Mitral regurgitation after anthracycline-based chemotherapy in an adult patient with breast cancer
A case report
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Abstract
Rationale: Anthracyclines cardiotoxicity characterized by dilated myocardopathy has been well described in the literature. However, anthracyclines-induced valvular diseases have been seldom reported.

Patient concerns: In this study, we present the case of a 62-year-old Chinese female patient with breast cancer developing severe mitral regurgitation after anthracycline exposure.

Diagnoses: The patient was diagnosed with mitral regurgitation with preserved left ventricular ejection fraction and normal cardiac chamber dimensions in the sixth month after the last course of anthracycline-containing chemotherapy. However, continued decrease in LVEF with normal left ventricular wall thickness, and serial increases in left atrial and ventricular dimensions were observed in the follow-up echocardiography.

Interventions: Treatments with oral itraconazole at a dose of 75 mg/day and local wound care with ciclopirox olamine ointment were administered.

Outcomes: The patient responded well to the treatment with perindopril, metoprolol succinate, spirolactone, and furosemide, and symptoms associated with heart failure were dramatically relieved.

Lessons: The incipient mitral regurgitation may serve as an early sign of myocardial dysfunction that can facilitate a timely recognition of cardiotoxicity, which is crucial to a timely change of chemotherapy regimen and an appropriate initiation of antiremodeling therapy that could limit anthracycline cardiotoxicity and improve overall outcome.

Abbreviations: AR = aortic regurgitation, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, MV = mild mitral valve, TTE = transthoracic echocardiography.

Keywords: anthracycline, cardiotoxicity, chemotherapy, heart failure, mitral regurgitation

1. Introduction
Chemotherapy has been a mainstay for treating malignant tumor and can bring a significant survival benefit in various types of cancers. However, a growing population of cancer survivors is recognized to have an increased incidence of cardiovascular disease that is associated with a high degree of morbidity and mortality. Therefore, improving the prevention, recognition, and treatment of cardiovascular disease is an important priority to the overall health of this population. Anthracyclines cardiotoxicity characterized by dilated myocardopathy has been well established in the literature. However, anthracyclines-induced valvular diseases have been seldom reported. Only few long-term follow-up studies in childhood cancer survivors have observed that chemotherapy, particularly with anthracyclines, seemed to increase the risk of valvular heart disease. We present a rare case of an adult patient who developed severe MR with initially preserved left ventricular ejection fraction (LVEF) followed by a progressive decline of LVEF after anthracycline exposure.

2. Methods
An approval from the ethics committee of the Peking Union Medical College Hospital was obtained for this case report study. The detailed information regarding this study has been fully disclosed to the patient and informed consent has been obtained.

3. Case report
A 62-year-old Chinese female was admitted to Peking Union Medical College Hospital because of recurrent shortness of breath and leg edema for 1 year. She had a history of hyperlipidemia for 1 year, which was treated with pravastatin.
She had been diagnosed with hormone receptor-positive breast carcinoma in 2 years prior and received a right radical modified mastectomy. After surgery, the patient underwent 6 cycles of adjuvant chemotherapy with doxorubicin, cyclophosphamide, and docetaxel, followed by adjuvant anastrozole. During the following 6 months after the last course of chemotherapy, the patient developed a feeling of fatigue, leg edema, orthopnea, and exertional dyspnea consistent with New York Heart Association class III congestive heart failure. The prechemotherapy baseline transthoracic echocardiography (TTE) revealed nothing abnormal but a mild aortic regurgitation (AR), and TTE after the onset of symptoms revealed severe mitral regurgitation (MR), mild mitral valve (MV) thickening, mild LV segmental hypokinesia, and normal LVEF and chamber diameters. However, follow-up TTEs revealed continued decrease in LVEF with normal LV wall thickness, and serial increases in left atrial and ventricular dimensions (Table 1). After admission, repeat TTE showed mild AR, severe MR, left atrial and ventricular dilation, and generalized ventricular hypokinesia with a LVEF of 35% (Figs. 1–3). Cardiac magnetic resonance imaging revealed severe MR, left atrial and ventricular enlargement, and LV contractile dysfunction. Results of blood routine and serum tests for liver, kidney, and thyroid function, anti-nuclear antibodies, extractable nuclear antigens antibodies, immunoelectrolytes, and immuno fixation electrophoresis were within normal range. Physical examination revealed a holosystolic murmur. The patient was started on 2 mg of perindopril once daily, 71.25 mg of metoprolol succinate once daily, 20 mg of spironolactone once daily, and 20 mg of furosemide once daily, and placed on a sodium-restricted diet. The patient responded well to the treatment and heart failure symptoms were significantly relieved.

4. Discussion

Anthracyclines have been shown to be associated with dose-dependent cardiotoxicity, characterized by dilated cardiomyopathy and progressive myocardial dysfunction.[1] In contrast with the often-reported impairment of myocardial contractile function, this single case study describes an incipient MR with initially preserved LVEF and a normal ventricular chamber dimensions in a patient with breast cancer after anthracycline exposure. The patient later developed progressive LV chamber dilation and reduced systolic function, which responded well to treatment with perindopril, metoprolol, and spironolactone.

Only few studies have reported an increased risk of developing valvular dysfunction following treatment with anthracyclines independent of radiation therapy.[2–6] However, the underlying mechanisms remain poorly understood. The most likely cause is that anthracycline-induced regional myocardial dysfunction may be demonstrated as subclinical abnormalities in regional myocardial contractile function, despite normal LVEF.[7] In our case, the anthracycline-associated insult to the papillary muscle, like ischemic myocardial injury, may cause papillary dysfunction that impairs lateral shortening between the papillary muscles that tethers the leaflet edges, leading to incomplete leaflet

|     | LAD, mm | LVEDD, mm | LVPWD, mm | LVEF | MR     |
|-----|---------|-----------|-----------|------|--------|
| June 2015 | 36      | 42        | 9         | 60%  | None   |
| April 2016 | 41      | 52        | 10        | 58%  | Severe |
| May 2016  | 45      | 52        | 9         | 57%  | Severe |
| June 2016 | 51      | 48        | 10        | 48%  | Severe |
| May 2017  | 51      | 55        | 10        | 51%  | Severe |

LAD = left atrium diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVPWD = left ventricular posterior wall thickness, MR = mitral regurgitation, MV = mitral valve.
closure and significant MR, even in the absence of LV and mitral annular dilatation.\(^\text{19}\) Although previous reports suggested that valve regurgitation may be secondary to chemotherapy-related ventricle systolic function impairment and left ventricular remodeling,\(^\text{11,12}\) our findings of inconsistence between MR and ventricular remodeling argued against that explanation. Similarly, Allen et al.\(^\text{\ Ref 12}\) showed that MR occurs more often in children after anthracycline exposure compared to normal controls, and may herald the later development of overt anthracycline cardiomyopathy.

Another explanation for the incipient MR is that the valvular aging process may be accelerated by anthracycline toxicity. MR is seen in a considerable proportion of the general population and is thought to be related to aging.\(^\text{9,10}\) Klaus et al.\(^\text{4}\) found that age > 50 years at primary treatment was an independent risk factor for valvular dysfunction in lymphoma patients. In our case, MV thickening was observed in the TTEs after the onset of symptoms, which suggested that degenerative changes in the mitral valves played a role in the development of MR.

Mechanisms underlying anthracycline-induced myocardial damage are still less established. Proposed mechanisms include generation of toxic oxygen-free radicals, induction of apoptosis, inhibition of protein synthesis, and DNA damage through interaction with topoisomerase II.\(^\text{11}\) As exact mechanisms remain unclear, no specific agents that prevent the anthracycline-induced cardiotoxicity have been developed yet. However, early detection and prompt treatment, as suggested by Daniela et al.\(^\text{12}\) is of great importance in the preservation and restoration of cardiac function, especially in patients with the onset of LVEF reduction occurring within first 12 months after chemotherapy. Heart failure symptoms were significantly relieved in our patient by the therapy with furosemide, beta blocker, angiotensin-converting enzyme inhibitor, and aldosterone antagonist, and the good initial response to medical treatment delayed an aggressive upfront surgical correction of MR, which, as far as we are concerned, will cause a rapid increase in LV afterload and in turn, may precipitate cardiomyopathy with reduced LVEF.

The incipient MR may serve as an early sign of myocardial dysfunction, which may be insidiously latent and not develop for several months, years or even decades after the last course of chemotherapy. By the time symptomatic ventricular dysfunction occurred, the myocardial injury is hardly reversible and often progresses even after cessation of chemotherapy. Thus, close attention should be paid to a new-onset MR, and increased efforts are needed for the early detection of cardiotoxicity, which is crucial to a timely change of chemotherapy regimen and an appropriate initiation of anti-remodeling therapy that could limit anthracycline cardiotoxicity and improve overall outcome.

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