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【 CASE REPORT 】

Reversible Cancer Therapeutics-related Cardiac Dysfunction Complicating Intra-cardiac Thrombi

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Abstract:

Epirubicin-based chemotherapy carries a risk of inducing heart failure, although the frequency is rare. Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, has recently been widely used in patients with recurrent breast cancer as a first-line chemotherapeutic agent. Heart failure or arterial thromboembolism has been reported as a rare cardiovascular complication of bevacizumab. We herein report a breast cancer patient with reversible cancer therapeutics-related cardiac dysfunction associated with bevacizumab and epirubicin complicating intracardiac thrombi in the left atrium and left ventricle. This case underscores the importance of tailored medical planning according to the individual status in patients receiving anti-cancer therapies.

Key words: epirubicin, bevacizumab, cardiotoxicity, heart failure, thrombus

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Introduction

Anthracycline, including epirubicin-based chemotherapy, improves the survival of breast cancer patients but is associated with an increased risk of heart failure (1).

In recent years, systemic therapy targeting vascular endothelial growth factor (VEGF) and its receptors has proven to be a successful strategy in patients with cancer. Bevacizumab is a widely used anti-VEGF monoclonal antibody targeting the VEGF ligand. Although it has been shown to improve clinical outcomes in several malignancies including advanced breast cancer (2), its use has been associated with many cardiovascular events (3-5).

We herein report a breast cancer patient with reversible cancer therapeutics-related cardiac dysfunction associated with bevacizumab along with epirubicin complicated by intracardiac thrombi in the left atrium and left ventricle.

Case Report

A 65-year-old woman with a history of postoperative chemotherapy for right breast cancer was referred to our department due to congestive heart failure. The breast cancer had been graded as clinical stage IIa, triple-negative invasive ductal carcinoma [estrogen receptor 0%, progressive receptor 0%, and human epidermal growth factor receptor 2 (HER2) immunohistochemistry 0%], and the Ki-67-positive cell index was 98.6%. She had received 4 courses of epirubicin (total dose: 327 mg/m^2) and cyclophosphamide (total dose: 2,183 mg/m^2) followed by paclitaxel (total dose: 727 mg/m^2) and bevacizumab (total dose: 546 mg/m^2).

Nine months after the end of epirubicin administration and three months after the end of bevacizumab administration, she developed dyspnea on exertion despite denying any history of cardiovascular diseases. Three months later, car-

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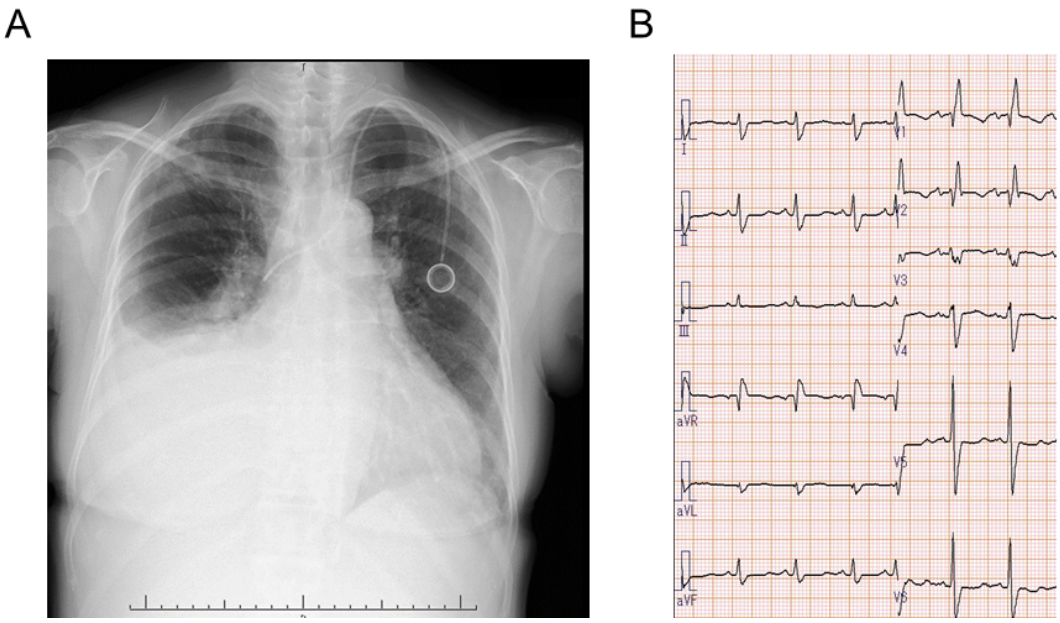

Figure 1. **(A) Chest X-ray at admission showing lung congestion with apparent cardiomegaly and pleural effusion. (B) The electrocardiogram at admission showing sinus tachycardia with complete right bundle branch block.**

diac enlargement with pleural effusion and intracardiac thrombi were detected by contrast-enhanced computed tomography (CT). Subsequently, she was introduced to our department and admitted for the management of heart failure and intracardiac thrombi.

On admission, she showed a blood pressure of 150/101 mmHg, pulse rate of 102/min, and transcutaneous oxygen saturation of 98% in room air. A clinical examination revealed jugular vein distension, third heart sound, and abdominal fullness. Chest X-ray showed lung congestion with apparent cardiomegaly and pleural effusion (Fig. 1A). The electrocardiogram showed sinus tachycardia with complete right bundle branch block (Fig. 1B). The serum N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) level was markedly increased to 7,648 pg/mL. Transthoracic echocardiography showed diffuse severe hypokinesis of the left ventricular (LV) wall [ejection fraction (EF): 24%] with a mildly enlarged cavity and LV hypertrophy (Fig. 2A). Mural thrombus with a radius of 2 cm was observed in not only the LV apex but also the left atrium (Fig. 2B, C), which was confirmed by contrast-enhanced CT taken after admission (Fig. 3A, B). The patient was diagnosed with heart failure caused by cancer therapeutics-related cardiac dysfunction (CTRCD), and intravenous carperitide (0.025 μg/kg/min) and furosemide (40 mg/day) were initiated along with unfractionated heparin to maintain an activated partial thromboplastin time of 60 seconds followed by warfarin.

Soon after the infusion therapy, the congestion was relieved, and medication was switched to oral cardioprotective drugs, such as enalapril (up to 2.5 mg/day) and carvedilol (up to 10 mg/day). A coronary angiogram performed at the 10th day showed no coronary artery lesions, and the pathological findings in an endomyocardial biopsy specimen obtained from the right side of the interventricular septum showed mild cardiomyocyte hypertrophy and no myocardial fibrosis or findings specific for secondary cardiomyopathy. Anticoagulation therapy with warfarin was continued in order to maintain a prothrombin time international normalized ratio ≥2.0, resulting in the disappearance of the intracardiac thrombi on echocardiography on the 19th day without any thromboembolic events. As a result, the patient was discharged on the 32nd day without any residual cardiovascular symptoms.

Despite the favorable course of cardiovascular disease, local recurrence of breast cancer was found thereafter, and reoperation was performed 52 days after the discharge without any cardiovascular events. Nevertheless, lymph node metastasis was found two months after the reoperation. Accordingly, postoperative chemotherapy with capecitabine was planned. A repeat echocardiogram showed a reduction in the LV size and an increase in the LV EF to 52%, and contrast-enhanced CT showed no intracardiac thrombus. Because of the potential interaction of capecitabine with warfarin, we decided to discontinue warfarin based on the low estimated risk of recurrent thromboembolism thanks to the recovered cardiac function.

Eight months after discharge, chest-X ray showed normal findings in the heart (Fig. 4A), the serum NT-pro-BNP level had decreased to 89 pg/mL, and an echocardiogram showed a normal LV systolic function (LV EF: 63%) (Fig. 4B). Contrast-enhanced imaging confirmed no intracardiac thrombus (Fig. 4C). She is now receiving a new chemotherapy regimen with a low risk of cardiotoxicity.

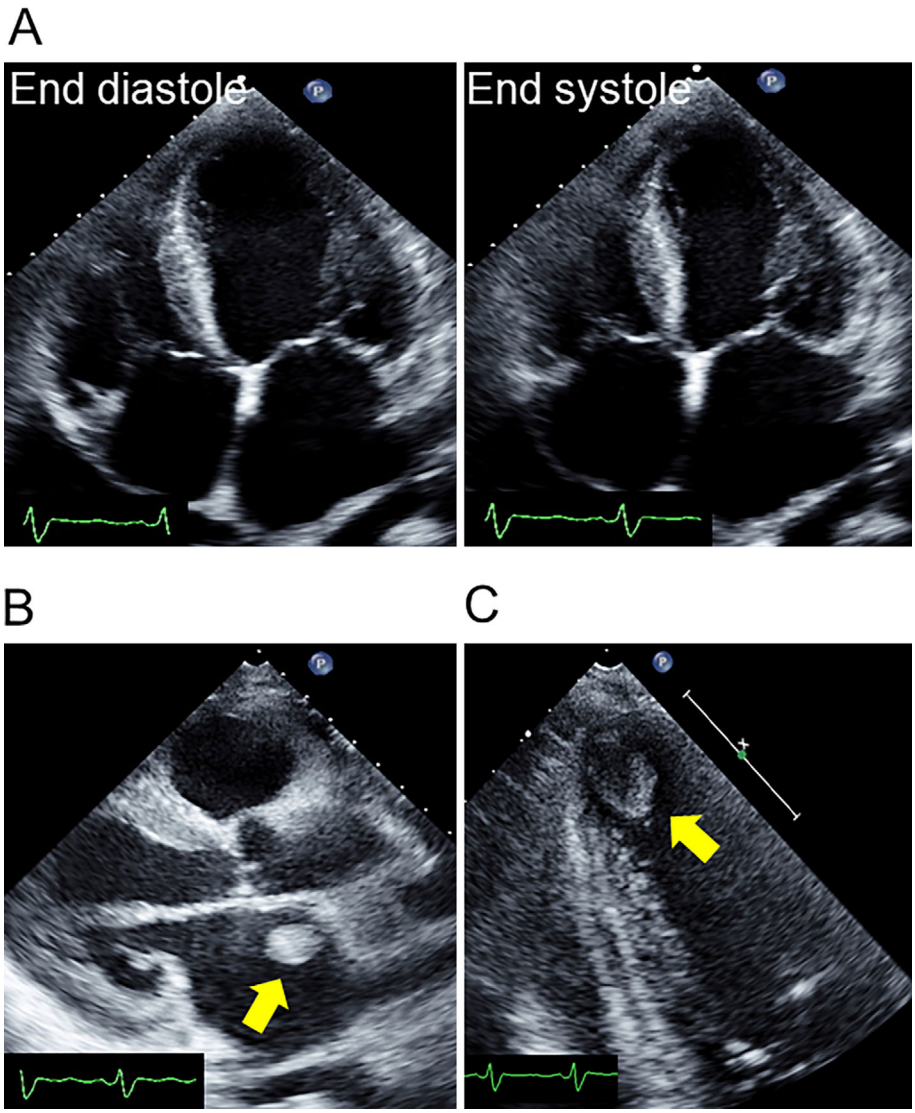

Figure 2. **(A) Apical four-chamber echocardiographic view at end diastole (left) and end systole (right) at admission showed a mildly enlarged left ventricle (left ventricular end-diastolic diameter: 57 mm), left ventricular hypertrophy (left ventricular mass index: 136 g/m^2), and diffuse severe hypokinesis of wall motion (ejection fraction: 24%). (B) Parasternal long-axis view showing thrombus formation (yellow arrow) in the left atrium. (C) Zoomed image of the apical four-chamber view focusing on the left ventricular apical thrombus (yellow arrow).**

Discussion

In the treatment of breast cancer, anthracyclines are established as a main component of cancer therapy regimens, even though they have dose-dependent cardiotoxicity. The incidence of heart failure after high-dose epirubicin exposure (approximately 900 mg/m^2) is known to exceed 5-10%, but substantial cardiotoxicity may occur at even lower doses, depending on the individual susceptibility (6). Heart failure due to epirubicin typically manifests within several years after exposure (7). However, anthracyclines can also cause myocardial injury in the acute (immediately after exposure) and subacute (within one year after exposure) phases, even though their frequencies are rare (acute: <1%; subacute: 1-6%) (8).

However, in recent years, anti-VEGF monoclonal antibodies, such as bevacizumab, have become one of the first-line therapies for human epidermal growth factor receptor type 2-positive breast cancers (2). The use of bevacizumab is associated with class-effect adverse events, including hypertension, arterial thromboembolism, and congestive heart failure (3, 4), and the incidence of clinically significant heart failure is reported to be approximately 2-4% (9). Cyclophosphamide also induces acute heart failure with an incidence of 2-17%, although this often occurs within 48 hours after the administration and sometimes within 2 or 3 weeks (10, 11). Cardiac toxicity caused by paclitaxel takes the form of sub-acute or acute bradycardia, heart block, and atrial or ventricular arrhythmia with an incidence of 0.5%, and paclitaxel itself does not induce heart failure (12).

In this particular patient, the time difference between the

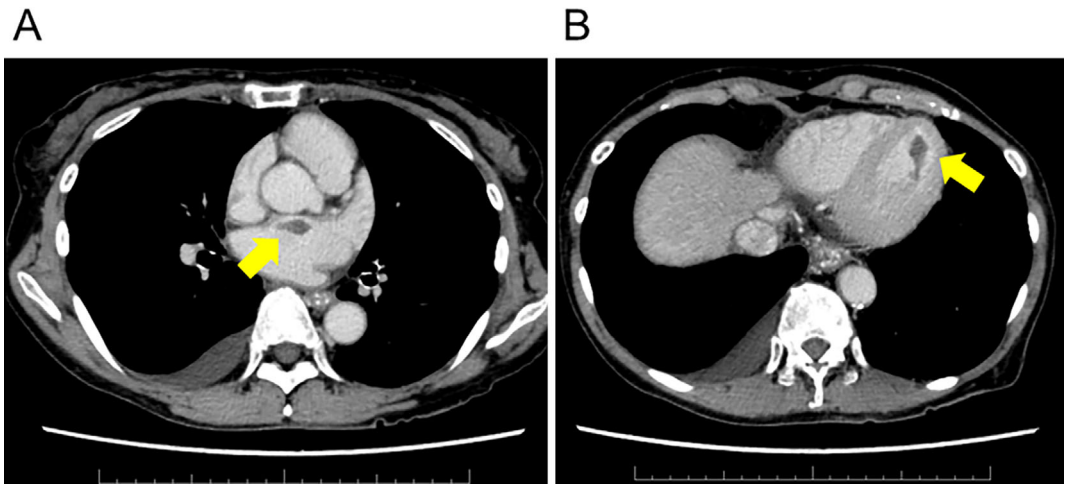

Figure 3. **Contrast-enhanced computed tomography at admission showing left atrial thrombus (A, yellow arrow) and left ventricular apical thrombus (B, yellow arrow).**

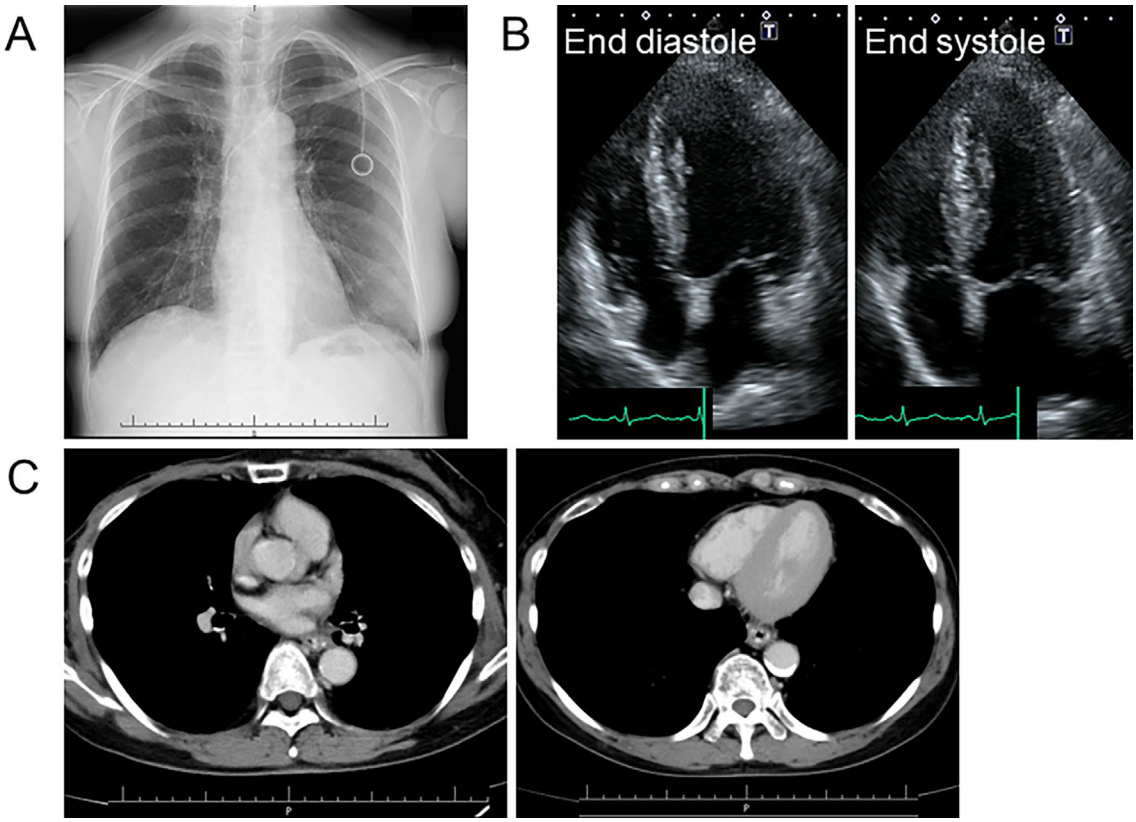

Figure 4. **(A) Chest X-ray at eight months after discharge showing normal findings in the heart. (B) Apical four-chamber echocardiographic view at end diastole (left) and end systole (right) eight months after discharge showed a decrease in the left ventricular size (end-diastolic left ventricular diameter: 46 mm) and increase in the ejection fraction to 63%. (C) Contrast-enhanced CT findings eight months after discharge showing no intracardiac thrombus.**

occurrence of heart failure symptoms and the final course of epirubicin administration (9 months) and low amount of total use (327 mg/m^2) suggest a relatively low probability of epirubicin-associated heart failure, although the patient might have suffered from epirubicin-induced subacute myocardial injury. As there were no data concerning cardiac biomarkers and echocardiography during epirubicin administration, the latter could not be completely denied. These findings, together with the short duration from the final course of bevacizumab administration to the onset of heart failure, suggested that bevacizumab was the main cause of the incidence of LV systolic dysfunction and subsequent

heart failure.

Bevacizumab therapy for breast cancer is reported to carry a substantially high risk of heart failure due to prior or concomitant exposure to other cardiotoxic medications (4). In addition, consistent with the typical manifestation of bevacizumab-associated heart failure (13), the present patient showed an elevated blood pressure and hypertrophied LV, which also suggested probability of bevacizumab-associated heart failure. Anthracyclines directly cause cell death, leading to irreversible myocyte destruction, even though anthracycline-induced subacute myocardial injury may occasionally be reversible when cardioprotective therapy is administered (14). In contrast, VEGF inhibitors alter the normal cellular function by affecting the mitochondrial system and reducing protein synthesis, leading to reversible myocyte destruction (5). Cyclophosphamide and paclitaxel were unlikely to be involved in heart failure in the present case, given the time course and their reported cardiac toxicity.

Fortunately, the patient was able to be successfully treated, and the LV systolic function recovered after standard therapy using angiotensin-converting enzyme inhibitors and beta blockers, which is recommended by the guidelines (15, 16).

In summary, the cause of cardiac dysfunction and heart failure in this case was considered to be CTRCD associated with bevacizumab along with epirubicin that showed a response to cardioprotective therapy. Importantly, the present case was complicated by intracardiac thrombi at the time of worsening heart failure. A case of epirubicin-associated heart failure with LV apical thrombus has been reported (17), and combination treatment of bevacizumab and anti-cancer agents is known to be associated with an increased risk of arterial thromboembolism, although the underlying mechanism remains unclear (5). Some researchers have suggested that bevacizumab might reduce the anti-inflammatory effects of VEGF exposure, leading to increased inflammation and thrombus formation (18). In addition to these agent-specific reasons, the hypercoagulation status during the decompensated heart failure and intracavity blood stasis due to severe LV and left atrial dysfunction may have been associated with thrombus formation, according to Virchow's triad.

To our knowledge, this is the first report of reversible CTRCD associated with bevacizumab and epirubicin showing both left atrial and LV thrombus in a breast cancer patient. In addition, it is noteworthy that the thrombi were able to be managed using anticoagulation therapy, and the medication was ultimately able to be discontinued without any thromboembolic events owing to the recovered cardiac function, which aided in the management of her breast cancer. This was an educational case suggesting the importance of cardiology intervention in oncology and collaboration between cardiologists and oncologists.

Conclusion

We experienced a case of reversible CTRCD associated with bevacizumab along with epirubicin showing intracardiac thrombi in a breast cancer patient. This case emphasizes the importance of tailored medical planning according to the individual status in patients receiving anti-cancer therapies.

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

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