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Coronary artery disease associated with radiation therapy

Case Report

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Abstract: Recent advancements in curative-intent therapies have led to dramatic improvements in breast cancer-specific mortality but at the direct expense of increased risk of cardiovascular-related mortality. The use of radiation therapy has led to significant improvements in survival for patients treated for breast cancer. However, as patients live longer, the potentially serious adverse effects of radiation on the heart have raised concerns. Coronary artery disease following irradiation is encountered rarely but is one of the most devastating treatable complications.In this article we review the cardiac complications associated with radiation therapy.

Keywords: *Radiation therapy • Breast cancer • Acute myocardial infarction*

1. Introduction

The use of radiation therapy (RT) has led to significant improvements in survival for patients treated for breast cancer, Hodgkin's disease, and numerous other malignancies [1]. However, as patients live longer, the potentially serious long term adverse effects of radiation on the heart have raised concerns. Irradiation of a substantial volume of the heart to a sufficiently high dose can damage virtually any component of the heart including the pericardium, myocardium, heart valves, coronary arteries, capillaries and conducting system. Pericarditis is the typical acute manifestation of radiation injury, while chronic pericardial disease, coronary artery disease, cardiomyopathy, valvular disease and conduction abnormalities can manifest years after the original treatment. Analyses have shown that therapeutic benefits from RT may be offset to some extent by delayed effects on the heart.

2. Pathophysiology

The clinical spectrum of cardiac injury directly resulting from radiation includes the following abnormalities: Acute pericarditis during therapy (rarely associated with treatment of juxtapericardial cancer); delayed pericarditis that can present abruptly or as chronic pericardial effusion or constriction; pancarditis, which includes pericardial and myocardial fibrosis with or without endocardial fibroelastosis; cardiomyopathy in the absence of significant pericardial disease; diastolic dysfunction and other abnormalities (functional valve injury, conduction defects, Coronary artery disease (CAD)) [2].

The histologic hallmarks of radiation associated cardiotoxicity are diffuse fibrosis in the intersititium of the myocardium with normal appearing myocytes and narrowing of capillary and arterial lumens [3]. Irregularities of endothelial cell membranes, cytoplasmic

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swelling, thrombosis, and rupture of the walls are present. The ratio of capillaries to myocytes is reduced by approximately 50 percent and this reduction leads to myocardial cell death, ischemia, and fibrosis. Dense collagen and fibrin replace the normal adipose tissue of the outer layer of the heart leading to pericardial fibrosis [4].

The essential charecteristics of the radiation-induced CAD are premature CAD, disproportionate number of coronary ostial lesions, and predilection for the right coronary (RCA) , left main and proximal left anterior descending coronary arteries [5]. Since the greatest amount of radiation exposure occurs in the anterior wall of the chest during irradiation, radiation-induced CAD has been frequently detected in the proximal parts of all epicardial coronary arteries. In histopathologic examination, fibrointimal thickening without a lipid core is common in radiation-induced injury.

The cusps and valve leaflets may undergo fibrotic changes with or without calcification. Myocardial fibrosis can compromise cardiac compliance leading to diastolic dysfunction and fibrosis of cells in the conduction system may predispose to dysrhythmia.

3. Clinical Course and Management

Exposure at a young age, anterior irradiation without shielding, a high dose of total irradiation, and the presence of other radiation induced heart diseases are the risk factors in thedevelopment of radiation induced CAD [6].

In the late 1980s, data demonstrated that older radiotherapy techniques resulted in increased rates of cardiac morbidity and mortality. A meta-analysis of nearly 20,000 women with breast cancer enrolled into 40 randomized trials before 1990 showed that radiotherapy reduced the annual mortality from breast cancer by 13%, but increased the annual mortality rate from other causes by 21%, mostly from vascular causes [7]. Similarly, another review of nearly 8,000 cases from 10 randomized trials of mastectomy with or without radiotherapy initiated before 1975 and found the standardized mortality ratio was significantly higher for patients treated with radiotherapy compared with controls [3]. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group that included 78 randomized trials of breast or chest wall irradiation after surgery examined the risk of death from breast cancer and non–breast cancer causes [8]. In this analysis, there was an excess of non–breast cancer deaths among women who received radiation, mainly due to heart disease and lung cancer. The excess mortality was seen only after 5 years after treatment, and was not age dependent. The studies included were conducted between 1961 and 1995, and many of the older trials used outdated radiation techniques that exposed more volume of heart and lung to larger doses of irradiation than current standard tangential beams, accounting for the excess cardiovascular mortality. Hooning et al. examined the long-term cardiovascular disease (CVD) risk according to specific radiation fields and interaction with known CVD risk factors among 4,414 10-year survivors of breast cancer treated from 1970 through 1986 in the Netherlands [9]. After 18 years' median follow-up, 62.9 excess cases per 10,000 patient years of cardiovascular events were observed compared with the general female population. In addition, radiotherapy to either the left or right side of the internal mammary chain was associated with increased cardiovascular disease for 1970 to 1979 compared with patients who received no radiotherapy. After 1979, radiation in combination with chemotherapy was associated with a greater risk of heart failure than patients who received radiotherapy only. Finally, when combined, smoking and radiotherapy were associated with an additive effect on risk of Myocardial Infarction (MI) [9]. Giordano et al. reported that the 15-year CVD mortality rate was significantly greater for left-sided versus right-sided tumors for women diagnosed and treated between 1973 and 1979 (13% vs. 10.2%) [10]. However there were no significant differences for women diagnosed and treated after 1984 with newer radiotherapy techniques. Although modern radiation techniques provide lower cardiac mortality risks than older techniques, cardiopulmonary damage does nonetheless occur. Prospective studies report cardiac perfusion defects in 50% to 63% of women and radiologic evidence of irreversible lung fibrosis and associated pulmonary disorders with left-sided breast cancer 6 to 24 months after radiotherapy [11]. Focal impairment of cardiac perfusion in the left ventricle has been described after chest wall irradiation [12]. The frequency with which this might occur was addressed in a report of 114 patients: perfusion defects were seen in 10 to 20% of patients when less than 5% of the left ventricle was included in the radiation field, versus 50 to 60% when more than 5% was included. These perfusion defects were associated with wall-motion abnormalities but not a reduction in left ventricular ejection fraction. Risk factors for radiation-induced cardiovascular morbidity and mortality go beyond the myocardial and/or pulmonary volume in the field and the dose delivered to that field (dose-volume histogram), to include the presence of pre-existing CVD risk factors and use of anthracyclines [13].

Controversy over whether radiation exposure of the heart results in coronary artery stenosis existed as aresult of a high prevalance of the disease. However, a number of large cohort studies have demonstrated that the incidence of CAD is significantly higher in patients with prior radiation therapy compared with age-matched control groups with a preponderance of very charecteristic lesions [3,4,14]. Relative risk in those studies is reported to be varied between 3 to 40, depending the age of the cohort. In animal models, the primary target of radiation for this complication is the endothelial cell. The presence of other risk factors such as dyslipidemia, may have an impact on the development of radiation-induced cardiac injury. As an example, an increase in coronary atherosclerosis has been noted when animals are fed a high cholesterol diet and then exposed to radiation [1]. In humans, CAD, usually involving the left anterior descending artery, has been observed after radiation doses of 24 Gy or higher (1). In addition, patients receiving 1.6 to 3.9 Gy to the heart for treatment of benign conditions were observed to have an increased risk of late coronary heart disease [15]. The muscular coronary arteries are large enough to escape damage by therapeutic doses of thoracic radiation, and coronary thrombosis is a relatively infrequent occurrence. However, radiation therapy can cause endothelial dysfunction, a result of endothelial cell death and a decreased availability of nitric oxide; this may contribute to the subsequent development of arterial occlusion and vascular events [16]. A number of pro-inflammatory molecules have been reported to be upregulated by endothelial cell irradiation in vitro and in vivo. These are adhesion molecules, including E-selectin (a mediator of leukocyte rolling), ICAM (a mediator of leukocyte arrest), and PECAM-1 (involved in leukocyte transmigration). These pro-inflammatory events may be the molecular correlate of early radiation-induced ultrastructural changes observed in the microvessels of the myocardium [17]. Besides induction of adhesion molecules, up-regulation of some cytokines (namely IL-6 and IL-8) has been observed after endothelial cell irradiation in a time- and dose-related fashion [18]. Also, there is evidence of prothrombic effects of radiation, which may be the cause of the increased platelet adherence and thrombus formation observed in irradiated capillaries and arteries [19]. The carotid arteries of apolipoprotein-negative mice have been monitored for the development of atherosclerotic plaques for up to 9 months after high doses of irradiation. Irradiation had no influence on cholesterol levels, markers of systemic inflammation, or atherosclerotic lesions in the non-irradiated renal arteries, but initial plaque formation began earlier and the rate of plaque growth was faster in irradiated than in non-irradiated carotid arteries. Histologically, the carotid arteries showed typical signs of plaque instability, such as intra-plaque haemorrhage and macrophage accumulation. The interaction of radiation-induced changes in endothelial function with the initial events of atherosclerotic lesion formation in these animals was believed to result in chronic inflammation, favouring the development of a vulnerable plaque [20].

On the other hand, concurrent chemotherapy administration can also influence radiation toxicity on the heart. Combinations of doxorubicin and radiation resulted in additive but not synergistic effects in a rabbit model [21]. Oxidative damage to the heart, induced both by radiation and doxorubicin, may be a pathogenic factor [22]. In humans, prior mediastinal radiation may increase the susceptibility to anthracycline cardiotoxicity by inducing endothelial cell damage and eventual compromise in coronary artery blood flow [1].

The management of radiation induced CAD is similar to commonly occurring CAD. Although surgery is effective, it is often complicated by mediastinal fibrosis in the majority of patients with the history of prior anterior irradiation [2]. Therefore PCI in those patients may be primary treatment option especially when bypass surgery is difficult to perform [2].

4. Conclusion

The risk of developing adverse cardiac events is among one of the long term complications of chest RT which may limit the benefits of the therapy. Although safer ways to irradiate the chest are being studied and developed, the long term morbidity and mortality associated with modern techniques are still to be determined. Since the latency period for the cardiovasvular complications may take more than a decade to become clinically manifested, long term clinical screening studies are necessary to establish the safety profiles of the newer RT methods.

References

[1] Chung T. Cardiac effects of radiation therapy for malignancy . In: UpToDate, Rose, BD (ed). UpToDate, Wellesley, 2007

[2] Lee PJ, Mallik R . Cardiovascular effects of radiation therapy: practical approach to radiation therapy-induced heart disease. Cardiol Rev. 2005; 13: 80-6

[3] Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12: 447-53

[4] Hooning MJ, Aleman BM, Van Rosmalen AJ, et al. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow up study. Int J Radiat Oncol Biol Phys 2006; 64: 1081

[5] Hancock SL, Tucker MA, Hoppe RT . Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA. 1993; 270: 1949-55

[6] Glanzmann C, Huguenin P, Lutolf UM, Maire R, Jenni R, Gumppenberg V . Cardiac lesions after mediastinal irradiation for Hodgkin's disease. Radiother Oncol. 1994; 30: 43-54

[7] Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 2000; 355: 1757-70

[8] Early Breast Cancer Trialists' Collaborative Group: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of randomized trials . Lancet 2005; 366: 2087-2106

[9] Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007; 99: 365–75

[10] Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005; 97: 419–24

[11] Marks LB, Yu X, Prosnitz RG, Zhou SM, Hardenbergh PH, Blazing M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys 2005; 63: 214 –23

[12] Seddon B, Cook A, Gothard L, Salmon E, Latus K, Underwood SR, Yarnold J. Detection of defects in myocardial perfusion imaging in patients with early breast cancer treated with radiotherapy. Radiother Oncol 2002; 64: 53-63

[13] Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, Solin LJ. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006; 24: 4100–6

[14] Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer. 1992; 69: 1241-1247

[15] Carr ZA, Land CE, Kleinerman RA, Weinstock RW, Stovall M, Griem ML, Mabuchi K. Coronary heart disease after radiotherapy for peptic ulcer disease. Int J Radiat Oncol Biol Phys. 2005; 61: 842-50

[16] Beckman, JA, Thakore, A, Kalinowski, BH, Harris JR, Creager MA. Radiation therapy impairs endothelium-dependent vasodilation in humans. J Am Coll Cardiol 2001; 37: 761

[17] Hendry JH, Akahoshi M, Wang LS, Lipshultz SE, Stewart FA, Trott KR. Radiation-induced cardiovascular injury. Radiat Environ Biophys. 2008; 47: 189-93

[18] Van der Meeren A, Squiban C, Gourmelon P, Lafont H, Gaugler MH. Differential regulation by IL-4 and IL-10 of radiationinduced IL-6 and IL-8 production and ICAM-1 expression by human endothelial cells. Cytokine 1999; 11: 831–838

[19] Verheij M, Dewit LG, Boomgaard MN, Brinkman HJ, van Mourik JA. Ionizing radiation enhances platelet adhesion to the extracellular matrix of human endothelial cells by an increase in the release of von Willebrand factor. Radiat Res 1994; 137: 202–207

[20] Stewart FA, Heeneman S, te Poele J, Kruse J, Russel NS, Gijbels M, Daemen M. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. Am J Pathol 2006; 168 : 649–658

[21] Eltringham JR, Fajardo LF, Stewart JR. Adriamycin cardiomyopathy: enhanced cardiac damage in rabbits with combined drug and cardiac irradiation. Radiology 1975; 115: 471-2

[22] Dalloz F, Maingon P, Cottin Y, Briot F, Horiot JC, Rochette L. Effects of combined irradiation and doxorubicin treatment on cardiac function and antioxidant defenses in the rat. Free Radic Biol Med. 1999; 26: 785-800