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Case Report

A Case of Asymptomatic Left Ventricular Dysfunction during the Treatment of Metastatic Breast Cancer with Trastuzumab

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We report a case of 29-year-old Japanese female with a history of resection of primary carcinoma of the right breast. After a partial response by chemotherapy with pirarubicin and docetaxel for lung metastasis, the patient developed multiple brain and bone metastases. As the degree of overexpression of human epidermal growth factor receptor-2 (HER2) was (2+), trastuzumab was administered in combination with paclitaxel. Asymptomatic left ventricular (LV) systolic dysfunction evaluated by echocardiography was observed ten weeks after the beginning of the treatment. After two weeks of discontinuation of the therapy, however, LV function showed rapid recovery and the resumed use of trastuzumab did not cause further cardiac deterioration. The patient died of sudden respiratory failure due to cerebral herniation and not to heart failure.

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Introduction

Trastuzumab (Herceptin) is a humanized anti-human epidermal growth factor-2 (HER2) monoclonal antibody which was approved by the United States Food and Drug Administration (FDA) in September 1998, and more than 25,000 patients have been treated. This therapy has proved effective and well tolerated in patients with HER2-positive metastatic breast cancer.[1] Retrospective analysis revealed that infusion-related reactions and cardiotoxicity emerged as the two main safety concerns with the use of trastuzumab. The incidence of serious adverse effects attributable to trastuzumab was low, however, the occurence of cardiac toxicity was high especially in patients previously or concomitantly treated with anthracyclines.[2] Clinical use of trastzumab has become available since June 2001 in Japan. We herein describe a Japanese patient with progressive metastatic breast cancer who showed a mild systolic dysfunction evaluated by echocardiogram during the administration of trastuzumab.

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Case Report

A 29-year-old female was introduced to our outpatient clinic for evaluating the basic cardiac function before the use of trastuzumab.

The patient visited our hospital because of right breast mass and was diagnosed as a breast cancer (T1aN1M0, Stage I) on December 25, 1998. The results of a quantitative analysis of estrogen receptors and progesterone receptors in the specimen were negative. After resection of primary tumor, the patient underwent radiation therapy (50 Gy), followed by chemotherapy consisting of pirarubicin 20 mg/month for three months because of high chemosensitiveness by MTT assay.

On May 9, 2001, lung metastasis (Fig.1) was detected and the patient was given six courses of chemotherapy consisting of pirarubicin 30 mg/month and docetaxel 80 mg/month. However, multiple brain and bone metastases were detected by brain magnetic resonance image (November 14, 2001) (Fig. 2A,B) and

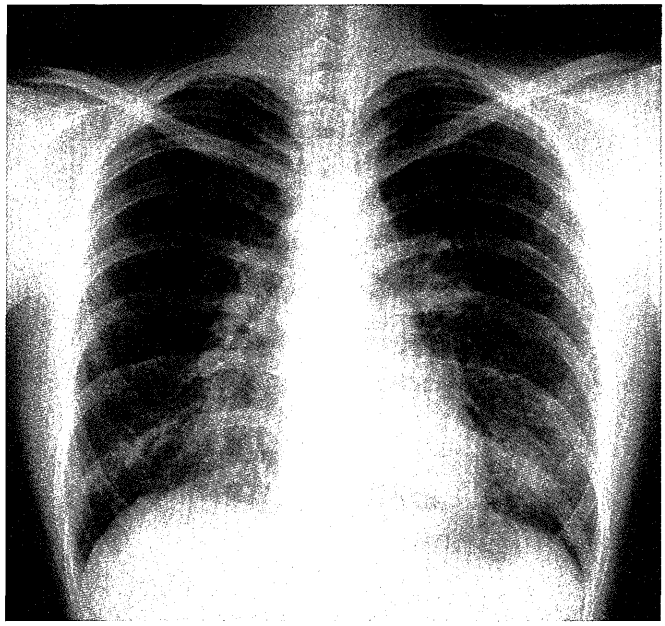

Fig. 1. Chest roentgenogram performed on May 18, 2001 showing infiltrative shadow in bilateral lower lobes, suggesting lung metastases.

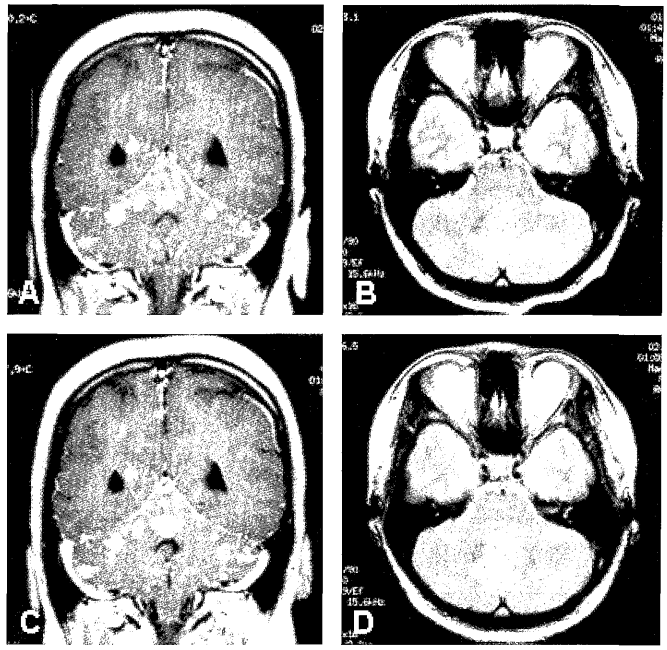

Fig. 2. Brain magnetic resonance images of enhanced coronal T1-weighted images (A, C) and axial T2-weighted images (B, D). Upper panels (A, B) performed on November 14, 2001 showing meningeal dissemination, multiple cerebellar, cerebral, and brainstem metastases. The number and size of brain metastases were not changed (C), however, an edema of cerebellar hemisphere was slightly reduced on January 16, 2002 (D).

bone scintigraphy (October 31, 2001) (Fig. 3A) respectively. Radiation therapy could not be continued because of the increase of brain edema. Immunohistochemical staining for the HER2 was moderately positive on the surface of primary tumor cells (referred to as a score of 2+), therefore trastuzumab 2 mg/kg/week was administered in combination with paclitaxel 300 mg/month on November 21, 2001. The patient showed partial response transiently because the uptake of right 11th rib and the edema of

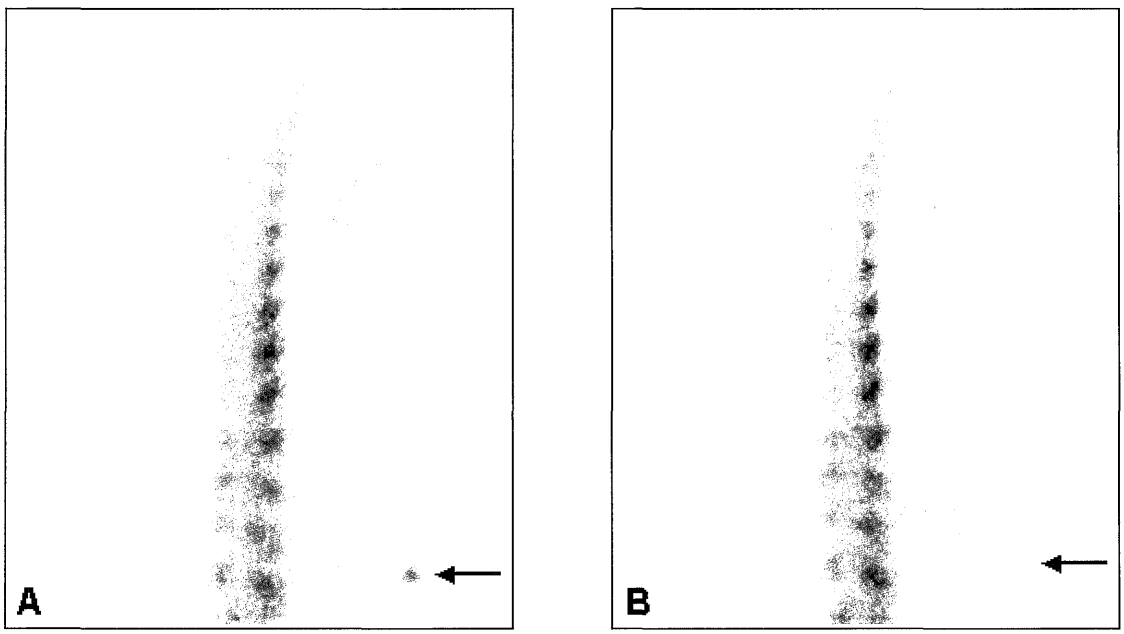

Fig. 3. ^{99m}Tc-HMDP bone scintigraphy performed October 31, 2001 demonstrating an intense uptake at right 7th and 11th ribs, moderate uptake at right sacroiliac joint and left iliac wing, suggesting bone metastases (A). The uptake of right 11th rib was decreased on January 17, 2002 (B).

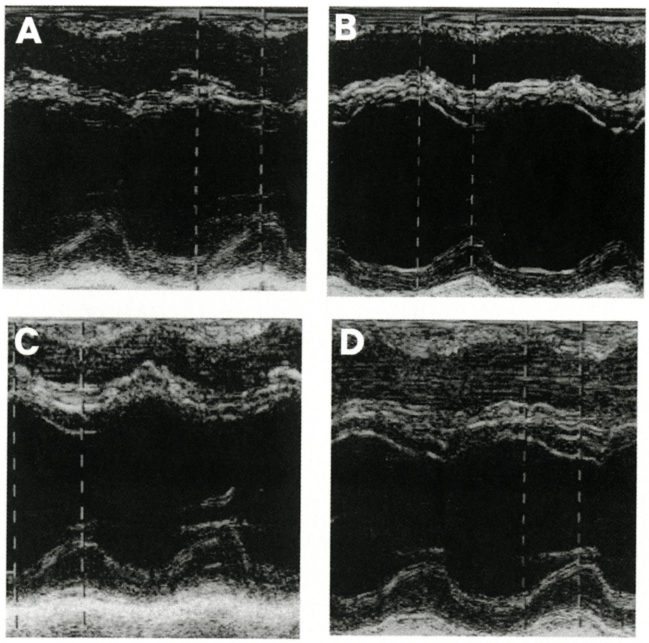

Fig. 4. Transthoracic echocardiogram performed (A) just before the beginning of the administration of trastuzumab (LVDd, 45 mm; LVDs, 27 mm; LVEF, 70%; FS, 40%), (B) 10 weeks after the administration of trastuzumab (LVDd, 49 mm; LVDs, 33 mm; LVEF, 61%; FS, 33%), (C) 2 weeks after discontinuation of the administration of trastuzumab (LVDd, 48 mm; LVDs, 31 mm; LVEF, 65%; FS, 36%), and (D) resumed use of trastuzumab, a week before her death (LVDd, 45 mm; LVDs, 29 mm; LVEF, 65%; FS, 36%). EF: ejection fraction, FS: fractional shortening, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension.

cerebellar hemisphere were reduced (Fig. 2C,D, 3B).

Echocardiogram performed just before the use of trastuzumab showed left ventricular diastolic dimension (LVDd): 45 mm, left ventricular systolic dimension (LVDs): 27 mm, and left ventricular ejection fraction (LVEF): 70%, fractional shortening (FS): 40% (Fig.4A). Ten weeks after the beginning of treatment with trastuzumab and paclitaxel, LV systolic fuction was declined; LVDd: 49 mm, LVDs: 33 mm, LVEF: 61%, FS: 33% (Fig.4B) although the patient had no symptoms of heart failure. Two weeks of discontinuation of the combined chemotherapy, LV function showed partial recovery; LVDd: 48 mm, LVDs: 31 mm, LVEF: 65%, FS: 36% (Fig.4C). Then we resumed combined chemotherapy and her LV function did not show a further deterioration; LVDd: 45 mm, LVDs: 29 mm, LVEF: 65%, FS: 36% (Fig.4D).

On April 10, 2002, twenty weeks after the initial administration of trastuzumab, the patient died of sudden respiratory failure due to cerebral herniation. Autopsy was not performed because permission was not obtained.

Discussion

Trastuzumab (Herceptin), an IgG monoclonal antibodies against the extracellular domain of the HER-2, has proved to increase the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. Trastuzumab demonstrated enhanced anti-tumor activity when used in combination with cisplatin, doxorubicin, and especially paclitaxel in preclinical models.[3] From a phase III clinical trial, paclitaxel response rate was significantly improved in patients with breast cancer when erbB2 was downregulated by trastuzumab.[4] Long-term survival of women with congestive heart failure (6 years, 33%)[5] is superior to that of women with breast cancer and distant metastases (5 years, 22%)[6], yet it is far worse than that of women with breast cancer and regional metastases (5 years, 77%)[6] or women without identifiable metastases (5 years, 97%)[6]. Moreover most women who developed heart failure after trastuzumab administration showed symptomatic improvement with appropriate therapy[7]. At this moment, we have no option but to try trastuzumab for her advanced metastatic breast cancer. Before the use of this therapeutic antibodies, genotyping tumor samples for the expression of HER-2 (based on a 0-3+ scale) is required. Our patient fortunately showed the 2+ level of overexpression of HER-2 in her tumor samples (Fig.5), therefore administration of trastuzumab in combination with paclitaxel was commenced and at least transiently, partial respose was achieved.

Cardiac dysfunction was an unfavorable and serious side effect of trastuzumab. The incidence was greatest

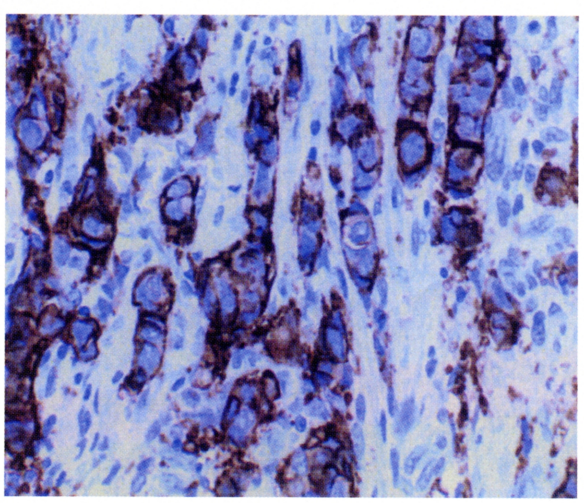

Fig. 5. Immunohistochemical staining for the HER2 gene product was moderately positive (score 2+) on the primary tumor cell membrane (x200). HER2: human epidermal growth factor receptor-2.

in patients receiving trastuzumab and anthracycline plus cyclophosphamide concomitantly (27%). The risk was substantially lower in patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (5%).[2] HER2 overexpression has been associated with the development of breast cancer, however HER2 receptors themselves seem to be cardioprotective because they mediate the activation of cardiac survival pathways and trastuzumab increases susceptibility of myofilaments to doxorubicin.[8] Using ventricular-restricted ErbB2 deficient mice, Crone et al. demonstrated that ErbB2 signaling in cardiomyocytes was essential for the prevention of dilated cardiomyopathy.[9]

The cardiac review and evaluation committee (CREC) was established to obtain independent and unbiased estimates of cardiac dysfunction risk for patients receiving trastuzumab. According to CREC criteria, cardiac LVEF data for low absolute values (<50%) or significant decrease (>20% relative to baseline) was used as cardiac dysfunction. And the CREC also established following criterion to confirm or revise a preliminary diagnosis of cardiac dysfunction as; decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms. Our patient demonstrated mild systolic LV dysfunction (12.9% decrese in LVEF) associated with LV dilatation evaluated by echocardiography after 10 weeks treatment with trastuzumab and paclitaxel. In this case, decline of LVEF and dilatation of LVDd after treatment of trastuzumab were small, which did not satisfy CREC criteria of cardiac dysfunction. And yet it potentially possessed variability problem, although recording of echocardiogram was performed by the same doctor. Biological markers such as brain natriuretic peptide or troponin T might be a sensitive and specific markers of trastuzumab-induced cardiac dysfuction, although the usefulness of them has not been defined.

Unfortunately, we could not continue a long-term follow up because the patient suddenly died of cerebral herniation. Our patient showed a partial improvement of LV systolic function after two weeks discontinuation of trastuzumab administration. Moreover, one week before her death, echocardiography did not demonstrate a further deterioration of LV systolic funcftion, despite the fact that the administration of trastuzumab and paclitaxel was resumed. It was reported that trastuzumab was discontinued because cardiac dysfunction had been observed in 18 out of 235 patients (8%) overall, and most of these patients received an anthracyclines, cyclophosphamide, and trastuzumab.[4] These suggest that trastuzumab plus previous use of anthracycline may be related to LV dysfunction in this case. It is imperative that physicians perform long-term follow-up of the patient who is receiving trastuzumab, especially one who is given anthracyclines previously or simultaneously, by evaluating LV systolic function by echocardiogram noninvasively.

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