

Subendocardial Late Gadolinium Enhancement in Two Patients with Anthracycline Cardiotoxicity Following Treatment for Ewing's Sarcoma

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ABSTRACT

Cardiotoxicity is a well-known consequence of anthracycline chemotherapy. We report CMR findings not previously described in two patients with anthracycline cardiotoxicity following treatment for Ewing's sarcoma. Subendocardial enhancement on late gadolinium contrast-enhanced CMR was present in both cases, with histological correlation in one case.

INTRODUCTION

Cardiotoxicity is a well documented adverse consequence of anthracycline chemotherapy. Agents such as doxorubicin are thought to produce their toxic effects on the myocardium by generation of oxygen free radicals, leading to oxidative stress and lipid peroxidation of cell membranes. Irreversibly damaged myocytes become replaced by fibrous tissue.

Cardiotoxicity may occur acutely during chemotherapy with symptoms including arrhythmias, pericarditis-myocarditis syndrome and ventricular dysfunction (1). These symptoms are uncommon and usually transient. Early onset cardiotoxicity presents as heart failure soon after chemotherapy. Late onset cardiotoxicity presents as a non-ischemic cardiomyopathy with a delay in the development of symptoms for up to 15 years post chemotherapy (1, 2). Late onset cardiotoxicity occurs with a high incidence in survivors of anthracycline chemotherapy. Pein et al. (3) report severe cardiac dysfunction in 39% of patients given adriamycin 15 to 25 years previously.

Late gadolinium enhancement CMR imaging has become a useful technique for identifying irreversibly damaged myocardium. Gadolinium-based contrast diffuses into extracellular spaces and accumulates in areas of non-viable myocardium

(4, 5). Late enhancement of the subendocardium is predominantly associated with ischemic heart disease (6). In non-ischemic conditions, contrast enhancement has been recorded in a variety of locations other than the subendocardium (6).

We report two cases of subendocardial enhancement on late gadolinium contrast-enhanced CMR associated with anthracycline cardiotoxicity following treatment of Ewing's sarcoma. Neither patient had clinical evidence of ischemic heart disease.

CASE 1

The first case was a 36-year-old man who presented with decompensated heart failure requiring cardiac transplantation. At 26-years of age, he was diagnosed with Ewing's sarcoma of the T12 vertebral body and received a curative 6 month course of adriamycin. During the final cycle of chemotherapy he developed early onset cardiotoxicity. The single cardiac risk factor was a prior smoking history. The patient's heart condition was managed conservatively for 10 years, and cardiac function remained poor but stable until recently.

CMR at this point showed a dilated heart with mild enlargement of all four chambers and globally reduced contractility. There was global thinning of the left ventricular wall with an ejection fraction of 15%, BSA-indexed end diastolic volume of 145 mL/m² and BSA-indexed end diastolic mass of 55 g/m². Late gadolinium enhancement imaging showed diffuse subendocardial enhancement of the anterior, inferior and septal walls involving 25–50% of wall thickness. (Fig. 1A & B).

The patient underwent cardiac transplantation. Pathology on the removed heart confirmed dilated cardiac chambers with endocardial thickening in the anterior left ventricular wall. The myocardium showed patchy interstitial fibrosis, myocyte hypertrophy and endocardial fibrosis in several areas. Sections of the coronary arteries showed no significant atherosclerosis and no evidence of stenosis or thrombosis. There was no evidence of

Received 2 January 2006; accepted 12 March 2006

Keywords: late gadolinium enhancement; CMR; anthracycline; Cardiotoxicity; Ewing's sarcoma.

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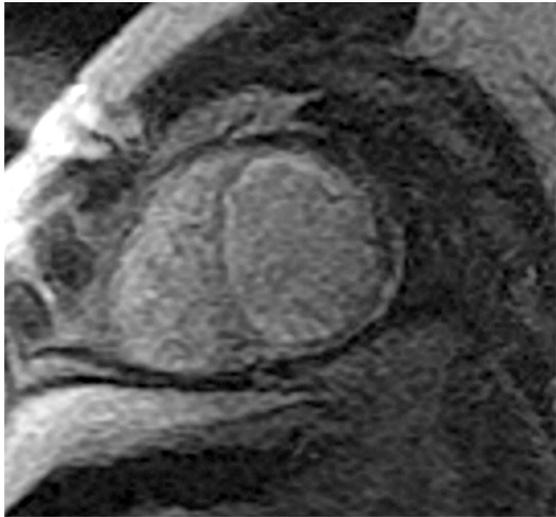
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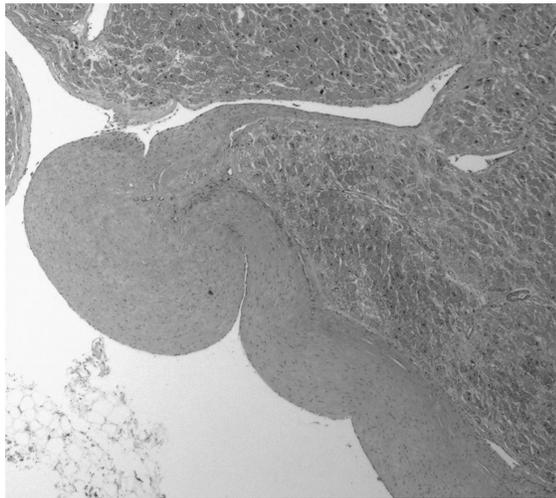
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(A)



(B)



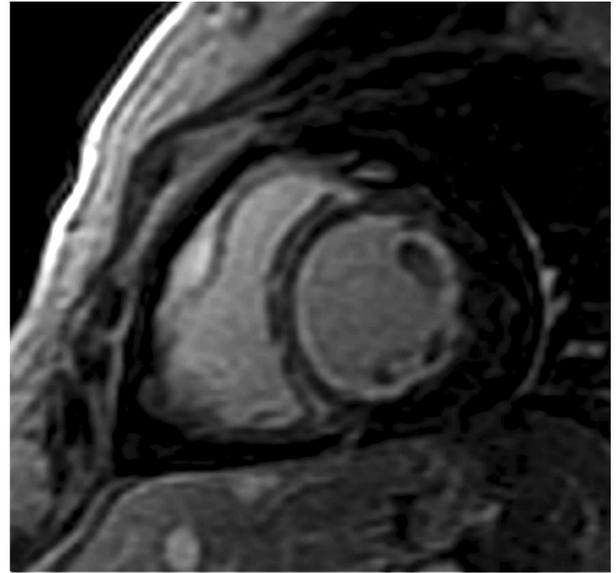
(C)

Figure 1. (A and B) Short axis and vertical long axis late gadolinium enhancement images showing diffuse subendocardial enhancement of the left ventricle. (C) Pathological section of the same heart showing prominent endocardial fibrosis with mild interstitial fibrosis in the underlying myocardium.

myocarditis and no evidence of recent or previous myocardial infarction. (Fig. 1C).

CASE 2

The second case was a 37-year-old female with late onset anthracycline cardiotoxicity. She was diagnosed at the age of 23 with Ewing's sarcoma of the left 3rd and 4th ribs and was



(A)



(B)

Figure 2. (A and B) Short axis and vertical long axis late gadolinium enhancement images showing diffuse subendocardial enhancement of the left ventricle.

curatively treated with a 6 month course of doxorubicin and adriamycin, followed by radiation therapy to the left hemithorax. Cardiac function was normal during, and for seven years following, treatment. Routine echocardiography seven years post treatment identified the onset of mild restrictive cardiomyopathy with mild left ventricular systolic dysfunction and normal heart size. Subsequent echocardiograms have noted steady deterioration in cardiac function.

Recent echocardiography (14 years post treatment) showed biatrial enlargement, left ventricular ejection fraction of 38%, moderate pulmonary hypertension, mild pericardial effusion, and severe hypokinesis of the anteroseptal and anteroapical walls. The patient had no risk factors for coronary artery disease, and catheter angiography showed no evidence of coronary artery disease.

CMR showed a mild reduction in systolic function, akinesis of the interventricular septum and a left ventricular ejection fraction of 41%, BSA-indexed end diastolic volume of 90 mL/m², and BSA-indexed end diastolic mass of 33g/m². Late gadolinium enhancement imaging showed diffuse subendocardial enhancement of the left ventricle and some areas of subendocardial enhancement of the right ventricle. (Fig. 2A & B).

DISCUSSION

Patterns of late gadolinium enhancement on CMR are useful in differentiating myocardial diseases. The subendocardium always shows enhancement in acute and chronic myocardial infarction although this is not a specific finding (6–8). In non-ischemic myocardial diseases (e.g., myocarditis, fibrosis, sarcoidosis, cardiomyopathy), late gadolinium enhancement occurs in a variety of regions within the myocardium (6).

A description of the enhancement pattern in dilated cardiomyopathy is provided by McCrohon et al. (8) as mid-wall enhancement not in the territory of a coronary artery and not subendocardial. They describe a group of dilated cardiomyopathy patients with subendocardial enhancement; however, each of these patients had strong risk factors for coronary artery disease.

Subendocardial enhancement in anthracycline cardiotoxicity has not been previously described. In both patients this enhancement was identified in the confirmed absence of large vessel ischemic heart disease. The mechanism of injury for anthracycline cardiotoxicity is presumed to be the result of oxygen free radicals and lipid peroxidation of cell membranes leading to myocardial fibrosis. The findings from these case reports suggest that anthracyclines may cause irreversible small vessel ischemia affecting the subendocardium.

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