

Toxic Cardiomyopathy in a Young Patient Treated for Her2-Positive Early Breast Cancer: Case Report and Literature Review

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Abstract

Objective. We present the case of toxic cardiomyopathy in a healthy thirty-eight-year-old female patient treated for Her2-positive early breast cancer. **Case Report.** During the neoadjuvant treatment, the patient received four cycles of AC regimen and four cycles of docetaxel in combination with trastuzumab biosimilar. Two days after she received the ninth dose of trastuzumab biosimilar, she reported febleness, palpitation, and dyspnoea. A heart ultrasound was performed and was normal without changes in the ejection fraction (EF) compared to previous checks. Three days later she reports worsening of her symptoms that were highly suggestive of heart failure. A cardiologist was consulted who insisted that the patient's symptoms were the consequence of the disease progression. A CT scan showed signs of heart failure. A heart ultrasound was done and the EF dropped to 30%. Drainage of the right pleural cavity was performed and pharmacotherapy for heart failure was started. The treatment led to clinical improvement, but eighteen months later EF is still not back to normal. **Conclusion.** This is a rare case of toxic cardiomyopathy in a young, previously healthy, patient who received anthracyclines followed by trastuzumab biosimilar in combination with taxanes. All the medications this patient received are potentially cardiotoxic. However, the overall presentation is not typical for any of these medications since the patient presented with symptoms and signs of heart failure with significant dilatation of the right atrium, which persists eighteen months after its onset, with only a small increase in the EF. There is also a possibility that the antineoplastic therapy the patient received only facilitated dilatative cardiomyopathy, while the main causative factor was intrinsic or extrinsic.

Key Words: Breast Cancer ▪ Anthracyclines ▪ Trastuzumab ▪ Toxic Cardiomyopathy.

Introduction

Breast cancer has the highest incidence and prevalence among malignant diseases (1). Its rising prevalence can be attributed to better screening methods and the development of innovative therapeutic options that are available for all types of breast cancer. Consequently, the absolute number of patients that experience adverse events (AE) of antineoplastic therapy is increased (2). Most AE are easily controlled and the prevalence of serious AE is relatively low, but they can significantly impact the clinical outcomes. Cardiotoxicity is common in breast cancer patients. Patients treated for breast cancer are more susceptible to heart

failure compared to the general population (3) but there is evidence that the incidence of heart failure is higher in patients older than 65 and those with previous cardiovascular disease (CVD) (4).

The objective of this article is to present a rare case of cardiotoxic cardiomyopathy with atypical clinical features in a previously healthy young patient.

Case Presentation

We report the case of a patient who was diagnosed with breast cancer at the age of thirty-eight. She had no comorbidities. In the previous six years, she had been regularly examined by a radiologist

because of positive family history of breast cancer and fibrocystic dysplasia. She underwent an ultrasound examination every four to six months. On several occasions, a fine needle aspiration biopsy (FNAB) was performed and cytological findings were always benign.

In July 2020, the breast ultrasound was without any change in comparison to the previous, but there was a new lymph node in the right axillary region, which was of malignant ultrasound characteristics. The FNAB was performed and malignant cells were found. The CT of the neck, thorax, and abdomen was normal, except for the multicentric expansive lesion of the right breast with a maximal diameter of 10 mm and a pathologic lymph node in the right axillary region. This expansive lesion was previously verified at the ultrasound examination as a fibrous plaque with stationary dimensions of 11×4 mm. A CORE biopsy was performed and moderately differentiated, ER, PgR, and Her2 positive invasive ductal carcinoma was confirmed. Before the onset of the neoadjuvant treatment, heart ultrasound was normal with the ejection fraction (EF) of 60%.

The patient received neoadjuvant chemotherapy, four cycles of the AC regimen (doxorubicin – 60 mg/m² and cyclophosphamide – 600 mg/m²) followed by four cycles of docetaxel (75 mg/m²) with trastuzumab biosimilar (loading dose of 8 mg/kg, then 6 mg/kg q3w). The dose of medications was reduced after two cycles of therapy according to the AC regimen because of prolonged grade four neutropenia. During the neoadjuvant treatment, in February 2021, the patient had a mild form of COVID-19. The patient experienced only mild rhinopharyngitis that lasted for less than five days. In April 2021, she had a right mastectomy and a prophylactic left mastectomy. A complete pathologic response (pCR) was confirmed. In the adjuvant setting, the continuation of trastuzumab biosimilar for up to one year was planned as well as hormone therapy (GnRH agonist and tamoxifen) and adjuvant radiotherapy together with regular follow-up.

In July 2021, two days after the patient received the ninth dose of trastuzumab biosimilar, she was

referred to an oncologist because of febleness, palpitation, and dyspnoea. The oncologist suggested an examination by a cardiologist, so the heart ultrasound, which was normal with the EF of 60%, was performed. There was no change in comparison to the baseline ultrasound and ultrasounds that were performed every three months since the onset of systemic treatment for breast cancer. The chest X-ray (Figure 1) showed bilateral pulmonary infiltration with minor pleural effusions bilaterally. The patient was also examined by a pulmonologist that prescribed antibiotics. Three days later, the patient was again referred to an oncologist because of her worsening condition, this time with the obvious clinical signs of heart failure. Even though all symptoms and clinical signs suggested heart failure, in a patient receiving cardiotoxic therapy, the cardiologist insisted that it was impossible since the heart ultrasound had been normal three days before and that the patient's state must have been the consequence of disease progression. In order to prove that the disease progression was the least possible scenario, a CT of the thorax and abdomen



Figure 1. The chest X-ray that demonstrates bilateral pulmonary infiltration and minor pleural effusions.

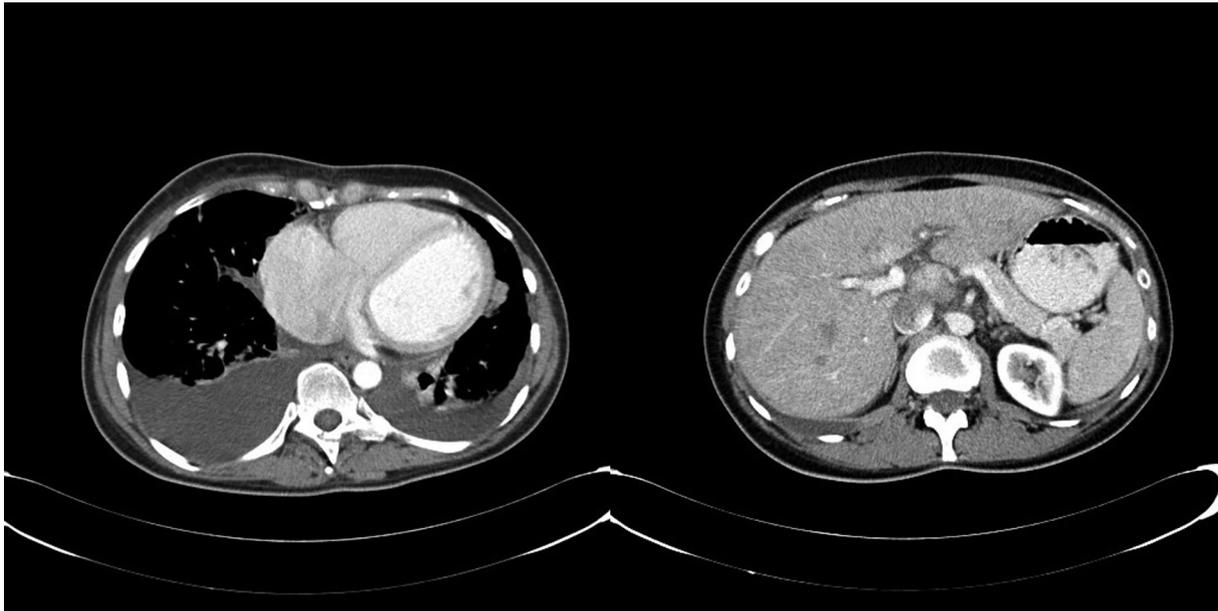


Figure 2. Enlarged heart, pleural effusions, and periportal oedema as signs of heart failure on CT of thorax and abdomen.

was performed (Figure 2). It showed an enlarged heart, especially the right atrium, with pleural effusion bilaterally, periportal edema, and ascites. There were no radiologic signs of dissemination of malignant disease.

In the lab findings, the liver enzymes were three times ULN, with hypoalbuminaemia and consequent hypocalcaemia. Heart biomarkers were normal. Since the D dimer was high (3 mg/mL), a CT angiography was performed and there were no signs of pulmonary thromboembolism. The thoracic drainage was done on the right. The heart ultrasound showed global heart dilatation with global hypokinesia and consequent dilatation of the inferior vena cava as well as the EF of 30%. The pharmacotherapy for heart failure was started with diuretics (furosemide and spironolactone), ACE inhibitor, beta-blocker (carvedilol), and low

molecular weight heparin. Instead of tamoxifen, letrozole was prescribed with the continuation of GnRH agonists. The therapeutic response was achieved and after fifteen days the patient was discharged from hospital stable.

When she recovered, she received radiotherapy without any adverse events. Now, the patient is on hormonotherapy and since the EF did not go back to normal, the treatment with trastuzumab was discontinued. She has regular follow-ups, every four months. All her lab and radiological findings are normal, except for the heart ultrasound where the global heart dilatation is still present with the EF of 45%. The patient still tolerates activity poorly. The summary of important clinical events and heart ultrasound findings are shown in Figure 3 and Figure 4.

<p>Sep-2020</p> <ul style="list-style-type: none"> - Stage II invasive ductal carcinoma (Er, PgR and Her2 positive) 	<p>Oct-2020 to Apr-2021</p> <ul style="list-style-type: none"> - Neoadjuvant therapy - Mild form of COVID-19 in Feb-2021 	<p>Apr-2021</p> <ul style="list-style-type: none"> - Surgery (pCR) 	<p>Apr-2021 to Jul-2021</p> <ul style="list-style-type: none"> - Continuation of trastuzumab biosimilar - Adjuvant hormonotherapy from May-2021 	<p>Jul-2021</p> <ul style="list-style-type: none"> - Syptomatic heart failure
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Figure 3. The summary of important clinical events.

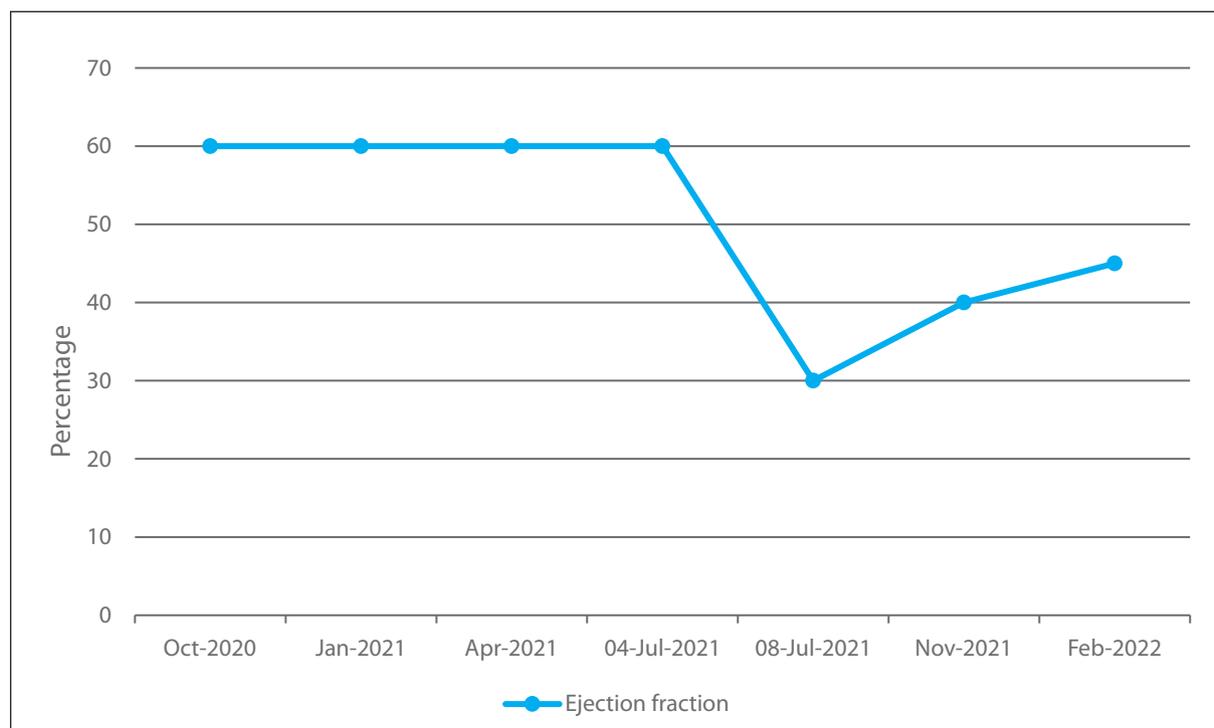


Figure 4. Patient's heart ultrasound findings from the beginning of her treatment until 2022.

Discussion

Cardiotoxicity of antineoplastic therapy led to the fast development of cardio-oncology, which is very important in the treatment of breast cancer, especially Her2-positive breast cancer. A study that included more than 63 000 patients with breast cancer, from 1992-1995, showed that CVDs are the leading cause of death in this population with 15.9%, while breast cancer is the second with 15.1% (5). The incidence of CVDs is higher in women with breast cancer, as well as the mortality caused by them, showed the study that included almost 82 000 patients with breast cancer with a median follow-up of seven years (3). The same study showed that patients treated for breast cancer have a higher risk of developing heart failure, especially patients treated with anthracyclines and trastuzumab with a hazard ratio (HR) of 3.68. HR is higher in patients treated with both anthracyclines and trastuzumab than in patients who only get anthracyclines, 2.53 vs. 1.84. Patients who received adjuvant radiotherapy for breast cancer, as

well as those who are treated with aromatase inhibitors, are also at higher risk.

Clinical trials NeoSphere and CLEOPATRA confirmed that the addition of pertuzumab to trastuzumab does not change its safety profile regarding cardiotoxicity (6, 7). The safety profile of the clinical trial TRYPHAENA is comparable to those in NeoSphere and CLEOPATRA (8).

OHERA is an observational study that brought real-world data and showed that the incidence of symptomatic heart failure in patients treated with anti-Her2 therapy is 2.8% with a median onset of 5.7 months since the start of the treatment and complete recovery in 72.6% of patients (4). This study also showed that the incidence of heart failure is higher in patients older than 65 and those with previous CVD. We here have the patient, who is, unlike presented in the results above, young, without comorbidities, with normal heart ultrasound before the onset of the neoadjuvant therapy and EF that was stable during the treatment.

ESMO consensus recommends baseline ultrasound before the start of cardiotoxic treatment as

well as a check-up every three months and active surveillance for at least three years after the end of cardiotoxic treatment (9). Taking into account the fact that this case shows a young patient with no comorbidities, who had heart ultrasounds regularly during the treatment and had no deflection from the baseline EF, not even when the first symptoms occurred, a logical question to arise is whether there is another way to screen the patients with the higher risk of heart failure. The biomarkers, mostly hs-troponins, BNP, and NT pro-BNP, are tested, but ESMO consensus still has not found evidence strong enough to recommend their routine use.

Primary prevention could decrease the incidence of heart failure, which would be particularly important for patients, who, like the patient in this case, are not diagnosed with heart failure while still asymptomatic. Some studies test the cardioprotective effect of certain medications. OVERCOME is a study that showed that the combination of enalapril and carvedilol can decrease the incidence of systolic dysfunction of the left ventricle in patients treated with cardiotoxic chemotherapy (10). MATICORE 101 – Breast showed that bisoprolol decreases the incidence of left ventricle's EF decrease in patients treated with trastuzumab (11).

It is still an open question what led to the heart failure with significant dilatation of the right atrium, which persists eighteen months after its onset, with only a small increase in the EF, in such a young patient. Cardiotoxicity caused by anthracyclines and trastuzumab differs in a way that anthracyclines cause structural damage to cardiomyocytes with consequent cell death, while trastuzumab inhibits signal transmission during DNA reparation (12). Therefore, the cardiotoxicity of anthracyclines is dose-induced and irreversible, while the cardiotoxic effect of trastuzumab is not dose-induced and is usually reversible. One should not a priori omit the possibility that, in this case, dilatative cardiomyopathy is facilitated by the antineoplastic therapy, while the main causative factor was intrinsic (e.g., TTN gene mutation) or some other extrinsic factor (e.g., previous SARS-CoV-2 infection) that we were not able to foresee or prevent.

Conclusion

In conclusion, this is a rare case of a toxic cardiomyopathy in a previously healthy young patient who received anthracyclines followed by trastuzumab biosimilar in combination with taxanes for the treatment of early Her2-positive breast cancer. All the medications this patient received are potentially cardiotoxic. However, the overall presentation is not typical for any of these medications since the patient presented with symptoms and signs of heart failure with significant dilatation of the right atrium, which persists eighteen months after its onset, with only a small increase in the EF. There is also a possibility that the antineoplastic therapy the patient received only facilitated dilatative cardiomyopathy, while the main causative factor was intrinsic or extrinsic.

What Is Already Known on This Topic:

Both anthracyclines and trastuzumab are known to be cardiotoxic. The cardiotoxicity caused by anthracyclines is irreversible, while the cardiotoxicity caused by trastuzumab is reversible in more than 70% of the cases. The incidence of cardiotoxicity is higher in patients older than 65 years and those with CVD. There is evidence that supports the primary prevention of heart failure in patients receiving cardiotoxic therapy.

What This Study Adds:

Something that can be learned from this case is how fibrocystic and fibroadenomatous breast changes, even though they do not show a statistically significant correlation with the incidence of breast cancer, could be misleading during the diagnostic procedure, so the breast ultrasound, which is a diagnostic method of choice in young patients, could be insufficient and needs a correlation with other methods. Secondly, regular follow-up of heart function must not overshadow the importance of clinical signs and symptoms that patients report. Therefore, a medical oncologist should play a central role in the follow-up of cancer patients and always point out possible adverse events of antineoplastic therapy in order to increase the efficacy of collaboration with clinicians of other specialties. In this case, we can observe a bad habit of some clinicians to attribute all symptoms of cancer patients to disease progression. Finally, one should think about primary prevention even in young patients without comorbidities.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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