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Case Report

Radiation Induced Valvular Heart Disease: A Case Report and Review of the Literature

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2. Keywords

Radiotherapy; Valvular heart disease; Radiation induced valvular heart disease

1. Abstract

1.1. Aims: This is a case report that well exemplifies the radiation-induced heart disease and a review of the literature with the purpose to identify its prevalence, pathophysiology, diagnostic modalities, and treatment options.

1.2. Case Report: We report the case of a 70-year-old female patient with a personal history of left breast cancer treated with radiotherapy and chemotherapy 30 years ago who presented to the cardiology Service referring progressive dyspnea. Transthoracic (TTE) and Transesophageal (TEE) echocardiography were performed and showed an expanded calcification of aortic and mitral valves that compromises the Left Ventricle Outflow Tract (LVOT), aorto-mitral curtain and mitral annulus resulting in hemodynamically significant aortic regurgitation and mitral and aortic stenosis. Aortic and mitral valve replacement surgery was the management strategy selected and successfully executed in this case.

This patient experienced cardiovascular complications, specially involving the left side heart valves, that must be attributed to the radiotherapy treatment received during cancer treatment in the past.

1.3. Conclusions: Thoracic radiotherapy can develop complications at different levels of the cardiovascular system. This case report exemplifies the valvular involvement and its associated morbidity in the, so-called, radiation induced heart disease.

3. Introduction

Chemotherapy agents and radiotherapy techniques have improved overall survival of patients with neoplastic diseases; however, these therapies can cause significant side effects. One of the most important of them, worsening morbidity and mortality, is the Radiation Induced Heart Disease (RIHD), that usually apears 20 to 40 years after initial treatment in survivors and can involve, almost, any cardiovascular structure [1].

Thoracic radiotherapy may directly affect heart valves, leading to both stenotic and regurgitant valve diseases. Due to the progressive nature of this entity, although valvular heart changes are found in most patients with RIHD, there exists a long latency until the valvular damage becomes symptomatic. Therapeutic management is challenging in these cases because of the high rates of perioperative morbidity and mortality [2].

4. Methods

We present a patient who experienced cardiovascular complications of thoracic radiotherapy, specially involving the left side heart valves, who was referred to our center to complete the diagnostic evaluation and treatment. Based in this case report we carry out a bibliographic review. We searched for publications containing terms 'valvular' or 'valve', 'cardiac' or 'cardiovascular' and one of the terms 'radiotherapy', 'radiation', or 'cancer'. All publications from 2000 onwards were screened for use in this review.

5. Case Report

A 70-year-old female with a personal history of left breast cancer, treated with surgery, local radiotherapy and, simultaneous, chemotherapy 30 years ago, was admitted to our center due to progressive dyspnea in the last three months. The patient received anterior mantle radiation therapy with a cumulative dose of approximately 35 Gy and associated chemotherapy. We have no additional information on the chemotherapy regimen because she had been treated of her malignant disease at a different center.

The electrocardiogram showed sinus tachycardia and complete right bundle branch block (Figure 1). A TTE was performed showing eccentric left ventricular hypertrophy with normal systolic function. Aortic valve was severely thickened and calcified with reduced opening. Doppler echocardiography showed severe aortic regurgitation (large central jet occupying 60% of the LVOT with a pressure half time of 200 msec) and moderate to severe aortic

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stenosis (mean gradient of 30 mmHg and an aortic valve area, calculated by the continuity equation, of 0.85 cm2). Mitral valve was thickened with mitral annulus and mild valvular calcification, resulting in moderate mitral stenosis (mean gradient of 6 mmHg) associated with mild mitral regurgitation. Also, there was noticed a severe calcification of the LVOT which extends to the aortic ring and the mitro-aortic curtain (Figure 2).

TEE was performed to complete the evaluation of the mitral valve disease and revealed severe calcification of the mitral annulus and the base of the mitral leaflets. However, the commissures and the tips of the valve appeared uninvolved (Figure 3).

The patient underwent multi-slice computer tomography to rule out significant coronary artery disease and the presence of an important structural alteration of the aortic wall, such as the porcelain aorta, that could rule out the conventional surgical approach (Figure 4).

Figure 1: Electrocardiogram showing Sinus tachycardia with complete right bundle branch block.

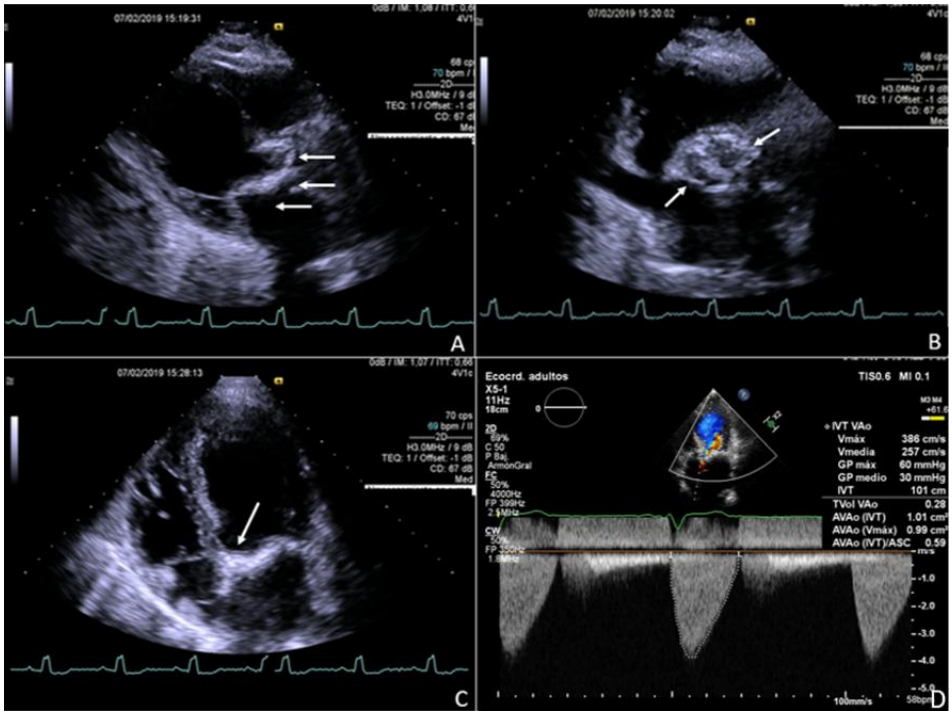

Figure 2: Transthoracic echocardiogram shows severe thickening and calcification of the aortic root, aortic valve, aorto-mitral curtain and the anterior mitral leaflet (arrows) on Long axis parasternal view (**A**), Short axis parasternal view (**B**) and Apical 4 Chambers view (**C**). Continuous-wave Doppler mode on the Apical 5 chambers view, reveals aortic regurgitation and an increased gradient across the aortic valve, with peak velocity near 4 m/s (**D**).

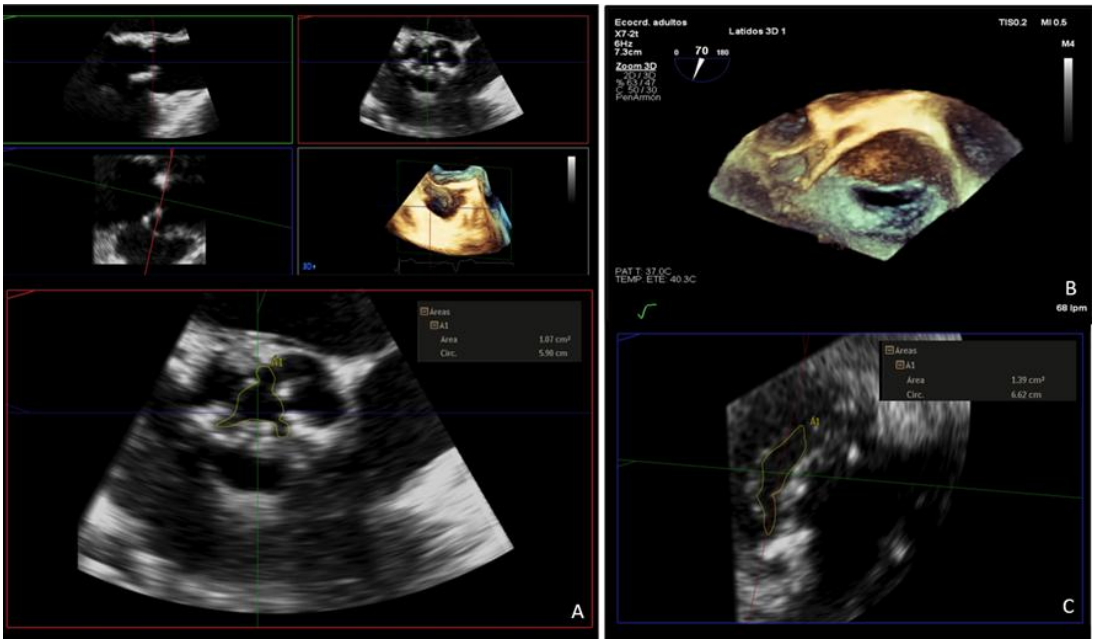

Figure 3: Transesophageal echocardiogram. A: Aortic valve area by three-dimensional planimetry was evaluated; the patient had moderate to severe stenosis. B: Three-dimensional TEE of the mitral valve as visualized from the left atrium reveals thickened leaflets with no commissural fusion. C. Mitral valve area by multiplane reconstruction of a 3D-TEE was assessed; the patient had moderate stenosis.

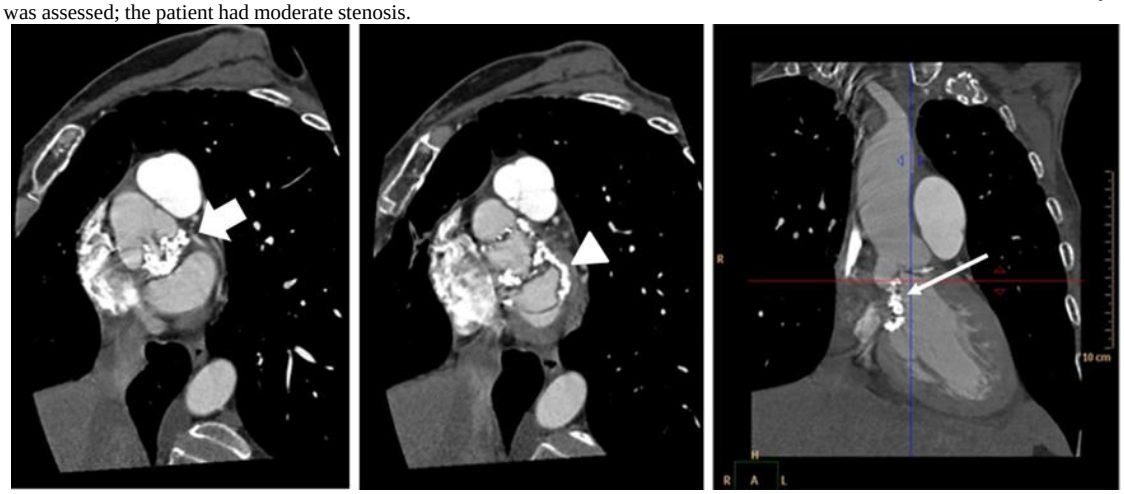

Figure 4: Multislice Computed tomographic imaging demonstrating extended calcification that affects the aortic and mitral valve with extension to the LVOT (thick arrow), the mitral ring (arrow head) and the mitro-aortic curtain (thin arrow).

The patient was referred for aortic and mitral valve replacement surgery with biological prostheses, Carpentier-Edwards Nº 21 in aortic position and Carpentier-Edwards Nº 27 in mitral position

Postoperatively, the transvalvular gradients decreased significantly.

6. Discussion

RIHD involves a spectrum of deleterious cardiovascular effects in patients who have undergone thoracic radiotherapy and may affect any cardiac structure, including the pericardium, myocardium, valves, conduction system and coronary arteries. It can manifest in different ways, ranging from preclinical histopathologic findings to symptomatic clinical disease [1].

Mediastinal radiotherapy is used as part of the treatment regimen for a wide range of mediastinal cancers. Since RIHD may occur decades after radiotherapy, it becomes especially relevant for patients suffering from malignant diseases with good prognosis such as breast cancer or Hodgkin´s lymphoma with a 20-year-survival now approaching to 80%. Among these patients, cardiovascular disease is the most common non-malignant cause of death [3-6].

Risk factors for RIHD are: anterior or left chest irradiation location, high cumulative dose of radiation (over 30 Gy), younger age (less than 50 y/o) at the time of radiation therapy, inadequate or absent shielding, concomitant chemotherapy, conventional cardiovascular risk factors and preexisting cardiovascular disease [7-11].

In the 1980s the radiation dose was higher when high dose, wide-field radiation therapy in thoracic portals were the norm and minimization of cardiovascular irradiation was not necessarily prioritized. Contemporary radiation regimens incorporate techniques

to optimize radiation delivery to the tumor, while minimizing repeated irradiation of surrounding normal structures, including the heart. Although these measures will likely reduce the risk of cardiovascular toxicity, current outcomes in RIHD still remain considerably influenced by historical practices [10,11].

Acute cardiac inflammation can occur at the time of treatment, resulting in myocarditis or pericarditis. Late cardiovascular effects manifest decades after treatment and result from diffuse interstitial fibrosis and collagen deposition [12,13]. This can result in a variety of cardiovascular complications including the following: myocardial fibrosis, valvular heart disease, vasculopathy including Coronary Artery Disease (CAD), pericardial disease, and conduction system dysfunction.

The pathophysiology of radiation-induced valvular disease is not completely clarified: cellular injury, combined with pressure-related trauma, may cause valvular fibrosis and calcification. Irradiation seems to trigger a degenerative process that lasts for years and results in leaflet retraction, fibrotic thickening and late calcification [14].

The incidence of valvular abnormalities associated with mediastinal radiation therapy increases significantly after 20 years after irradiation when mild aortic regurgitation is seen in up to 45%, moderate or severe aortic regurgitation in up to 15% and aortic stenosis in up to 16% of patients. Left-sided valves are the more commonly affected, with stenotic lesions being more frequent in the aortic valve. Although radiation-induced valvular heart disease is common more than 70% of patients have no symptoms. Over time, valvular damage may ultimately progress to severe and clinically significant dysfunction, requiring consideration of intervention. There is a reported incidence of clinically valve disease of 1% at 10 years, 5% at 15 years and 6% at 20 years after radiation exposure [15, 16].

Diagnosis involves identifying anatomical valve abnormalities, valve dysfunction and assessing the functional consequences on the ventricle. TTE is the recommended first line imaging technique whereas TEE is indicated when TTE is non-diagnostic or when further information is required. Cardiac MRI can provide complementary information where echocardiographic data are incomplete and can provide assessment of myocardial fibrosis. CT is used to identify other sequelae of radiation heart disease such as coronary artery disease, aortic calcification and pericardial thickening/calcification and it is also very useful to evaluate extra-cardiac structures for surgical planning [15].

The echocardiographic findings are characteristic but nonspecific. Radiation-associated valvular thickening and calcification are extensive and may affect multiple valves. Surrounding structures, such as the valve annulus, sub-valvular apparatus, and aorto-mitral curtain, are also frequently involved [15, 17]. Increasingly, aorto-mitral curtain thickening/calcification is being recognized as a hallmark of previous heart irradiation and its extent is strongly associated with mortality in subjects undergoing cardiac surgery [18, 19].

The combination and variable degree of thickening and calcification leads to restricted motion and either valve stenosis or regurgitation. Importantly, unlike rheumatic valve disease, there is a lack of commissural fusion [20].

The case we present in this opportunity illustrates some of the chronic cardiac complications of mediastinal irradiation, such as disorders of atrioventricular conduction and, particularly, symptomatic mitral and aortic valve disease.

A common feature between the patients in most series and our case is the long delay since mediastinal irradiation and the symptoms onset. Most notably, aortic stenosis has been described to develop after 20 years after mediastinal irradiation, suggesting that stenosis of the aortic valve takes a considerably longer time to develop than either aortic or mitral regurgitation. Therefore, mitral valve stenosis, which was also present in our patient, may take a longer time to develop than other valvular lesions after mediastinal irradiation.

Due to multiple comorbidities related to the effects of radiation on mediastinal structures, cardiac surgery in RIHD is often complex and, therefore, best undertaken by experienced surgeons. Replacement is favored over repair because irradiated valve tissue is abnormal and tends to progressively fibrose and calcifies. Given the susceptibility to calcification of the valves and surrounding structures, it should be considered to replace both valves in the same surgical procedure, even if the disease of one of them is only mild or moderate. Due to the increased risks of reoperation, mechanical prostheses are preferred, especially for younger patients [21]. It has been recently demonstrated that the prognosis of patients with RIHD undergoing cardiac surgery is significantly worse compared with age and sex-matched patients undergoing similar cardiac surgeries (55% vs. 28%), despite a low perioperative mortality [22].

Percutaneous valve techniques offer an alternative strategy for patients at high risk of cardiac surgery, including those with a ‘hostile’ thorax (mediastinal fibrosis, chest wall deformities) and porcelain aorta. Patients with radiation-induced heart valve disease had a high procedure success rate (94%) with no mortality at 6 months post procedure [23].

Serial evaluation of cancer survivors with appropriate screening programs is recommended in the expert consensus document [15]. The guidelines call for aggressive cardiac risk-factor modification program in addition to early detection of RIHD. Baseline comprehensive TTE is performed in all patients before starting radiotherapy to detect cardiac abnormalities. Beyond this, an annual physical examination looking after symptoms and signs of cardiopulmonary disease that should justify the evaluation with TTE. Due to its late presentation, screening for valvular disease in asymptomatic

patients is delayed until 10 years after radiotherapy, with subsequent imaging then performed at 5-year intervals (35).

7. Conclusions

Due to significant improvements in overall cancer survival, radiotherapy-induced heart disease has become an increasingly recognized adverse reaction that, potentially, may have a major impact on outcomes. Specifically, the natural history and physiopathology of radiation-associated valve disease are significantly different from other causes of valve dysfunction such as rheumatic or degenerative injury. Therapeutic management is a challenge, requiring complex surgical procedures or the transcatheter approach.

8. Conflict of Interest

Authors do not declare any financial support or relationship that may pose a conflict of interest.

References

1. Desai M, Jellis C, Kotecha R, Johnston D, Griffin B. Radiation-Associated Cardiac Disease: A practical approach to diagnosis and management. J AM Coll Cardio Img. 2018; 11: 1132-49.
2. Gujral D, Lloyd G, Bhattacharyya S. Radiation-induced heart disease. Heart. 2015; 0: 1-8.
3. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. Blood. 2008; 111: 2977-83.
4. Ng AK, Bernardo MP, Weller E, Backstrand K, Silver B, Marcus K et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol. 2002; 20: 2101-8.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet. 2000; 355: 1757-70.
6. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourgut A, Jager J et al, European Organization for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomized phase 3 trial. Lancet Oncol. 2015; 16: 47-56.
7. Jarwoski C, Mariani J, Wheeler G, Kaye D. Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013; 61: 2319-28.
8. Schellong G, Riepenhausen M, Bruch C, Kotthoffs S, Vogt J, Boliug T et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodkin disease in children and adolescents: report from the longitudinal GPOH follow up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer. 2010; 55: 1145-52.
9. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W et al: Modifiable risk factors and ma¬jor cardiac events among adult survivors of childhood cancer. J Clin Oncol. 2013; 31: 3673-80.
10. Landau D, Adams EJ, Webb S, Ross G. Cardiac avoidance in breast radiotherapy: a comparison of simple shielding techniques with intensity-modulated radiotherapy. Radiother Oncol. 2001; 60: 247-55.
11. Hodgson DC. Late effects in the era of modern therapy for Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2011: 323-9.
12. Yarnold J, Vozenin Brotons MC: Pathogenetic mechanisms in radiation fi¬brosis. Radiother Oncol. 2010; 97: 149-61.
13. Spetz J, Moslehi J, Sarosiek K. Radiation-induced cardiovascular toxicity: Mechanisms, prevention, and treatment. Curr Treat Options Cardiovasc Med. 2018; 20: 31.
14. Brand M, Abadi C, Aurigemma G, Dauerman H, Meyer T. Radiation associated valvular heart disease in Hodkin´s disease is associated with characteristic thickening and fibrosis of the aortic-mitral courtain. J Heart Valve Dis. 2001; 10: 681-5.
15. Lancellotti P, Nkomo V, Badano L, Bergler J, Bogaert J, Davin L et al. Expert Consensus for Multi-Modality Imaging Evaluationof Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2013; 26: 1013-32.
16. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003; 42: 743-9.
17. Hering D, Faber L, Horstkotte D. Echocardio graphic features of radiation-associated valvular disease. Am J Cardiol. 2003; 92: 226-30.
18. Brand M, Abadi C, Aurigemma G, Dauerman H, Meyer T. Radiation-associated valvular heart disease in Hodgkin's disease is associated with characteristic thickening and fibrosis of the aortic-mitral curtain. J Heart Valve Dis. 2001; 10: 681-5.
19. Desai M, Wu W, Masri A, Popovic Z, Agarwal S, Smedira N et al. Increased aorto-mitral curtain thicknes independently predicts mortality in patients with radiation associated cardiac disease undergoing cardiac surgery. Ann Thorac Surg. 2014; 97: 1348-55.
20. Krapf L, Dreyfus J, Cueff C, Lepage L, Brochet E, Vahanian A et al. Anatomical features of rheumatic and non-rheumatic mitral stenosis: potential additional value of three-dimensional echocardiography. Arch Cardiovasc Dis. 2013; 106: 111-15.
21. Handa N, McGregor C, Danielson G, Anderson B, Schomberg P, Puga F et al. Valvular heart operation in patients with previous mediastinal radiation therapy. Ann Thorac Surg. 2001; 71: 1880-4.
22. Donnellan E, Masri A, Johnston D, Pettersson G, Rodriguez L, Popovic Z et al. Long-term outcomes of patients with mediastinal radiation-associated severe aortic stenosis and subsequent surgical aortic valve replacement: a matched cohort study. J Am Heart Assoc 2017; 6: e005396.
23. Dijos M, Reynaud A, Leroux L, Redant P, Cornolle C, Roudaurt R et al. Efficacy and follow-up of transcatheter aortic valve implantation in patients with radiation-induced aortic stenosis. Open Heart 2015; 2: e000252.