Reversible Cardiomyopathy After Epirubicin Administration

Norimichi Koitabashi, MD, Yoshiaki Ohyama, MD, Rieko Tateno, MD, Masashi Arai, MD, Nana Rokutanda, MD, Jun Horiguchi, MD, and Masahiko Kurabayashi, MD

Summary

Anthracycline-containing chemotherapy can cause irreversible and progressive left ventricular dysfunction. Epirubicin, which is widely used for breast cancer chemotherapy, is an anthracycline that has less cardiac toxicity than doxorubicin. The present report describes the case of a 70-year-old woman with breast cancer who developed severe congestive heart failure and severe cardiac dysfunction at 6 weeks from epirubicin final administration. Left ventricular function gradually improved after intensive treatment for heart failure and recovered completely within 2 months. To the best of our knowledge, this is the first report to describe epirubicin-induced subacute reversible cardiotoxicity. (Int Heart J 2015; 56: 466-468)

Key words: Anthracycline cardiac injury, Breast cancer

Anthracycline chemotherapies are effective against a wide spectrum of malignancies, including lymphoma, gastric cancer, small cell lung cancer, sarcomas, and breast cancer. Commonly used anthracyclines include doxorubicin, daunorubicin, and epirubicin. Unfortunately, these agents also have the most well-recognized cardiotoxic profile among all cancer treatments, which often limits their utility. Cardiomyopathy induced by anthracyclines is characterized by a dose-dependent, symptomatic, or asymptomatic progressive reduction in ventricular systolic function, which often results in congestive heart failure. The cardiomyopathy can be acute, subacute, or late. Acute toxicities during or immediately after drug administration are generally rare. Subacute cardiomyopathy typically occurs up to 8 months after the final dose, with peak onset of symptoms at 3 months. Late cardiomyopathy presents 5 or more years after therapy with an anthracycline. The latter two presentations are usually irreversible and progressive. Early retrospective studies showed that subacute and late cardiomyopathy were associated with poor outcomes and a mortality rate greater than 40%. Even though recent progress in the treatment of congestive heart failure has resulted in improved outcomes in affected individuals, the cardiotoxicity of anthracyclines still limits its overall utility in the treatment of cancer.

Epirubicin (4’-epidoxorubicin) was developed in an effort to identify an anthracycline with less cardiotoxicity. The cumulative dose of chemotherapy at which cardiotoxicity occurs is higher for epirubicin (900 to 1000 mg/m²) than for doxorubicin (450 to 500 mg/m²). Several studies have shown that epirubicin produces anti-tumor responses similar to doxorubicin, but is associated with a lower cardiotoxicity rate in women with breast cancer. Epirubicin-based adjuvant chemotherapy (fluorouracil 500 mg/m², cyclophosphamide 500 mg/m², and epirubicin 100 mg/m² [FEC100]) is the most effective and standard epirubicin-based regimen for women with node-positive breast cancer.

The present report describes a rare case of a female patient with breast cancer who developed severe cardiomyopathy and congestive heart failure after FEC100 followed by paclitaxel, but subsequently experienced complete cardiac recovery.

Case Report

A 70-year-old woman with right breast cancer (T3N1M0, stage IIIA) was scheduled to undergo adjuvant therapy in November 2010. Histological assessments indicated that the tumor was positive for estrogen receptor and negative for both progesterone receptor and HER-2. Four cycles of FEC100 (cumulative epirubicin dose, 400 mg/m²) followed by 12 courses of paclitaxel were scheduled before mastectomy. She had no previous history of cardiac disease or related symptoms. Her electrocardiogram (ECG) and echocardiogram were both normal before chemotherapy. FEC100 was administered every 3 weeks without any adverse events; however, it was discontinued after the third course of paclitaxel because the patient developed severe diarrhea and appetite loss. The diarrhea and appetite loss continued, even after the termination of chemotherapy. In April 2011, the patient was hospitalized with fever, appetite loss, and diarrhea. Marked hypoproteinemia was observed on blood testing; therefore, hydration and albumin infusion were given. Three days after admission, she suffered progressive dyspnea, and chest x-rays revealed massive pulmonary congestion and pleural effusion (Figure 1A). At
that time, her pulse was 130/min, blood pressure was 94/54 mmHg, and body temperature was 38°C. Auscultation showed coarse crackles and no murmur. Bilateral lower leg edema was present. Electrocardiography revealed sinus tachycardia with low voltage and diffuse T-wave abnormalities in the limb leads and poor R-wave progression in the precordial leads (Figure 1B). Echocardiography revealed diffuse severe hypokinesis in the left ventricular (LV) wall (Figure 1C). The estimated ejection fraction was 24%. The serum B-type natriuretic peptide and troponin I levels were 1825.5 pg/mL and 0.29 ng/mL, respectively. C-reactive protein level was 15.27 mg/dL, which indicated infective or inflammatory disease. Later, Clostridium difficile stool testing was positive, and she was thus diagnosed with presumed pseudomembranous enterocolitis.

Even though treatments for heart failure were given with diuretics, dobutamine, and carperitide (atrial natriuretic peptide), respiratory failure worsened, and artificial ventilation with intratracheal intubation was required on day 6. After intensive treatments with high dose catecholamines (ie, norepinephrine, dopamine, dobutamine), type III phosphodiesterase inhibitor, and carperitide for 4 days, pulmonary congestion gradually decreased. Interestingly, serial echocardiograms showed that the LV wall motion gradually improved as well. Artificial ventilation was terminated on day 11. Thereafter, her respiratory condition was maintained in response to oral furosemide and spironolactone therapy (Figure 1D). LV wall motion continued to improve, normalizing by day 21.

Coronary angiography on day 24 showed no significant stenosis. Subsequently, we performed acetylcholine stress testing, because coronary vasospasm may trigger transient cardiomyopathy. However, coronary spasm occurred in the left coronary artery only with high-dose acetylcholine (100 μg), and there were no relevant symptoms or ischemic ECG changes. These findings were interpreted as negative for vasospastic angina. Myocardial biopsy of the left ventricle showed mild infiltration of mononuclear cells (Figure 2A). No obvious myofibrillar loss, vacuolization, or interstitial myocardial edema was observed. On day 32, contrast-enhanced cardiac magnetic resonance (CMR) showed late gadolinium enhancement (LGE) in a small area at the posterolateral wall (Figure 2B). Two months later, she was asymptomatic, and both her ECG and her echocardiogram were nearly normal (Figure 2C, D); therefore, she underwent mastectomy. The surgery was successfully performed without any adverse events.

**DISCUSSION**

The clinical differential diagnosis for “reversible” cardiomyopathy is as follows: 1) stunned myocardium induced by ischemic heart disease (IHD); 2) stress-induced cardiomyopathy (Takotsubo cardiomyopathy); and 3) acute myocarditis. In the current case, neither symptoms nor angiographic findings suggestive for IHD were observed, even though the troponin I level was high.
level was elevated. IHD-related reversible cardiomyopathy, such as myocardial stunning, was still unlikely to be present in this case, since the troponin I level has been shown as an acute cardiac injury marker in anthraccline cardiomyopathy.\textsuperscript{79} Regarding stress-induced cardiomyopathy,\textsuperscript{78} a typical ventricular wall motion abnormality for Takotsubo cardiomyopathy (apical ballooning with basal hyperkinesis) was not observed. Of note in this case, myocardial biopsy showed mild mononuclear cell infiltration without obvious degeneration of cardiomyocytes. Typical pathological changes in anthraccline cardiomyopathy include myofibrillar loss and vacuolization,\textsuperscript{75} but these were also not observed. CMR imaging has recently been used as a diagnostic tool for myocarditis.\textsuperscript{79} Since the patient was hemodynamically unstable, we could not perform CMR at acute phase of heart failure. CMR at recovery phase showed small LGE in the posterolateral wall but no obvious myocardial edema in T2-weighted imaging. Because of lack of biopsy and CMR in acute phase, we could not rule out the possibility of acute myocarditis in this case. However, if acute myocarditis would be the cause of severe cardiac dysfunction, we believe that biopsy and CMR should show more pathological changes such as inflammatory cell infiltration, fibrosis, and myocardial edema even in biopsy samples of subacute phase. Psaltis, \textit{et al.} reported that doxorubicin induces myocardial inflammatory infiltrates as well as fibrosis and cardiomyocyte degeneration in the area of LGE in an experimental sheep model.\textsuperscript{100} Taken together, it was difficult to distinguish this case between subacute anthraccline-induced cardiotoxicity and acute myocarditis from pathological and CMR data. Because this case did not clinically experience any symptoms suggestive of myocarditis or preceding viral infection, we concluded that epirubicin could be a primary cause of the cardiomyopathy.

Previous reports suggest that anthraccline cardiomyopathy might be reversible in some cases.\textsuperscript{11,12} However, the duration for functional recovery took 4 to 12 months in previous reports.\textsuperscript{11,12} In contrast, our case showed a complete recovery within 2 months after heart failure. Hengel, \textit{et al.} described a patient with subacute (17 days after chemotherapy) anthraccline cardiotoxicity who showed transient cardiac hypertrophy, diastolic dysfunction, and biopsy-proven interstitial myocardial edema.\textsuperscript{75} Increased production of pro-inflammatory cytokines might contribute to the development of myocardial edema.\textsuperscript{75} We suggest that myocardial edema might contribute to the quick recovery in our case as well, if the marked hypoproteinemia could worsen tissue edema by lowered colloid osmotic pressure. However, myocardial biopsy and CMR could not support this idea since they were demonstrated after improvement of hypoproteinemia.

Congestive heart failure was revealed after paclitaxel treatment in this case. Although paclitaxel has been shown to be safe for patients with cardiomyopathy, its combination with anthracclines is associated with an increase of anthraccline cardiotoxicity.\textsuperscript{14} In addition, cyclophosphamide has also been reported to have an additive effect for anthraccline-induced cardiomyopathy although cyclophosphamide itself was not associated with cardiotoxicity and myocarditis at the dose of FEC100 protocol.\textsuperscript{14} Therefore, it is possible that paclitaxel or cyclophosphamide administration(s) might be related to the additive toxicity of epirubicin.

In summary, subacute cardiotoxicity can rarely occur in the context of epirubicin-based chemotherapy. Aggressive supportive therapy is important to reverse this phenomenon in affected individuals.

\textbf{References}