patient's general condition was fine, and her vital signs were normal. Her laboratory findings and chest X-ray did not show any abnormality. She was 162.6 cm in height and 59 kg in weight. Physical measurements and laboratory values are summarized in Table 1. Basal electrocardiography showed normal sinus rhythm with a heart rate of 84 beats per minute. The baseline two-dimensional echocardiography indicated normal-sized cardiac chambers with normal global left ventricular systolic function with a left ventricular (LV) ejection fraction of 62%. Apart from cardiologic evaluations, other pre-transplantation baseline studies demonstrated no abnormalities, including pulmonary function test (FEV_1 97%, FVC 98%), X-ray of paranasal sinuses, and dental evaluations.

The regimen of treosulfan/cyclophosphamide/etoposide was selected as conditioning chemotherapy. The patient was intravenously started on 12 mg/m^2 treosulfan for 3 days, 15 mg/kg etoposide for 2 days, and 60 mg/kg cyclophosphamide for 2 days with Uromitexan (Mesna) protection for hemorrhagic cystitis. Intrathecal methotrexate (15 mg) injection was administered. Sibling bone marrow transplantation was performed (CD34 2.3×10^6/kg) on January 17th with no complications. On the third day after transplantation (day 3), she had a syncope after standing up in a bathroom, and her vital signs were blood pressure 96/70 mmHg, heart rate 89/min, and percutaneous oxygen saturation 99%. Then, the arterial blood gas analysis, chest X-ray, and EKG revealed no difference, so we considered it to be a vasovagal syncope or orthostatic hypotension. On day 4 in the morning (7 days after cyclophosphamide infusion), her blood pressure suddenly dropped to 87/65 mmHg and was not responsive to normal saline (20 mg/kg) loading. Chest X-ray showed mild cardiomegaly with CT ratio of 0.60 compared to the previous X-ray with a ratio of 0.43 (Fig. 1). Electrocardiography showed sinus rhythm

Table 1. Vitalsigns and laboratory characteristics of the day of admission, day 7 and day 10 after cyclophosphamide infusion

	On admission	7 days after cyclophosphamide infusion	10 days after cyclophosphamide infusion
Blood pressure (mmHg)	112/61	87/65	113/80
Heart rate (beats/min)	63	121	124
Hemoglobin (g/dL)	10.7	11.6	10.2
AST/ALT (IU/L)	16/10	29/14	1,409/1,932
Creatinine (mg/dL)	0.54	0.89	2.24
CK (IU/L)/CK-MB (ng/mL)		149/15.2	1,740/10.9
NT-pro BNP (pg/mL)		7,489	60,161
Troponin-T (pg/mL)		1,612	2,894

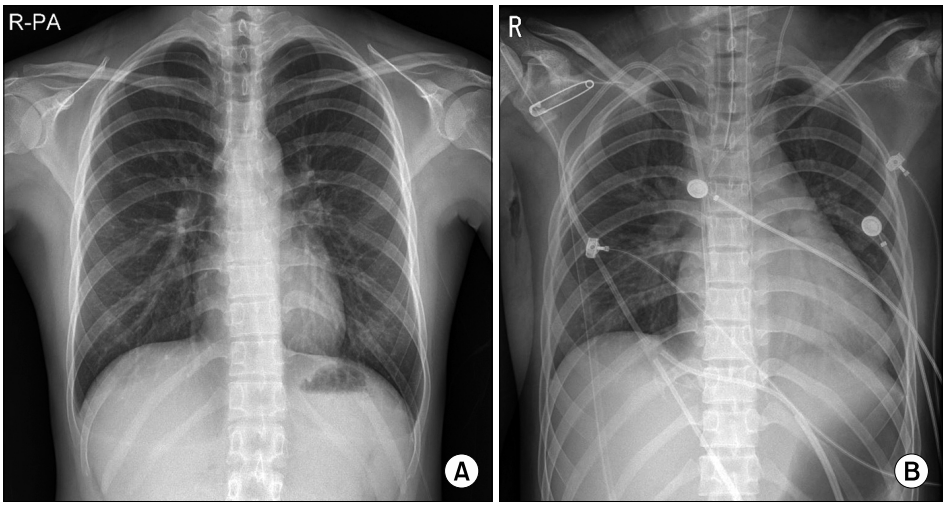

Fig. 1. Comparison of chest radiography between the day of admission (A) and day 7 after cyclophosphamide infusion (B). The CT ratios were 0.43 (A) and 0.60 (B), respectively.

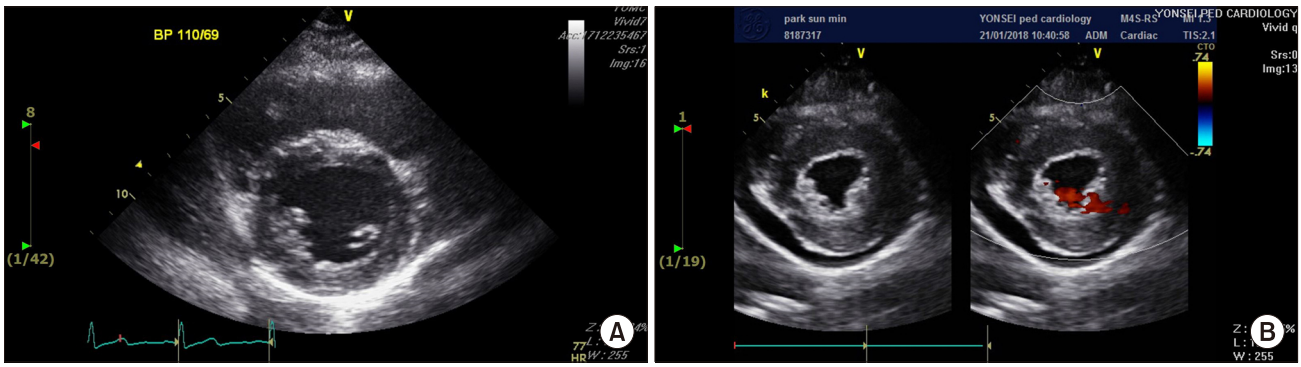

Fig. 2. Comparison of echocardiography at the baseline and at day 7 after cyclophosphamide infusion. (A) Baseline echocardiography shows normal left ventricular septum and chamber size. (B) Echocardiography on day 7 shows severe thickness of left ventricular septum and increased pericardial effusion.

with a short PR interval and rightward axis deviation with a heart rate of 73 beats per minute. Urgent 2D-echocardiography found severe thickening of the myocardium with an LV mass of 154 g/m^2 and a 10-12 mm-sized pericardial effusion without the evidence of tamponade physiology. The LV ejection fraction was 50.0% (Fig. 2). The level of troponin T was 134 pg/mL (0-14 pg/mL) and that of NT-pro BNP was 8,134 pg/mL (0-130 pg/mL); these levels drastically elevated within two days to 2,031 pg/mL and >70,000 pg/mL, respectively. The patient did not complain of upper respiratory or gastrointestinal symptoms, viral rash, or other systemic symptoms indicative of an infection. Drug-induced cardiomyopathy was suspected. Intravenous furosemide was started to reduce preload, and inotropic agents (milrinone, dopamine, and epinephrine) were administered to raise blood pressure. Blood pressure was maintained at systolic BP of over 90 mmHg; however, tachycardia with a heart rate of 160 beats per minute persisted, and the patient complained of severe chest discomfort and nausea. Meanwhile, oliguria due to low cardiac output developed and continuous renal replacement therapy (CRRT) was administered. Shortly after the initiation of CRRT, the patient became unconscious and developed supraventricular tachycardia which was resolved by performing synchronized direct-current (DC) cardioversion (Fig. 3). We intubated her and she underwent intensive care including mechanical ventilator, CRRT, arterial blood pressure monitoring, and daily echocardiography with proper intravenous fluid replacement for the following days. On day 7, we extubated her, and despite the remaining pericardial

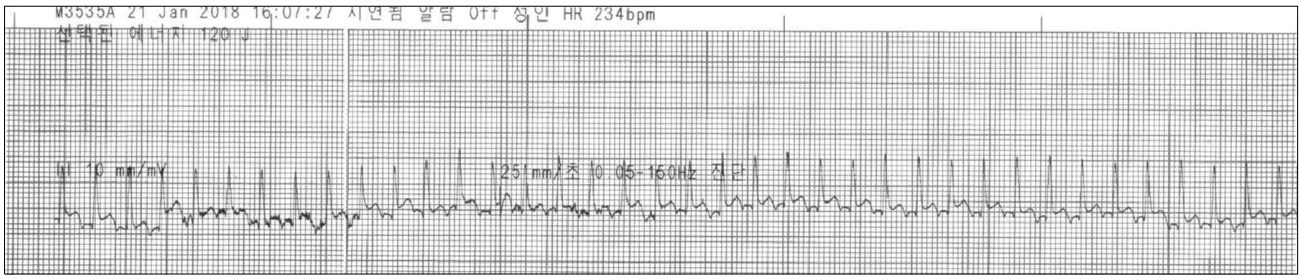

Fig. 3. Electrocardiography showing supraventricular tachycardia terminated by synchronized DC cardioversion.

Table 2. Comparison of the echocardiography indices at the baseline and day 7 after cyclophosphamide infusion

	Baseline evaluation	7 days after cyclophosphamide infusion
Left ventricular ejection fraction	62.0%	50.0%
Interventricular septum diameter in diastole	8.1 mm (Z score 0.33)	17.9 mm (Z score 4.08)
Left ventricular diastolic and systolic diameter	48 mm (Z score 0.44)	40 mm (Z score −1.39)
	32 mm (Z score 0.92)	26 mm (Z score −0.72)
Left ventricular mass	71.5 g/m^2	154 g/m^2
Pericardial effusion	None	10-12 mm

effusion with (diameter, 10-12 mm) and thickened myocardium with an LV mass of 133 g/m^2, blood pressure and heart rate became stabilized without inotropics. Elevated laboratory findings, such as serum aspartate aminotransferase, alanine aminotransferase, and creatinine concentrations, gradually decreased which was probably due to poor organ perfusion. On day 23, sibling bone marrow was engrafted, revealing complete donor chimerism in post-BMT DNA evaluation. On day 24, kidney function had completely recovered and CRRT was removed. On day 63, echocardiography showed that left ventricular hypertrophy had resolved with an LV mass of 73 g/m^2 and decreased pericardial effusion (diameter, 8-10 mm). She is still in remission and has mostly returned to normal general condition, and we are planning to discharge her shortly.

Discussion

Cyclophosphamide-induced cardiotoxicity is a fatal condition that may lead to acute heart failure, pericardial effusion with tamponade, cardiogenic shock, and possibly death [1]. Heart failure has been associated with cyclophosphamide therapy in 7-28% of patients. The risk of cardiotoxicity is apparently dose-related (>150 mg/kg and 1.5 g/m^2/day) and occurs within 10 days of the administration of the first dose of cyclophosphamide [6-9]. The risk factors also include the prior or concomitant use of other cardiotoxic agents, such as anthracyclines, previous mediastinal radiation, and pre-existing heart diseases [10]. Although this patient did not have known risk factors and the total dose of cyclophosphamide was modest at 120 mg/kg, the morphological findings in the echocardiography —thickened myocardium, increased pericardial effusion, and a rather decreased ejection fraction—were compatible with cyclophosphamide-induced toxic myocarditis.

Considering the lack of established risk factors and the rapid progression of cyclophosphamide-induced cardiotoxicity, early detection of cardiac insult is of high interest. The most commonly used noninvasive method of monitoring cardiac toxicity from chemotherapeutic agents is echocardiography. Diastolic dysfunction, including a change in the E/A ratio, the interventricular septal thickness in diastole, and increased left ventricular diastolic and systolic diameters, are considered as the earliest predictors of cyclophosphamide damage [11,12]. The patient showed a marked increase in the interventricular septal thickness in diastole and a marginal decrease in the left ventricular diastolic and systolic diameters (Fig. 2, Table 2). Circulatory

cardiac markers may also be a valuable predictor of chemotherapy-induced cardiac toxicity. B-type natriuretic peptide is perhaps the most promising indicator since it is elevated within the first 24 hours of therapy, and monitoring highly sensitive plasma cardiac troponin I or T may also have some advantages in predicting chemotherapy-induced myocardial damage [12]. The patient suffered from a sudden decline in blood pressure, and simultaneously, laboratory findings showed a significant increase in NT-pro BNP and troponin-T.

The exact pathophysiology of cyclophosphamide-induced cardiomyopathy has not been established, and the treatment should not be different from the symptomatic treatments. Conservative management, such as proper intravenous fluid replacement, applying continuous renal replacement therapy for oliguria, and mechanical ventilation for pulmonary edema, were successfully implemented to ensure patient survival. Drug-induced cardiotoxicity should always be taken into consideration when administering cyclophosphamide therapy, and cardiac evaluations in advance are indispensable. Routine vital sign check-ups, laboratory cardiac markers, and echocardiography should be conducted when a patient develops cardiovascular symptoms of syncope, chest discomfort, or tachycardia.

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