A case of multifactorial late left ventricular dysfunction after cancer treatment

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Abstract

A case of hypokinetic cardiomyopathy in a young lady previously treated with anthracyclines and mediastinal radiotherapy (RT) is described. The dysfunction was first considered due to anthracyclines cardiomyopathy, possibly with superimposed myocardits, and treated with enalapril and betblockers obtaining an improvement in left ventricular function. After a nine-year follow-up, left ventricular dysfunction worsened and inducible silent myocardial ischemia was detected. When coronary artery disease (CAD) was diagnosed and cured by angioplasty and stenting, left ventricular function improved. In this patient, CAD was likely secondary to both RT and dyslipidemia, and was probably a co-factor of left ventricular dysfunction. Patients treated with chest radiotherapy are at increased risk of CAD, and any other risk factors (with particular attention to metabolic factors) should be thoughtfully searched and promptly treated. This is mostly important in long-term survivors, and in patients treated more than 30 years ago, when RT techniques were not yet planned to reduce radiation-induced heart disease.

Keywords: cardiotoxicity; radiotherapy; left ventricular dysfunction; Hodgkin's disease; coronary artery disease; dyslipidemia

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Case Report

Case report

A 40-year-old woman, a former smoker with family history of hypertension and diabetes, was first seen in our outpatient clinic in June 2001. Her past clinical history included Hodgkin disease stage III (supraclavear and mediastinal lymph nodes, spleen) at age 14 (in 1974), treated with splenectomy, six courses of chemotherapy with adriamycin (ADM), bleomycin, vinblastine, dacarbazine (ABVD) up to a total dose of 300 mg/sm of ADM, and mantle field radiotherapy (RT) (30 Gy). In January 2001, after traveling in Thailand, she was admitted to a general hospital with fever and worsening dyspnoea. Chest x-rays revealed bilateral pneumonitis, immunological tests resulted positive to mycoplasma pneumonia. At that time electrocardiography (ECG) revealed complete left bundle branch block (LBBB).

In June 2001, the patient was asymptomatic, without cardiac murmurs or other pathologic findings. The ECG showed sinus rhythm, with LBBB. At echocardiography the left ventricle (LV) showed normal dimensions, with asynchronous contraction, septal hypokinesis and slightly reduced ejection fraction (EF): 43%. Cytomegalovirus antibodies were elevated; other routine blood tests were negative. Enalapril 5 mg/day was started. The patient took a treadmill stress test in August 2001 and attained a workload of 9.3 metabolic equivalent units (METS), without symptoms (ECG not evaluable for LBBB). The patient refused coronary angiography

and myocardial biopsy (to rule out coronary artery disease and myocarditis), and nuclear imaging tests.

Up to 2008, the patient remained asymptomatic, with EF ranging from 51% to 56% and mild diastolic dysfunction (mitral E/A <1 at pulsed Doppler) on yearly echocardiograms. Treadmill stress tests, repeated every 3 years, were always clinically negative, with the patient able to perform >9 METS. Therapy included enalapril and beta-blockers at the highest tolerated dose (enalapril 7.5 mg, bisoprolol 2.5 mg: up-titration was difficult because of hypotension). In 2004, blood tests revealed dyslipidemia (total cholesterol 350 mg/dL), and we prescribed atrovastatin 20 mg, which was changed to rosuvastatin 10 mg/day in 2006. In November 2007, the patient underwent mastectomy for left breast carcinoma, followed by hormone therapy (tamoxifen and triptorelin). After surgery, the patient spontaneously stopped rosuvastatin. In November 2009, she was still asymptomatic, with echocardiographic EF at 52%, but further impairment of diastolic function (pseudonormal pulsed Doppler mitral flow pattern, E/E'= 22). A myocardial perfusion stress test showed reduced septal perfusion, partially reversible at rest. The patient finally accepted coronary angiography in June 2010: a 95% ostial stenosis of the right coronary artery was detected and treated with angioplasty and stenting. At echocardiography, one month later both systolic and diastolic functions were improved (EF 57%, mitral E/A <1).

Comments

The cardiotoxicity of both ADM and RT may become clinically evident years after treatment, mostly in patients treated at age <18 (as our patient was) and in those who received both treatments [1, 2]. The intracellular accumulation of doxorubicinol, an ADM metabolite, may act as a toxic reservoir potentiating the damage of further cardiac insults [3]. The heart was formerly considered resistant to radiation, but from the late 1970s more and more reports about the late sequelae of chest RT have been published [4–6]. Radiation-induced damage of normal tissues depends on dose and volume: according to predictive algorithms, new RT techniques have been developed in the past 30 years in order to concentrate the radiation beam on the tumor, sparing the surrounding structures [7–10]. Since therapeutic plans have changed over time, the risk of cardiac damage is obviously higher for patients treated earlier and lower for those treated more recently [11]. Long-term adverse cardiac effects of RT include dilated and/or restrictive cardiomyopathy, pericarditis, valvular disease, arrhythmias and coronary artery disease (CAD) [12, 13]. The pathophysiological link between RT and accelerated atherosclerosis is the radiation-induced inflammatory reaction followed by endothelial and fibroblast proliferation, lipid deposition, fibrosis, and formation of inflammatory plaque [14–16]. The clinical incidence of CAD is relevant after 10 years, and increases thereafter. A study of 1998 reports an increased prevalence (2.9% after 10 years, 13.7% after 20 years, 24.7% after 25 years) in the subgroup of patients with additional classic cardiovascular risk factors only; in a study of 2003 hypertension and hypercholesterolemia were significant risk co-factors; in a study of 2007 stress-induced ischemia was found in 18.4% of patients, and among them CAD was detected in 40% of those examined <10 years and in 58% of those examined >10 years after RT, without any difference between the patients with and those without additional risk factors; in all studies the risk was higher in males than in females [17–19].

Since the initial stress test in 2001 did not induce clinical ischemia in our patient, and she had no additional risk factors, we considered LV dysfunction probably due to late ADM cardiomyopathy, possibly with myocarditis as co-factor. On enalapril and beta-blockers the patient remained asymptomatic and had clinically negative stress tests for years. When dyslipidemia was first detected, we prescribed a statin, which was later discontinued by the patient. This decision could have accelerated the progression of CAD. Hormonal therapy for breast cancer, on the contrary, had probably no role on coronary pathology: tamoxifen has a beneficial effect on lipid profiles and on cardiac risk; for triptorelin no effect is reported [20, 21].

A peculiarity of radiation-induced CAD is the frequency of ostial lesions and the high prevalence of silent ischemia, and this was also the case for our patient, who was asymptomatic but whose LV diastolic function had worsened over time, suggesting a progression of CAD. In fact, when the ostial lesion was detected and cured with angioplasty, an improvement in systolic and diastolic function was obtained. Thus, cardiac dysfunction, in this particular patient, was probably multifactorial and included ADM myocardial toxicity, radiation-induced myocardial damage (both as direct insult and as increased sensitivity to other stress factors) and coronary artery subclinical damage by RT

leading to early development of CAD (with dyslipidemia as co-factor), which further impaired LV function.

Conclusion

The late cardiotoxicity of anticancer therapies is relevant in long-term survivors, mostly in case of curable malignancies of young patients, leading to a large cohort of subjects at increased risk of cardiac disease in early adulthood. Antracyclines irreversibly damage the myocites, and prevention of late cardiac disease implies the prevention of other factors potentially affecting cardiac function, as hypertension, diabetes and ischemic heart disease. RT may cause myocardial, valvular, pericardial and coronary artery damage. In patients having undergone mediastinal or left chest wall RT, prevention should also include the control of risk factors such as dyslipidemia. The highest risk for radiation-induced heart disease in general and of CAD in particular regards subjects treated before 1980–1985, for several reasons: at that time radiation techniques were not yet planned to prevent the possible long-term adverse cardiac effects, it was possible that dyslipidemia was not promptly treated (its role as CAD risk factor was still under debate and powerful therapeutic agents like statines were not available yet), and the incidence of heart disease increases anyway over time.

All the patients who had been cured by RT for mediastinal lymphomas (or other thoracic tumors) and for left breast carcinomas should absolutely avoid smoking and should be frequently screened, and promptly treated, for any other CAD risk factor, with particular attention to diabetes and dyslipidemia. Moreover, a regular follow-up with echocardiography and stress test is recommended. •

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