

## CASE REPORTS

# Trastuzumab induced diastolic heart failure

Haoyi Zheng<sup>1</sup>, Alex Reyentovich<sup>2</sup>, Mary Lynn Nierodizik<sup>2</sup>, Stuart D Katz<sup>2</sup>

1. Saint Francis Hospital, Roslyn, New York, USA. 2. New York University Langone Medical Center, New York, USA

**Correspondence:** Haoyi Zheng. Address: Cardiac Imaging, The Heart Center, Saint Francis Hospital, 100 Port Washington Blvd, Roslyn, New York, NY 11576, USA. Email: haoyi.zheng@chsli.org

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## Abstract

**Background:** Trastuzumab-induced cardiotoxicity has been well accepted. Cardiotoxicity especially with concomitant or sequential use of anthracycline has been clinically identified as decreased left ventricular ejection fraction with or without symptoms of heart failure. Acute diastolic heart failure has not been reported.

**Case report:** A 62-year-old female patient with HER2<sup>+</sup> positive breast cancer presented to the emergency room with acute heart failure symptoms after trastuzumab use. Chest X-ray and CT demonstrated acute pulmonary edema. Echocardiography showed normal left ventricular ejection fraction, elevated left ventricular filling pressure, and moderate pulmonary hypertension, which are consistent with acute diastolic heart failure. The patient symptoms resolved quickly with diuretic therapy and Trastuzumab was discontinued. A follow-up echocardiography showed normal left and right ventricular function and a follow-up right heart catheterization demonstrated normal cardiac filling pressure and normal cardiac index.

**Conclusions:** Trastuzumab induced cardiac toxicity could occur in a spectrum-from transient diastolic heart failure to systolic heart failure. The monitoring of both diastolic and systolic function during the course of trastuzumab treatment with or without other chemotherapy agents should be considered.

## Keywords

Breast cancer, Trastuzumab, Diastolic heart failure

## 1 Introduction

Trastuzumab (Herceptin), an anti-HER-2 monoclonal antibody, is now part of the standard treatment of HER-2 positive breast cancer. Cardiac toxicity limits its use, with higher risk reported when combined with anthracycline and paclitaxel therapy<sup>[1]</sup>. In the past studies, cardiac toxicity has been clinically identified as decreased left ventricular ejection fraction (LVEF) with or without clinical symptoms of heart failure. We now describe a case of acute heart failure associated a normal LVEF after administration of trastuzumab as a treatment of metastatic breast cancer. To our knowledge, no such case of heart failure with preserved LVEF associated with trastuzumab has been previously reported in the literature.

## 2 Case report

A 62-year-old Caucasian woman with history of metastatic breast cancer (ER positive and HER2 positive) and no modifiable risk factors for heart disease presented with progressive shortness of breath and tachycardia for 5 days. She had

been treated with trastuzumab (3 doses of trastuzumab with initial dose of 8 mg/kg intravenous infusion and subsequent dose of 6 mg/kg every three weeks). The last dose of trastuzumab was administered one week prior to the hospitalization. The patient had not received chemotherapy with anthracyclines or taxanes.

Physical examination revealed a blood pressure 107/55 mmHg, tachycardia, tachypnea, and hypoxia with oxygen saturation 82% on room air. There were signs of biventricular congestive heart failure as evidenced by increased jugular venous pressure, hepatojugular reflux, bilateral pulmonary rales, and bilateral lower extremity edema. Laboratory findings were notable for normal cardiac enzymes and elevated B-type natriuretic peptide (BNP) 278 pg/ml. ECG showed sinus tachycardia with T wave inversion in precordial leads. Chest X-ray showed normal sized cardiac silhouette and bilateral infiltrates consistent with pulmonary edema. A pulmonary CT angiography study ruled out proximal pulmonary embolism, and confirmed bilateral pulmonary edema. Echocardiography revealed normal LVEF of 60%, increased left ventricular wall thickness, left ventricular Doppler filling pattern consistent with an elevated left atrial pressure, moderate pulmonary hypertension, right ventricular dilatation, and elevated right atrial pressure.

The clinical diagnosis of acute heart failure was made and the patient was treated with intravenous furosemide (40 mg). Dyspnea and clinical and radiographic signs of biventricular congestion improved rapidly with diuretic therapy. She was discharged and trastuzumab was discontinued.

A follow-up echocardiogram two months later showed normal LVEF, normal left ventricular wall thickness, mild right ventricular dilatation unchanged from the first echo, normal right atrial pressure. A right heart catheterization performed at the same time demonstrated a normal right ventricular systolic pressure, normal cardiac filling pressures and normal resting cardiac index. A repeat echocardiogram 12 months later showed normal LVEF, normal LV wall thickness, normal RV dimension, and normal RA pressure. There were no recurrent signs or symptoms of heart failure.

### 3 Discussion

Trastuzumab, a monoclonal antibody, selectively binds to the tyrosine kinase receptor ErbB2 and inhibits neuregulin-1 signaling. When used with conventional chemotherapy (anthracycline and cyclophosphamide), trastuzumab therapy significantly improves overall survival of patients with Her2 positive breast cancer <sup>[2-4]</sup>. Since the neuregulin-1 signaling pathway is also present in cardiomyocytes, trastuzumab therapy is associated with a known risk of cardiotoxicity <sup>[5]</sup>. Trastuzumab-induced cardiotoxicity has been extensively reported and studied. The cardiotoxicity has been defined as decreased LVEF with or without symptoms of heart failure. In randomized clinical trials, trastuzumab therapy is associated with an absolute increase in the risk of new heart failure by 1.6% and new decrease in LVEF by 7.2% <sup>[6]</sup>. The incidence of trastuzumab-induced cardiotoxicity in clinical practice appears to be substantially higher than that reported in the trials. Patients who received both trastuzumab and anthracycline had an absolute 23.8% higher risk <sup>[7]</sup>.

Our case demonstrates that trastuzumab-related cardiac injury with associated clinical heart failure syndrome can occur in the absence of a measurable change in LVEF. The absence of other known risk factors for heart failure (including previous exposure to anthracyclines or taxanes), rapid improvement in response to furosemide therapy, and complete restoration of normal cardiac function after withdrawal of trastuzumab support a putative role of trastuzumab as the cause of transient diastolic dysfunction with symptomatic heart failure. To our knowledge, this is the first case reported as acute diastolic heart failure after use of trastuzumab without prior treatment with anthracycline. It has been reported that the majority of trastuzumab-induced LV systolic dysfunction are reversible <sup>[8]</sup>. The current case also showed a reversible course of diastolic heart failure induced by trastuzumab. In this case, LVEF remained in the normal range, but other abnormal echocardiographic findings normalized, and right heart catheterization demonstrated normal hemodynamic parameters after withdrawal of trastuzumab.

Trastuzumab is thought to induce cardiac injury and left ventricular dysfunction by inhibition of neuregulin-1 signaling in the myocardium<sup>[5]</sup>. While previous reports have characterized the effects of trastuzumab on systolic function<sup>[9]</sup> (as assessed by LVEF), neuregulin-1 signaling can also impact diastolic function. Diastolic dysfunction defined by decreased E/A ratio (mitral inflow E velocity and A velocity ratio) and decreased E' velocity (mitral annular E' velocity) without measurable change of LVEF was reported in breast cancer patients who had received adjuvant treatment with trastuzumab<sup>[10]</sup>.

Our case demonstrates that trastuzumab-related cardiac injury with associated clinical heart failure syndrome can occur in the absence of a measurable change in LVEF. Clinicians should be aware that a stable LVEF does not by itself rule out heart failure as the cause of dyspnea in a patient receiving trastuzumab chemotherapy for breast cancer. The monitoring of both diastolic and systolic function during the course of trastuzumab treatment with or without other chemotherapy agents is recommended by the recently published the ASE/EAC expert consensus statement (the American Society of Echocardiography/the European Association of Cardiovascular Imaging)<sup>[11]</sup>.

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