Diastolic heart failure is a new clinical entity of trastuzumab-induced cardiotoxicity: a Case Report

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Learning points

➢ Cancer therapy-related cardiac dysfunction (CTRCD) is defined as a decrease in the left ventricular (LV) ejection function of >10% points to a value below the lower limit of normal after cancer treatment.

➢ Trastuzumab is associated with significant cardiotoxicity characterized by LV systolic dysfunction.

➢ Decompensated heart failure resulting from diastolic dysfunction-dominant trastuzumab-induced cardiotoxicity can also occur.

➢ Perspectives on diastolic dysfunction are mandatory for the management of CTRCD, including pretreatment screening, monitoring for cardiotoxicity, follow-up after anti-cancer agents, and evaluation of the effectiveness of the therapy.
<table>
<thead>
<tr>
<th>TIME</th>
<th>EVENT</th>
</tr>
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<tbody>
<tr>
<td>September 2021</td>
<td>The patient underwent mammectomy for stage IIb breast cancer with HER-2 overexpression. The patient received adjuvant therapy with trastuzumab, 1 dose (6 mg/kg) every 3 weeks.</td>
</tr>
<tr>
<td>9 weeks later</td>
<td>Bilateral leg oedema and diarrhea were noted.</td>
</tr>
<tr>
<td>15 weeks later</td>
<td>Dyspnea, fatigue, orthopnoea, and anorexia developed. The patient was diagnosed with heart failure.</td>
</tr>
<tr>
<td>Admission</td>
<td>Admitted to hospital for bilateral leg oedema, orthopnoea. Diagnosed with decompensated heart failure and treated with diuretics, arteriodilators, and venodilators. Trastuzumab was discontinued.</td>
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<tr>
<td>3 weeks later</td>
<td>After volume reduction, the patient underwent cardiac catheter examination. Mean pulmonary artery wedge pressure was 18 mmHg without systolic dysfunction, indicating LV diastolic dysfunction.</td>
</tr>
<tr>
<td>12 weeks later</td>
<td>The patient’s heart failure symptoms improved to New York Heart Association functional class I. Diastolic function improved as seen on Doppler echocardiography.</td>
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Abstract

Background:

Cancer therapy-related cardiac dysfunction (CTRCD) is defined as a decrease in the left ventricular ejection function (LVEF) of >10% to a value below the lower limit of normal or relative reduction in global longitudinal strain (GLS) >15% from baseline after cancer treatment. However, the possibility of the development of isolated diastolic dysfunction has never been considered in the clinical presentation of CTRCD.

Case summary:

An 81-year-old woman was admitted to our institution presenting with prominent bilateral leg edema, orthopnea, and 8 kg of weight gain after administration of the anti-human epidermal growth factor receptor 2 (HER-2) antibody, trastuzumab, for HER-2 positive breast cancer. Transthoracic echocardiography showed a preserved LVEF of 62% without a significant reduction in GLS compared to results obtained before anti-HER-2 targeted therapy. Doppler echocardiography distinctly revealed a newly developed significant left ventricular diastolic dysfunction with evidence of elevated filling pressure. After successful achievement of volume reduction, the patient underwent cardiac catheter examination, revealing an elevated pulmonary artery wedge pressure of 18 mmHg.
Subsequently, trastuzumab was discontinued and the patient was treated with diuretics, arteriodilators and venodilators, until the signs and symptoms of heart failure completely disappeared.

Discussion:

In the management of CTRCD, including pre-treatment screening, cardiotoxicity monitoring, follow-up after anti-cancer agents, and evaluation of the effectiveness of the therapy, too much emphasis has been paid exclusively to the development of systolic dysfunction; however, perspectives for diastolic dysfunction may be needed. A comprehensive multidisciplinary team approach composed of breast surgeons, oncologists, onco-cardiologists, and echocardiography specialists is required.
Introduction

Trastuzumab is a humanized monoclonal antibody that is effective for 20% to 25% of all breast cancers, wherein human epidermal growth factor receptor 2 (HER-2) protein is overexpressed. In HER-2 positive breast cancer, trastuzumab administered concomitantly with chemotherapy has significantly modified the natural course of the disease by improving response rates and survival. Consequently, trastuzumab is now recognized as a “game changer” in the field of breast cancer. On the other hand, several clinical studies have demonstrated that trastuzumab is associated with clinically significant cardiotoxicity characterized by left ventricular (LV) systolic dysfunction in approximately 34% of patients when co-administered with anthracycline, and in 0.6% to 4.5% of patients even without concomitant anthracycline therapy.

Cancer therapy-related cardiac dysfunction (CTRCD) has been defined as a decrease in the LV ejection function (EF) of >10% to a value below the lower limit of normal after cancer treatment according to several clinical guidelines. More recently, over 15% relative reduction in global longitudinal strain (GLS) has been proposed as a novel criterion for the diagnosis of CTRCD. In this way, special attention has been focused...
exclusively on the reduction of ventricular contractility, while little consideration has been paid to the effect of CTRCD on the diastolic function.

Here, we report a case of decompensated heart failure due to a relatively pure diastolic dysfunction without overt contractile impairment, a condition that falls outside the clinical concerns of CTRCD in the current guidelines.

Case presentation

An 81-year-old woman was admitted to our institution due to prominent bilateral leg oedema and orthopnoea concomitant with 8kg of weight gain in three months after four courses of trastuzumab therapy to treat HER-2 overexpressing breast cancer. She was prescribed with irbesartan 100 mg/day, amlodipine 10 mg/day, febuxostat 10 mg/day, and ibandronate 100mg/month for hypertension, hyperuricaemia, and osteoporosis, respectively. In September 2021, she underwent mammectomy for stage IIb breast cancer with high proliferative activity (Ki 67, 63%), negative hormone receptors and HER-2 overexpression. After surgery, she received adjuvant therapy with trastuzumab (loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg) at one dose every three weeks. She noted bilateral leg oedema and diarrhea, nine weeks after the initiation of anti-
HER-2 targeted therapy, which progressively worsened after four courses of treatment. Although she was referred to a general cardiologist, the patient was not diagnosed with CTRCD due to the absence of LV systolic dysfunction (LVEF of 70%) paired with a nonspecific elevation of brain natriuretic peptide (BNP) level of 57.3 pg/mL. After 15 weeks of treatment with trastuzumab, dyspnoea, general fatigue, orthopnoea, and anorexia developed, and the patient was eventually diagnosed with heart failure.

On admission, her blood pressure was 176/68 mmHg, heart rate was 69 beats/min, and oxygen saturation was 93% (room air). Physical examination revealed hepatomegaly, jugular vein distension, and prominent bilateral leg oedema. On auscultation, a SIII gallop with no cardiac murmur was observed. On admission, the NT-proBNP concentration was 1525 pg/mL (normal value <125 pg/mL) and the Troponin I level was 32.6 pg/mL (normal value <26.2 pg/mL). Electrocardiography indicated a normal sinus rhythm with first-degree atrioventricular block and a nonspecific T-wave inversion on precordial leads. Chest radiography and computed tomography revealed bilateral pleural effusion with significant cardiomegaly (Fig. 1a and b), in comparison to the patient’s preoperative images which did not show any pleural effusion (Fig. 1c and d). Transthoracic echocardiography revealed that LV contraction was preserved without any ventricular remodelling (Fig. 2), and the LVEF
was calculated at 62% using the bi-plane Simpson’s method (Video S1, S2, and S3).

Moreover, no significant reduction in GLS was observed compared to results obtained before anti-HER-2 targeted therapy (from -16.5% to -14.6%; relative reduction of 11.5%, Fig. 3). In contrast, the left atrial volume index (LAVI) and tricuspid valve regurgitant jet velocity increased from 48.8 mL/m² to 85.1 mL/m² and 2.5 m/sec to 3.2 m/sec, respectively. Doppler echocardiography showed that the transmitral flow pseudonormalized (E/A ratio; from 0.70 to 1.30), e’ velocity was reduced (e’ septal 5.1 cm/sec and e’ lateral 6.0 cm/sec), E/e’ ratio was elevated from 14.3 to 19.1, and pulmonary venous flow changed from a systolic component dominant to a diastolic component dominant pattern (Fig. 4), all of which indicated elevated ventricular filling pressure as a result of the development of LV diastolic dysfunction. The patient was consequently diagnosed with decompensated heart failure, and combined treatment with diuretics (torasemide 8 mg/day, spironolactone 25 mg/day, and trichlormethiazide 2 mg/day for 14 days), arteriodilators (amlodipine 5 mg/day and olmesartan 20 mg/day) and venodilators (carperitide 0.125 μg/kg/min for 7 days), was introduced, resulting in the complete disappearance of pleural effusion and peripheral oedema concurrent with a reduction in body weight of 8kg in over three weeks. After successfully achieving volume reduction, the patient underwent cardiac catheter
examination to further assess her haemodynamic status (Table 1). Notably, the mean pulmonary artery wedge pressure was elevated to 18 mmHg without any systolic dysfunction or LV dilation, indicating LV diastolic dysfunction.

After a thorough discussion with her breast surgeon, trastuzumab was discontinued. At discharge, the patient was treated with 3.75 mg of tolvaptan, 200 mg of sacubitril valsartan, 5 mg of amlodipine, 25 mg of spironolactone, and 30 mg of azosemide. At 12 weeks after the interruption of trastuzumab administration, her heart failure symptoms significantly improved to New York Heart Association functional class I; thus, maintenance medication was reduced to 5 mg of amlodipine and 200 mg of sacubitril valsartan. As shown in Figure 4, Doppler echocardiographic parameters of diastolic function, including E/A of 0.60, E/e’ of 14.3, and LAVI of 57.1 ml/m², significantly improved.

**Discussion**

Generally, HER-2 positive breast cancer has a less favourable response to traditional chemotherapy due to the aggressive growth rate of malignant cells. However, owing to the emergence of humanized monoclonal anti-HER-2 antibody, trastuzumab, the
natural course of HER-2 positive breast cancer has been dramatically improved. However, with the widespread use of trastuzumab, myocardial toxicity has emerged as a prominent side effect, manifesting as asymptomatic LV contractile dysfunction or symptomatic heart failure in some cases. Although the exact mechanism of trastuzumab-induced cardiotoxicity is not fully understood, HER-2 inhibition appears to result in the structural and functional modification of contractile proteins and mitochondria without apparent myocardial cell death. Based on the findings of various in vitro and animal experiments, trastuzumab-induced cardiotoxicity has long been recognized as ventricular systolic dysfunction with subsequent pump failure. To date, clinical guidelines from various societies have defined trastuzumab-induced cardiotoxicity as a decrease in LVEF of more than 10%, to a value below the lower limit of normal, and only those who met this criterion have been "certified" or "endorsed" as having definitive CTRCD. The patient reported here developed significant diastolic dysfunction after trastuzumab therapy, as evidenced by findings from comprehensive Doppler echocardiographic assessment, which eventually resulted in haemodynamic decompensation without a significant reduction in LVEF and GLS. Although the possibility
of incidental development of decompensation unrelated to trastuzumab could not be
completely excluded, the patient had no history of heart failure or related symptoms prior to
trastuzumab administration. In the process of disease screening, diagnosis, and follow-up of
CTRCD, too much emphasis has been assigned to impaired systolic function. In contrast,
little attention has been paid to diastolic dysfunction, which is another clinically critical
aspect of cardiac dysfunction. Therefore, it is possible that there are CTRCD patients with
diastolic dysfunction who are not having appropriate heart failure therapy, or who
continued anticancer agents, because of the the preserved systolic function. Modifications
of clinical guidelines may be needed to broaden the clinical entity of the CTRCD for early
detection of patients who may benefit from appropriate heart failure therapy and timely
interruption of anticancer agents.

LV diastolic performance is often assessed using Doppler echocardiography, and,
more recently, the usefulness of LA speckle-tracking strain analysis is gaining prominence
in the assessment of diastolic capacity; thus, a detailed and appropriate interpretation is
highly specialized and technically demanding. Therefore, when assessing cancer therapy-
related cardiotoxicity, a comprehensive multidisciplinary team approach composed of
breast surgeons, oncologists, onco-cardiologists, and echocardiography specialists should
be mandatory. Thus far, although the possibility of the development of isolated diastolic
dysfunction has never been considered in the clinical presentation of CTRCD, a more
comprehensive haemodynamic assessment with special attention to diastolic function may
be necessary.

Conclusion

We encountered a case of heart failure resulting from diastolic dysfunction-
dominant trastuzumab-induced cardiotoxicity. Perspectives on diastolic dysfunction are
mandatory for the management of CTRCD, including pretreatment screening, monitoring
for cardiotoxicity, follow-up after anti-cancer agents, and evaluation of the effectiveness of
the therapy.

Patient consent statement:
The authors confirm that written consent for the submission and publication of this case
report, including images and associated text, has been obtained from the patient in line with
the COPE guidance.
References


Figure Legends

Figure 1: Chest radiography and computed tomography of an 81-year-old woman.

Pre-operative chest radiography did not reveal any pleural effusion or congestion (a).
Computed tomography performed before mammectomy did not indicate any pleural effusion (b). After trastuzumab treatment, bilateral pleural effusion concomitant with Kerley’s B-line was apparent (c). A modest amount of pleural effusion, along with an enlarged heart, is clearly depicted on chest computed tomography (d).

Figure 2: M-mode echocardiography at the onset of decompensated heart failure.

Left ventricular contraction is preserved without evidence of ventricular remodelling after receiving trastuzumab therapy.

Figure 3: Polar map presentation of global longitudinal strain of an 81-year-old woman.

The global longitudinal strain value did not significantly change from -16.5% to -14.6% after trastuzumab treatment.
Figure 4: Doppler echocardiograms of an 81-year-old woman at baseline and after receiving trastuzumab.

Before receiving trastuzumab, the patient’s E/A ratio of the left ventricular (LV) inflow was 0.70 and the E/e’ ratio was 14.3. The pulmonary venous flow pattern did not indicate an elevated LV filling pressure (left panel). After receiving trastuzumab, both the E/A ratio and E/e’ ratio significantly increased to 1.3 and 19.1, respectively. Moreover, pulmonary venous flow converted to a diastolic flow-dominant pattern, indicating an elevated ventricular filling pressure (middle panel). Twelve weeks after the interruption of trastuzumab, Doppler echocardiographic parameters of diastolic function significantly improved (middle panel).

TMF, transmitral flow; TDI, tissue Doppler imaging; PV, pulmonary vein; PVS, pulmonary venous flow in systole; PVD, pulmonary venous flow in diastole; Ar, pulmonary venous atrial reversal flow.
Figure 1

Before chemotherapy

After chemotherapy

(a)  (c)

(b)  (d)
Table 1: Pressure data obtained during cardiac catheter examination

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP: $a$ wave / $v$ wave (mean), mmHg</td>
<td>19 / 25 (18)</td>
</tr>
<tr>
<td>mPAP: systolic / diastolic (mean), mmHg</td>
<td>40 / 13 (24)</td>
</tr>
<tr>
<td>RVP: systolic / diastolic / end-diastolic pressure, mmHg</td>
<td>46 / 6 / 11</td>
</tr>
<tr>
<td>RAP: $a$ wave / $v$ wave (mean pressure), mmHg</td>
<td>10 / 10 (9)</td>
</tr>
<tr>
<td>Aortic pressure: systolic / diastolic (mean), mmHg</td>
<td>148 / 64 (92)</td>
</tr>
<tr>
<td>Stroke volume, mL (stroke volume index, mL/m$^2$)</td>
<td>89.3 (64.7)</td>
</tr>
<tr>
<td>Cardiac output, L/min (cardiac index, L/min/m$^2$)</td>
<td>4.59 (3.42)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes/sec/cm$^3$</td>
<td>185</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes/sec/cm$^3$</td>
<td>2557</td>
</tr>
</tbody>
</table>

PCWP, pulmonary capillary wedge pressure; mPAP, mean pulmonary artery pressure; RVP, right ventricular pressure; RAP, right atrial pressure.