CASE REPORT

Radiation induced valvular disease: the internist's prospective

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SUMMARY

Radiation-induced cardiac injury entails a wide spectrum of cardiovascular complications such as cardiomyopathy and valvular diseases among others. We present the internist's perspective and the challenges faced in managing these patients. There are guidelines addressing radiation-induced valvular disease (RIVD) including screening and treatment, but are often unrecognised by most internist's practice. A thorough cardiovascular examination and screening echocardiography may detect RIVD at an earlier stage. Early screening with transthoracic echocardiogram should be considered in asymptomatic or low-risk patients and more frequently in symptomatic and high-risk patients. The internists should educate their patients with prior chest irradiation, regarding the possible radiation related adverse cardiovascular effects and recommended screening. Lifestyle changes and aggressive cardiovascular risk modification should be emphasised, as concomitant hypertension, coronary artery disease and cardiomyopathy can have unfavourable effects in these patients.

BACKGROUND

Radiation-induced cardiac injury, well studied over the past six decades, entails a wide spectrum of cardiovascular complications such as cardiomyopathy, pericardial diseases, valvular diseases, accelerated atherosclerosis and abnormalities of the conduction system. We present a case where a patient with previous radiation therapy to the chest and abdomen was found to have a radiation-induced valvular disease (RIVD). Here we present an internist's perspective and challenges faced in managing these patients. The primary care physicians and other internists serve as the gatekeeper to diagnosing subclinical presentations of progressive

cardiovascular complications resulting from prior radiation therapy and have a crucial role in managing these patients.

CASE PRESENTATION

A 53-year-old Caucasian female with a history of Hodgkin's lymphoma (stage IIB), treated with mantle radiation with a dose of 39.6 Grey m²/s² to the chest and abdomen at the age of 18 years, presents to our ambulatory clinic for the routine annual follow-up. The patient did not receive any chemotherapy for Hodgkin's lymphoma as she was considered to have early favourable disease. Review of symptoms reported occasional palpitations; otherwise, she denied chest pain, dyspnea and other cardiovascular symptoms. On physical examination, the patient was found to have ejection systolic murmur at the right second intercostal space near sternal border without radiation to the neck. Given her prior history of radiation and new physical examination findings, she underwent a transthoracic echocardiogram and the findings were compared with the transthoracic echocardiogram from two and half years ago. The echocardiographic finding revealed progressive aortic stenosis (from a prior aortic valve area of 1.5 cm² to a valve area of 1.1 cm²) along with extensive calcification of aorto-mitral fibrosa and the anterior mitral leaflet (figure 1A,B). The echocardiogram also suggested increased right ventricular systolic pressure to 54 mmHg in the absence of pulmonic stenosis or regurgitation. A 24 hours Holter monitoring performed for palpitations showed some episodes of supraventricular tachycardia (SVT) and she was started on beta-blocker therapy. A shared decision was made to perform regular interval surveillance for any progression in valvular disease with echocardiography or further cardiac testing if new or worsening symptoms arise.

Figure 1 (A and B) Echocardiographic findings of calcification of aorto-mitral (A) and anterior mitral leaflet (B) both suggestive of radiation-induced valvulopathy.

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Figure 2 Adapted from the current 2013 EACVI and ASE guidelines for RIVD screening (with written permission from Elsevier).

INVESTIGATIONS

A transthoracic echocardiogram was performed (figure 1) which revealed valvular calcifications as described.

A 24 hours Holter monitoring was performed revealing two brief episodes of non-sustained runs of SVT.

DIFFERENTIAL DIAGNOSIS

Rheumatic valvular disease was considered, but excluded. Unlike rheumatic valvular disease RIVD spares mitral valve commissure and leaflet tips.

Carcinoid-associated valvular disease was excluded due to absence of right-sided valve damage and exclusive involvement of left-sided valves typically seen in RIVD.

Bicuspid aortic valve and other congenital valvular abnormalities were excluded based on echocardiogram results.

TREATMENT

The patient was started on beta-blocker therapy for symptomatic palpitations.

OUTCOME AND FOLLOW-UP

The patient is currently asymptomatic regarding her heart valve disease consistent with American College of Cardiology/American Heart Association (ACC/AHA) stage B status. She will receive serial echocardiograms every one to two years to assess the disease progression per guidelines. Intervention will be planned when patient develops symptoms or meets other appropriate criteria for valve intervention.

DISCUSSION

Radiation-related valvular disease typically involved aortic and mitral valves, with progressive calcification and valve thickening, ultimately leading to stenosis or regurgitation. Cardiac CT and MRI can provide valuable diagnostic information, but echocardiography remains the most widely used imaging modality

for screening and monitoring of RIVD. Management of RIVD depends on disease severity and patient related factors and varies from conservative approach to open surgical, percutaneous or a hybrid approach.

With an improvement in life expectancy after cancer treatment and improved diagnostic modalities, more cases of radiation-induced valve damage are being recognised. The usual latent period between radiation exposures to clinical disease is around 10 to 20 years. The effects of radiation-induced valvular damage depend on radiation dose, duration, concurrent chemotherapy and latency since radiation. The risk of RIVD increases steadily after dose greater than 30 Grey m^2/s^2 . However, RIVD can also occur at any dose of radiation.

The aortic valve appears to be the predominant valve involved. A plausible explanation is high flow pressure across the aortic valve along with its proximity to the radiation treatment field in many cases. Increased incidence over time is likely related to worsening fibrosis, micro and macrocalcifications and thickening of the valves. Valvular calcification is secondary to changes at molecular levels, with radiation inducing ontogenesis in valve interstitium.¹ RIVD spares mitral valve commissure and leaflet tip distinguishing it from rheumatic valve disease. Perioperative morbidity and overall survival in the patients with previous mediastinal radiation undergoing cardiac surgery are adversely affected compared with patients who do not receive radiation.² Risk prediction scores predict higher perioperative surgical mortality in patients with radiation-induced heart disease.

This case enlightens some important questions that can be raised while managing such patients and can be challenging for primary care providers in routine clinical practice.

1. Can RIVD progression be delayed or prevented? Is there a role of limiting or minimising radiation dose?

To date, there are no proven methods that may prevent radiation-induced valvular damage. Higher doses of radiations increase the incidence of RIVD. However, dose reduction may not be an ideal option for many patients with active malignancy with risk for progression and metastasis. Limiting dose of radiation, limiting the field of radiation and using newer techniques, such as intensity-modulated radiotherapy and proton therapy, may be helpful in reducing the mean dose to cardiac structures. This approach may prevent or delay the progression of radiation-related cardiac injury.³ However, further studies are needed to quantify the impact and clinical implications of these modalities.

2. Does it warrant more vigilance and regular screening approaches through the primary care providers of such patients?

It is well known that the effects of radiation therapy are long-term that usually manifests after an average of 10 to 20 years. By this time, the primary care physicians have assumed an active and pivotal role in the care of such patients, as many patients are believed to be 'cured' of their primary malignancy and are lost to follow-up with their oncologist. Radiation at young age, pre-existing cardiovascular diseases, exposure to high doses of radiation, concomitant chemotherapy, anterior or left chest irradiation location and the absence of shielding to heart are associated with the highest risk for RIVD and such patients are likely to benefit the most from regular screening echocardiogram.⁴ In our case, the patient did not receive any chemotherapy, added effects of which could have been detrimental. Anthracycline-based chemotherapy regimen can lead to cardiomyopathy and worsening of underlying cardiac functions. It is hence important for the internist to be vigilant in terms of long-term follow-up of these patients to observe for radiation-associated complications. Common consensus between

European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) also lays down a comprehensive and systematic approach (figure 2) to screening such patients to help early diagnosis and timely management. This consensus recommends a pre-radiotherapy screening for any underlying risk factors, detailed history and physical examination along with baseline echocardiogram in all patients to identify any baseline cardiac abnormalities. On follow-up assessments, annual comprehensive history and physical examination are aimed to diagnose any signs or symptoms of cardiac disease. Asymptomatic patients with no new findings on examination or history can have a screening echocardiogram after 10 years of radiation therapy, while those at 'high risk' (patients who underwent anterior or left side chest irradiation with at least one risk factors for RIVD) an early screening echocardiogram at five years post-radiation is recommended.

Follow-up surveillance imaging in all patients is recommended at five years after initial screening study or on the onset of new symptoms (whichever is earlier). If the initial echocardiographic results are equivocal or require further enhanced studies, cardiac MRI or cardiac CT can be utilised. However, these modalities do not have an established role for primary screening in suspected patients.⁴

3. Screening in patients with prosthetic valves when compared with the native valve?

We encounter patients with prosthetic valves in our clinical practice. There are no specific recommendations regarding the patients with prosthetic valves that develop RIVD. These patients are at higher risk for cardiovascular complications compared with people with normal valves. This raises the valid question regarding more aggressive screening approach in this population.

4. Treatment options and guidelines for the surgical approach to affected valves in RIVD?

There are no separate guidelines for valvular surgery (open/minimally invasive) in a patient with previous mantle radiation. Studies have shown patients with previous mediastinal radiation have higher perioperative mortality and morbidity. We believe the future guidelines should address this specific population.

Learning points

- ▶ The primary care providers are gatekeeper for safe healthcare practices and can play pivotal role in early diagnosis and treatment of RIVD.
- ▶ A thorough cardiovascular examination and screening echocardiography may detect RIVD at an earlier stage.
- ▶ The internist can take a lead role in adopting a comprehensive multidisciplinary approach for better outcomes in patients with RIVD.
- ▶ Internist should emphasise lifestyle changes and aggressive cardiovascular risk modification in patient with previous exposure to mantle radiation.

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