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Cardiotoxicity with doxorubicin, trastuzumab, and development of the metabolic syndrome: Case report

Cardiotoxicidade com doxorrubicina, trastuzumabe e desenvolvimento de síndrome metabólica: Relato de Caso

Cardiotoxicidad con doxorrubicina, trastuzumab y desarrollo de síndrome metabólico: Reporte de un caso

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Abstract
The aim of this report is to present a case of a breast cancer patient who showed a reduction in the left ventricular ejection fraction and developed the metabolic syndrome after doxorubicin and trastuzumab use. It was analyzed if those drugs may be related to cardiotoxicity or be a possible cause for metabolic syndrome. With increased cancer survival, many patients may still develop metabolic syndrome, which has a multifactorial nature A 46-year-old female patient with infiltrated breast cancer exhibiting reduced left ventricular ejection fraction after chemotherapy neoadjuvant with doxorubicin and then with isolated trastuzumab. Chemotherapy was discontinued, and it was prescribed tamoxifen. The patient was referred to the cardiologist and nutritionist for a follow-up of the metabolic syndrome. Importance of early identification and monitoring of cardiotoxicity, avoiding the cardiovascular complications of cancer treatment and the preventing interruption of therapy**.**
Keywords: Cardiotoxicity; Doxorubicin; Trastuzumab; Metabolic Syndrome.

Resumo
O objetivo deste relato é apresentar o caso de uma paciente com câncer de mama que apresentou redução da fração de ejeção do ventrículo esquerdo e desenvolveu síndrome metabólica após o tratamento neoadjuvante com doxorrubicina, e em seguida de trastuzumabe. Foi analisado se esses medicamentos podem estar relacionados à cardiotoxicidade ou ser uma possível causa de síndrome metabólica. Com o aumento da sobrevida ao câncer, muitos pacientes ainda podem desenvolver síndrome metabólica, que tem uma natureza multifatorial. Paciente do sexo feminino, 46 anos, com câncer de mama infiltrante exibindo fração de ejeção ventricular esquerda reduzida após doxorrubicina e, em seguida, com trastuzumabe isolado. A quimioterapia foi suspensa e foi prescrito tamoxifeno. A paciente foi encaminhada ao cardiologista e nutricionista para acompanhamento da síndrome metabólica. O estudo ressalta a importância da identificação e monitoramento precoce da cardiotoxicidade, evitando as complicações cardiovasculares do tratamento do câncer e prevenindo a interrupção da terapia.

Palavras-chave: Cardiotoxicidade; Doxorrubicina; Trastuzumabe; Síndrome metabólica.

Resumen

El objetivo de este informe es presentar el caso de una paciente con cáncer de mama que presenta fracción de eyección ventricular izquierda reducida y síndrome metabólico tras tratamiento neoadyuvante con doxorrubicina y trastuzumab. Se analizó si estos fármacos pueden estar relacionados con la cardiotoxicidad o ser una posible causa de síndrome metabólico. Con el aumento de la supervivencia al cáncer, muchas pacientes aún pueden desarrollar síndrome metabólico, que tiene una naturaleza multifactorial Paciente mujer de 46 años con cáncer de mama infiltrante que muestra fracción de eyección ventricular izquierda reducida tras doxorrubicina y luego con trastuzumab aislado. Se suspendió la quimioterapia y se prescribió tamoxifeno. El paciente fue derivado al cardiólogo y nutricionista para seguimiento del síndrome metabólico Importancia de la identificación y seguimiento precoz de la cardiotoxicidad, evitando las complicaciones cardiovasculares del tratamiento del cáncer y evitando la interrupción de la terapia.

Palabras clave: Cardiotoxicidad; Doxorrubicina; Trastuzumab; Síndrome metabólico.

1. Introduction

Breast cancer is one of the significant public health problems in Brazil and worldwide. Doxorubicin and trastuzumab represent the most commonly used drugs to treat breast cancer but have adverse effects such as myocardial damage, which can occur during therapy, months, and even years after (Hajjar et al, 2020).

Anthracyclines, a class of highly effective chemotherapy drugs formed by doxorubicin, daunorubicin, epirubicin and idarubicin is associated with the development of cardiotoxicity, and is characterized by ventricular dysfunction and heart failure (Hajjar et al, 2020; Mc Gowan et al, 2017; Nicolazzi et al, 2018).

Heart failure caused by anthracyclines is associated with a cumulative dose of the drug, and can occur in around 5% of patients receiving doses up to 400 mg / m^2 and can affect up to 50% of patients with doses above 700 mg / m^2 and may occur acutely, subacute, early or late, reversible or irreversible. (Henriksen 2018; Brant et al, 2017; Narezkina & Nasim, 2019).

Trastuzumab, a monoclonal antibody targeting the human epidermal growth factor 2 receptor Her 2 +, reduced cancer mortality (Slamon et al, 2011; Perez et al, 2014). However, its use is related to the increased incidence of cardiotoxicity, which is manifested by the asymptomatic decline in Left Ventricular Ejection Fraction (LVEF) and by the occurrence of symptomatic heart failure (Wang et al, 2014).

The general incidence of trastuzumab cardiotoxicity varies in the literature from 2 to 28%. 2% to 7%, when trastuzumab is used in monotherapy, reaching 27%, when used sequentially after the AC protocol (doxorubicin and cyclophosphamide) (Yeh & Bickford, 2009).

Breast cancer patients are at high risk for the development of cardiovascular disease (CVD) and have an additional risk of developing metabolic syndrome, due to excess adiposity and the effect of chemotherapy.Metabolic syndrome affects about 30% of the population of women over the age of 50 (Nahas et al, 2012; Rose & Stephenson, 2004)With increased cancer survival, many patients may still develop metabolic syndrome.

The purpose of this report is to present a case of a breast cancer patient who showed the reduction of the left ventricular ejection fraction with doxorubicin and trastuzumab, and still the metabolic syndrome. The article discusses a cardiotoxicity associated with the analyzed drugs, the use of algorithms for initial stratification and determination of causality and the possible causes for metabolic syndrome.

2. Methodology

This article is a unique, qualitative and descriptive case study (Pereira et al, 2018).Initially, the data were collected from medical records. Then, the patient was interviewed by the pharmacist to complement the information. The study was

carried out in a university hospital in the state of Rio de Janeiro. The project was approved to the Research Ethics Committee of the University, under the CAAE: 98429018.0.0000.5243. A Free and Informed Consent Form was obtained.

3. Case Report

Female patient, 46 years old, black, married, servant, with a family history of a mother with hypertension and sister with breast cancer. She started treatment in a quaternary hospital in 2015, diagnosed with infiltrating right breast carcinoma, Her 2 +. She reported a history of hypertension using enalapril 10 mg 2 times daily and spironolactone 25 mg 1 time daily and normal weight. She had a social history of smoking reduction (with 50 packs/year) and alcoholism (40.8 units of alcohol).

The chemotherapy with doxorubicin and cyclophosphamide (AC) began as early as 2015. She previously performed normal electrocardiogram and echocardiogram exams. After the first cycle, she presented nausea and vomiting and neutropenia, and the second cycle was postponed one week until the blood count improved. The second cycle was uneventful. After the third cycle, a new ECHO was performed, which showed a slight enlargement of the left atrium and mild systolic dysfunction without pericardial effusion and LVEF = 51%. Due to mild left ventricular dysfunction, the AC protocol was discontinued, associated with the use of doxorubicin (cumulative dose of 300 mg), and replaced by 4 cycles of docetaxel in 2016, without complications.

The patient was then submitted to segmentectomy and axillary emptying of the right breast. Chemotherapy with trastuzumab monotherapy in 12 sessions started in 2017, with a new ECHO with LVEF = 69%. After the 9th session, ECHO was performed with LVEF = 30%. Chemotherapy was discontinued, and another ECHO was performed 2 months later, with LVEF = 28%. Examination revealed enlargement of the left cavities, with significant left ventricular dysfunction due to diffuse hypokinesia. The analysis of diastolic function was impaired. Thickened mitral valve with tethering of its leaflets with moderate reflux and pulmonary hypertension and normal-sized inferior vena cava was observed. QT was discontinued, and tamoxifen 20 mg / 1 cp daily was prescribed. She was referred to the cardiologist and a nutritionist because, throughout the treatment, she had increased waist circumference, showed weight gain (grade II obesity), dyslipidemia, and increased blood glucose. She was being followed up in the smoking cessation program.

4. Discussion

The reported case shows cardiotoxicity attributed to the use of doxorubicin, an anthracycline with well-known cardiotoxicity (Hajjar et al, 2020; Cardinale et al, 2010). Cumulative doses ranging from 400 to 500 mg / m2 are well documented. However, there are already studies reporting doses of 300 mg, as found in the present report (Cardinale et al, 2010; Grunaldi et al, 2016). After discontinuation of treatment, LVEF normalized, and the patient started trastuzumab, a cardiotoxic drug that is independent of the dose administered (Ewer et al, 2005), with a significant reduction in LVEF = 28%, requiring cardiac follow-up. The patient presented cardiotoxicity to both drugs: doxorubicin and trastuzumab, at different times, making the analysis of the results easier. There was a significant reduction in LVEF, slight enlargement of the left atrium, mild systolic dysfunction and diffuse hypokinesia and asymptomatic condition. Cardiovascular adverse reactions were then analyzed by the Naranjo Algorithm (Naranjo et al, 1981), and the scores obtained were 5 for doxorubicin and 3 for

trastuzumab, with the causal class: probable and possible, respectively. The reactions were considered serious by the Brazilian Society of Oncology Pharmacists (SOBRAFO) Adverse Reaction Reporting Guide (Sobrafo, 2011).

According to the National Cholesterol Education Programs Adult Treatment Panel III (NCEP-ATP III), (James, 2001). Metabolic Syndrome is a set of clinical disorders characterized by the presence of three or more indicators, such as elevated waist circumference, elevated triglycerides, high blood pressure, high blood glucose, and this set of metabolic

disorders confer an increased risk of developing cardiovascular disease (James, 2001; Lorenzo et al, 2007; Feitosa et al, 2012). The criteria for metabolic syndrome are presented in Table 1.

Table 1 – Criteria for the definition of Metabolic Syndrome.

CRITERIA	DEFINITION
Abdominal obesity	
Men	
White and black	≥102cm
Asian	≥ 90cm
Women	
White and black	≥88cm
Asian	≥80cm
Triglicerides	≥150mg/dL or treatment for hypertriglyceridemia
HDL-cholesterol	
Men	<40mg/dL
Women	<50mg/dL
Fasting glucose	≥ 100 mg/dL or treatment for *diabetes mellitus*
Blood pressure	
Systolic	≥130mmHg or treatment for blood pressure
Diastolic	≥ 85mmHg or treatment for blood pressure

Legend: HDL-cholesterol: High density lipoprotein- cholesterol.
Adapted: Adult Treatment Panel III (ATP III)(James, 2001; Lorenzo et al, 2007; Feitosa et al, 2012).

The patient also presented metabolic alterations during treatment, such as increased waist circumference, weight gain (grade II obesity), dyslipidemia, and increased glycemia, which are components of the metabolic syndrome and may be induced by chemotherapy (Westerink et al, 2016). Studies have shown an increased frequency of Metabolic Syndrome in breast cancer patients (Feitosa et al, 2012; Westerink et al, 2016).

Recent studies show evidence of changes in lipid profile with the use of Selective Estrogen Receptor Modulators (MRSE) (Leite et al, 2018).Tamoxifen is the best-studied MSRE, and studies show that tamoxifen lowers cholesterol and low-density lipoprotein (LDL) levels, but increases serum triglyceride levels (Leite et al, 2018).

In 2014, Herrmann et al proposed the use of a Cardiotoxicity Risk Assessment Algorithm for breast cancer, including the main previous risk factors and totaling 14 scores (Herrmann et al, 2014). In the reported case, the use of this algorithm scored 9 due to female sex, previous use of anthracyclines, the use of trastuzumab, the use of docetaxel and hypertension before treatment. This score represents a extreme risk assessment for cardiotoxicity (Herrmann et al, 2014).

This reinforces the importance of early identification of individual patient risk stratification for cardiotoxicity, monitoring, and follow-up of these cardiovascular reactions. Although there is no validation in the scientific evidence of the periodicity of monitoring of ventricular function, in this case, ECHO was delayed after the use of trastuzumab in relation to the recommendations in the literature, which recommends ECHO before, after the third cycle and at the end (Plana et al, 2014).It was performed after the 9th cycle when LVEF was already extremely low with 30%, thus delaying the referral to cardiology.

The study also shows the need for teamwork in Cardio-oncology, valuing multidisciplinary action. An ongoing study in Canada advocates the importance of the oncologist, cardiologist, pharmacist, nutritionist, and physical education professionals in diagnosing, treating, monitoring, and preventing cardiotoxicity (Pituskin et al, 2016).

5. Conclusion

The use of algorithms may contribute to the initial stratification of the risk of cardiotoxicity and to the determination of the class of causality. The study emphasizes the importance of early identification and monitoring of cardiotoxicity to avoid treatment interruption and associates the use of tamoxifen with the development of the metabolic syndrome.

This report shows the need for early identification, monitoring, and control of cardiovascular adverse reactions caused by anticancer drugs, early referral to cardiologists, multidisciplinary work, and the importance of these studies for decision-making for safe therapy for patients.

In the near future, we hope to deepen the knowledge of the association between breast cancer, cardiovascular diseases and the metabolic syndrome in order to avoid the interruption of cancer treatment and promote the appropriate management of these patients.

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