

## Long-Term Radiotherapy-Induced Cardiac Complications: A Case Report

Department of Cardiology, University Hospital of the Canary Islands, Tenerife, Spain

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

EF **Néstor Báez-Ferrer**  
E **María Manuela Izquierdo-Gómez**  
E **Carima Beyello-Belkasem**  
A **Pablo Jorge-Pérez**  
DE **Martín J. García-González**  
F **Julio J. Ferrer-Hita**  
E **Alejandro De la Rosa-Hernández**  
EF **Javier García-Niebla**  
AEF **Juan Lacalzada-Almeida**

**Corresponding Author:** Juan Lacalzada-Almeida, e-mail: [jlacalzada@gmail.com](mailto:jlacalzada@gmail.com)  
**Conflict of interest:** None declared

**Patient:** Male, 48  
**Final Diagnosis:** Late cardiac complications postradiotherapy  
**Symptoms:** Chest pain • dyspnea • syncope  
**Medication:** —  
**Clinical Procedure:** Diagnostic and therapeutic techniques in cardiology  
**Specialty:** Cardiology

**Objective:** Unusual or unexpected effect of treatment

**Background:** Tumor disease has improved survival due to therapeutic advances and early diagnosis. However, anti-neoplastic treatment involves generating harmful side effects in the body, both in the short-term and in the long-term. One of the most important side effects is cardiovascular disease after radiotherapy, which in addition to being influenced by classic cardiovascular risk factors, can be also be influenced by anti-neoplastic therapy, and represents the main cause of death after a second cancer. We present a case that synthesizes the most relevant and determining aspects of radiotherapy-induced heart disease.

**Case Report:** We present the case of a 48-year-old male with a personal history of mediastinal Hodgkin lymphoma who was treated with local radiotherapy 20 years ago, and who was admitted to hospital due to dyspnea and oppressive chest pain with efforts. He was diagnosed with severe aortic stenosis, and a coronary angiography confirmed the existence of coronary disease. Two years before, he had been admitted to hospital due to syncope and a pacemaker had been implanted. This patient experienced several cardiovascular complications that could be attributed to the radiotherapy treatment received in his past.

**Conclusions:** Radiotherapy shows multiple cardiological complications, especially when applied at the thoracic level. This fact is very relevant, and this report can help determine the aspects of radiotherapy-induced heart disease affecting the mortality and morbidity of these patients.

**MeSH Keywords:** Arrhythmias, Cardiac • Breast Neoplasms • Coronary Artery Disease • Heart Valve Diseases • Hodgkin Disease • Radiotherapy Dosage

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/917224>

 2074   6  35



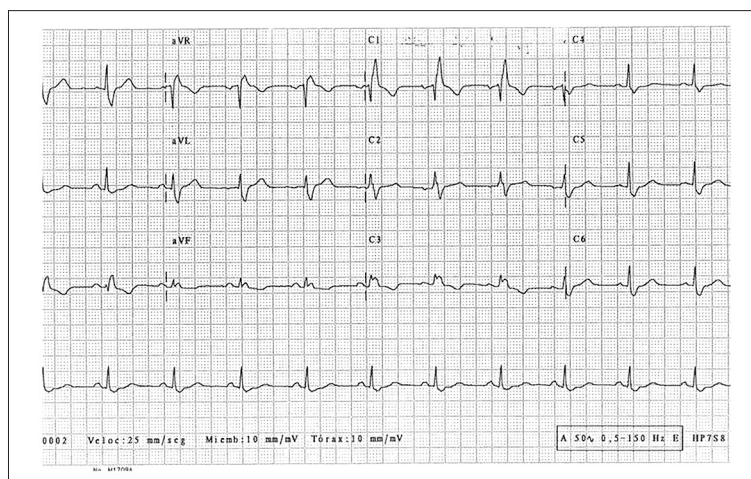
## Background

Nowadays, new chemotherapy agents and radiotherapy techniques have improved mortality and survival of patients with neoplastic diseases; however, new therapies can cause significant side effects [1]. Even though cancer treatment is focused on carcinogenic cells, healthy cells are exposed to secondary toxicity [2] and one of the most important side effects, worsening morbidity and mortality, is the so-called “radiation-induced” heart disease (RIHD). Cardiovascular disease is one of the main causes of mortality in oncologic patients and it could have subclinical cardiac alterations increasing risk of RIHD [1]. Breast cancer (BC) and Hodgkin’s lymphoma (HL) are often treated with chest radiotherapy and are directly related to the development of RIHD [1]. For patients with lymphoma who develop RIHD, it usually manifests 15 to 20 years after initial treatment and it seems that younger patients are more susceptible than older patients. Long-term survivors of Hodgkin’s lymphoma are at 4-fold to 7-fold increased risk of coronary artery disease compared to the general population and an accumulated incidence of cardiovascular disease up to 50% at 40 years after treatment. The risk of myocardial infarction in patients treated for Hodgkin’s lymphoma is increased (2-fold to 7-fold) compared with the general population, with a 30-years cumulative incidence of 10%. Acute pericarditis and chronic pericardial effusion might appear 6 to 12 months after radiotherapy, however, acute pericarditis is a rare complication with the use of more contemporary thoracic radiotherapy strategies. There have been reports of stenosis and regurgitation of the mitral and aortic valves. There might be fibrosis of the conduction system that causes disturbances of the rhythm [2,3]. Both breast cancer and Hodgkin’s lymphoma are the most common indications of thoracic radiotherapy in young people and this therapy improves their survival. The relative risk of fatal cardiovascular events in breast cancer and Hodgkin’s lymphoma is between 2.0 and 7.0 and between 1.0 and 2.2, respectively [3]. However, the current incidence is

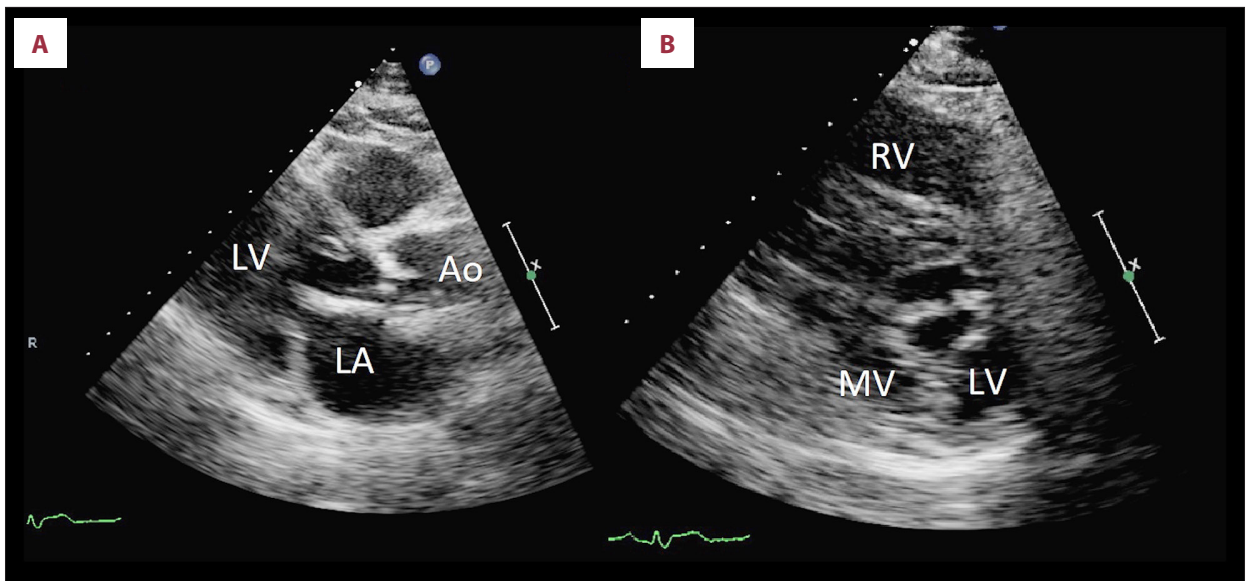
unknown because radiotherapy methods and protocols have changed significantly over time, so they have not been evaluated in the long-term. Here is a case report of a patient with multiple side effects on his cardiac function and structures after thoracic radiotherapy.

## Case Report

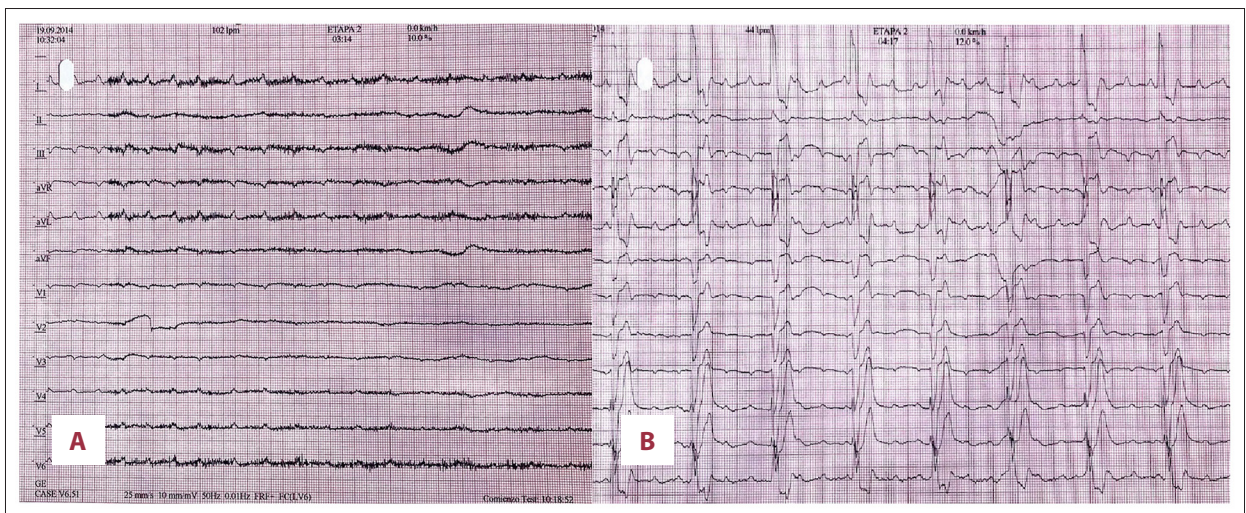
A 48-year-old male with a personal history of mediastinal Hodgkin’s lymphoma, type nodular sclerosis in stage II, treated with local radiotherapy and chemotherapy 20 years ago and without current evidence of recurrence, was admitted to our Cardiology Department due to progressive dyspnea and chest pain. The patient received mantle-type supradiaphragmatic radiation therapy with a cumulative dose of approximately 36 Gy and associated chemotherapy. We have no information on the chemotherapy regimen received by our patient, because he had been treated at a different center. The patient did not have any cardiovascular risk factor or known history of heart disease. Two years before the current admission, he had been admitted to the Cardiology Department of our hospital due to effort syncope, not preceded by prodromes, and without any other symptomatology. Clinical semiology of mild aortic stenosis and mild mitral valve regurgitation excelled in the physical examination, without clinical data of heart failure. The bilateral carotid sinus massage was negative. The electrocardiogram at that time showed sinus rhythm and complete right bundle branch block (Figure 1). Heart rate monitoring during admission was normal. A transthoracic echocardiogram (TTE) was performed showing slight left ventricular hypertrophy with diastolic dysfunction type I. Thickened aortic valve with isolated areas of calcification and slightly decreased opening, Doppler echocardiography mean gradient was 23 mmHg and an aortic valve area of 1.8 cm<sup>2</sup> was calculated, also showing mild-moderate aortic regurgitation. Mitral valve was thickened, with some areas of mild valvular and mitral ring calcification, and with mild



**Figure 1.** Electrocardiogram showing the basal rhythm of the patient. Sinus rhythm with complete right bundle branch block.



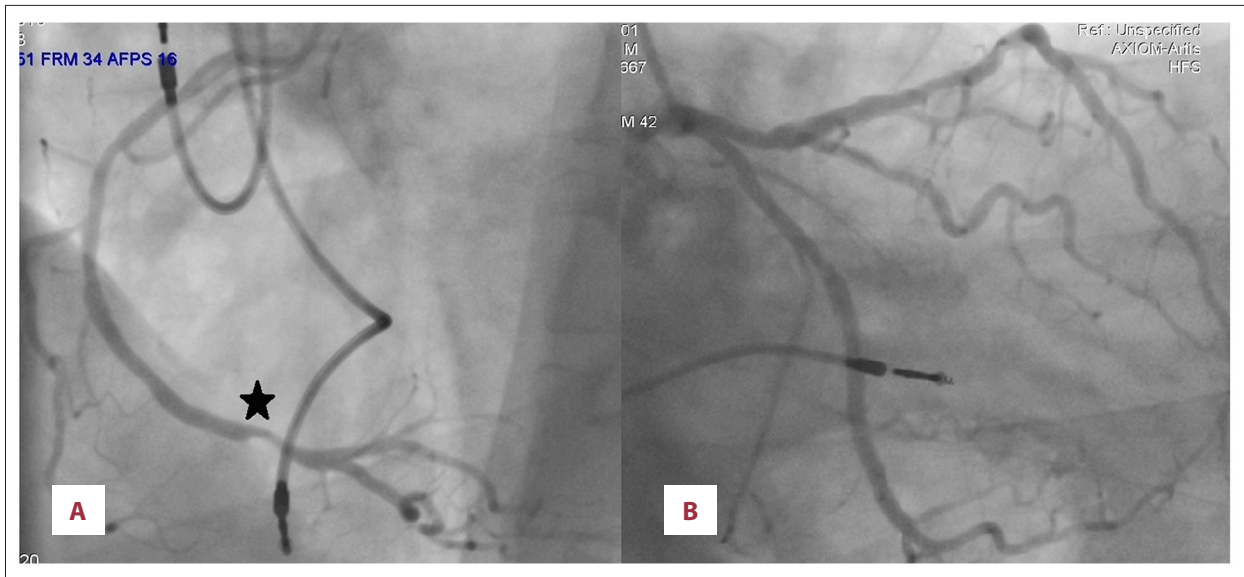
**Figure 2.** Transthoracic echocardiography. (A) Long axis parasternal view, with aortic and mitral valvular thickening. (B) Short axis parasternal view, mitral valve thickening, with some area of mild valvular and mitral ring calcification. Ao – aorta; LA – left atrium; LV – left ventricle; RV – right ventricle; MV – mitral valve.



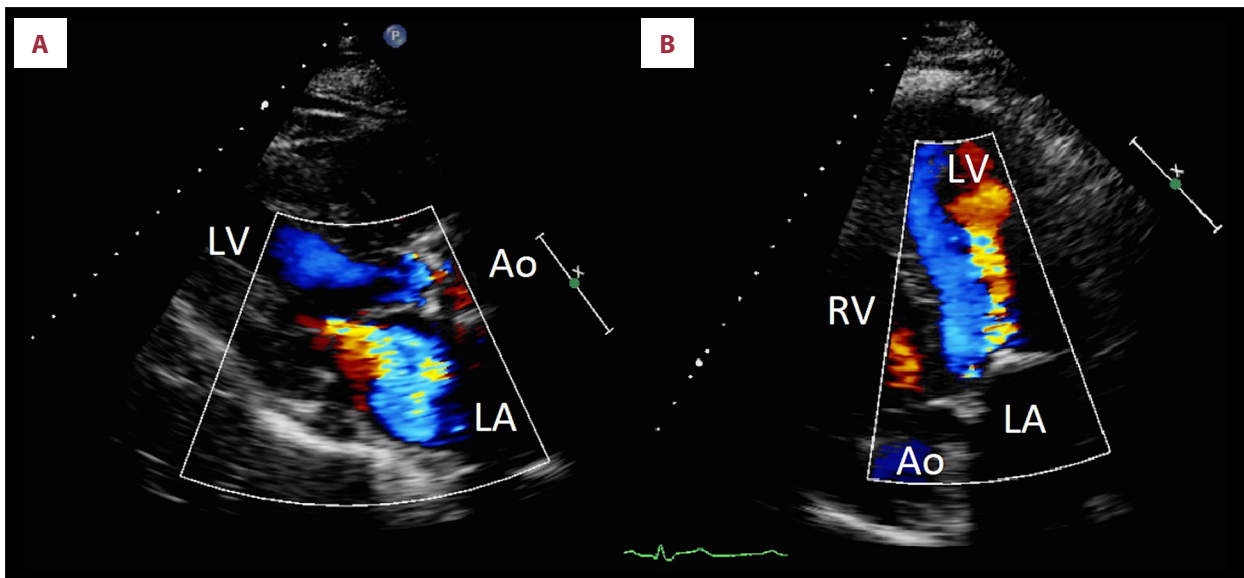
**Figure 3.** Electrocardiogram of the stress test. (A) Asystole during stage 2 of the stress test. (B) After cessation of stress test, recovery of ventricular activity showing complete atrioventricular block with complete left bundle branch block.

regurgitation (Figure 2). All these findings were attributed to former radiotherapy in the absence of any clinical history of interest. A tilt table test and electrophysiological study were performed, and both were normal. Since the clinical symptoms were presented in relation to exertion, a treadmill test was performed. During this test, the patient showed a complete atrioventricular block with a 10-second asystole (Figure 3A), recovering pulse once the test was stopped (Figure 3B). Coronary angiography was performed, and significant obstructive coronary lesions were ruled out. (Figure 4). The conduction disorder was attributed to a late complication of radiation therapy and a definitive bicameral pacemaker was implanted.

Two years later, he was readmitted due to dyspnea and progressive angina. In the examination, clinical semiology of left and right heart failure, with cardiac auscultation of double aortic lesion with severe stenosis and moderate mitral insufficiency excelled. A new TTE was performed that evidenced a hypertrophic left ventricle, with preserved left ventricular systolic function. The aortic and mitral valves showed more severe thickening of the leaflets and more extensive and intense areas of calcification, with a double aortic lesion with severe stenosis and mild regurgitation, and moderate mitral regurgitation, accompanied by mild pulmonary arterial hypertension (Figure 5). The angiographic and hemodynamic study



**Figure 4.** Coronary angiographic study and presence of pacemaker bicameral electrodes. (A) Right coronary artery with presence of non-significant obstructive lesion (asterisk). (B) Left coronary artery without significant obstructive lesions.



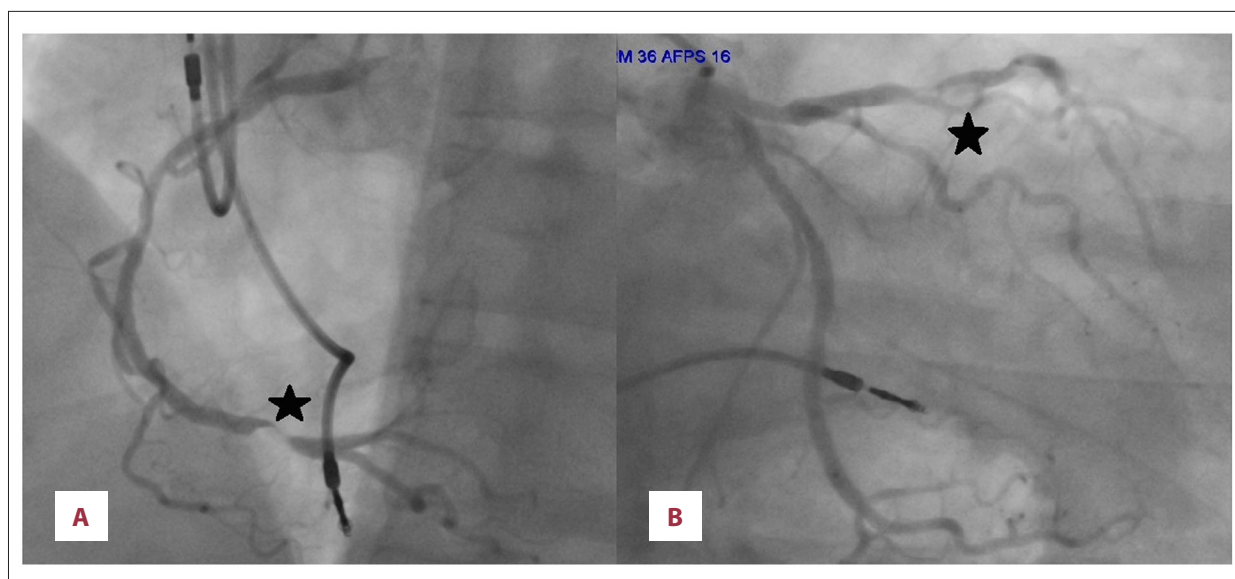
**Figure 5.** Transthoracic echocardiography. (A) Long axis parasternal view, with presence of jet of moderate mitral regurgitation. (B) Apical 5 chambers view, jet of mild aortic regurgitation. Ao – aorta; LA – left atrium; LV – left ventricle; RV – right ventricle.

evidenced coronary artery disease of 2 vessels, posterior descending coronary artery dependent on the right coronary artery (Figure 6A) and left anterior descending coronary artery (Figure 6B), with mild pulmonary arterial hypertension and severe pulmonary capillary hypertension with the presence of prominent V wave. The patient underwent aortic and mitral valve replacement surgery with mechanical prostheses, St. Jude n° 19 in aortic position and St. Jude n° 25 in mitral position, as well as complete myocardial revascularization by double coronary artery bypass grafting (left internal mammary artery to

left anterior descending coronary artery and saphenous vein graft to posterior descending coronary artery). The patient's postoperative course was satisfactory, being discharged and remaining asymptomatic until the present time.

## Discussion

Radiotherapy may significantly increase the risk of triggering obesity, hypertension, dyslipidemia, and diabetes, worsening



**Figure 6.** Coronary angiographic study and presence of pacemaker bicameral electrodes. (A) Right coronary artery with presence of significant obstructive lesion (asterisk). (B) Left coronary artery with significant obstructive lesion in anterior descending coronary artery (asterisk) and circumflex artery free of significant obstructive lesions.

cardiovascular risk [4]. The effects of radiation therapy on myocardial structures and function include vascular alterations, molecular interactions, induction of apoptosis, and deterioration of stem cells [2]. Long-term side effects have been seen in cardiomyocytes due to little regenerative capacity and at vascular histology, despite its extensive regeneration [5]. Radiation induces injury to single or double DNA chains, shortening telomeres and aging the cell, representing a significant impact on the development of RIHD [6]. This shortening in endothelial cells has been linked to the generation of atherosclerosis [7]. At a histologic level, radiotherapy generates vasodilatation with production of proinflammatory cytokines [8], resulting on a final fibrotic tissue formation response which would replace the native myocardium, triggering valvular alterations, conduction disturbances, cardiomyopathies, coronary artery disease, etc. [9,10]. However, in spite of everything, the pathophysiological mechanism that ultimately generates this cascade is still unknown.

Cardiac absorbed dose of radiotherapy is greater in patients with left side breast cancer than those with right side breast cancer with higher mortality rates in the first group [11]. Mediastinal radiotherapy for patients with Hodgkin's lymphoma triggered increased long-term cardiovascular events [12]. Nowadays, with 3-dimensional conformal radiotherapy and field-in-field techniques, we can reduce the patient's direct cardiac dose [11]. During the 1970s and 1980s, radiation absorbed by the heart was greater in patients with left side breast cancer than those who had neoplasia on the right side [11], and a higher cardiac dose was absorbed on the left side than on the right, around 13 to 17 Gy and 2 to 10 Gy respectively [13].

Currently with more precise measures, such as 3-dimensional conformal radiotherapy and field-in-field techniques, the direct cardiac dose of the patient can be reduced [11]. Other techniques such as image guided radiotherapy, intensity modulated radiotherapy, and stereotactic body radiotherapy determine better image and delimitation of tumor volume in order to reduce the dose of adjacent organs. Even techniques such as deep inspiration breath hold versus free breathing reduce cardiac exposure by 50%, assuming 2 to 3 Gy of the total dose absorbed. The therapies with x-rays and gamma particles accumulate electromagnetic radiation in depth. However, therapies with charged particles such as protons or heavy ions generate greater attenuation in deep layers where the therapeutic objective has been set [11].

## Cardiac alterations

### Valvular disease

Incidence of valvular disease ranges from 2% to 17% after radiotherapy and may be underestimated [14]. It is higher when applied to the left breast than to with right breast [15]. Incidence increases when absorbed cardiac dose is 30 Gy or greater in patients with Hodgkin's lymphoma treated with radiotherapy [14,16]. Radiotherapy generates calcification and fibrosis, with 90% mitral and aortic calcification at 20 years [17]. Left valves are more affected, and the aortic valve has a significant incidence of stenosis of 16% after 20 years of radiotherapy, as our clinical case. Surgical treatment should be considered for severe valvular disease and percutaneous valve replacement could be considered for patients at high surgical risk [18,19].

### **Coronary artery disease**

Radiotherapy alone is a risk factor for developing long-term coronary artery disease and pathological changes generated on medium and large caliber coronary vessels are similar to those produced by atherosclerosis [10]. Heidenreich et al., described coronary artery disease incidence around 10% after mediastinal radiotherapy, with an absorbed dose between 25 and 42 Gy [17]. The left anterior descending coronary artery is the most predisposed in up to 85% of cases, possibly in relation to the absorbed dose in the anterior face of the thorax [20]. Management of radiation-induced coronary artery disease follows therapeutic guidelines. However, thoracic fibrosis makes coronary artery bypass grafting (CABG) more difficult and the left internal mammary artery could be occluded [21]. Due to a possibly high mortality at follow-up by CABG [22] percutaneous revascularization and new drug-eluting stents might be an alternative, at least for patients at high surgical risk [23].

### **Conduction disturbances**

Conduction disturbances secondary to radiotherapy range from isolated ventricular extra systolic to atrioventricular conduction disorders [10]. Conduction block disorders are described immediately after radiotherapy [24] and most reported are of complete or incomplete blockage of right branch conduction [25]. Conduction disorders after radiotherapy have been described for the last 30 years, and atrioventricular block is associated with a dose around 52 Gy [26]. However, Santoro et al. described one case of atrioventricular block after 6 years of mediastinal radiation [27]. All evidence suggests higher doses of radiation induce conduction disturbances than other cardiac disorders [23]. Autonomic dysfunction generated by thoracic radiotherapy might increase heart rates [28]. Even our case was initially presented as an atrioventricular conduction disorder in relation to exertion [29].

### **Pericardial disease**

One of the RIHD after radiation is pericardial disease. This one is one of the earliest cardiac disorder after thoracic radiation and currently, near 5% to 6% of left breast cancer cases treated with radiotherapy could develop it [30]. Pericardial disease after radiotherapy is dose-dependent and the mean cardiac absorbed dose described is near 36 or 40 Gy. However, the incidence could be higher around 50 Gy and it improves

when cardiac absorbed dose is less than 26 Gy [30]. Radiation induces pericardial fibrosis after inflammatory and microvascular changes, hindering venous and lymphatic drainage [10]. Constrictive pericarditis usually appears after 12 months of radiotherapy which spontaneously resolves in most cases, but other cases progress to a restrictive disorder requiring pericardiectomy [21,31].

### **Cardiomyopathy and myocardial fibrosis**

After radiotherapy, there is an insufficient capillary proliferation due to microvascular damage generating fibrosis tissue [32]. Fibrosis tissue increases filling pressures in the left ventricle, and reduces the ejection fraction [10] and anterior face of the myocardium could have smaller compliance [33]. Gadolinium-enhancement magnetic resonance imaging may be useful for the early diagnosis [34] and final treatment usually focuses on cardiac transplantation [35].

## **Conclusions**

This unusual case illustrates several cardiac complications possibly secondary to radiotherapy, such as advanced disorders of atrioventricular conduction, coronary artery disease, and mitral aortic valve disease, which have never before been described in the same patient and in a short period of time of 2 years. Radiotherapy in neoplasms, especially in thoracic neoplasms, generates a significant cardiac absorbed dose. Improvement in survival after radiotherapy in oncological pathology implies development of RIHD, constituting one of the main causes of long-term mortality. Our case shows the importance of using new radiotherapy techniques to protect the heart and limit morbidity and mortality from cardiovascular diseases. Histopathological changes degenerate into vascular damage and myocardial fibrosis, determining a broad spectrum of cardiac pathology, often requiring surgical treatment and even cardiac transplantation. There are currently not enough studies related to this topic and therefore, more studies are needed to analyze new techniques of thoracic radiotherapy, current incidence of RIHD and how to prevent complications both cardiovascular and from other organs.

### **Conflict of interest**

None.

## References:

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al: Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*, 2013; 49(6): 1374–403
2. Abe JI, Martin JF, Yeh ETH: The future of onco-cardiology: We are not just 'side effect hunters'. *Circ Res*, 2016; 119(8): 896–99
3. Curigliano G, Cardinale D, Dent S et al: Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. *Cancer J Clin*, 2016; 66(4): 309–25
4. Armstrong GT, Oeffinger KC, Chen Y et al: Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*, 2013; 31(29): 3673–80
5. Tzahor E, Poss KD: Cardiac regeneration strategies: Staying young at heart. *Science*, 2017; 356(6342): 1035–39
6. Kaina B: DNA damage-triggered apoptosis: Critical role of DNA repair, double-strand breaks, cell proliferation and signaling. *Biochem Pharmacol*, 2003; 66(8): 1547–54
7. Minamino T, Komuro I: Vascular cell senescence: Contribution to atherosclerosis. *Circ Res*, 2007; 100(1): 15–26
8. Yarnold J, Vozenin Brotons MC: Pathogenetic mechanisms in radiation fibrosis. *Radiother Oncol*, 2010; 97(1): 149–61
9. Spetz J, Moslehi J, Sarosiek K: Radiation-induced cardiovascular toxicity: Mechanisms, prevention, and treatment. *Curr Treat Options Cardiovasc Med*, 2018; 20(4): 31
10. Taunk NK, Haffty BG, Kostis JB, Goyal S: Radiation-induced heart disease: Pathologic abnormalities and putative mechanisms. *Front Oncol*, 2015; 5: 39
11. Menezes KM, Wang H, Hada M, Saganti PB: Radiation matters of the heart: A mini review. *Front Cardiovasc Med*, 2018; 5: 83
12. Van Nimwegen FA, Schaapveld M, Janus CP et al: Cardiovascular disease after Hodgkin lymphoma treatment 40-year disease risk. *JAMA Intern Med*, 2015; 175(6): 1007–17
13. Taylor CW, Nisbet A, McGale P, Darby SC: Cardiac exposures in breast cancer radiotherapy: 1950s–1990s. *Int J Radiat Oncol Biol Phys*, 2007; 69(5): 1484–95
14. Gujral DM, Lloyd G, Bhattacharyya S: Radiation-induced valvular heart disease. *Heart*, 2016; 102(4): 269–76
15. McGale P, Darby SC, Hall P et al: Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*, 2011; 100(2): 167–75
16. Cella L, Liuzzi R, Conson M et al: Multivariate normal tissue complication probability modeling of heart valve dysfunction in Hodgkin lymphoma survivors. *Int J Radiat Oncol Biol Phys*, 2013; 87(2): 304–10
17. Heidenreich PA, Hancock SL, Lee BK et al: Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol*, 2003; 42(4): 743–49
18. Chang AS, Smedira NG, Chang CL et al: Cardiac surgery after mediastinal radiation: Extent of exposure influences outcome. *J Thorac Cardiovasc Surg*, 2007; 133(2): 404–13
19. Dijos M, Reynaud A, Leroux L et al: Efficacy and follow-up of transcatheter aortic valve implantation in patients with radiation-induced aortic stenosis. *Open Heart*, 2015; 2(1): e000252
20. Correa CR, Litt HI, Hwang WT et al: Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol*, 2007; 25(21): 3031–37
21. Filopei J, Frishman W: Radiation-induced heart disease. *Cardiol Rev*, 2012; 20(4): 184–88
22. Wu W, Masri A, Popovic ZB et al: Long-term survival of patients with radiation heart disease undergoing cardiac surgery: A cohort study. *Circulation*, 2013; 127(14): 1476–85
23. Cuomo JR, Javaheri SP, Sharma GK et al: How to prevent and manage radiation-induced coronary artery disease. *Heart*, 2018; 104(20): 1647–53
24. Orzan F, Brusca A, Gaita F et al: Associated cardiac lesions in patients with radiation-induced complete heart block. *Int J Cardiol*, 1993; 39(2): 151–56
25. Tötterman KJ, Pesonen E, Siltanen P: Radiation-related chronic heart disease. *Chest*, 1983; 83(6): 875–78
26. Slama MS, Le Guludec D, Sebag C et al: Complete atrioventricular block following mediastinal irradiation: A report of six cases. *Pacing Clin Electrophysiol*, 1991; 14(7): 1112–18
27. Santoro F, Ieva R, Lupo P et al: Late calcification of the mitral aortic junction causing transient complete atrio-ventricular block after mediastinal radiation of Hodgkin lymphoma: Multimodal visualization. *Int J Cardiol*, 2012; 155(3): e49–50
28. Moslehi JJ, Ng A, Forman DE et al: Abnormal exercise response in long-term survivors of Hodgkin lymphoma treated with thoracic irradiation. *J Am Coll Cardiol*, 2015; 65(6): 573–83
29. Jorge-Pérez P, García-González MJ, Beyello-Belkasem C et al: Radiotherapy-induced recurrent syncope. *Rev Esp Cardiol (Engl Ed)*, 2015; 68(11): 1033–34
30. Marinko T: Pericardial disease after breast cancer radiotherapy. *Radiol Oncol*, 2019; 53(1): 1–5
31. Barbetakis N, Asteriou C, Kleontas A, Tsilikas C: Radiation-induced constrictive pericarditis and waffle procedure. *Asian Cardiovasc Thorac Ann*, 2012; 20(2): 225
32. Chello M, Mastroberto P, Romano R et al: Changes in the proportion of types I and III collagen in the left ventricular wall of patients with post-irradiative pericarditis. *Cardiovasc Surg*, 1996; 4(2): 222–26
33. Stewart RJ, Fajardo LF: Heart disease: An update. *Prog Cardiovasc Dis*, 1984; 27(3): 173–94
34. Zhuang XF, Yang YM, Sun XL et al: Late onset radiation-induced constrictive pericarditis and cardiomyopathy after radiotherapy. *Medicine (Baltimore)*, 2017; 96(5): e5932
35. Saxena P, Joyce LD, Daly RC et al: Cardiac transplantation for radiation-induced cardiomyopathy: The Mayo Clinic experience. *Ann Thorac Surg*, 2014; 98(6): 2115–21