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Case Report

Considerations in cardio-oncology: Multiple mobile left-sided cardiac thrombi in chemotherapy-induced cardiomyopathy

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ABSTRACT

With advances in cancer chemotherapy, the importance of the new clinical discipline of cardio-oncology, which is concerned with the cardiac effects of chemotherapy, is increasing. Herein we describe the case of a 48-year-old woman with a history of breast cancer who presented with symptoms of heart failure due to chemotherapy-induced cardiomyopathy. Treatment for the patient's breast cancer had included surgery and chemotherapy with anthracyclines and trastuzumab. Echocardiography revealed multiple mobile thrombi in the left ventricle and atrium. In addition, brain magnetic resonance imaging revealed small acute cerebral infarctions due to embolization. Given the high risk of re-embolization, surgical thrombectomy was performed. Thus far, there are no standardized therapeutic guidelines for left-sided cardiac thrombi and the optimal treatment remains contentious. Although this patient was managed successfully with surgical thrombectomy, patients should be managed individually, taking into consideration embolization, bleeding, and surgical risks. With further improvements in cancer chemotherapy, there may be an increase in the incidence of complications such as multiple cardiac thrombi. From the cardio-oncology standpoint, we propose close interactions between cardiologists and oncologists for the optimal care of cancer patients.

1. Introduction

Considerable advances have been made in cancer chemotherapy in recent decades. However, chemotherapy can cause a variety of cardiovascular abnormalities, including heart failure (HF) due to left ventricular (LV) dysfunction or cardiomyopathy, which are the frequent and serious adverse effects [1]. Increased awareness of the cardiovascular complications of chemotherapy has led to the emergence of the clinical discipline of "cardio-oncology", which is the field of integrative medicine between cardiologists and oncologists and involves the early assessment and management of any cancer therapy-related cardiovascular abnormalities [2–4]. In the past, chemotherapy-induced cardiomyopathy was often associated with the use of anthracyclines; however, this complication has also been reported with the newly developed anticancer drug trastuzumab [1,5]. Here, we report on a patient who developed severe LV dysfunction following chemotherapy with anthracyclines and trastuzumab for breast cancer. In this case, multiple mobile cardiac thrombi were seen in the left ventricle and left atrium, and small acute cerebral infarctions developed due to embolization. In the absence of evidence-based guidelines for the treatment of left-sided cardiac thrombi, the best therapeutic strategy is still under debate. Individualized management of patients must take into account embolization, bleeding, and surgical risks. The patient in the present report was successfully managed by surgical thrombectomy after she had been assessed as being at high risk of systemic embolism. The incidence of complications such as multiple cardiac thrombi may increase with further improvements in cancer chemotherapy. Herein we also discuss the current controversies regarding the reversibility of trastuzumab-associated cardiotoxicity and the therapeutic options for left-sided cardiac thrombi.

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2. Case report

The patient was a 48-year-old woman who had undergone breast-conserving surgery for human epidermal growth factor receptor 2 (HER2)-positive cancer in her right breast 4 years previously. The histopathological diagnosis of the breast cancer was invasive ductal carcinoma. The patient subsequently received adjuvant chemotherapy with four cycles of docetaxel 93 mg in combination with cyclophosphamide 920 mg, and 17 cycles of trastuzumab 324 mg in addition to oral tegafur/uracil (tegafur 300 mg/day). Nevertheless, local recurrence was identified in the patient's right breast and she underwent a mastectomy 2 years previously. After the mastectomy, the patient received six cycles of epirubicin 150 mg in combination with fluorouracil 750 mg and cyclophosphamide 750 mg. Then, she received 14 cycles of trastuzumab 300 mg. The patient developed dyspnea and leg edema and was admitted to Kyorin University Hospital with worsening symptoms of HF.

On admission, the patient's blood pressure and pulse rate were 98/84 mmHg and 111 bpm, respectively. Auscultation revealed a moist rale at the base of the left lung, and pretibial pitting edema was observed. Laboratory values were as follows: hemoglobin 16.3 g/dL; hematocrit 49.7%; total protein 5.1 g/dL; serum albumin 2.8 g/dL; blood urea nitrogen 19.2 mg/dL; serum creatinine 0.74 mg/dL; aspartate aminotransferase 81 IU/L; alanine aminotransferase 68 IU/L; lactate dehydrogenase 517 IU/L; activated partial thromboplastin time 27.9 s; prothrombin time–international normalized ratio 1.05; D-dimer 7.21 μg/mL; fibrin degradation product 15.2 μg/mL; and plasma B-type natriuretic peptide 1441 pg/mL. Levels of protein C, protein S, antithrombin III, and lupus anticoagulant were within the normal range. Chest X-ray showed mild cardiomegaly with pulmonary congestion and pleural effusion (Fig. 1A). The electrocardiogram showed sinus tachycardia with a heart rate of 110 bpm and non-specific ST–T changes. Echocardiography revealed a dilated left ventricle [LV end-diastolic diameter (LVDd) 58 mm, LV end-systolic diameter (LVDs) 52 mm] with diffuse hypokinesis, an LV ejection fraction (LVEF) of 23%, and multiple mobile thrombi in the left ventricle and atrium (Fig. 2A and B; Supplementary Video 1). Moderate mitral and tricuspid regurgitation was observed, with the peak pressure gradient of tricuspid regurgitation at 31 mmHg. The inferior vena cava, with a diameter of 23 mm, showed decreased respiratory variation. Cardiac computed tomography (CT) confirmed multiple left-sided cardiac thrombi (Fig. 2C). Coronary CT angiography showed no significant coronary stenosis (Fig. 1B). Cardiac magnetic resonance imaging (MRI) revealed no late gadolinium enhancement. Importantly, brain MRI showed two small acute cerebral infarctions due to embolization (Fig. 3).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jiac.2017.02.003.

On the basis of these results, chemotherapy-induced cardiomyopathy was strongly suspected, suggesting that the acute cerebral infarctions were caused by embolism of the cardiac thrombi. The possibility of comorbid hypercoagulable state due to nonbacterial thrombotic endocarditis (NBTE) was also considered. Given the high risk of re-embolization, surgical thrombectomy was performed. Postoperative histological examination confirmed the diagnosis of the thrombi (Fig. 2D and E).

The patient discontinued trastuzumab therapy and received standard optimal medications for HF, including an angiotensin-converting enzyme inhibitor, beta-blocker, spironolactone, and diuretics. The patient was discharged in a clinically stable condition. At the 6-month follow-up, echocardiography revealed that the patient's LVEF had improved to 40% (LVDd 55 mm, LVDs 42 mm; Supplementary Video 2). The patient's breast cancer is currently in remission.

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3. Discussion

Cardiovascular diseases and cancer have been the major causes of death [6]. Cardio-oncology is a new field that is concerned with the management of cardiovascular complications of cancer treatment to optimize the care of cancer patients. In this context, the newly developed anticancer drug trastuzumab is of note. Currently, anthracyclines and trastuzumab are among the most frequently used chemotherapy drugs for the treatment of breast cancer [1]. According to the operational classification system proposed by Ewer and Lippman [7], anthracycline-associated cardiotoxicity is regarded as irreversible even after drug withdrawal. Conversely, trastuzumab-associated cardiotoxicity is considered to be reversible following the cessation of treatment [7]. However, the concept that trastuzumab-associated cardiotoxicity is reversible remains contentious. Based on follow-up data of large clinical trials, Telli et al. [8] reported that many patients exhibited persistent LV dysfunction after withdrawal of trastuzumab, calling into question the concept of the reversibility of trastuzumab-associated cardiotoxicity. Recent experimental studies also raised questions regarding this concept. For example, ElZarrad et al. [9] reported that trastuzumab-induced cardiac dysfunction was associated with enhanced myocardial apoptosis and ultrastructural changes to cardiomyocytes in a mouse model, whereas Barth et al. [10] reported that trastuzumab impaired the function of human resident cardiac stem cells. The pathophysiological mechanisms underlying the cardiotoxicity associated with trastuzumab remain ill defined and further investigations are needed to determine the reversibility

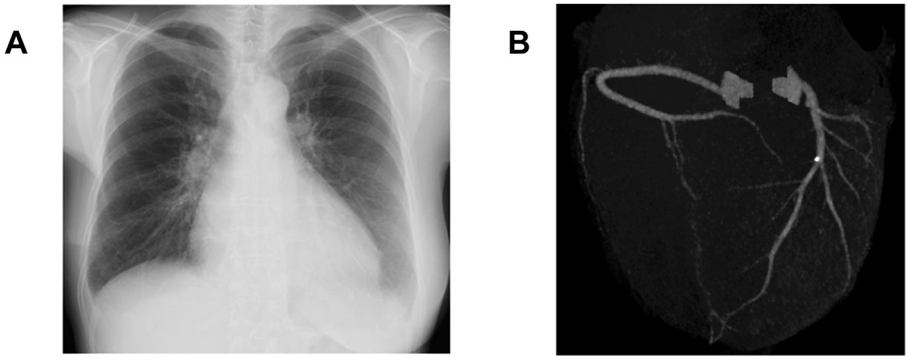

Fig. 1. Chest X-ray and coronary computed tomography (CT) angiography on admission. (A) Chest X-ray showed mild cardiomegaly with pulmonary congestion and pleural effusion. (B) Coronary CT angiography showed no significant coronary stenosis.