

Progressive late cardiac dysfunctions chemo- and radiotherapy related in a middle age woman with Hodgkin lymphoma – a case report

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ABSTRACT

Background. Elaborated chemotherapy protocols used for a broad spectrum of solid and haematological malignancies have a significant cardiotoxicity potential. Different biologic mechanisms generated by Doxorubicin used in ABVD protocol, induce irreversible myocardial alterations, like type I cancer therapeutics-related cardiac dysfunction. The present case-report highlights the importance of comprehensive diagnostic evaluation of a common mitral valve disease and emphasizes the importance of the accurate etiology in a case of late cardiomyopathy anthracycline + radiation related.

Case presentation. A 46-year-old Caucasian woman was admitted in sequence of 20 years prior anthracycline chemotherapy + radiotherapy protocols (five MOPP cycles, one cycle of ABVD, and three radiotherapy cycles of mantle Cobalt-60 therapy) for stage IIB Hodgkin lymphoma, medical investigations supporting a diagnosis of cardiotoxicity. The optimal pharmacological regimen for heart failure was prescribed with significant improvement of symptoms six months later. Consecutive four-year regular follow-up, complete clinical workup, lab tests and high-performance imaging studies endorsed a slow progression of cardiomyopathy with the appearance of a left bundle branch block and a balanced clinical status. Except cardiac and thyroid involvement, no relapse of Hodgkin lymphoma, musculoskeletal disease or other malignancies were identified 24 years after chemotherapy and radiation.

Pathogenesis of late-onset chronic development cardiotoxicity anthracycline-containing chemotherapy + mediastinal radiotherapy related remains unclear, resulting from multifactorial and complex mechanisms, and usually is considered irreversible. Notably, long-term survivors who experienced Hodgkin lymphoma in childhood or young age, appear to be susceptible and remain at increased risk of developing heart failure decades after.

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Conclusions. *From the setting-up of targeted therapy for Hodgkin lymphoma, cardio-oncology knowledge should be joined, avoiding the late stages, when symptomatic heart failure occurs. For Hodgkin lymphoma treated patients, serial follow-up and individualized approach are required to reduce the continuously increased risk of future CV events.*

Keywords: adult Hodgkin lymphoma survivor, late cardiotoxicity, heart failure, mitral regurgitation, cardiac conduction disorder, treatment, long term follow-up, case report

INTRODUCTION

Different chemotherapy protocols used for a broad spectrum of solid and haematological malignancies have a significant cardiotoxicity potential (1,2). The use of chemo- and radiotherapies may amplify the risk of cardiovascular (CV) events up to three times for cancer survivors in terms of medium and long term prognosis (3,4).

Although long-term cardiotoxicity is a well-recognized issue, anthracyclines are widely used in the treatment protocols of patients with Hodgkin lymphoma (HL) and contribute substantially to improving the prognosis of these patients. Doxorubicin, used in ABVD protocol, induce type I cancer therapeutics-related cardiac dysfunction (CTRCD) via reactive oxygen species, and other different biologic mechanisms; myocardial alterations are irreversible and dose-related, especially if the cumulative dose exceeds 400 mg/sqm (5,6). Late cardiac complications (heart failure, arrhythmias, valvular involvement, chronic coronary syndromes, pericardial disease, cerebrovascular disease) can occur variable (years or decades) after completion of anthracycline administration, expressly in adult patients who experienced cancer treatment in childhood (7,8).

CTRCD, defined as a decrease of more than 10% of the left ventricular ejection fraction (LVEF), compared with pre-chemotherapy values and drop to less than 53%, is associated with the occurrence of heart failure (HF) in 5% to 26% of cases, and 48% for left ventricular dysfunction, depending on the population and follow-up duration (9-13).

Anthracycline-induced cardiomyopathy (AICM) display a broad spectrum range from the asymptomatic decline in systolic function quantified through measurement of left ventricular ejection fraction (LVEF) to the development of heart failure.

The risk of AICM should be hypothesized in the presence of associated conditions such as female sex, Afro-American descendants, older age (> 65 years), pediatric population, chronic kidney disease, systemic hypertension, genomic variants, but factors triggering individual susceptibility are less known (9,10,12,13). Retrospective evaluation of long HL who encountered

combined therapy (anthracyclines plus early radiotherapy protocols) in childhood or adulthood underlines an unquestionably increased risk of development of any cardiovascular disease, coronary artery disease (CAD), and heart failure, after a median interval of 20 years (14).

Comparing AICM with the other forms of cardiomyopathies, this is associated with a poor prognosis, with a 1-year death rate of 50% up to 60% in the first two years after diagnosis, typically result from congestive heart failure (15). In 2000, Felker et al. reported a poor survival prognosis 3.5 in AICM patients compared to those with idiopathic dilated cardiomyopathy (DCM) (16).

The objective of this paper is to emphasize the importance of an appropriate etiological diagnosis of DCM and heart failure management in a middle-aged woman exposed to previous chemotherapies and radiotherapy (RT) for Hodgkin lymphoma along with relevant data regarding combined long term effects of appropriate therapies for this haematological malignancy.

CASE PRESENTATION

A 46-year-old Caucasian woman with a history of Hodgkin's lymphoma was admitted in 2015 for fatigue, palpitations, dizziness, shortness of breath, dyspnoea.

In 1995, she was diagnosed with HL stage IIB (Cotswold Modification of Ann Arbor staging system). No suggestive medical records (negative personal and family history for CV disease, rheumatic fever, recurrent viral infections, hormonal, and neoplastic disorders) were documented before cancer therapy. Chemotherapy (five cycles of MOPP and one cycle of ABVD) and RT (3 cycles of mantle therapy Cobalt-60) were started at the age of 22, attaining complete remission in November 1996.

Unfortunately, after more than two decades, there were no evidences regarding cumulative dose of chemotherapeutic agents used, or the total mediastinal radiation dose. DCM, mitral regurgitation and heart failure were diagnosed in ambulatory settings.

On admission, physical examination revealed orthopnoea, bilateral limbs oedema, bilateral pulmo-



FIGURE 1. 12-lead electrocardiogram (ECG) at first admission (2015)

nary crepitations, a regular cardiac rhythm, mitral holosystolic murmur, and blood pressure of 120/75 mmHg. The 6-minutes walk test highlighted a reduced exercise capacity, a 395 m 6-MWD, from a predicted value of 572 meters.

Routinely laboratory tests were within normal limits except total cholesterol (6.13 mmol/l), and fibrinogen (5.9 g/l). A baseline level of NT-proBNP was also assessed, showing a value of 953.5 pg/ml.

A possible RT-induced subclinical hypothyroidism (TSH: 9.3 mIU/ml, FT4: 1.09 ng/dl) was diagnosed. Serologic patterns suggestive for chronic B or C hepatitis, human immunodeficiency virus, *Borrelia burgdorferi*, *Treponema pallidum*, *Chlamydia* spp. were negative.

Rest electrocardiogram (BTL Industries Ltd, BTL-08MT Plus machine, UK) recording identified sinus rhythm with a heart rate of 72 bpm, first degree atrio-ventricular block (P-Q = 204 ms), patterns of myocardial ischemia in precordial leads (figure 1). Serial 24-hour Holter ECG recordings revealed rare, isolated supraventricular and ventricular extrasystoles.

Chest X-ray indicated a 2.5 x 3 cm inhomogeneous, egg-shaped, well-delineated, opacity located above the left pulmonary hilum.

2D transthoracic echocardiography was performed (GE Healthcare, GE Vivid™ E9 ultrasound system, Boston, MA, USA), according to guidelines recommendations (17). Off-line analysis of stored images showed a dilated left ventricle (LVED: 67mm), moderate/severe mitral regurgitation and a mild secondary pulmonary systolic hypertension (PAPs = 36mmHg), intermediate echocardiographic probability parameters of pulmonary hypertension. LV function was assessed, showing

reduced LV ejection fraction (LVEF: 30-35%, modified Simpson's biplane method), and reduced global longitudinal strain (GLS: -17.2%). No retractions, calcifications or fibrotic thickening of valves were noticed. Echocardiographic assessment of pericardium did not confirm pericardial thickening or pericardial effusion.

Cardiac testing with myocardial scintigraphy at rest and during exercise revealed a slightly enlarged LV, a fixed perfusion defect located at the level of the septum, middle and basal segment possible in a shorter interventricular context. Invasive coronary angiography (Allura Xper FD10 X-ray system, Koninklijke Philips N.V, Netherlands) displayed normal epicardial arteries without anatomic variances (figures 2 and 3).

Cardiac magnetic resonance (GE Healthcare, CMR, 1.5T Optima™ MR450w MRI scanner, Boston, MA, USA) revealed a hypertrabeculated, slightly dilated left ventricle with an improved LVEF (48%), the normalized end-diastolic volume of 101 ml/m², and end-systolic volume of 53 ml/m², with moderate mitral valve regurgitation (figure 4).

All data suggested cardiotoxicity related to prior anthracycline chemotherapy + RT protocols and a diagnosis of heart failure with reduced ejection fraction (HFrEF) NYHA III functional class, dilated cardiomyopathy, moderate mitral regurgitation, secondary systolic pulmonary hypertension was established. A systematic, rationale, work-up regarding different aetiologies of DCM in this index patient was also considered.

Optimal pharmacological regimen (Carvedilol 3.125 mg b.i.d., Ramipril 5 mg o.d., fixed-dose combination diuretics – Spironolactone 50 mg + Furosemide 20 mg o.d. and selective sinus node If channel inhibi-

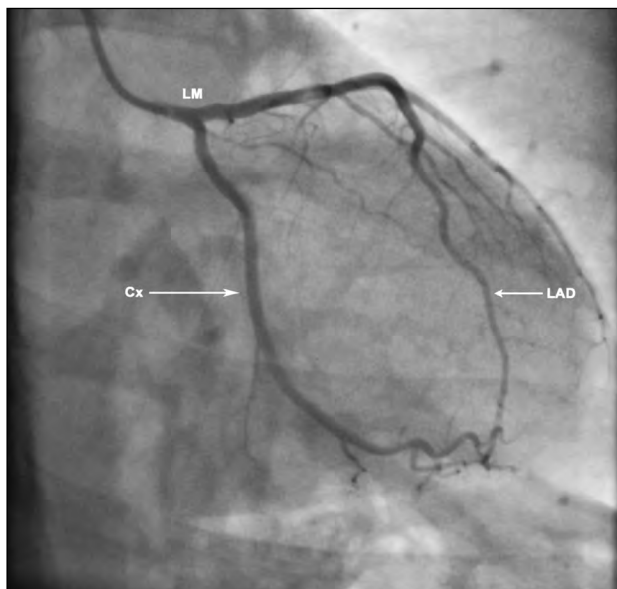


FIGURE 2. Angiographic aspect of left coronary artery (LM – left main coronary artery, LAD – left anterior descending artery, Cx – circumflex artery)

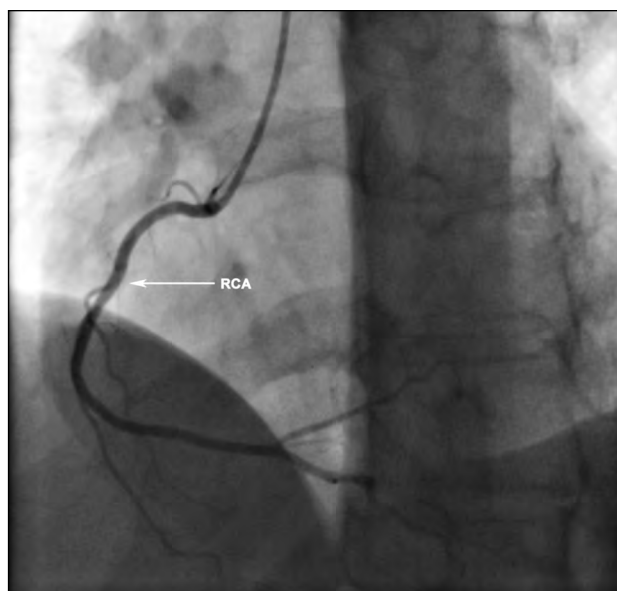


FIGURE 3. Angiographic aspect of right coronary artery (RCA – right coronary artery)

tor) was prescribed. Thyroid replacement therapy (Levothyroxine 50 micrograms o.d.) was considered appropriate for subclinical hypothyroidism.

Six months later, a significant improvement of symptoms was noticed, NYHA functional class II, 6-MWD: 530 m (87% out of predictive 6-MWD of 583 meters), and a 63.27% NT-proBNP decrease (350.2 pg/ml).

At four-years regular follow-up (2019), a complete clinical work-up, lab tests and imaging studies (echocardiography and CMR) was performed. Exercise capacity was enhanced (545 meters from a predictive 6-MWD of 567 meters – 96%) and NT-proBNP dis-

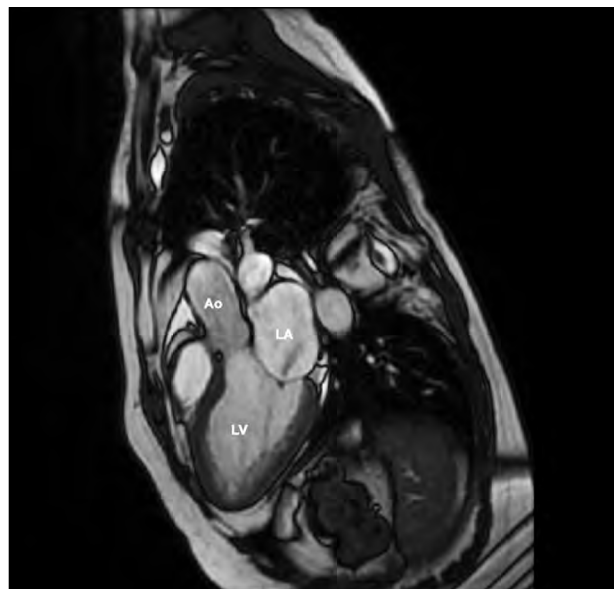


FIGURE 4. Cardiac magnetic resonance imaging at diagnosis (Ao – aorta, LA – left atrium, LV – left ventricle)

played a 237.3 pg/ml value (75% reduction from baseline).

The rest ECG recording showed sinus rhythm, and heart rate of 75 bpm, with new-onset of complete left bundle branch block (LBBB) and secondary ST-T changes (figure 5). Serial rest ECG and 24-hours Holter recordings didn't show malignant arrhythmias or Q-T prolongation.

Repeated late gadolinium enhanced CMR revealed DCM, myocardial fibrosis with non-ischemic distribution in myocardial segments 7, 8, 11, 14 and moderate mitral regurgitation with LVEF of 55%, the indexed end-diastolic volume of 118 ml/m² and end-systolic volume of 53 ml/m² respectively (figure 6).

Pharmacological regimen for HF was optimized, increasing the dose of Carvedilol up-to 6.25 mg b.i.d.; statins (Atorvastatin 40 mg o.d.) were added.

No relapse of HL, musculoskeletal disease or other malignancies were identified 24 years after chemotherapy and radiation.

DISCUSSIONS

Considering the previous medical data, the clinical work-up, lab tests and multimodality imaging, heart failure, dilated cardiomyopathy, mitral regurgitation and intraventricular conduction disturbances reflect late cardiotoxicity given by the chemotherapeutic regimens (MOPP+ABVD) combined with RT (Cobalt-60 mantle therapy). In addition, diffuse myocardial fibrosis without scarring may indicate specific cellular changes anthracycline-induced cardiomyopathy related (18).

Anthracycline-based chemotherapy is the key-element in HL and other malignancies. However, between



FIGURE 5. 12-lead electrocardiogram (ECG) at 4 years follow-up (2019)

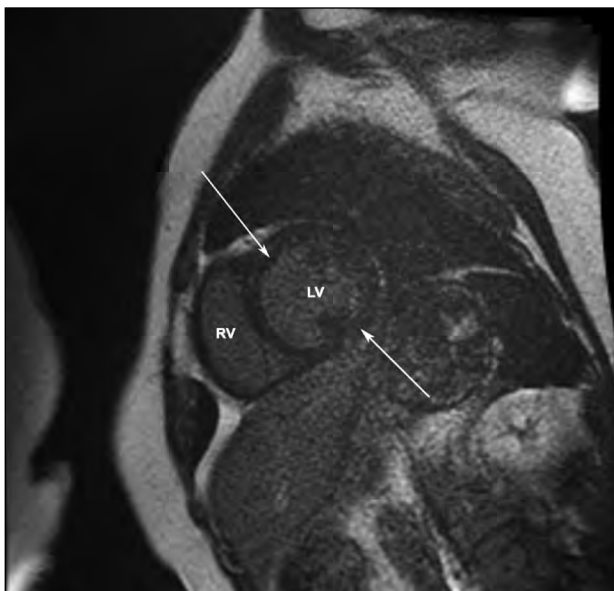


FIGURE 6. Late gadolinium enhanced CMR at 4 years follow-up (2019). Myocardial fibrosis is seen in segments 7, 8, 11, and 14 (arrows)

2 and 23% of patients receiving anthracyclines develop late heart failure, secondary to the induced cardiotoxicity. Despite the normal ejection fraction of the left ventricle, subtle abnormalities of systolic myocardial function are present in long-term survivors after anthracycline exposure.

Anthracyclines and/or RT are involved in the occurrence of mitral regurgitation, a timeframe of more than ten years being attributable to radiotherapy (9,19-21). Hull et al. reported in a retrospective study on 415 HL patients a 6.2% rate (25 cases) of significant valvular dysfunction after a median of 22 years, the aortic valve being most affected (22). The underlying

mechanisms of valvular disease secondary to cancer treatments are unclear. Based on imagistic studies performed, we consider that mitral regurgitation is secondary to annular dilation as a consequence of LV dysfunction and remodeling occurred later in the course of CRTCD.

Acute or late-onset of cardiac arrhythmias/conduction system disturbances represents a result of myocardial injury induced by chemo or RT, right bundle branch block is generally more common than LBBB (23,24). In our patient, the first-degree A-V block was present from the first presentation, and after two years follow-up, an asymptomatic left bundle branch block was identified.

Although pericardial disease induced by doxorubicin and radiotherapy is relatively frequent diagnosed (25,26) no features of pericardial involvement were detected by non-invasive imaging.

Treatment including beta-blockers, ACE inhibitors, aldosterone antagonists, statins is the recommended therapeutic regimen, similar to other types of cardiomyopathies with heart failure (20,27,28). Despite data published by Cardinale et al. (29), our patient presented a functional recovery of LV after initiation of personalized HF treatment. Long-term follow-up of cardiac status is desirable, to reduce overtreatment in case of permanently normalized LVEF. Advanced treatment options for HF (cardiac resynchronization therapy/implantable cardioverter-defibrillator) will be considered when advisable. Current evidence do not support the use of anticoagulation in this particular case (no active cancer or evidence of previous thrombotic events, DCM in sinus rhythm), despite the fact that HF confers a prothrombotic state. The hypothesis that FXa inhibi-

tion can reverse or improve early adverse cardiac remodeling is promising (30); despite the existing specific methods to determine the plasma concentration of direct oral anticoagulants, further research is needed in assumption that these techniques can be used to adjust the drug dosage (31,32).

Pathogenesis of late-onset chronic development cardiotoxicity anthracycline-containing chemotherapy + mediastinal RT related remains unclear, resulting from multifactorial and complex mechanisms, and usually is considered irreversible. Particularly, long-term survivors who experienced HL in childhood or young age, appear to be susceptible and remain at increased risk of developing heart failure decades after.

Previous therapies contribute to late cardiac involvement or further life-threatening conditions, although the occurrence rate is poorly known, as no precise guidelines are available (33-35).

CONCLUSIONS

From the setting-up of targeted therapy for Hodgkin lymphoma, cardio-oncology knowledge should be joined, avoiding the late stages, when symptomatic heart failure occurs.

Surveillance of Hodgkin lymphoma patients in complete remission, and personalized care approach are required in order to reduce the constantly increase risk of future cardiovascular events. Patients and doctors should be well-informed about this existing risk; cardioprotective agents are needed, succeeding to lower the enhanced morbidity-mortality incidence in Hodgkin's lymphoma patients, treated with anthracyclines and radiotherapy.

The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patient has given her signed consent for images and other clinical information to be reported in the journal.

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