DETECTION OF ADRIAMYCIN CARDIOXOTOXICITY WITH INDIUM-111 LABELED ANTIMYOSIN MONOCLONAL ANTIBODY IMAGING

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Myocardial imaging with indium-111 labeled antmyosin monoclonal antibody (antimyosin imaging) has been reported to be useful in the noninvasive detection of myocardial cell necrosis in dilated cardiomyopathy as well as in myocardial infarction and myocarditis. We used antimyosin imaging to detect myocardial damage in 2 patients with malignant lymphoma in whom adriamycin cardioxotoxicity was suspected. Patients were injected with 74 MBq of indium-111 labeled antimyosin (Fab. fraction). Forty-eight hours later, planar imaging and single-photon emission computed tomography were performed using a gamma camera with a medium energy general purpose collimator. Antimyosin imaging demonstrated diffuse myocardial uptake not only in one patient with congestive heart failure but also in another patient at the early stage without congestive heart failure.

Antimyosin imaging may be a sensitive method for noninvasive visualization of myocardial cell damage and useful in the early diagnosis of specific heart muscle disease.

MYOCARDIAL imaging with indium-111 labeled antmyosin monoclonal antibody (antimyosin imaging) has been used clinically to detect irreversible myocardial cell necrosis noninvasively in myocardial infarction1-7 and myocarditis4,8-10. Recently, myocardial uptake of antimyosin antibody in patients with dilated cardiomyopathy has been reported7,11-12. However, antimyosin imaging in patients with heart muscle disease due to adriamycin cardioxotoxicity has not been reported.

We used antimyosin imaging in 2 patients with malignant lymphoma treated with adriamycin to determine whether antimyosin imaging is useful in the detection of myocardial damage in adriamycin-induced heart muscle disease.

METHODS

Patients

Case 1 was a 50-year-old man, who had been receiving chemotherapy, including adriamycin, for malignant lymphoma (non-Hodgkin, diffuse mixed type) diagnosed more than 11 years earlier. He received the last chemotherapy including adriamycin 4 years before his admission to our hospital because of dyspnea on effort and foot

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Table 1: Clinical Data of Two Patients with Malignant Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>50</td>
<td>74</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>NHL</td>
<td>NHL</td>
</tr>
<tr>
<td>First Chemotherapy-AM scan (mos)</td>
<td>138</td>
<td>19</td>
</tr>
<tr>
<td>Total Dose of Adriamycin (mg/m²)</td>
<td>308</td>
<td>391</td>
</tr>
<tr>
<td>NYHA</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>Serum Cardiac Enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>35</td>
<td>63</td>
</tr>
<tr>
<td>GOT</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>LDH</td>
<td>368</td>
<td>247</td>
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<tr>
<td>Electrocardiography</td>
<td></td>
<td></td>
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<tr>
<td>low voltage in limb leads</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ventricular ectopic beat</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Q wave or ST-T change</td>
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<td>-</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>72</td>
<td>41</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>61</td>
<td>20</td>
</tr>
<tr>
<td>IVST (mm)/PWT (mm)</td>
<td>7/7</td>
<td>8/10</td>
</tr>
<tr>
<td>EF (%)</td>
<td>30</td>
<td>76</td>
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<tr>
<td>Thallium-201 Imaging</td>
<td></td>
<td></td>
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<tr>
<td>perfusion defect</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LV enlargement</td>
<td>+</td>
<td>-</td>
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</table>

NHL = non-Hodgkin Lymphoma; AM = anti-myosin; NYHA = New York Heart Association classification; CTR = cardiothoracic ratio; CK = creatine kinase; GOT = glutamic oxaloacetic transaminase; LDH = lactic dehydrogenase; LVDd = left ventricular diastolic dimension; LVDs = left ventricular systolic dimension; IVST = interventricular septum thickness; PWT = posterior wall thickness; EF = ejection fraction; LV = left ventricle

Edema. Although the total dose of adriamycin was moderate (308 mg/m²), cardiotoxicity was severe, and he developed congestive heart failure. The chest X-ray demonstrated moderate cardiomegaly (cardiothoracic ratio, 60%) and congested vessels. The electrocardiogram showed low voltage in the limb leads (Fig. 1), and the echocardiogram revealed marked dilatation of the left ventricle, wall thinning, and decreased ejection fraction. Serum cardiac enzymes; creatine kinase (CK), glutamic oxaloacetic transaminase (GOT) and lactic dehydrogenase (LDH) at admission were within the normal range (Table 1).

Case 2 was a 74-year-old man, admitted to our hospital for maintenance chemotherapy of malignant lymphoma (non-Hodgkin, diffuse mixed type) diagnosed 2 years earlier. At that time, the total dose of adriamycin was 391 mg/m² and the last administration of adriamycin was given 4 months previously. He had no cardiac symptoms, but his electrocardiogram showed ventricular ectopic beats. To rule out adriamycin cardiotoxicity, cardiac examinations were needed before further administration of adriamycin. The cardiothoracic ratio by chest X-ray was normal (49%). The electrocardiogram showed no other abnormalities, and the echocardiogram demonstrated normal left ventricular function. Serum cardiac enzymes; CK, GOT and LDH at admission were also within the normal range (Table 1).

Antimyosin Imaging
Antimyosin monoclonal antibody, R11D10, was developed by Khaw et al using a hybridoma technique. Antimyosin imaging was performed as previously described. In brief, patients were injected with 74 MBq of indium-111 labeled diethytriamine pentaacetic acid (DTPA)-anti-myosin monoclonal antibody-Fab (offered by Daiichi Radioisotope Laboratories, Ltd.,

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Adriamycin Cardiotoxicity Detected by Antimyosin

Fig. 2. Planar images of anterior view (left) and left anterior oblique (LAO) 45 degree view (right) of antimyosin imaging in case 1, 48 hours after administration of indium-111 antimyosin monoclonal antibody Fab (74 MBq). Definite myocardial uptake is seen in the left ventricle, particularly in the LAO view (arrows), and there is marked uptake in the liver or kidneys. L = liver; K = kidney.

Fig. 3. A series of vertical (top) and horizontal (middle) long axis slices and short axis slices (bottom) of antimyosin imaging in case 1. Vertical long axis images are displayed from septal to lateral region, horizontal long axis images from caudal to cranial region, and short axis images from apex to base. Diffuse and inhomogenous myocardial uptake is demonstrated in the left ventricle in these tomographic images.

Tokyo, Japan), if there was no flare reaction to the intradermal skin test with 0.05 mg of non-labeled DTPA-antibody. Forty-eight hours later, planar images (anterior, 45 degree left anterior oblique, left lateral) were obtained, each for 7 min, to collect
Fig. 4. Planar images of anterior view (left) and left anterior oblique 45 degree view (right) of antimitosin imaging in case 2 show diffuse myocardial uptake in the left ventricle (arrows). L = liver; K = kidney.

Fig. 5. A series of vertical (top) and horizontal (middle) long axis slices and short axis slices (bottom) of antimitosin imaging in case 2. The locations of tomographic are the same as figure 2. Diffuse myocardial uptake in the left ventricle is demonstrated.

300—500 kilocounts at both photopeaks of indium-111 (174 and 247 KeV) with a medium energy general purpose collimator. Single-photon emission computed tomography was performed after planar imaging. A series of 64 projection images was collected over 180 degrees at 5.6 degree increments for 30 sec each in 64 by 64 matrices and
stored for image analysis. A series of transaxial slices at 6 mm intervals was reconstructed by a filtered back-projection method. A series of vertical long axis, horizontal long axis, and short axis sections was also obtained.\textsuperscript{14}

Antimyosin images were displayed on a computer with 256 by 256 matrices without background subtraction and were independently interpreted by two experienced observers without knowledge of the clinical data. Myocardial uptake was evaluated quantitatively by calculating the heart/lung ratio\textsuperscript{11}; ratio of the average counts per pixel in the myocardium to the average counts of the lungs in the anterior image. The heart/lung ratio has been reported to correlate well with visual estimations.

\textit{Thallium-201 imaging}

Myocardial imaging using thallium-201 was performed. Each patient was injected with 74 to 111 MBq of thallium-201 chloride at rest. About 10 minutes later, planar images (anterior, 45 degree left anterior oblique, left lateral) were obtained, each for 5 minutes to collect 400 kilocounts at a photo-peak of thallium-201 (80 KeV) with a high resolution parallel hole collimator.

RESULTS

Antimyosin imaging in case 1 demonstrated diffuse but definite myocardial uptake in the left ventricle (Fig. 2). The heart/lung ratio was 2.12, although high uptake by the liver and kidneys was also demonstrated. Single-photon emission computed tomography demonstrated diffuse and inhomogenous antimyosin radioactivity in the left ventricular wall (Fig. 3).

Antimyosin imaging in case 2 demonstrated diffuse uptake in the left ventricle (Fig. 4). The heart/lung ratio was 1.91. High uptake by the liver and kidneys was noted. Single-photon emission computed tomography demonstrated diffuse antimyosin radioactivity in the left ventricular wall and no blood pool radioactivity (Fig. 5).

Neither patient had a history of ischemic heart disease. Thallium-201 imaging showed no perfusion defect in either (Fig. 6), while enlargement of left ventricle was demonstrated in case 1.

DISCUSSION

A high incidence of positive antimyosin imaging has been reported in dilated cardiomyopathy.\textsuperscript{7,11-12} Obador et al reported that the mean heart/lung ratio of dilated cardiomyopathy in antimyosin imaging was 1.83 ± 0.36, whereas the mean heart/lung ratio of patients with congestive heart failure not due to dilated cardiomyopathy was 1.46 ± 0.04.\textsuperscript{11} The heart/lung ratio of our patients exceeded their mean heart/lung ratio of dilated cardiomyopathy, and single-photon emission computed tomography demonstrated diffuse myocardial uptake in the left ventricular wall and no blood pool activity. Figulla et al reported that 52% of patients with dilated cardiomyopathy showed significant antimyosin uptake, and that up to 35% of myocytes demonstrated antimyosin uptake immunohistochemically in en-
ary myocardial biopsy specimens. We recently reported a good correlation between antiyosin uptake and myocardial damage in a murine model of experimental viral myocarditis. Therefore, antiyosin uptake in patients with dilated cardiomyopathy may be due to ongoing changes of myocytes.

Specific heart disease is defined as myocardial disease due to known cause. It includes conditions of infective, metabolic, alcoholic and toxic origins. Severe heart failure sometimes occurs in adriamycin-treated patients. It is important to detect adriamycin cardiotoxicity as early as possible, because it can occur suddenly and irreversibly. A dose-relationship between the total dose of adriamycin and cardiotoxicity has been reported, and less than 550 mg/m² is the recommended dose. However, cardiotoxicity is also related to other factors, such as synergic cardiotoxicity with other anti-tumor drugs, radiation therapy, and old age. Minow et al reported that even 55 to 220 mg/m² of adriamycin can induce cardiotoxicity. Bristow et al reported that 27 of 29 biopsied patients treated with doses less than 240 mg/m² had doxorubicin (adriamycin)-associated degenerative changes identified by right ventricular endomyocardial biopsy. Therefore, the total dose of adriamycin is not an absolute marker of critical cardiotoxicity. Actually, both of our patients had received less than 550 mg/m² of adriamycin, but showed positive antiyosin imaging suggesting myocardial cell damage. Case 1 had congestive heart failure, while case 2 had normal left ventricular function. Although metastatic lesions of lymphoma cells cannot be denied, the clinical course was compatible with adriamycin cardiotoxicity. Antiyosin imaging may be a more sensitive method of detecting adriamycin-induced myocardial cell necrosis than other diagnostic methods and may give us valuable information as to whether adriamycin treatment should be continued or discontinued. Although endomyocardial biopsy was not performed in either patient due to clinical condition or age, further study is necessary to correlate antiyosin imaging and histopathological findings on endomyocardial biopsy.

Adriamycin cardiotoxicity evaluated with two other radionuclide methods has also been reported: technetium-99m pyrophosphate (Tc-PYP) myocardial imaging and rediunucleic angiocardigraphy. Chacko et al found that 9 patients out of 15 treated with adriamycin for neoplasia showed myocardial accumulation of Tc-PYP. 99mTc-PYP uptake is reported to be related to the accumulation of Ca²⁺ in the myocytes. Azuma et al reported that enhanced Ca²⁺ influx into myocytes could be a factor in the Ca²⁺ overload associated with adriamycin-induced cardiomyopathy. Antiyosin antibody, however, is highly specific for myocardial cell necrosis, and antiyosin imaging is considered to be superior to 99mTc-PYP in the detection of myocardial damage. Radionuclide cardiography has also been reported to be useful in monitoring adriamycin cardiotoxicity. Since antiyosin imaging detected myocardial cell necrosis before congestive heart failure developed (case 2), antiyosin imaging may be a more sensitive method than radionuclide cardiography.

This study indicates that antiyosin imaging may provide useful and sensitive information in the detection of irreversible myocardial cell necrosis caused by adriamycin not only in congestive heart failure but also in an early stage before congestive heart failure develops. It may lead to the monitoring of myocardial damage in specific heart muscle diseases due to adriamycin as well as in myocarditis.

REFERENCES


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