CASE REPORT

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Pathological changes of the myocardium in reworsening of anthracycline-induced cardiomyopathy after explant of a left ventricular assist device

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ABSTRACT

We herein report the long-term changes in cardiac function and pathological findings after successful explantation of a left ventricular assist device in a 42-year-old patient with anthracycline-induced cardiomyopathy with reworsening heart failure. Endomyocardial biopsy samples revealed that the cardiomyocyte diameter decreased and collagen volume fraction increased just after left ventricular assist device explantation. The collagen volume fraction decreased after 6 months, despite preserved systolic function. At 5 years after left ventricular assist device explantation, the systolic function markedly decreased and cardiomyocyte diameter increased. Pathological changes of the myocardium may enable the identification of cardiac dysfunction prior to echocardiographic changes in patients with reworsening heart failure after left ventricular assist device explantation.

Keywords: anthracycline-induced cardiomyopathy, left ventricular assist device, cardiac pathology, reworsening heart failure

Abbreviations:
AIC: anthracycline-induced cardiomyopathy
HF: heart failure
LV: left ventricular
LVEF: left ventricular ejection fraction
LVDD: left ventricular end-diastolic diameter
LVAD: left ventricular assist device
BNP: brain natriuretic peptide
CD: cardiomyocyte diameter
CVF: collagen volume fraction

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INTRODUCTION

Anthracycline-induced cardiomyopathy (AIC) is a well-known cause of heart failure (HF) with reduced left ventricular (LV) ejection fraction (LVEF).[1,2] One of the treatments recommended for patients with refractory HF with reduced LVEF is continuous unloading via a left ventricular assist device (LVAD). Some patients experience successful reverse remodeling and subsequent LVAD explantation.[3,4] However, LVAD explantation occasionally causes their cardiac function to gradually deteriorate again.[5,6] Previous studies reported that the histopathological findings were changed before versus after LVAD support.[7,8,9] However, the serial changes of pathological characteristics in the myocardium long after explantation of a LVAD have not been well investigated in the process of reworsening cardiac function. Herein, we describe the long-term changes in cardiac function and pathological findings of the myocardium after LVAD explantation in a patient with reworsening AIC.

CASE REPORT

A 42-year-old female presented with progressive shortness of breath and decreased LVEF. She had been diagnosed with acute promyelocytic leukemia at 32 years of age, and received anthracycline chemotherapy (idarubicin and daunorubicin) for 5 months. The cumulative dose was equivalent to 350 mg/m^2 of doxorubicin. Complete remission was attained 1 month after chemotherapy commenced. However, she had dyspnea on exertion, leg edema, and weight gain. A chest roentgenogram revealed cardiomegaly and pulmonary congestion, and echocardiography demonstrated a reduced LVEF of 32%. Furthermore, the plasma brain natriuretic peptide (BNP) level was elevated to 782 pg/mL. The patient was diagnosed with AIC and received HF guideline-directed medical therapy including a beta-blocker, angiotensin-converting enzyme inhibitor, and mineralocorticoid receptor antagonist. After optimal medical therapy, she remained in a stable condition of HF (New York Heart Association functional class I or II) for 4 years. However, the cardiac function gradually deteriorated; at 36 years of age, the patient had a LVEF of 11% with severe functional mitral regurgitation, and a left ventricular end-diastolic diameter (LVDD) of 61 mm. The plasma BNP level was elevated to 1,214 pg/mL. Despite in-hospital inotropic treatment, the patient's hemodynamics remained unstable, and so she received extracorporeal LVAD therapy with an inflow conduit from the LV apex and an outflow conduit to the ascending aorta (Gyro centrifugal pump and Bio-console, Medtronic Inc., Minneapolis, MN, USA). Along with LVAD support, cardioprotective agents were increased to maximum doses (20 mg/day carvedilol, 10 mg/day enalapril, and 25mg/day spironolactone). The cardiac function and hemodynamics then improved. After 1 year of LVAD support, the LVEF had improved to 52%, and the LVDD was 36 mm with mild functional mitral regurgitation (Fig. 1). The BNP level had improved to 24.4 pg/mL, and the LVAD was successfully explanted. Six months later, the cardiac function was maintained with a LVEF of 51%, LVDD of 55 mm, and mild functional mitral regurgitation. There was no readmission for exacerbation of HF for 5 years. However, the cardiac function gradually deteriorated again to a LVEF of 28%, and LVDD of 56 mm with moderate functional mitral regurgitation. The plasma BNP level was elevated to 366.2 pg/mL.

We performed endomyocardial biopsy of the right ventricular septum and evaluated the cardiomyocyte diameter (CD) and collagen volume fraction (CVF) at four timepoints: just before LVAD implantation, just after LVAD explantation, and at 6 months and 5 years after LVAD explantation. Three or four samples were obtained and analyzed at each timepoint. Six microscopic fields were randomly chosen per specimen slide, at 400× magnification. The CD was

	LVAD-implant	LVAD-explant	6 months	5 years
LVEF (%)	10.8	52.2	51.2	28.4
LVDD (mm)	60.8	36.0	55.5	56.3
BNP (pg/mL)	1,214	24	96	366

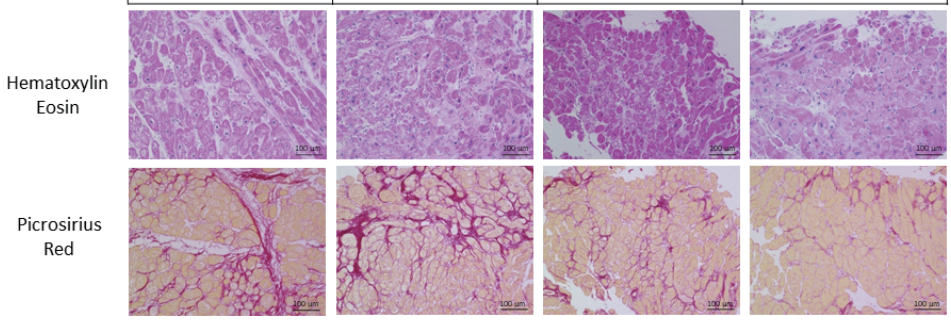

Fig. 1 Echocardiographic data, plasma BNP level, and myocardial pathology images.
LVEF: left ventricular ejection fraction, LVDD: left ventricular end-diastolic diameter, BNP: brain natriuretic peptide, LVAD: left ventricular assist device, LVAD-implant: just before LVAD implantation, LVAD-explant: just after LVAD explantation, 6 months: 6 months after LVAD explantation, 5 years: 5 years after LVAD explantation.

measured in cross-sectional view at the level of the nucleus, with the smallest measurement in each case used to represent the CD; thirty cardiomyocytes per microscopic field were measured and then averaged. The CVF is the ratio of collagen-specific staining to the total area of the myocardium in each biopsy sample, except in subendocardial or perivascular areas; this was calculated as an index for interstitial collagen using automated image analysis software (BZ 9000; KEYENCE Co. Ltd., Osaka, Japan). The measurements of CD and CVF were performed in a blinded manner by two independent observers. Statistical analyses were performed by repeated measured ANOVA using software PASW Statistics 18.0 (SPSS, Chicago, IL, USA). The patient provided informed consent for endomyocardial biopsy, and the procedure was approved by the Ethical Review Board of our institute based on the Helsinki Declaration.

At just before LVAD implantation, the mean CD and CVF were 31.3 μm and 7.16%, respectively. At just after LVAD explantation, the CD had markedly decreased (19.8 μm) and the CVF had significantly increased (18.07%) with reverse remodeling. At 6 months after LVAD explantation, the CD was maintained (18.1 μm) with preservation of LVEF, whereas the CVF had substantially decreased (11.51%) with LV re-enlargement. At 5 years after LVAD explantation, the CD had increased again (24.5 μm) and the CVF was approximately the same (8.96%) (Fig. 2A, 2B).

DISCUSSION

This is the first report focusing on the long-term histopathological changes of the myocardium after LVAD explantation in a patient with reworsening HF with AIC. After LVAD explantation, the change in the CVF (but not the CD) occurred prior to the alteration of LVEF.

Hemodynamic unloading by LVAD support leads to structural and functional reverse remodeling. Although there was controversy regarding the change in the myocardium during LVAD support, some previous studies demonstrated significant decreases in cardiomyocyte volume, length, and diameter, in contrast with a significant increase in interstitial fibrosis after LVAD support in dilated cardiomyopathy.[3,4] Furthermore, LVAD therapy induces morphological changes

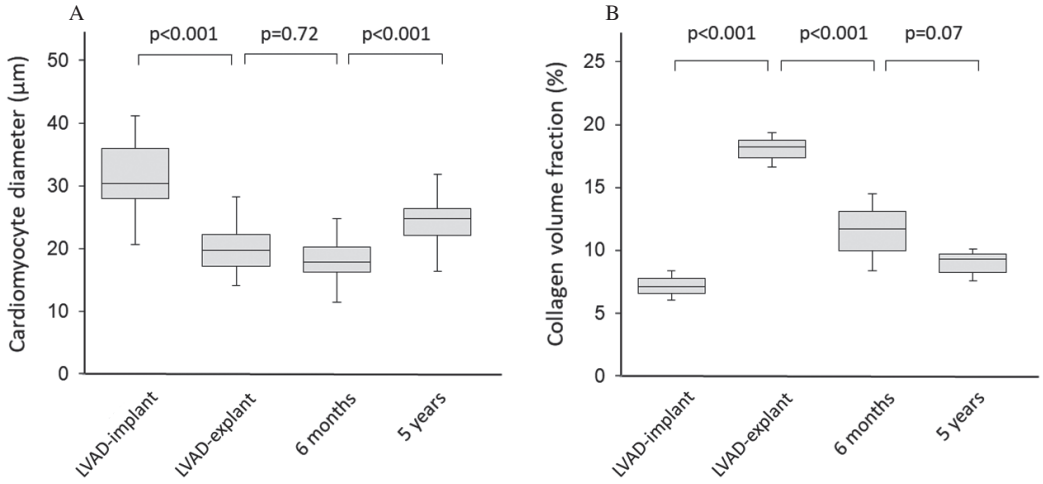

Fig. 2 Endomyocardial biopsy samples revealed changes in cardiomyocyte diameter (A) and collagen volume fraction (B).
Data are expressed in box plots; box, interquartile range; horizontal line, median; whiskers, range.
LVAD: left ventricular assist device, LVAD-implant: just before LVAD implantation, LVAD-explant: just after LVAD explantation, 6 months: 6 months after LVAD explantation, 5 years: 5 years after LVAD explantation.

at an intracellular ultrastructural level, such as in the cardiomyocytic mitochondria.[10] In the present case, the CD significantly decreased and the CVF markedly increased after LVAD support.

Cardiotoxicity is notably associated with some anticancer drugs, and can result in severe HF with reduced LVEF. Anthracycline-induced type I cardiotoxicity causes irreversible and dose-related cardiomyocyte injury,[1,2] and is thought to occur through several mechanisms.[11,12] Furthermore, even in a heart that has recovered LVEF via reverse remodeling, the cardiomyocytes undergo remission rather than true recovery because of potential damage at the molecular and/or cellular level.[5,6] In the present case, despite the maintained CD with preserved LV systolic function at 6 months after LVAD explantation, the CD increased with reduced LVEF at 5 years after LVAD explantation. Although the detailed mechanism of redecreased LVEF after LVAD explantation is still unclear, it might not only be due to the mechanical stretch from pressure and volume overload, but may also be due to the "legacy effect" of anthracycline on myocardium that leads to the irreversible collapse of myofibrils and cardiomyocyte hypertrophy.

The collagen matrix is part of the connective tissue, and is considered an important determinant of myocardial structural integrity. A previous study demonstrated increases in total collagen content, collagen cross-linking, and the ratio of collagen type I to type III during LVAD support.[13] The disorder of the extracellular collagen matrix (such as the attenuation of collagen cross-linking and the change in collagen subtypes) might precede cardiomyocyte damage, and LV re-enlargement might exceed the increase in total collagen content, resulting in a decreased CVF at 6 months after LVAD explantation. The increase in interstitial fibrosis may aid in maintaining both the structure and function of the whole heart without LVAD support. More importantly, both the quantity (structure) and quality (function) of the cardiomyocytes and myocardial interstitial tissue might change in accordance with each situation: before, during, or after LVAD support.

While a few patients with reverse remodeling experience temporarily successful LVAD explantation, they often need LVAD support again.[14] A previous study reported that prompt initiation of angiotensin-converting enzyme inhibitors and beta-blockers were associated with LV

recovery in patients with AIC.[15] However, the management of HF with recovered LVEF has not been established.[5,6] Even though the present patient received optimal medical therapy for HF and maintained a healthy lifestyle after achieving temporary recovery of LVEF, these interventions were not enough to prevent the progression of reworsening cardiac function. It is possible that the present patient will need LVAD support again in the future. It might be important to evaluate cardiac function based on myocardial pathological findings from the early stage of HF, as patients with AIC have a poor prognosis. In addition, the serial assessment of myocardial pathology by repeated endomyocardial biopsy might help clinicians to judge whether patients with AIC have undergone successful LVAD explantation or need LVAD support again.

CONCLUSION

We described a case of reworsening HF with AIC after explant of a LVAD. Although endomyocardial biopsy is invasive, the evaluation of pathological changes of the myocardium may enable the identification of cardiac dysfunction prior to echocardiographic changes in reworsening HF with AIC after LVAD explantation.

DISCLOSURE STATEMENT

The authors declare no conflicts of interest associated with this manuscript.

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