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Case Report

ANTHRACYCLINE CARDIOTOXICITY IN NON-HODGKIN'S LYMPHOMA MEDIASTINAL MASS: A CASE REPORT

Elisabetta Chiodi[1], Maria Teresa Cannizzaro[1], Marcello Natali[2], Zairo Ferrante[2], Bruna Malta[2], Clorinda Montalto[2], Melchiore Giganti[2], Giorgio Benea[1]

Summary

Anthracycline is often used for treatment of hematologic malignancies and solid tumors, and the damage it causes to the heart muscle has long been known; therefore, the cardiac toxicity, one of the treatment-related co-morbidities, has become an issue for cancer survivors. Cardiotoxicity has been defined using various classifications. In this paper we report the case of a man affected by follicular non-Hodgkin's lymphoma, which was first diagnosed in 2006 and had a second recurrence in 2012 with a mediastinal mass: the patient was subjected to a new cycle of chemotherapy with anthracycline, the follow-up exam showed a significant reduction of the mass, but the clinical condition worsened and the ejection fraction of the left ventricle had a progressive reduction, as seen in the cardiac-MRI test. Then, it was decided to discontinue therapy with anthracycline, resulting in a clear recovery of systolic function of the left ventricle, as seen in the following echocardiogram.

Case report

A 66 year old man, with HBV chronic hepatitis on interferon therapy, nephrectomized due to a sports trauma, and follicular non-Hodgkin's lymphoma grade 1 (stage IV, Follicular Lymphoma International Prognostic Index 1/5, low risk) was first diagnosed in 2006, threated with a cycle of chemotherapy with RCVP x 8 (rituximab with cyclophosphamide, vincristine and prednisone), with first recurrence in the 2008 that was threated with second-line therapy, which resulted in a complete remission. Then, the patient was monitored with follow-up examinations. In March 2012, the patient was admitted because of mild asthenia, fever and cough. The Thoracic-Radiography results were negative **(Figure 1)**, so he started a cycle of antibiotic therapy (amoxicillin/clavulanic acid) without any clinical improvement. After a few days, upon clinical observation a congestion of jugular veins was found. The echocardiogram showed a pericardial thickening with liquid effusion involving all of the ventricular chambers, and a maximal thickening around the right atrium, the segmental kinetics appeared

Address of the authors:
1. Radiology Department, Arcispedale Sant'Anna, Cona (Ferrara), Italy.
2. Universitary Radiology Department, Arcispedale Sant'Anna, Cona (Ferrara), Italy.

Send correspondence to: *Marcello Natali, ntlmcl@unife.it*

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normal. The CMR showed a mediastinal mass (6x4 cm) compressing the left atrium, the left ventricle, and the left pulmonary artery, also infiltrating the pericardium and the sub-epicardial fat. Heart kinetics was stable and ejection fraction was above 58%. After administration of contrast (gadolinium medium) a late enhancement of the mass appeared. CMR also confirmed the presence of a conspicuous liquid effusion in the pericardial (maximum thickness 2.5 cm) and pleural spaces (**Figure 2a and Figure 2b**). TC confirmed the resumption of the disease and shows the mediastinal mass (6x4 cm) and the presence of a liquid effusion in pericardial and pleural space (**Figure 3a and Figure 3b**).

The patient was then subjected to a new cycle of chemotherapy with anthracycline

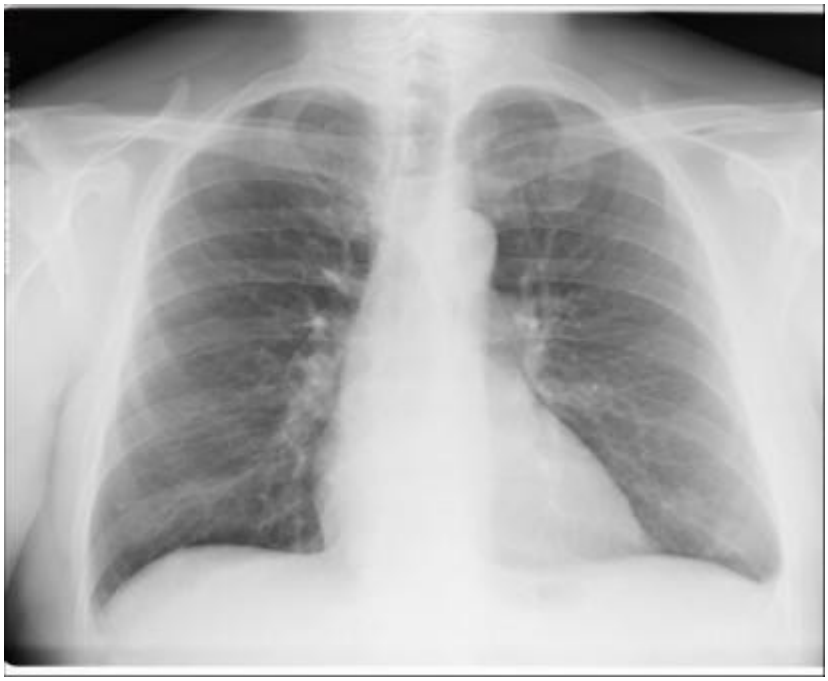

Figure 1: Thoracic X-rays (08 March 2012).

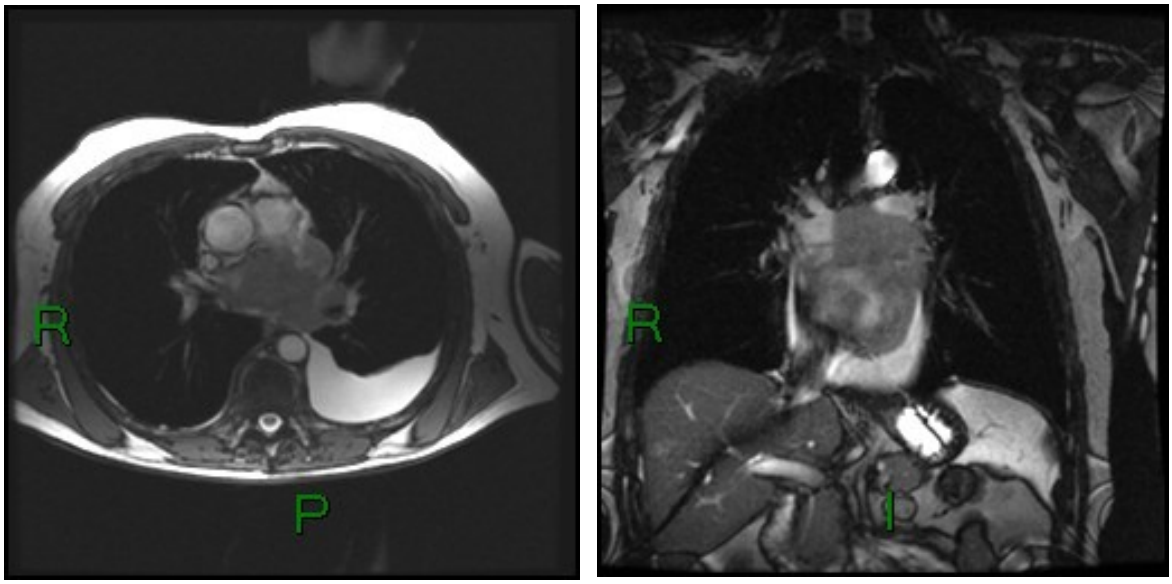

Figure 2a (left) – 2b (right): CMR shows liquid effusion in pericardial and pleural spaces (13 April 2012).

and followed very closely; also the TC test confirmed a significant reduction of the mass, minimal residual of pericardial effusion and the resolution of pleural effusion (**Figure 4**). In the following months the patient showed a worsening of the clinical condition with a marked weakness and dyspnea, also follow-up seriate echocardiogram exams showed a progressive reduction of eject fraction of the left ventricle (EF 31.9%). CMR test showed a marked reduction of the contractility of the left ventricle, particularly in the septal segments (EF 19%); the

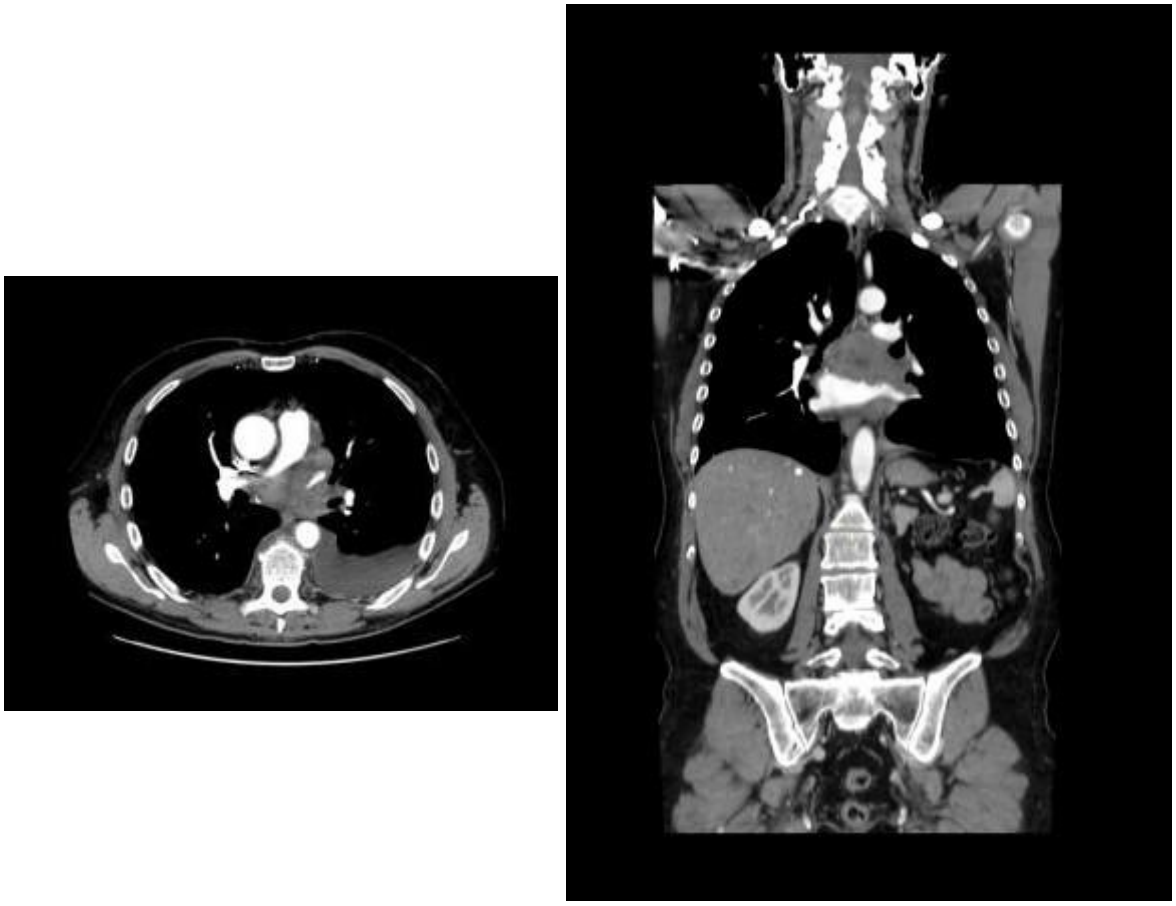

Figure 3a (left) – 3b (right) : TC: mediastinal mass, liquid effusion in pericardial and pleural space (16 Apr 2012).

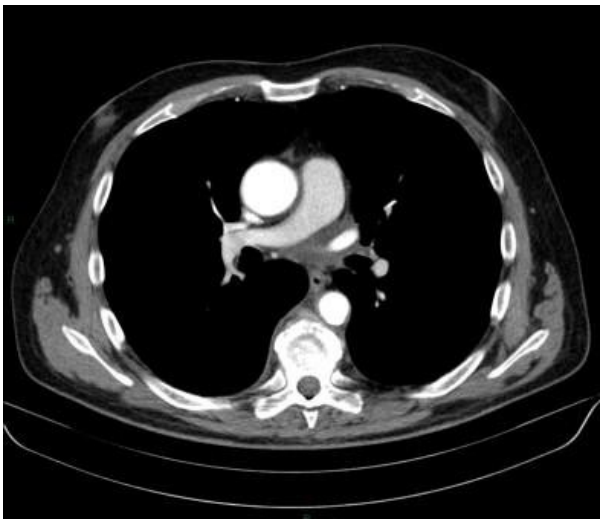

Figure 4: TC after chemotherapy with anthracycline (18 Jun 2012).

STIR sequence showed septal edema and post-contrastographic sequences showed septal late enhancement without coronary distribution, pleural and pericardial effusions were also visible, and in particular a thickening of apical pericardium was evident (**Figure 5**). After theses exams confirmed the massive myocardial damage, therapy with anthracycline was discontinued, resulting in a clear recovery of the left ventricle's systolic function, confirmed by the following echocardiogram tests.

Discussion

With new anticancer therapies, many patients have an increased life expectancy. Anthracycline is often used in polychemoterapeutic regimens for treatment of hematologic malignancies and solid tumors, and the damage inflicted to the heart muscle, from chemotherapy with anthracycline, has long been known [(1)], as well as the Cardiotoxicity, one of the treatment-related co-morbidities, have become an issue for cancer survivors. More than 50% of patients treated with anthracycline will show cardiac dysfunction [(2, 3)] along with a 2-year survival rate of 40%[(4)]. Cardiotoxicity has been defined using various classifications: guidelines suggest that a reduction of LVEF >5% to LVEF <55% with symptoms of heart failure, or an asymptomatic reduction of LVEF of >10% to a LVEF<55%, constitute cardiotoxicity [(5)]. This effect is to be referred to as oxidative stress, which is generated in myocytes from this drug. Cardiac abnormalities include dilated and restrictive cardiomyopathy and subtler changes in cardiac function: in some cases it may be so important as to affect the ventricular contractility, resulting in congestive heart failure, sometimes years after completion of chemotherapy [(6)].

Detection of anthracycline-induced cardiotoxicity is usually performed by echocardiography, looking for an impairment in the LV ejection fraction; especially in early stages the changes may be subtle, so, there is a need for other functional parameters that more reliably depict early anthracycline cardiotoxicity: modern functional parameters, such as speckle tracking echocardiography (STE) to measure strain rate (SR), have been proven to be more sensitive than conventional functional parameters to detect early ventricular dysfunction in patients after cardiotoxic chemotherapy. However, functional metrics alone provide limited insight into the underlying myocardial damage. Cardiovascular magnetic

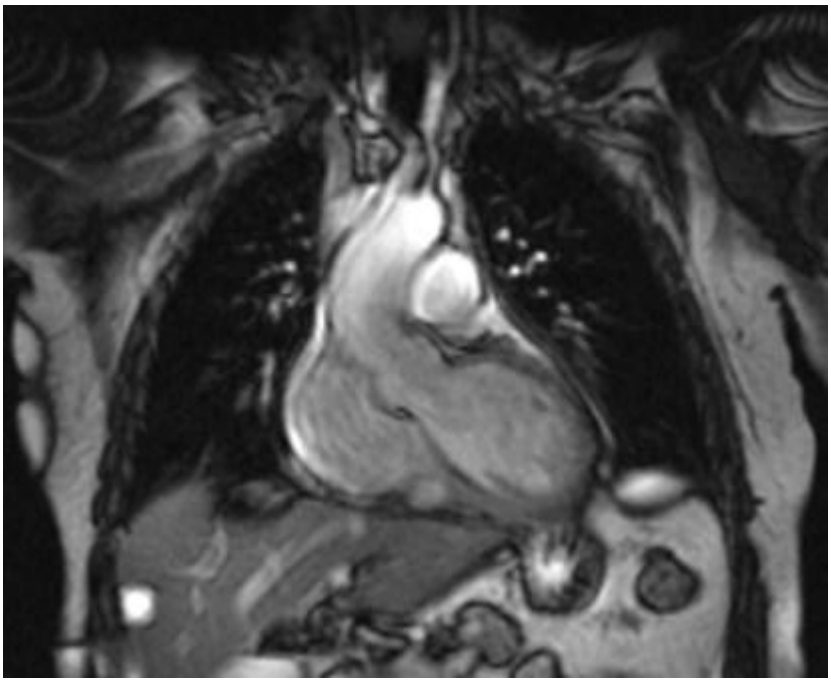

Figure 5: CMR four months after therapy (25 Oct 2012).

resonance (CMR) is a sensitive and reproducible technique with the ability to characterize myocardial tissue using T_1 and T_2 mapping techniques [7, 8], and to demonstrate subclinical myocardial changes prior to the onset of LV dysfunction. Quantitative T_1 imaging can be used to calculate the myocardial extracellular volume fraction (ECV), a measure of microscopic myocardial remodeling that has been associated with underlying diffuse fibrosis: scarring found using CMR with late gadolinium enhancement (LGE) is a strong predictor of outcomes in patients with a cardiomyopathy [9, 10]. The role of the CMR is better explored for anthracycline-induced toxicity than for the other chemotherapeutic agents cardiotoxicity, such as high-dose cyclophosphamide, even if data on the typical CMR findings and the presence detected by LGE, specifically in patients with anthracycline-cardiomyopathy, are limited [11]. Studies show that the CMR-derived LV mass helped further quantify risks in patients with anthracycline-cardiomyopathy and provided additional prognostic information; characteristics frequently found are different: myocardial scar demonstrated by LGE was an infrequent finding, an inverse correlation was found between anthracycline dose and LV mass, cardiac edema using T2-weighted imaging was an uncommon finding, the cardiovascular event rate in the follow-up exams was high for patients with anthracycline-cardiomyopathy [12].

Conclusion

Different imaging techniques have allowed us to follow the effects of therapy upon recurrence of the disease, in particular the CMR imaging has provided crucial information. The CMR has allowed us to initially define the cardiac involvement of tumor recurrence and, during follow-up, the damage on the heart muscle. With this case report we believe we have provided a clear demonstration of the utility of CMR in identifying the extent of myocardial damage during treatment with anthracycline.

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