

[ CASE REPORT ]

## The Effective Use of Digoxin in a Patient with Metastatic Breast Cancer and Anthracycline-induced Cardiomyopathy

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### Abstract:

Anthracyclines have cardiotoxic side effects. Cardioprotective drugs such as angiotensin-converting enzyme inhibitors and beta-blockers are therefore recommended for patients with anthracycline-induced cardiomyopathy. We herein present a 54-year-old woman with recurrent metastatic breast cancer who developed heart failure (HF) with a left ventricular ejection fraction (LVEF) of 22% after undergoing epirubicin chemotherapy. However, her HF symptoms and low LVEF persisted despite 5 months of cardioprotective therapy and additional oral pimobendan. Pimobendan was discontinued because of ventricular arrhythmia and hypotension. After the start of low-dose (0.125 mg daily) digoxin, her LVEF increased to 42%, and her HF symptoms improved with no adverse events.

**Key words:** anthracycline, cardiotoxicity, digoxin, heart failure, left ventricular ejection fraction

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### Introduction

Anthracyclines were one of the first discovered chemotherapeutic agents and they remain in use as a class of chemotherapy drugs for metastatic breast cancer (1). Anthracyclines are an effective anticancer drug but they also have some cardiotoxic side effects. The cardiotoxicity of anthracyclines, especially impaired left ventricular (LV) function and heart failure (HF), is the most common problem that worsens the prognosis or limits the options for further treatment (2, 3). Cardioprotective medications such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers and beta-blocker treatment are recommended for patients who develop symptomatic HF or asymptomatic LV dysfunction either during or after chemotherapy (3). However, HF is difficult to treat in patients who show no recovery in LV dysfunction despite undergoing cardioprotective therapy.

Digoxin is an oral inotropic drug that improves the symptoms and decreases hospitalization in patients with HF with no effect on mortality (4). Digoxin has class IIa recommendations for treating HF with reduced ejection fraction

(HFrEF) patients in Japan (5). Recently, however, digoxin use in HFrEF patients has decreased because many doubts, especially regarding its safety and very narrow therapeutic window, have been raised (6, 7). We herein present a patient with metastatic breast cancer who, following anthracycline administration, developed HF with severe LV dysfunction, which both improved by low-dose digoxin in addition to cardioprotective therapy.

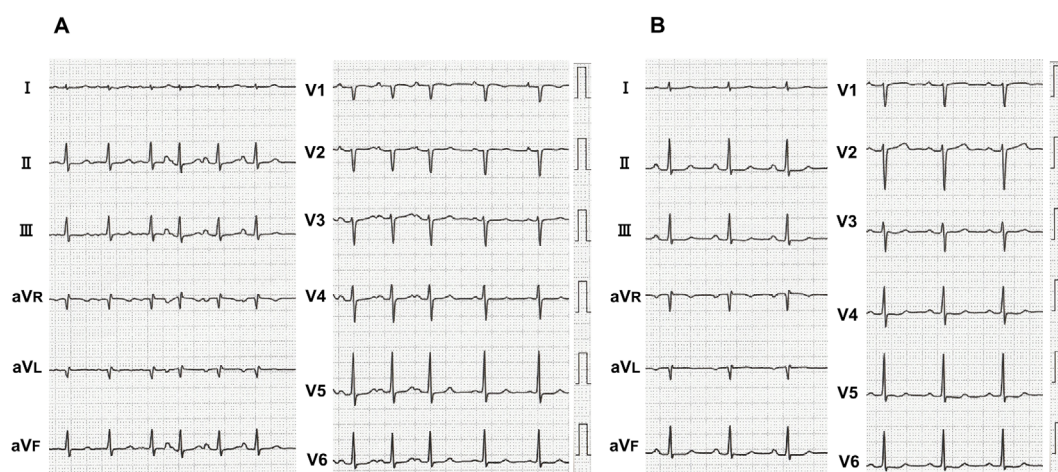
### Case Report

A 54-year-old woman with recurrent metastatic breast cancer and HF was referred to our hospital. She underwent left-sided mastectomy 4 years ago in a cancer hospital. Estrogen and progesterone receptors were both positive, and human epidermal growth factor receptor 2 was negative. She received tamoxifen as adjuvant therapy. However, a metastatic workup with a positron-emission tomography/computed tomography (PET/CT) scan revealed left axillary lymph node metastasis and isolated liver metastasis (segments IV and V, 78 mm in diameter) 2 years ago. Therefore, paclitaxel and bevacizumab chemotherapy was started. This treatment was temporarily interrupted at her request, and anas-

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**Figure 1.** Twelve-lead electrocardiograms obtained before (A) and 5 months after the start of digoxin treatment (B).

trozole was used alternatively for 3 months. After 24 cycles of paclitaxel and bevacizumab chemotherapy, a follow-up PET/CT scan showed a deceased liver metastasis size (segments IV and V, 46 mm in diameter).

Combination chemotherapy with cyclophosphamide, epirubicin (75 mg/m<sup>2</sup>) and fluorouracil (CEF) was started one year ago. Before the CEF therapy, her plasma B-type natriuretic peptide (BNP) concentration and serum troponin I level were 7.8 pg/mL (normal range <18.4 pg/mL) and 1.9 pg/mL (normal range <26.2 pg/mL), respectively, and her echocardiography showed a 70% of LV ejection fraction (LVEF) with no structural abnormalities. At the completion of CEF treatment (repeat every 21 days×8 cycles), echocardiography showed a 69% of LVEF. Her cumulative dose of epirubicin was 600 mg/m<sup>2</sup>.

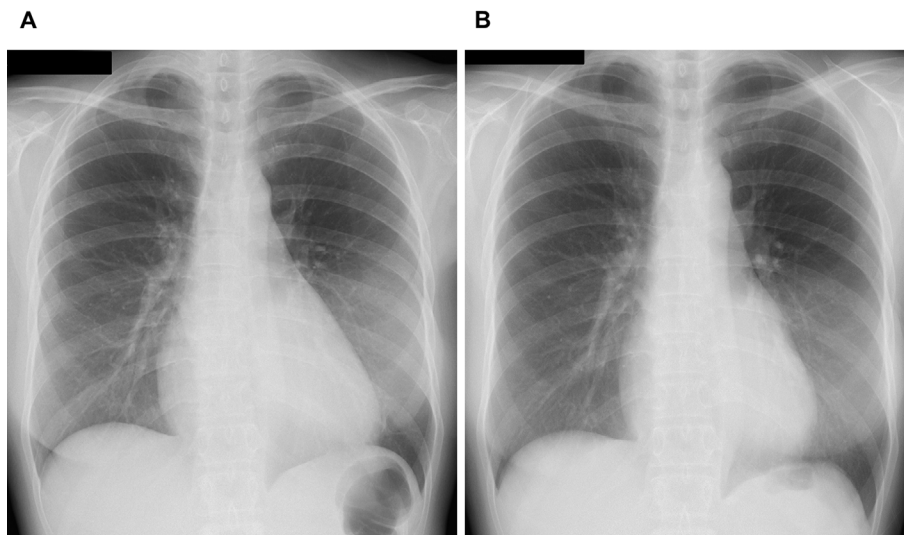
She developed dyspnea on exertion and was diagnosed with HF 1 month after completion of therapy; her plasma BNP concentration and serum troponin I were elevated to 843.0 pg/mL and 96.6 pg/mL, respectively, and echocardiography revealed a severely reduced LVEF of 28%. Therefore, she was referred to a cardiologist in another hospital 5 months ago. She was started on 20 mg daily furosemide, 50 mg daily spironolactone, 2.5 mg daily enalapril and 2.5 mg daily of carvedilol. Coronary angiography revealed no significant stenosis. Left ventriculography revealed an enlargement (LV end-diastolic volume index 107 mL/m<sup>2</sup>) and a low LVEF of 17%. Right ventricular endomyocardial biopsy was also performed. Histopathological examinations revealed atrophy of myocytes, myocytolysis, interstitial edema and fibrosis but no inflammatory cell infiltration, consistent with anthracycline-induced cardiomyopathy. The carvedilol was titrated up to 10 mg daily, and 5 mg daily pimobendane was added. She also received a wearable cardioverter-defibrillator (WCD) because of the occurrence of nonsustained ventricular tachycardia (NSVT) (22 beats, 150 bpm) with low LVEF.

She remained in New York Heart Association (NYHA) functional class III, and she felt dizzy and respiratory dis-

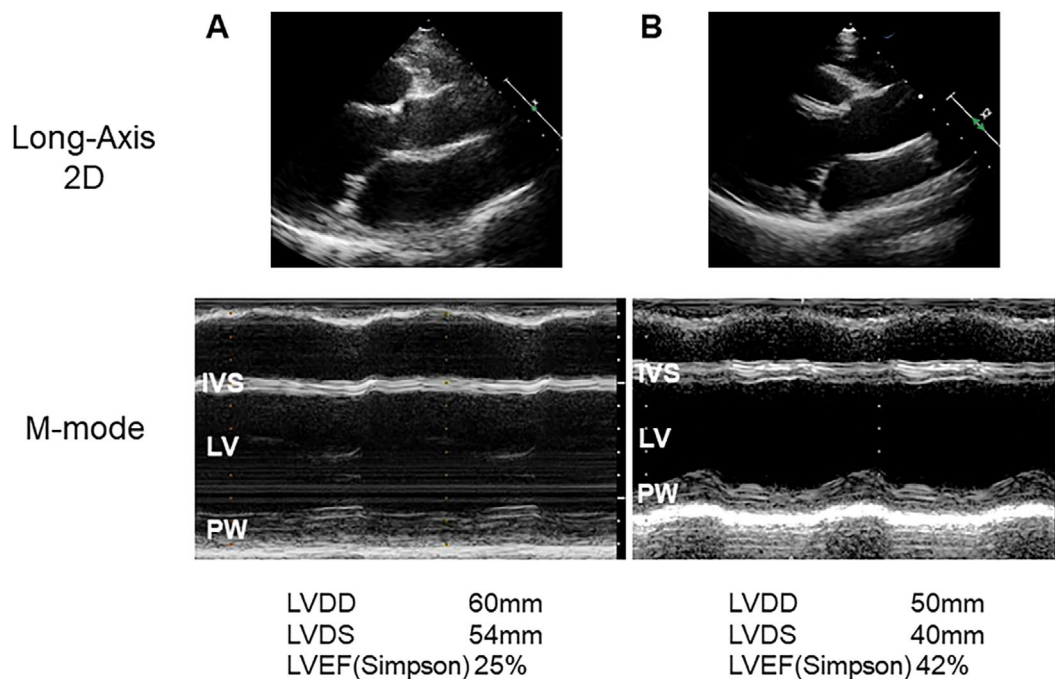
comfort on exertion. She was referred to the HF clinic in our hospital. Her blood pressure was 74/54 mmHg, and 12-lead electrocardiography (ECG) revealed a sinus rhythm with a heart rate of 94 bpm, poor R wave progression in leads V2-3, a transitional zone between V4 and V5 and a short run of atrial tachycardia (Fig. 1A). Chest radiography revealed cardiomegaly and a cardiothoracic ratio of 54% (Fig. 2A), and her plasma BNP concentration and serum troponin I were 554.9 pg/mL and 11.7 pg/mL, respectively. Echocardiography showed a large LV dimension in diastole (LVDD) of 60 mm, and LVEF (according to the biplane Simpson's method) was 25% (Fig. 3A).

After admission, the dose of pimobendane was tapered off for 4 days because of recurrent NSVT and persistent hypotension. Her systolic blood pressure increased to 80-90 mmHg. However, she complained of palpitation and chest discomfort; the mean heart rate was 96 bpm on Holter monitoring, and her plasma BNP concentration was 482.9 pg/mL. Daily digoxin (0.125 mg) was started to improve her symptoms due to HF; her estimated glomerular filtration rate was 68 mL/min/1.74 m<sup>2</sup> and her trough serum digoxin concentration was 0.34 ng/mL after 5 days of treatment. No drug-related adverse events were observed, and she was discharged from our hospital. Her WCD, during which time she did not receive any defibrillation shock, was discontinued. Atrial fibrillation was not detected during hospitalization.

One month after discharge, she was in NYHA functional class II, her plasma BNP concentration was 239.1 pg/mL, and her LVEF had increased to 34% (Fig. 4). Combination therapy with capecitabine and eribulin was also started. She returned to work and maintained her ordinary home life. After 5 months of digoxin therapy, 12-lead ECG showed a reduced heart rate and higher QRS voltage complexes in the limb leads than before the administration of digoxin and a normal transitional zone between V3 and V4 (Fig. 1B). Chest radiography revealed a cardiothoracic ratio of 47% (Fig. 2B), and echocardiography revealed an LVDD of 50



**Figure 2.** Chest radiographs obtained before (A) and 5 months after the start of digoxin treatment (B).



**Figure 3.** Echocardiography before (A) and 5 months after the start of digoxin treatment (B). IVS: interventricular septum, LV: left ventricle, LVEF: left ventricular ejection fraction, LVDD: left ventricular internal dimension in diastole, LVDS: left ventricular internal dimension in systole, PW: posterior wall

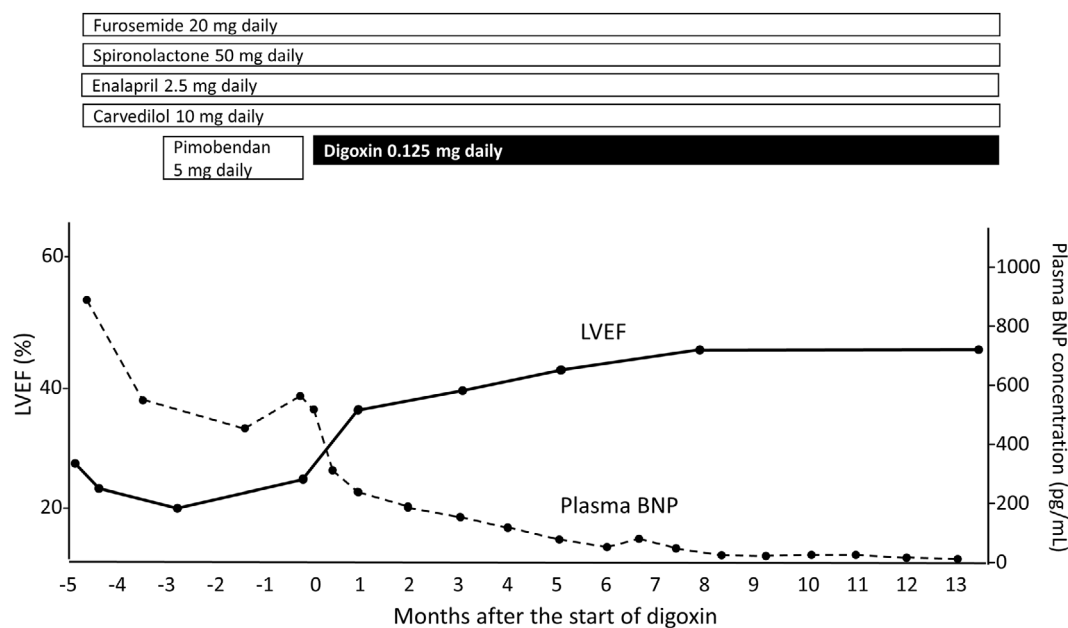
mm and an LVEF of 42% (Fig. 3B). Plasma BNP was 76.9 pg/mL (Fig. 4).

One year after discharge, she continued to receive digoxin therapy and had maintained NYHA functional class II without signs of worsening HF. Her trough serum digoxin concentration was 0.60 ng/mL. Her LVEF was 45% and plasma BNP was 34.1 pg/mL (Fig. 4). Thereafter, she received palliative care and died from metastatic breast cancer 3 months later. Digoxin and enalapril were discontinued 3 weeks before death to avoid digitalis toxicity, but she did not experi-

ence worsening HF symptoms.

## Discussion

Anthracycline-induced cardiomyopathy was formerly thought to be irreversible, and the median time to a reduction in LVEF from the end of chemotherapy was reported to be 3.5 months (8). However, the LVEF could recover if cardioprotective therapy including ACE inhibitors and beta-blockers was started within 2 months after the end of che-



**Figure 4.** Changes in the left ventricular ejection fraction (LVEF) and plasma B-type natriuretic peptide (BNP) concentration during cardioprotective therapy combined with low-dose digoxin.

motherapy (9). In this case, LVEF was normal at the completion of CEF therapy, but a severely reduced LVEF with HF symptoms was observed soon after the diagnosis. Despite 5 months of cardioprotective therapy, including carvedilol, enalapril and spironolactone, her LVEF did not recover.

A recent case report showed that intravenous levosimendan, a calcium sensitizer, increases LVEF in a patient with doxorubicin-induced cardiomyopathy (10). An experimental study demonstrated that the inotropic effects of levosimendan can be mainly explained through its inhibition of phosphodiesterase (PDE) 3 (11). Pimobendan, which is used only in Japan, has positive inotropic and vasodilator effects mainly through PDE 3 inhibition and slight calcium sensitization (12). However, no improvement in LVEF was observed in this patient despite the use of oral pimobendane, but she did demonstrate a higher heart rate in sinus rhythm and recurrent NSVT.

Digoxin has a positive inotropic effect as well as neurohormonal effects, including vagomimetic activity, the ability to improve baroreceptor sensitivity, decrease the norepinephrine serum concentrations and the activation of the renin-angiotensin system, a direct sympathoinhibitory effect and the ability to increase the release of natriuretic peptides with no effect on blood pressure (13). One month after the start of digoxin, despite no changes in her other medications, the patient's LVEF remarkably increased and her plasma BNP concentration decreased, changes that persisted over 1 year. The current guidelines recommend a combination of the maximum tolerated doses of beta-blockers and ACE inhibitors as the optimal medical therapy (14), but it takes a long time to titrate up to the maximum tolerated dose for HF patients with low LVEF. Although a more long-term cardioprotective therapy might have improved HF symptoms and

LVEF, this patient did not have much time left and therefore desired other types of chemotherapy. Recently, the  $I_f$ -channel inhibitor ivabradine was recommended for symptomatic HF patients with LVEF  $\leq 35\%$  and a resting heart rate  $\geq 75$  bpm in sinus rhythm despite the use of cardioprotective therapy (14). However, there is no evidence regarding the effect of ivabradine on outcomes in patients with anthracycline-induced cardiomyopathy. The fast hemodynamic benefit of digoxin, which has an inotropic effect in addition to a reverse remodeling effect by reducing the heart rate, might have led to the improvement in the HF status in this patient.

The patient received paclitaxel and bevacizumab before CEF. Paclitaxel and bevacizumab, which are mostly used as concurrent chemotherapy, are also known to induce cardiotoxicity (3, 15). Chemotherapy-induced cardiotoxicity is usually observed during treatment or, in some cases, after treatment. In this patient, the LVEF just after the completion of paclitaxel and bevacizumab chemotherapy was normal, but these drugs might have potentially contributed to the development of anthracycline-induced cardiotoxicity.

Although the mechanisms of anthracycline-induced cardiomyopathy are not fully understood, the inhibition of topoisomerase 2 $\beta$  in cardiomyocytes by anthracycline increases the production of reactive oxygen species via increased deoxyribonucleic acid (DNA) breaks and mitochondrial dysfunction and results in cellular damage in the form of oxidative stress (16). It is unclear how digoxin affects this mechanism. Ezzat et al. reported that the cardenolide glycoside acovenoside A protected against adriamycin-induced cardiotoxicity in mice by inhibiting oxidative stress and inflammation (17). Wann et al. reported that digoxin exhibited antitumor activities on non-small-cell lung cancer A549 and H1299 cells by inhibiting DNA repair and promoting reactive oxygen species while also inhibiting efforts to slow

DNA repair in cardiomyocytes but not in tumor in a nude mouse A549 xenograft model. These results suggested that compared with adriamycin alone, cotreatment with digoxin enhances antitumor efficacy and reduces cardiotoxicity in a cell context-dependent manner (18). It thus remains unclear whether digoxin can inhibit anthracycline-induced cardiomyopathy in humans.

In this patient, the trough serum digoxin concentration was maintained at less than 1.0 ng/mL to avoid digitalis toxicity (13, 19). Low-dose/low-concentration digoxin might exert a positive inotropic effect without excessive calcium overload in cardiomyocyte when combined with beta-blockers. Although her LVEF did not recover to normal levels, her HF symptoms and quality of life improved, and she was able to start chemotherapy with other regimens. Digoxin does not improve survival in HFrEF patients but may improve the quality of life by reducing HF symptoms and hospitalizations. (4, 5, 19) If severely low LVEF and HF symptoms persist in anthracycline-induced cardiomyopathy despite cardioprotective therapy, low-dose digoxin may be a useful tool as an adjunctive therapy. From the viewpoint of palliative care, this approach can also help relieve suffering and improve the quality of life in cancer patients with HF.

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

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