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Long Term Follow-Up of Cardiotoxicity in Breast Cancer Treatment: A Case Report

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Abstract

Background: Cardiac toxicity is currently defined as a symptomatic decrease in Left Ventricular Ejection Fraction (LVEF) of more than 5% or an asymptomatic decrease of at least 10% to a value of under 50% in repeated evaluations on conventional transthoracic echocardiogram (TTE), as well as a Global Longitudinal Strain (GLS) value < −18% or a relative reduction of 15% from baseline in any of the follow-up 2D-speckle tracking echocardiogram. **Aims:** To highlight using GLS rather than modified Simpson 2D-LVEF for the evaluation of long-term cardiotoxicity. **Case Presentation:** The case concerns a 73-year-old female patient with a history of breast cancer chemotherapy and anthracyclines-based therapy who presented symptoms of late cardiac toxicity related to the chemotherapeutic treatment. In the following years, the patient remained asymptomatic with a 2D-LVEF of 48%, dilation of the left atrium was found, and the reservoir phase strain was severely decreased. **Conclusion:** The preferred method for evaluating cardiovascular complications associated with chemotherapy is the TTE, which is performed prior to the start of treatment, during therapy, and in the follow-up. Myocardial deformation as a predictor of cardiotoxicity allows the identification of subclinical heart failure.

Keywords

Cardiotoxicity, Breast Cancer, Global Longitudinal Strain, Left Ventricular Ejection Fraction, Heart Failure

1. Introduction

Cardiac toxicity is currently defined as a symptomatic decrease in Left Ventricu-

lar Ejection Fraction (LVEF) of more than 5% or an asymptomatic decrease of at least 10% to a value of under 50% in repeated evaluations on conventional transthoracic echocardiographic (TTE) imaging techniques, as well as a Global Longitudinal Strain (GLS) value < −18% or a relative reduction of ≥15% from baseline in any of the follow-up 2D-speckle tracking echocardiograms [1] [2] [3].

In a study of over 43,000 patients with breast cancer, followed over a median of 53 months, anthracycline chemotherapy was associated with an adjusted hazard risk of 1.26 for the development of heart failure (HF) in women aged 66 - 70 years [4]. On the other hand, after cancer therapy, the St. Jude Lifetime Cohort Study showed that the prevalence of cardiac dysfunction, defined by decreased GLS, was 31.8% at a median interval of 23 years from diagnosis in long-term adult survivors of childhood cancers treated with anthracyclines, chest radiation, or both [2].

The aim of this manuscript is to highlight using GLS rather than modified Simpson 2D-LVEF for the evaluation of long-term cardiotoxicity.

2. Case Presentation (Table S1 in Supplementary Material 1)

A 73-year-old female patient was diagnosed in 1990, at the age of 52, with stage IIB left breast cancer. A radical mastectomy was performed, followed by radiotherapy and adjuvant chemotherapy based on anthracyclines.

The patient was referred to this hospital in December 2012, after presenting an episode of syncope and, atypical chest pain. She had presented a four-month functional class deterioration evidenced by NYHA class III. Two-dimensional TTE revealed left atrial (LA) dilation with left ventricular (LV) diffuse hypokinesia and a 2D-LVEF of 45%, severe mitral, moderate tricuspid, and mild aortic regurgitation. NT-ProBNP was 2080 pg/ml. These findings were compatible with dilated cardiomyopathy and HF probably secondary to anthracyclines.

In the following years, the patient remained asymptomatic with a 2D-LVEF of 48%. Follow-up TTE in 2020 reported diffuse LV hypokinesia, eccentric hypertrophy, severe mitral and tricuspid regurgitation, and 2D-LVEF of 40%. Medical treatment based on Metoprolol, Losartan and Furosemide was initiated and the patient was discharged.

Follow-up TTE in 2021 reported LV eccentric hypertrophy, diffuse hypokinesia of the LV, moderate tricuspid regurgitation and severe mitral regurgitation (**Video S1** and **Video S2**), tricuspid annular plane systolic excursion (TAPSE) 17 mm, LV end-diastolic hypertension with E/e'-24, 2D-LVEF of 39%, GLS −14% (**Figure 1**) and peak tricuspid regurgitation velocity of 3.01 m/s with intermediate probability of pulmonary hypertension (pulmonary arterial systolic pressure (PSAP) of 56 mmHg).

Last follow-up TTE in 2022 reported an NT-ProBNP of 1280 pg/ml. 2D-LVEF of 38%, GLS −10.9% with a reduction of 24% in comparison to previous TTE, LV end-diastolic hypertension with E/e'-25, LA reservoir strain 9.5% (**Video S3-S5**), TAPSE 19 mm, free-wall right ventricular longitudinal strain of −19.35% (**Video S6**) and intermediate probability of pulmonary hypertension (PSAP of 47 mmHg) (**Figure 2**).

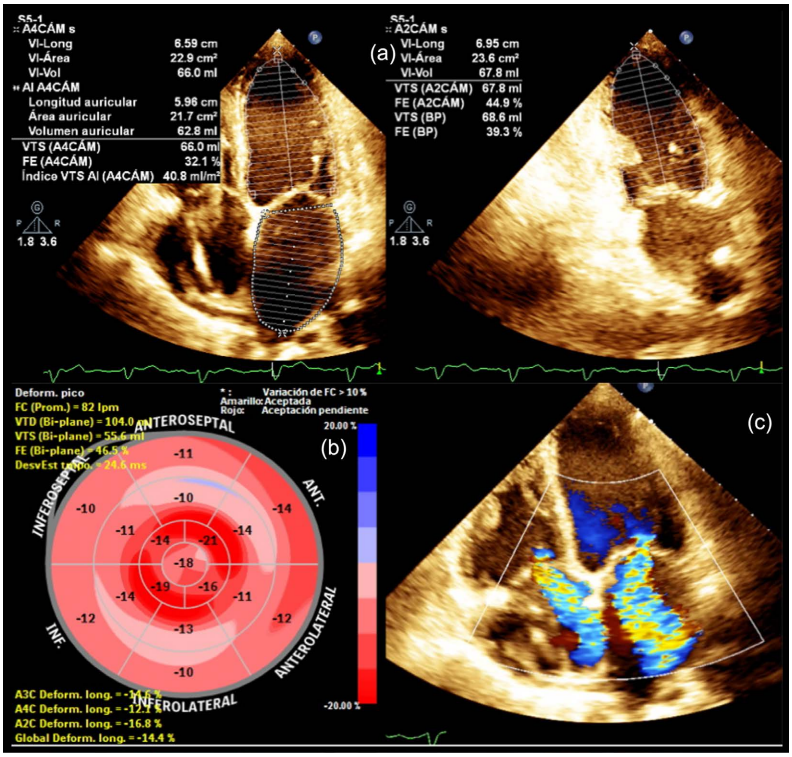

Figure 1. Simpson Modified transthoracic LVEF (a), Left ventricular GLS (b). Both studies performed in 2021 reported a LVEF of 39% and a GLS of −14.4%. (c) Dilation of the heart cavities with severe mitral and moderate tricuspid regurgitation.

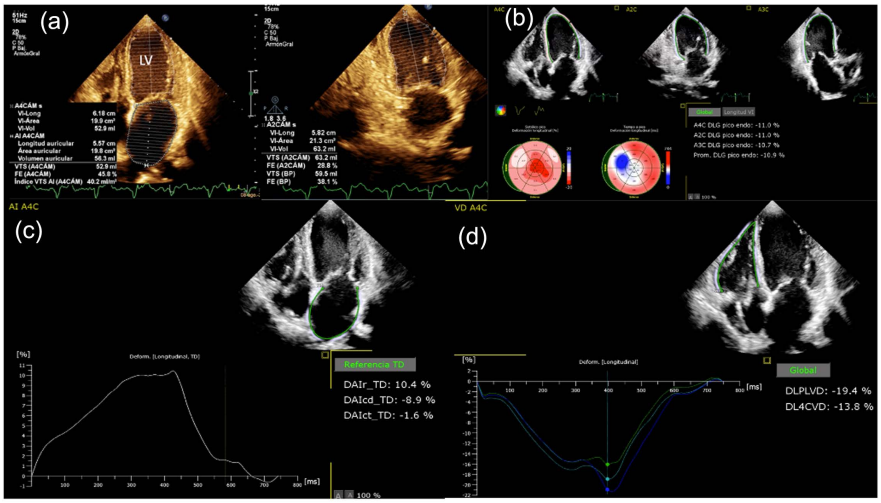

Figure 2. Echocardiographic follow-up in 2022. (a) 2D LVEF by Simpson modified method of 38.1%; (b) Left ventricular GLS of −10.9%; (c) Left atrial reservoir longitudinal strain: 9.5%; (d) Free wall-right ventricular longitudinal strain −19.4%. Abbreviations: LV: left ventricle.

On follow-up the patient remains asymptomatic with a NYHA functional class II and is currently receiving optimal treatment for HF based on sacubitril/valsartan + spironolactone + bisoprolol + furosemide + dapagliflozine, with a clear clinical and echocardiographic response.

3. Discussion

For most patients, chemotherapy is one of the pillars of therapy, along with surgery, and is associated with very high response rates [1].

The most common forms of cardiotoxicity include arrhythmias, myocardial necrosis (dilated cardiomyopathy), vasospasm/vaso-occlusion (angina and myocardial infarction), pericardial disease, sudden dead and heart failure.

The preferred method for evaluating cardiovascular complications associated with chemotherapy is TTE, which is performed prior to the start of treatment, during therapy and in the follow-up [5] [6].

The problem with LVEF is that it tends to decline in late clinical stages when reduction in cardiac events may not be achieved despite aggressive treatment. For this reason, the two-dimensional strain has been proposed as an optimal measure for the early detection of HF (subclinical HF).

This patient allows emphasizing the superiority of GLS in relation to modified Simpson 2D-LVEF in the evaluation of cardiotoxicity. The patient's GLS reports were expected in accordance with the literature on cardiotoxicity induced by anthracyclines and trastuzumab, demonstrating that the GLS should be regularly evaluated for follow-up, as suggested by the new guidelines.

LA strain has also been shown to provide beneficial information in patients with HF [7]. The changes in LA deformation that appear before any increase in LA volume underscores the value of looking beyond LA size [8] [9]. In our patient, dilation of LA was found, and the reservoir phase strain was severely decreased.

The change in myocardial strain values in different situations has greater sensitivity to detect subclinical HF compared to the measurement of LVEF. Also, it has been shown that the early reduction of GLS in the speckle tracking 2D-TTE during chemotherapy can predict subsequent cardiotoxicity [6]. This makes the myocardial strain, especially the systolic GLS, the most useful parameter for the prediction of cardiotoxicity and subclinical HF [1].

Elevation of cardiac biomarkers may also be a way to identify patients who are already at high cardiovascular risk [10].

The 2022 ESC Guidelines on Cardio-oncology suggest that long term surveillance in asymptomatic cancer survivors with moderate risk should be made with TTE every 5 years. In high and very high risk the evaluation should be performed at years 1, 3 and 5 after the cardiotoxic cancer therapy has been administered, with subsequent follow-up every 5 years [3].

The most accepted pathophysiological mechanism of cardiotoxicity induced by most chemotherapeutic agents as anthracyclines is due to lipid peroxidation of the cell membrane by reactive oxygen species, which leads to cardiomyocyte damage and replacement with scar tissue [11].

In patients with modified Simpson 2D-LVEF decreased more than 50%, angiotensin-converting enzyme inhibitors and beta-blockers are the recommended treatment to prevent further LV dysfunction and the development of symptomatic HF [12].

4. Conclusions

Myocardial deformation as a predictor of cardiotoxicity allows the identification of HF, since the main limitation of 2D-LVEF is that its decrease occurs when HF is already established, and the cardiovascular events are often no longer preventable despite treatment.

GLS currently represents an important source for early diagnosis of cardiotoxicity, and atrial strain should be further studied since it represents an important prognostic factor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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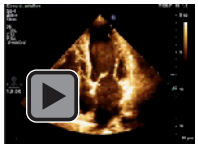
Supplementary Material 1

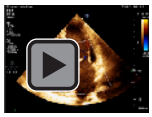
Table S1. Timeline cardiotoxicity.

Day	Event
January 1990 (First presentation)	Admission with stage IIB left breast cancer. A radical mastectomy was performed, followed by radiotherapy and adjuvant chemotherapy based on anthracyclines
December 2012 (Second presentation)	Admission after an episode of syncope, and atypical chest pain
April 2013	2D-echocardiography revealed left atrial dilation with left ventricular diffuse hypokinesia and a LVEF of 45%, severe mitral regurgitation, moderate tricuspid regurgitation and mild aortic regurgitation.
May 2013	Medical treatment based on metoprolol, losartan and furosemide and the patient was discharged.
December 2013	Admission due a new episode of syncope, and dyspnea 12-lead electrocardiogram showed a complete left bundle branch block and a Mobitz II atrioventricular block
December 2013	Heart Team: Implantation of a dual chamber pacemaker, and was discharged
December 2013 to January 2020	Following 2D-echocardiography (3) showed a LVEF of 48%
January 2020	2D-echocardiography reported diffuse left ventricular hypokinesia, eccentric hypertrophy, severe mitral and tricuspid regurgitation, and LVEF of 40%.
January 2021	Follow-up echocardiogram demonstrated LV eccentric hypertrophy, diffuse hypokinesia of the LV and mild tricuspid and severe mitral regurgitation, LVEF of 39%, GLS −14%, and intermediate probability of pulmonary hypertension (PSAP of 56 mmHg).
January 2022	Last follow-up 2D-echocardiography reported an LVEF of 38%, GLS −10.9%, left atrial reservoir strain 9.5%, free-wall right ventricular longitudinal strain of −19.35% and PSAP of 47 mmHg.
February 2022	Outpatient clinic visit: The patient remains asymptomatic with a NYHA functional class II and is currently receiving optimal treatment for heart failure based on sacubitril/valsartan + spironolactone + bisoprolol + furosemide + dapagliflozine

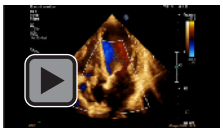
Supplementary Material 2



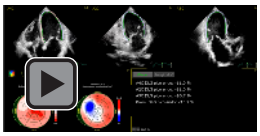
Video S1. 2D-TTE Apical four-chamber view. Dilation of the right chambers and global left ventricular hypokinesia. Pacemaker wires can also be observed in the right chambers.



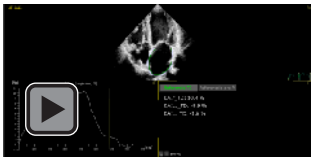
Video S2. 2D-TTE Apical four-chamber view with colour flow. A severe mitral and moderate tricuspid regurgitation are observed.



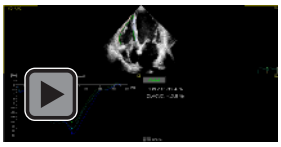
Video S3. 2D-TTE Apical four-chamber view with colour flow. Global left ventricular hypokinesia, and severe mitral and moderate tricuspid regurgitation.



Video S4. 2D-TTE Apical four, three and two-chambers view. The left ventricular GLS is severely decreased (−10.9%), showing a 24% reduction compared to the previous value reported in 2021.



Video S5. 2D-TTE Apical four-chamber view. Left atrial reservoir longitudinal strain markedly diminished (9.5%).



Video S6. 2D-TTE Focused right ventricular apical four-chamber view. The free wall-right ventricular longitudinal strain is mildly decreased (−19.4%).