A Case of Epirubicin-Associated Cardiotoxicity Progressing to Life-Threatening Heart Failure and Splenic Thromboembolism

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Abstract

We present the case of a 42-year-old Japanese woman who developed acute heart failure after chemotherapy with epirubicin for breast cancer. Echocardiography revealed a cardiac dysfunction with left ventricular thrombus. Serial serum troponin T tests were positive over a 5-week period, and an endomyocardial biopsy demonstrated ultrastructural lesions which were similar to those caused by cardiotoxicities due to doxorubicin. Although the patient developed splenic thromboembolism, her cardiac function recovered gradually, and she regained full range of her activities. This case report demonstrates that epirubicin-associated cardiotoxicity causes life-threatening heart failure and supportive care is important until the patient recovers from acute intoxication.

Key words: epirubicin, cardiotoxicity, thromboembolism

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Case Report

A 42-year-old Japanese woman complained of shortness of breath in July 2010, 5 weeks after she received a final dose of epirubicin for chemotherapy for breast cancer. She was diagnosed with mild congestive heart failure and prescribed furosemide and enalapril. One month later, she developed dyspnea, general fatigue, and loss of appetite, and she was admitted to our hospital with orthopnea in August 2010. A chest radiograph showed cardiomegaly and pulmonary congestion (Fig. 1B). Electrocardiogram showed low voltage in extremity leads and poor R-wave progression in precordial leads (Fig. 2B). The patient’s height was 153 cm and weight 57 kg. At the time of hospital admission, she had gained 3 kg in weight since her last regular medical check-up 4 weeks earlier. Physical examination showed third heart sound, hypotension, and tachycardia (Fig. 3).

The patient had been diagnosed in November 2008 with cancer of the left breast and metastasis to local lymph nodes and ilium. She had received 9 months of combined endocrine therapy with ovarian suppressant drugs and tamoxifen, a selective estrogen receptor modulator; however, the therapy was ineffective. After cardiovascular screening, the patient received 13 cycles of 60 mg/m² epirubicin (cumulative dose of 780 mg/m²) in combination with 600 mg/m² cyclophosphamide (cumulative dose of 7,800 mg/m²) every 3 weeks from August 2009 through June 2010. The patient did not receive mediastinal irradiation. Echocardiography showed normal left ventricular ejection fraction (LVEF) and LV size (Fig. 3). The patient did not display any clinical symptoms of heart failure during chemotherapy. After chemotherapy, the tumor size was reduced to a level below the sensitivity of detection of computed tomography; the concentration of the tumor markers CEA and CA15-3 decreased and then remained within their normal ranges. These results clearly indicated that the chemotherapy was effective.

On hospital admission in August 2010, N-terminal pro-B-type natriuretic peptide was elevated at 9,677 pg/mL (Fig. 3). A test for serum troponin T (TnT; Elecsys® troponin T STAT test) was positive, but creatine kinase levels were normal. Platelet counts, prothrombin time, activated

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Figure 1. Chest X-rays before administration of epirubicin (October 29, 2008; A) and at the time of hospital admission (August 10, 2010; B), at which point cardiomegaly and pulmonary congestion were indicated.

Figure 2. Electrocardiograms before chemotherapy (October 29, 2008; A), at the time of hospital admission (August 10, 2010; B), and 1 year later (September 28, 2011; C). Heart rates were 65, 105, and 50 beats/min, respectively. Electrocardiogram showed low voltage in extremity leads and poor R-wave progression in precordial leads at hospital admission (B). One year later, the electrocardiogram was almost normalized and it was similar to that recorded before chemotherapy (A, C).

tial thromboplastin time, and concentrations of fibrinogen, fibrin degradation products, and D-dimer were within their normal ranges. Echocardiography revealed a dilated and severely hypokinetic LV.

The patient was diagnosed with acute heart failure, and she was administered oxygen, diuretics, and vasodilators. Intravenous dobutamine also was initiated at 5.0 μg/kg/min because hypoperfusion and pulmonary and liver congestion were observed. Ambulatory monitoring showed frequent runs of non-sustained ventricular tachycardia. On the 8th hospital day, echocardiography showed LV hypokinesis associated with mural thrombus (Fig. 4A). Laboratory testing for thrombophilia, including concentrations of plasma antithrombin III, activated protein C, protein S, anti-cardiolipin β2-glycoprotein-I, and dilute Russell viper venom time, was normal. Although unfractionated heparin and warfarin were administered and reduced the size of the LV thrombus, the patient developed splenic thromboembolism associated with acute pain in her left hypochondrium on the 18th hospital day (Fig. 4B).
performed on day 17 after hospital admission. The patient had been treated with intravenous dobutamine at 5.0 μg/kg/min and intravenous furosemide at 20 mg every 6 hours.

Cardiac catheterization and endomyocardial biopsy were performed on day 17 after hospital admission. The patient had been treated with intravenous dobutamine at 5.0 μg/kg/min and intravenous furosemide at 20 mg every 6 hours.

![Figure 3](image-url)

**Figure 3.** Clinical course. Systolic blood pressure in mid-July 2010, when the patient developed mild congestive heart failure, was lower than that measured during chemotherapy in August 2009 through June 2010. Sinus tachycardia continued for the first 5 weeks after admission. The cardiothoracic ratio and LV diastolic dimension increased and the LVEF decreased after chemotherapy. N-terminal pro-B-type natriuretic peptide reached as high as 15,213 pg/mL. Serial serum TnT tests were positive over the first 6 weeks after hospital admission. After the serum TnT test turned negative, all indicators of heart failure improved. A surge in D-dimer was observed during the development of LV thrombus. APTT/control: activated partial thromboplastin time/control time, LVEF: left ventricular ejection fraction, NT-pro BNP: N-terminal pro-B-type natriuretic peptide, PT-INR: prothrombin time-international normalized ratio, TnT: troponin T

![Figure 4](image-url)

**Figure 4.** Echocardiogram and computed tomography after hospital admission. (A) Echocardiogram on day 8 after hospital admission showed a thrombus in the LV (arrowhead). The size was 27×13 mm. (B) Computed tomography on day 18 after hospital admission showed a splenic infarction (arrowhead). LV: left ventricle, RA: right atrium, RV: right ventricle
Mean pulmonary artery wedge pressure, pulmonary artery pressure, and cardiac index by thermodilution were 19 mmHg, 26 mmHg, and 1.4 L/min/m², respectively. The patient’s coronary arteries were normal. Endomyocardial biopsy from the right ventricle showed myocyte degeneration, interstitial myocardial edema, fibrosis, and slight infiltration of mononuclear cells, most of which were positive for CD45RO (Dako) (Fig. 5) and negative for CD15. Some myocytes were not stained by desmin (Dako). Electron micrographs showed myofibrillar loss, swollen mitochondria with loss of compact cristae, and dilated sarcoplasmic reticulum (Fig. 6).

On the 25th hospital day, the patient was examined by ²⁰¹Tl and ¹²³I-beta-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) myocardial single-photon emission computed tomography (SPECT) (Fig. 7). Myocardial uptake of ²⁰¹Tl was preserved, but that of ¹²³I-BMIPP significantly decreased in the anteroseptal and inferior walls of the LV. The distribution of ²⁰¹Tl in the SPECT showed blood flow in the LV walls and that of ¹²³I-BMIPP showed fatty acid metabolism in the myocardium. Therefore, her myocardial metabolism seemed impaired. She also underwent ⁶⁷Ga scintigraphy on the 35th hospital day, and no accumulation was observed in the myocardium.

Intravenous dobutamine was continued until day 35 after hospital admission (i.e., 12 weeks after the last dose of epirubicin), when the serum TnT test became negative. Cardiac function gradually recovered, and the patient was discharged on day 73 after hospital admission, with a LVEF of 43%. She had taken enalapril 2.5 mg, furosemide 80 mg, spironolactone 50 mg, warfarin 1.5 mg, digoxin 1.25 mg, pimobendan 5.0 mg, and amiodarone 50 mg daily. One year later, the patient had resumed her full range of social and familial activities. She had no recurrence of breast cancer. Electrocardiogram findings were almost normalized and similar to those recorded before chemotherapy (Fig. 2A, C). She had taken enalapril 5.0 mg, warfarin 2.5 mg, pimobendan 2.5 mg, and bisoprolol 2.5 mg daily, and her LVEF had recovered to 52%. A repeat endomyocardial biopsy was not performed.

**Discussion**

Long-term administration of anthracycline-like agents such as doxorubicin and epirubicin is known to cause life-threatening heart failure owing to drug-associated myocardial damage—a phenomenon called anthracycline-associated cardiotoxicity (ACT). Acute ACT occurs during treatment,
Electron micrographic images after endomyocardial biopsy. (A) Myofibrillar disruption and loss, different sized clusters of mitochondria, and distorted Z-bands were observed (arrows). (B) Vacuolar changes, myofibrillar loss, and peripheral Z-band remnants in an apparently intact myocyte in the lower left side of the image were observed (arrows). (C) Some of the mitochondria appeared swollen with loss of compact cristae. (D) Dilatation of transverse tubules was observed (arrows).

Figure 7. Dual SPECT with $^{201}\text{Tl}$ and $^{123}\text{I-BMIPP}$ on the 25th hospital day. Although a slight decrease in $^{201}\text{Tl}$ accumulation was observed in the anterior and inferior wall of the LV, $^{201}\text{Tl}$ distribution was preserved in the LV myocardium (upper image). Distribution of $^{123}\text{I-BMIPP}$ significantly decreased in the anteroseptal and inferior walls (lower image). Arrow-shaped accumulation at 8 o’clock in the lower image was an artifact created by the central venous catheter through which $^{123}\text{I-BMIPP}$ was injected.

often immediately after the first dose, and manifests itself predominantly in the form of arrhythmias and rarely in the form of pericarditis, myocarditis, or acute LV failure (1). Chronic ACT, which is typically manifested as clinical heart failure or subclinical LV dysfunction, presents early, within one year after termination of chemotherapy, or late, years or even decades after termination of chemotherapy (2). The incidence of ACT depends on the cumulative dose of the drug (2).

Epirubicin is less cardiotoxic than doxorubicin on a milligram per milligram basis; it is considered the preferred anthracycline for solid-tumor chemotherapy (3). In patients with metastatic breast cancer, however, an increased cumulative dosage of epirubicin can cause cardiotoxicity. Ryberg et al. reported that the risk of developing congestive heart failure increased during the first 6 months after discontinuation of epirubicin treatment and reached a near plateau by the end of the 2.5-year follow-up period (4). The risk for a 40-year-old woman was 5% if the patient was treated with 800 mg/m$^2$ epirubicin. Previous anti-hormonal treatment was one risk factor for cardiotoxicity that exacerbates the condition. We suspected, therefore, that epirubicin might have caused life-threatening heart failure due to ACT in the present patient.

Biopsy-proven ACT due to epirubicin has been reported rarely. Torti et al. used endomyocardial biopsy to examine
29 patients at high risk of ACT and reported that epirubicin caused less myocardial injury than doxorubicin, when compared at the same doses (5). At a dose of 450 mg/m² or greater, moderate to severe ACT was observed in 65% of patients who received doxorubicin compared to 15% of patients who received epirubicin. The authors estimated that approximately 180 mg/m² more epirubicin than doxorubicin could be administered before a similar degree of cardiac injury would occur. In the present patient, the histopathological findings were consistent with ACT, as described (5, 6). A significant accumulation of epirubicin might cause myocardial injury and ongoing toxic reaction even 2 months after the termination of chemotherapy.

Desmin is an intermediate filament abundantly expressed in cardiac muscle. Desmin filaments surround the Z discs connecting the entire contractile apparatus to cytoskeletal network, nucleus and cytoplasmic organelles (7). These networks provide maintenance of cellular integrity, force transmission, and mechenochemical signaling. Because desmin disappears fast in damaged myocytes, desmin stain is a valuable tool to detect early myocardial ischemia/infarction (8). In the present case, a substantial number of myocytes was not stained properly with antibodies against desmin (Fig. 5C). We suspected that there was diffuse degeneration of myocytes and that myocyte dysfunction caused the heart failure.

Mononuclear infiltrates, which were infrequently observed in the myocardium and thus were not indicative of a diagnosis of myocarditis, were characterized by immunohistochemistry. Those cells were stained not by CD15 antibody but by CD45RO antibody (Fig. 5D). As granulocytes are stained by CD15 antibody and T lymphocytes are stained by CD45RO, those infiltrates were identified as T lymphocytes. Eosinophils, which are often observed in drug-induced myocarditis, were not observed in the present case. Accordingly, we concluded that myocytes were injured not by drug allergy but by drug toxicity.

Myocyte damage has been attributed to the production of toxic oxygen free radicals and an increase in oxidative stress, which causes lipid peroxidation of membranes, leading to vacuolation and irreversible damage (1, 9). Wojnowski et al. reported that NAD(P)H oxidase and multidrug-resistant protein gene polymorphisms are associated with ACT, and those genetic variants might underlie variations in individual sensitivity to ACT (1). Myocarditis was observed in both acute and chronic ACT cases (9, 10). Gaudin et al. reported 4 cases of biopsy-proven myocarditis in 11 patients who had been treated with doxorubicin at a dose of approximately 500 mg/m² (11). Although myocarditis usually is not associated with ACT, and the role of inflammatory infiltrates in ACT is controversial, the authors noted that some patients had a course more typical of patients with myocarditis than patients with ACT alone.

For the present patient, the clinical manifestations of epirubicin-associated cardiotoxicity, including reversal of systolic dysfunction, clot formation in the LV cavity, frequent ventricular arrhythmia, sustained elevation of serum TnT for several weeks, and myocardial injury associated with mononuclear cells, were similar to those observed for myocarditis. However, mononuclear cells were comparatively few, even though the ultrastructural damage was significant. Although her heart failure was extremely severe and sustained for three months, this patient fully recovered one year later. We believe that the supportive care was important until the patient recovered from acute intoxication.

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

References