CASE PRESENTATION

Complex cardiovascular disease after Hodgkin lymphoma treatment

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Abstract: Extended survival in cancer patients raises the problem of late cardiotoxicity. Hodgkin lymphoma survivors are at increased risk of therapy-related cardiac complications, risking premature morbidity and death. We report the case of a 43 years old woman that, after successful combined therapy for Hodgkin lymphoma, has developed, during the next fifteen years, multiple cardiac involvements: pericardial tamponade and constriction, valvular and myocardial dysfunction. Combined diagnostic techniques have been used to clarify the nature of cardiac disease and to exclude local lymphoma recurrence, and specific medical and surgical treatment solutions were approached. Healthcare providers must be aware that screening for early detection of cancer treatments cardiotoxicity is mandatory, and is able to ensure better patient outcomes.

Keywords: Hodgkin lymphoma, cardiotoxicity, anthracycline, radiotherapy, cardiovascular risk

Rezumat: Creșterea speranței de viață a pacienților neoplazici ridică problema cardiotoxicității pe termen lung. Supraviețuitorii limfomului Hodgkin prezintă un risc crescut de complicații cardiace legate de terapie, riscând morbiditate prematură și deces. Prezentăm cazul unei femei de 43 de ani care, după succesul terapiei combinate pentru limfomul Hodgkin, a dezvoltat, în următorii cincisprezece ani, multiple afectări cardiace: tamponadă cardiacă și constricție pericardică, disfuncție valvulară și miocardică. Tehnici combinate de diagnostic au fost utilizate pentru a clarifica natura bolii cardiace și a exclude recidiva limfomului, și au fost abordate soluții specifice de tratament medical și chirurgical. Medicii trebuie să fie conștienți de faptul că screening-ul pentru depistarea precoce a cardiotoxicității tratamentului este obligatoriu și este capabil să asigure un prognostic mai bun al pacientului.

Cuvinte cheie: limfom Hodgkin, cardiotoxicitate, antracicline, radioterapie, risc cardiovascular

BACKGROUND

Cardiovascular disease (CVD) and cancer are the two leading causes of morbidity and mortality worldwide[1]. Early diagnosis and improvement of treatment have both contributed to increased survival in many cancer patients[2]. As a result, there are now close to 30 million cancer survivors worldwide, and the numbers are increasing[3]. Unfortunately, many cancer treatments carry a great risk of complications and, as life expectancy grows, the associated morbidity and mortality will also increase.

Hodgkin lymphoma (HL) is now curable in more than 75% cases[4]. HL survivors are at increased risk of therapy-related complications (especially cardiac disease) that may present years after treatment and may generate premature morbidity and death[4,5]. This may be the result of cardiotoxicity (direct toxic effect of the cancer treatment on heart structure and function) or may be due to accelerated development of CVD, especially in the presence of traditional cardiovascular (CV) risk factors[5,6].

Healthcare providers must take into account these complications, since screening can improve early detection that may lead to better management with favorable outcomes.

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CASE PRESENTATION

We report the case of a 43 years old woman who was first admitted to the Cardiology Clinic of Emergency Clinical Hospital of Constanta in January 2016, for evaluation of dyspnea and fatigue. The symptoms appeared at moderate physical exertion and had a slow progression during the last year. She also accused dry cough and negate having angina.

Her past medical history was significant by being diagnosed in July 2000 with stage IIB nodular sclerosis HL. She was treated with combined chemotherapy and radiotherapy (RT). Chemotherapy consisted of two cycles of ABVD (A for Adriamycin - doxorubicin, B for bleomycin, V for vinblastine and D for dacarbazine) and two cycles of AVD and lomustine. Following chemotherapy, in March and April 2001, extended field RT was given to the mantle field (which included lymph node areas in the neck, chest, and armpits). Her CV history begins in April 2002 when, at the chest computed tomography (CT) performed for follow-up, a small pericardial effusion was noted together with pulmonary fibrosis. The pericardial fluid accumulated gradually until October 2004, when the patient was admitted for cardiac tamponade and treated by emergency pericardiocentesis followed by anterior interphrenic pericardiectomy. The pericardial biopsy taken at the time of the surgery was negative for neoplastic involvement. During the prolonged hospitalization period she experienced an episode of deep vein thrombosis of the left lower limb, with favorable outcome under anticoagulant therapy. After year 2005 she had no cardiologic follow-up until September 2015 when she was referred to our clinic with the suspicion of heart failure (HF). Regarding the patient's lifestyle, we mention that she is a former occasional smoker.

The physical examination on the admission revealed an overweight patient (BMI=29.6 Kg/m^2) with a post-sternotomy scar and interscapular hyperpigmentation (due to radiation dermatitis). She was nonfebrile, with a blood oxygen saturation level of 98%, respiratory rate of 16 breaths per minute, blood pressure of 115/60 mmHg and a regular heart rate of 100 bpm. The auscultation of the heart revealed a grade 2/6 diastolic murmur at the aortic area and grade 3/6 systolic murmur on the left lower sternal border and apical region. The exam of the peripheral arteries was normal and the signs of systemic or pulmonary congestion were absent.

The ECG revealed sinus rhythm with a heart rate of 84 bpm, left anterior fascicular block, complete right bundle branch block, right ventricle hypertrophy, ST-T secondary changes and prolonged corrected QT interval (504 ms) (Figure 1).

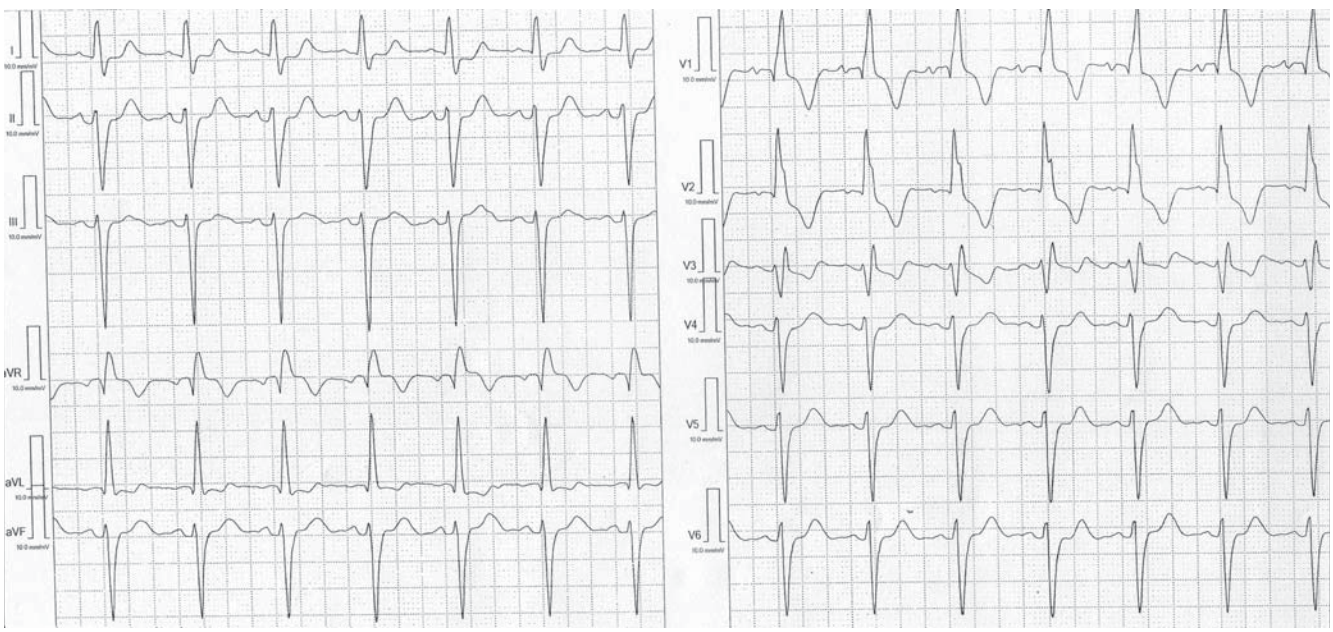

Figure 1. Electrocardiography. Sinus rhythm, 84 bpm, bifascicular block (left anterior fascicular block + complete right bundle branch block), right ventricular hypertrophy (qR pattern in V1), secondary ST-T changes, corrected QT interval = 504 ms.

Laboratory tests showed normal values of myocardial necrosis markers and D-dimer, elevated NT proBNP (485 pg/ml), slightly elevated LDL-cholesterol, hyperuricemia, and high values of thyroid stimulating hormone. The complete hemogram, liver function tests, renal function tests and ionogram were in normal limits.

Transthoracic (TTE) and transesophageal (TEE) echocardiography revealed normal cardiac chambers size with mild septal hypertrophy, normal diastolic function, mild left ventricle systolic dysfunction (left ventricle ejection fraction - LVEF of 50%) with slight hypokinesis and paradoxical motion of the interventricular septum. The aortic, mitral, tricuspid valves and the remaining pericardium were thickened; there were nodular calcifications of the aortic cusps, mitral chordae and posterior mitral annulus extended to the basal portion of the posterior mitral leaflet and an endocardial calcification at the level of left ventricular ejection tract. There was aortic sclerosis and moderate to severe aortic insufficiency (Figure 2A), moderate mitral insufficiency (Figure 2B), severe tricuspid insufficiency with two regurgitant jets and mild pulmonary hypertension (pulmonary artery systolic pressure of 39 mmHg).

The pulmonary function test revealed a moderate mixed respiratory dysfunction with a 26% decrease in total lung capacity, moderate obstructive ventilatory dysfunction, severe distal obstructive syndrome and a diffusing capacity for carbon monoxide at the lower normal range.

A high-resolution CT and CT pulmonary angiography showed no signs of pulmonary embolism, confirmed the presence of pleuro-pulmonary fibrosis and revealed a mass at the level of posterior mediastinum that raised suspicion of lymphoma relapse.

The patient was started on bisoprolol, perindopril (switched to candesartan due to cough), spironolactone, furosemide, atorvastatin, aspirin and levothyroxine, and referred to the Hematology Department to further investigate the mediastinum mass. Due to the high risk of bleeding associated with biopsy, an evaluation with positron emission tomography – CT scan was preferred and based on this investigation and on stationary aspect of the mass the lymphoma relapse was excluded. After the discharge the patient was lost to follow-up until November 2017 when she was readmitted to our clinic. The symptoms progressed and she had fatigue and dyspnea at mild effort. The physical exam and ECG revealed the same pathological findings as the previous ones. Laboratory tests showed higher values of NT-proBNP (612 pg/ml), normalized lipid profile and uric acid levels; the complete hemogram, liver function tests, renal function tests, ionogram and myocardial necrosis markers were in normal limits. The pulmonary function test showed similar results to the previous one. The changes at TTE from the previous exam were: mild dilated right chambers, mild left ventricle systolic dysfunction (LVEF of 45%) and mitral and tricuspid Doppler flow patterns suggestive of constrictive pericarditis (Figure 3). To further elucidate the suspicion of constrictive pericarditis a CT scan (Figure 4) and a cardiac magnetic resonance imaging (MRI) (Figure 5) were performed, but the results were inconclusive in regard to the pericardial involvement, due to extensive

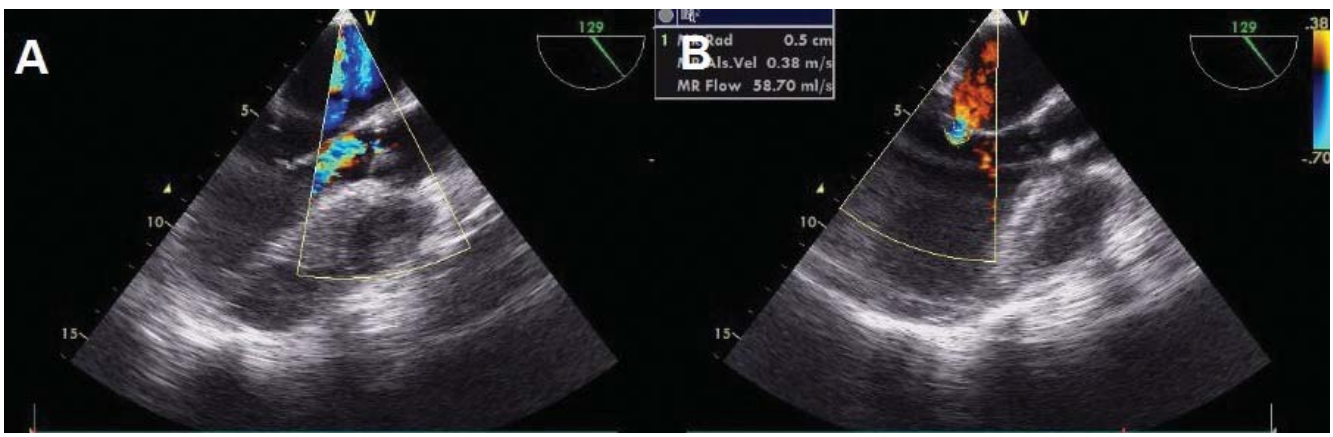

Figure 2. Transesophageal echocardiography. Midesophageal 129-degree view. Color Doppler at the level of aortic valve – eccentric aortic regurgitation (AR) with a jet width ratio relative to left ventricular outflow tract of 48% (qualitative parameter that can underestimate the severity of AR in eccentric jets) corresponding to moderate AR (panel A). Color Doppler at the level of mitral valve - measure of the proximal isovelocity surface area radius (0.5 cm). This value was used to calculate the effective regurgitant orifice area (0.2 cm^2) and regurgitant volume (37 ml), quantitative parameters indicative of moderate mitral regurgitation (panel B).

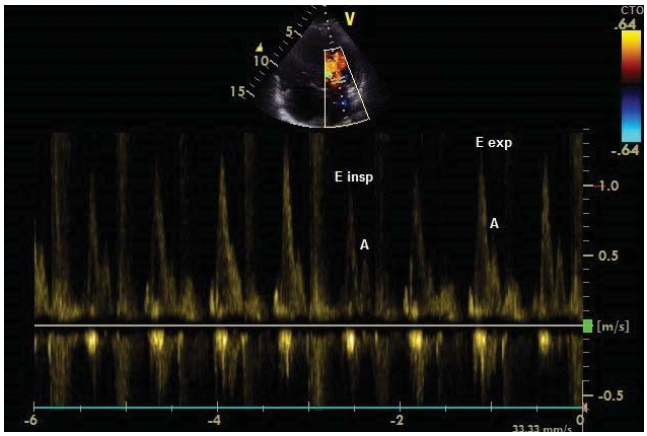

Figure 3. Transthoracic echocardiography. Mitral inflow pulsed-wave spectral Doppler showing restrictive pattern (E/A ratio >2) and respiratory variations - a decrease of peak flow velocity with >25% (from 1.27 to 0.9 m/s) during inspiration (insp – inspiration, exp – expiration).

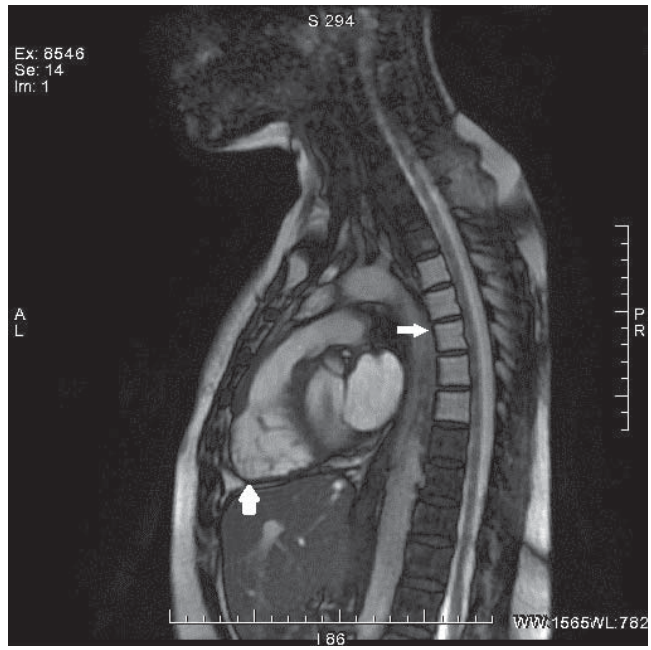

Figure 5. Cardiac MRI FIESTA RVOT showing segmental myocardial thinning at the level of the free wall of the right ventricle, with T1/T2 hyposignal with progressive contrast enhancement, having fibrotic substrate (big arrow); the bodies of T2-T6 thoracic vertebrae with hypersignal T1/T2 compatible with radiation-induced bone marrow degeneration (small arrow).

mediastinal fibrosis. Because the non-invasive testing was inconclusive she was transferred to "Prof. Dr. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases where she underwent cardiac catheterization which confirmed the diagnosis of constrictive pericarditis. The coronarography performed on this occasion revealed normal epicardial coronary arteries. The patient was referred for surgery, and given the severity of the associated valvulopaties, the heart team decided in favor of complex intervention with pericardial stripping and concomitant aortic, mitral and tricuspid valve surgery. At the moment she is admitted to "Prof. Dr. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases in the I Cardiovascular Surgery Clinic recovering after she successfully underwent surgery.

DISCUSSIONS

We presented this case to highlight the risk of CV complications that can appear years after finishing the treatment for HL and thus, the importance of syste-

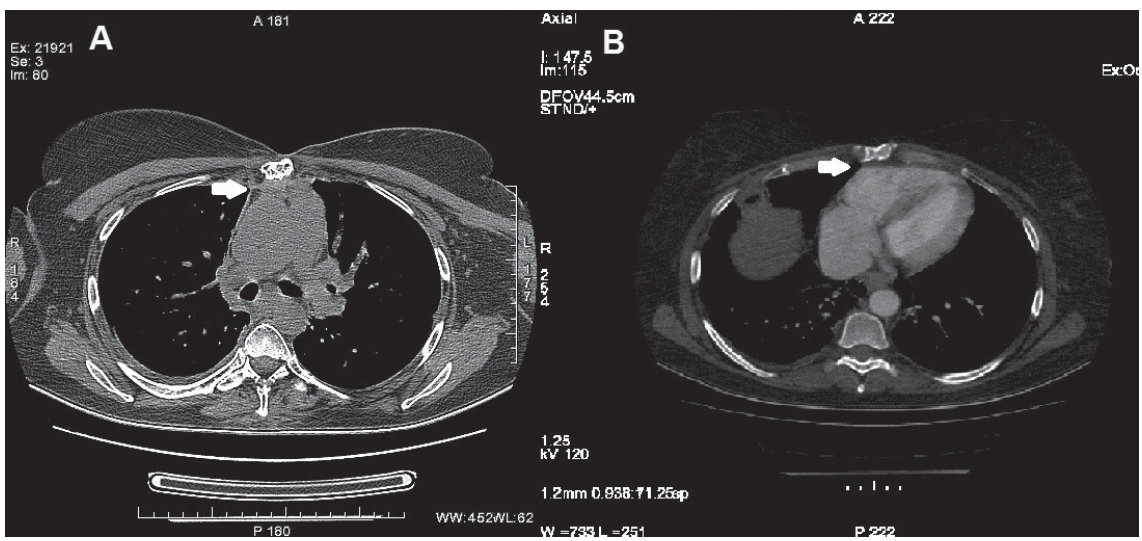

Figure 4. Chest spiral CT scan with radiocontrast agent showing reduction till extinction of the fat from the anterior mediastinum, which is being replaced by high-density strips with minimal contrast stain, indicative of fibrosis (arrow), that cause pleuro-pericardial joining to the anterior thoracic wall (panel A) with minimal retractile effect on the right ventricle (panel B).

matic follow-up of patients who received cardiotoxic therapies.

The long-term survivors of HL must be monitored periodically not only for disease recurrence but also for long-term complications related to the treatment[4]. Since 2000s most patients are treated with ABVD chemotherapy with or without RT, and those may generate various long-term sequelae (second malignancy, CVD, pulmonary fibrosis, thyroid dysfunction, infertility, muscle atrophy etc)[4]. From these, CVD is the most common non-malignant cause of death in long-term survivors of HL[4]. Long-term CV complications are mainly due to doxorubicine-based chemotherapy and RT, with an additive effect when both are used[7]. HL survivors will experience more than twice the number of CVD, nearly five times the number of more severe CV conditions and, on average, have one severe, life-threatening, or fatal CV condition, when compared to community controls[8].

Anthracyclines (eg, doxorubicin) induce cardiotoxicity mainly by oxidative stress, the generation of reactive oxygen species and lipid peroxidation of the cell membrane damaging the cardiomyocites[5]. This cardiotoxicity may be classified in acute (immediately after infusion), early (within the first year of treatment) or late (median of 7 years after treatment) and is mainly related to the total dose used during the treatment[4,5,9]. A dose of 400 mg/m^2 of doxorubicin is associated with a 5% incidence of congestive HF, and higher doses lead to an exponential increase in risk[10]. Anthracycline induced cardiotoxicity usually consist in a continuous progressive decline in LVEF that is initially asymptomatic[5]. If this dysfunction is detected early and treated with HF medications, patients usually have a good functional recovery, but if it's identified later, HF is typically difficult to treat[11].

The incidence of RT- induced cardiotoxicity is difficult to evaluate but the risk is related to the volume of the heart irradiated and the dose received[5,12]. Supradiaphragmatic RT, that include portions of the heart, can generate acute or delayed pericardial disease, myocardial ischemia (through the development of severe atherosclerotic and non-atherosclerotic disease), cardiomyopathy (restrictive cardiomyopathy due to myocardial fibrosis), heart failure, valvular abnormalities, or conduction defects (bradycardia, sick sinus syndrome and heart block)[3]. From those, the most common are valvular disorders, angina pectoris and myocardial infarction[12]. The median time to diagnosis is 19 years after treatment and the risk of CVD persists for at least 25 years after the initial treatment[12,13]. A clinically significant valvular disease can appear in up to 40% of HL survivors and gradually progresses in time[12]. It can involve the aortic, mitral and tricuspid valves with aortic insufficiency being the most prevalent one[12]. Cardiac valve surgery is challenging in these patients due to mediastinal fibrosis, impaired wound healing and associated coronary artery, myocardial and pericardial disease[5]. The transcatheter valve implantation may be an attractive option in this situation[5]. Pericardial disease (pericardial effusion with or without tamponade and pericardial constriction), rarely occurs nowadays, due to lower doses and modern RT techniques[12]. In this patients the diagnosis of constrictive pericarditis is very challenging due to the difficulty to identify the degree of underlying restrictive cardiomyopathy, so these patients may require multimodal imaging (including echocardiography, CT, and cardiac MRI) and invasive hemodynamic catheterization to assess elevation in filling pressures with diastolic equalization, ventricular interdependence and intrathoracic-intracardiac dissociation[14,15].

Our patient experienced complex early (effusive pericarditis with cardiac tamponade) and late CV complications (multiple valvulopaties, mild left ventricle - LV - systolic dysfunction, bifascicular block, prolonged QT and constrictive pericarditis) and we believe that extended-field RT was the main cause as the total dose of doxorubicin administered was less than 300 mg/m^2.

The HL survivors are also at increase risk of respiratory complications, as was the case of our patient. The pulmonary toxicity is mainly generated by bleomycin and RT. They both can generate pneumonitis and pulmonary fibrosis associated with increased mortality[3]. There are also emerging data that chest RT may be associated with pulmonary hypertension through pulmonary vascular damage, but the connection is not as clearly established as the one with pulmonary fibrosis[3]. The presence of pulmonary fibrosis in our patient is a confounding factor in establishing the severity of symptoms attributable to the cardiac involvement and negatively impacts survival.

HL survivors must be screened similar to other high-risk populations and offered lifelong surveillance. Patients must undergo an annually exam at their family doctor with a clinical exam, serum measurements of lipid profiles and glucose levels[3]. A cardiology exam (with ECG and TTE) must be made at the beginning of the treatment, periodically during the treatment

and after the completion of treatment (that serves as baseline evaluation for further exams). After this, the patient must be referred to a cardiologist whenever there are symptoms and signs suggestive of CVD, at 1 and 5 years after completion of cancer treatment (if they received ≥300 mg/m^2 of doxorubicin or equivalent[5], or if they developed cardiotoxicity during chemotherapy), and regularly after 5 years from RT (at least every 5 years thereafter, even if asymptomatic). TTE remains the method of choice for the detection of myocardial dysfunction, the two-dimensional (2D) biplane Simpson method being recommended for estimation of ventricular volumes and LVEF (unless three-dimensional - 3D - echocardiography is available, which is the best echocardiographic method for LVEF measurement)[5]. Cancer therapeutics-related cardiac dysfunction is defined as a decrease in more than 10% of the LVEF, to a value below 50%[5]. Additional diagnostic studies can help the diagnosis: contrast echocardiography, 3D echocardiography, 2D and 3D speckle tracking echocardiography, nuclear imaging, MRI, cardiac biomarkers (troponin and natriuretic peptides), noninvasive stress testing or coronary angiography[3,5,16]. Whenever possible, myocardial deformation parameters measured by tissue Doppler imaging or speckle tracking echocardiography should be used to identify early myocardial injury and to anticipate ventricular dysfunction[17]. A relative percentage reduction in peak systolic global longitudinal strain (GLS) of >15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction[5,17]. Cardiac MRI is a useful tool if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline[5]. It also serves to evaluate the pericardium (especially after RT) and can detect diffuse myocardial fibrosis using T1/T2 mapping and extracellular volume fraction evaluation[5]. The cardiac biomarkers may be considered in order to detect early cardiac injury, abnormal results being indicative of an increased risk of cardiotoxicity[5]. New elevation of high-sensitivity-cardiac troponin predicts subsequent LV dysfunction with poor prognosis in patients receiving anthraciclines[5,18]. Although the use of natriuretic peptides to detect HF is widely established, in the context of chemotherapy, their role in routine surveillance to define the high-risk patients needs further investigation[5]. An increase in cardiac biomarkers in patients receiving anthracyclines identifies those who may benefit from angiotensin converting enzyme inhibitor (ACEI)[5].

Since the CV complications in these patients are frequently complex and need multiple diagnostic techniques that are rarely available in the same hospital, delays in the diagnosis will occur, as in the case of our patient. We want to emphasize the need for centers of excellence with cardio-oncological expertise with readily available adequate diagnostic technologies.

To minimize the lost to follow-up, patients should be encouraged to take a more active role, and this can be achieved by informing them of their increased risk of CVD and of the importance of adherence to screening practice, early reporting of signs and symptoms of CVD and risk-reducing behavioral modification[4,5]. Cardiac risk factors (hyperlipidemia, hypertension, diabetes mellitus, smoking, obesity, sedentary lifestyle) should be actively screened and aggressively controlled as they increase the risk of CV disease after HL. The LDL-cholesterol targets in HL survivors is 100 mg/dL (or lower) and the recommended therapy is a statin[3,4]. Some authors recommend for prevention of atherosclerosis in cancer survivors the daily administration of aspirin (at least 81 mg)[3]. Patients who develop asymptomatic LV dysfunction or HF during or after cancer therapy will benefit from ACEI or angiotensin II receptor blockers and beta-blockers[5,19].

In our patient case, after a severe early complication, a long asymptomatic period followed, with the onset of symptoms 14 years after the cancer therapy. Once the symptoms appeared they progressed despite optimal medical therapy. This highlights the importance of regular follow-up for early diagnosis and treatment which can have a significant impact on prognosis[20]. The choice of medical treatment in our patient was in accordance with current practice guidelines for heart failure (an ACEI substituted by an angiotensin II receptor blocker due to side effects, a beta-blocker, a loop diuretic and antialdosteronic agent) and prevention of atherosclerotic disease in cancer survivors (aspirin 100 mg/day and statin with a LDL-cholesterol target <100 mg/dL)[3-5,21]. Surgical treatment was decided for constrictive pericarditis, early pericardiectomy with complete decortication (if technically feasible) being the mainstay of treatment, before severe constriction and myocardial atrophy occur[22,23]. Although none of the valvular lesions had the criteria to warrant surgery by themselves, their association, together with the need for pericardiectomy and the risks associated with a possible further reintervention, prompted the decision for combined surgery, in order to address all issues with a one-time complete operation[24]. Even in experienced centers, the outcomes of patients with radio-induced heart disease undergoing cardiac

surgery are significantly worse than a comparable matched population[25]. In patients with undergoing valve surgery the most important predictor for perioperative mortality is the presence of constrictive pericarditis, these patients having a 30-day mortality rate of 40%[26]. Thus, the prognosis of our patient remains reserved given the complex heart involvement, the severe fibrosis of the mediastinum that may interfere with the surgery ("*frozen mediastinum*") and the associated pulmonary disease.

CONCLUSIONS

As the life expectancy of HL patients increases, the focus on cardiovascular health becomes a priority. It is imperative to raise awareness of possible CVD among cancer survivors as well as to provide appropriate follow-up of such patients in clinical practice in order to minimize the burden of late CV morbidity and mortality.

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Conflict of interest: none declared

Abbreviations:

2D	Two-dimensional
3D	Three-dimensional
ABVD	Adriamycin, Bleomycin, Vinblastine, Dacarbazine
ACEI	Angiotensin Converting Enzyme Inhibitor
AR	Aortic Regurgitation
AVD	Adriamycin, Vinblastine, Dacarbazine
BMI	Body Mass Index
bpm	beats per minute
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
ECG	Electrocardiogram
GLS	Peak Systolic Global Longitudinal Strain
HF	Heart Failure
HL	Hodgkin Lymphoma
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
MRI	Magnetic Resonance Imaging
RT	Radiation Therapy
RVOT	Right Ventricle Outflow Tract
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography

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