¹¹¹In Monoclonal Antimyosin Antibody Imaging: Imaging of Myocardial Infarction and Myocarditis

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A new scintigraphic method to detect myocardial necrosis has been developed using antimyosin monoclonal antibody Fab labeled with indium-111. Using this method, we studied 35 patients with myocardial infarction, 5 patients with myocarditis and 3 patients with angina pectoris. ¹¹¹In antimyosin Fab was administered intravenously and antimyosin images were recorded by planar and single photon emission computed tomography (SPECT) 48 hours after injection. Planar images showed discrete localization of ¹¹¹In antimyosin in 25 of 26 patients within 14 days after the onset of acute myocardial infarction. In 14 of these patients creatine kinase, glutamic oxaloacetic transaminase and lactic dehydrogenase had already normalized. Positive scans were also obtained in 6 of 12 patients between the third week to the ninth year after the onset of the disease.

Three patients with acute myocarditis had positive scans 2 and 4 weeks after the onset of the disease.

Thus, ¹¹¹In antimyosin imaging may be a useful noninvasive method for the diagnosis of coronary diseases and myocarditis. Although the mechanism of persistent positive antimyosin images in the chronic stage remains to be clarified, ¹¹¹In antimyosin scintigraphy holds potential promise as a non-invasive method for the detection of myocardial injury in the subacute to chronic stage as well as in the acute stage.

WHEN radiolabeled antimyosin antibodies bind to cells whose plasma membranes have lost their integrity, intracellular myosin is exposed to extracellular fluid when the membrane degenerates.¹⁻³

Recently, antibody imaging technique was

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developed using antimyosin monoclonal antibodies and was found to be useful in the diagnosis of acute myocardial infarction,⁴⁻⁷ myocarditis^{8,9} and heart allograft rejection.^{10,11} However, myocardial uptake has not been studied in the subacute to chronic stage of the disease. The present study was performed to evaluate further the applicability of this technique in the diagnosis of acute myocardial infarction and myocarditis especially in the later phase of the disease.

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TABLE 1 ^{111}In ANTIMYOSIN IMAGING IN 35 PATIENTS WITH MYOCARDIAL INFARCTION

Onset-injection	n	^{111}In Antimyosin		Positive (%)
		+	-	
Day 1 - Day 7	16	15	1	94%
Day 8 - Day 14	10	10	0	100%
Day 15 - 2 months	6	4	2	67%
3 months - 8.5 years	6*	2	4	33%

*Prior infarction of recurrent cases was included

Fig.1. Myocardial images in anterior and left anterior oblique (LAO) and lateral projections in a patient with anterior wall myocardial infarction 3 days after the onset. Positive image is seen in the anterior wall.

METHODS

Patients

Thirty-five patients with acute myocardial infarction, 5 patients with myocarditis and 3 patients with angina pectoris were studied. Criteria for selection of the patients with acute myocardial infarction were precordial chest pain typical of cardiac ischemia of at least 30 min duration, ST elevation of at least 0.1 mV in 2 or more leads of the electrocardiogram with subsequent evolution of an electrocardiographic infarct pattern, and elevation of creatine kinase

(CK). Thirty-four patients underwent cardiac catheterization and selective coronary artery cineangiography. Five patients with histories and clinical findings suggestive of myocarditis were also studied. Four patients underwent cardiac catheterization, right and left endomyocardial biopsies using Konno-Sakakibara biptome or Cordis biptome. Two of them had definite myocarditis with myocardial necrosis and cellular infiltration and were demonstrated to have normal coronary arteries by selective coronary artery cineangiography. The remaining one patient had recent onset of congestive heart

TABLE II ^{111}In ANTIMYOSIN IMAGING IN 5 PATIENTS WITH MYOCARDITIS

Age (yr)	Sex	Clinical presentation	Biopsy finding	Onset-injection	^{111}In -antimyosin imaging
33	M	3° AV block	Acute myocarditis	14 Days	+
63	M	3° AV block	Acute myocarditis	14 Days	+
52	F	T wave inversion	Not done	1 Month	+
60	F	Pacemaker Congestive heart failure	Healed myocarditis	Unknown	—
50	M	Congestive heart failure	Healed myocarditis	1.5 Year	—

Fig.2. Light microscopy of right ventricular endomyocardial biopsy specimen, taken 4 days after the onset of acute myocarditis in a 33-year-old male patient. Mononuclear cell infiltration and necrosis of myocytes are prominent. Hematoxylin and eosin stain $\times 180$.

failure of unknown cause preceded by flu-like illness with fever, and elevation of creatine kinase and diffuse ST-T abnormalities on the electrocardiogram. All 3 patients with angina pectoris did not have elevation of creatine kinase.

Indium 111-monoclonal antimyosin Fab cardiac imaging

We used monoclonal antibody R11D10 (directed against cardiac myosin) coupled to DTPA for radiolabeling with ^{111}In (offered by Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan). After informed consent was obtained, the radiolabeled, pyrogen-free conjugate was

administered to the patients. To test for hypersensitivity 0.05 mg of the monoclonal antibody was administered intradermally. If no wheal or flare was observed within 15 min, 500 μg of antimyosin Fab labeled with 2 mCi (74 MBq) of ^{111}In was administered intravenously. Planar and single photon-emission tomography (SPECT) images were obtained at 48 hours after administration of ^{111}In antimyosin. Planar images were recorded in the anterior, 45 and 70 degree left anterior oblique and left lateral views with each 7 min, collecting 300–500 kilocounts each into 256 by 256 matrices using both photo peaks of indium-111 (174 and 247 KeV) and a medium

Fig.3-A. Myocardial images in anterior and left anterior oblique (LAO) projection in a patient with acute myocarditis 14 days after the onset. Diffuse positive image is seen in the left ventricle.

Fig.3-B. A series of vertical (top) and horizontal (middle) long-axis slices and short-axis slices (bottom) in the same patient as shown in Fig. 3-A. 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. Note diffuse myocardial uptake in the left ventricle in these tomographic images.

energy general purpose collimator. In SPECT study, a series of 64 projection images were collected over 360 degrees at 5.6 degree increments for 30 sec each into a 64 by 64 matrices and was stored for subsequent analysis. A series of transaxial slices with 6 mm intervals were reconstructed by a filtered back-projection method. A series of vertical long axis, horizontal long axis and short axis sections were also

obtained.

Planar and SPECT antimyosin images were interpreted directly from the computer video display by at least 2 observers who had no knowledge of the clinical data and biopsy results.

RESULTS

Skin tests before administration of antimyosin

were negative in all patients studied. ^{111}In antimyosin Fab was administered without untoward reaction in all subjects.

Antimyosin Imaging of Myocardial Infarction

The results of ^{111}In antimyosin imaging in 35 patients with myocardial infarction are listed in Table I. Electrocardiograms localized the infarct to the anterior wall in 17 patients, to the inferior wall in 13 and to the lateral wall in 5.

Planar images showed discrete localization of antimyosin in 25 of 26 patients (96%) within 14 days after onset of the disease in 14 of whom CK, GOT or LDH had already normalized. Antimyosin scans showed positive uptake in 4 of 6 patients (67%) between the third week and the second month after the onset and in 2 of 6 patients (33%) between the third month and the ninth year including cases of prior infarction of recurrent cases. Positive scan was seen as long as 9 months after onset in whom ventricular dyskinesia developed. Fig. 1 shows a planar ^{111}In antimyosin image from a patient.

Antimyosin Imaging of Myocarditis

Right and left ventricular biopsies were diagnostic for acute myocarditis in 2 patients and healed myocarditis in 2 patients. In patients with positive scans, CK GOT or LDH had already normalized and acute inflammatory reaction had subsided. Table II shows clinical findings and results of myocardial biopsy and antimyosin imaging. Results of ^{111}In antimyosin imaging were positive in all 3 patients. Antimyosin imaging. Results of ^{111}In antimyosin imaging were positive in 3 patients. Antimyosin imaging was positive 1 month after onset of the disease. Fig. 2 shows histologic finding and Fig. 3 illustrates antimyosin imaging of a patient with acute myocarditis.

All 3 patients with angina pectoris showed negative antimyosin scans.

DISCUSSION

In our study, ^{111}In antimyosin scans were positive in 96% of the patients with acute myocardial infarction before 14 days after onset. Among these patients, CK had already normalized in 14 patients (56%) at the time of antimyosin injection. Positive scans were seen as long as 9 months after the onset of myocardial infarction in a patient with dyskinetic area. These results indicate that ^{111}In antimyosin

imaging may detect myocardial infarction in the subacute to chronic stage as well as in the acute stage. As circulating ventricular myosin heavy chain has been shown to remain elevated for as long as 12 days after myocardial infarction,¹² persistent uptake of ^{111}In antimyosin uptake may reflect persistent exposure of myosin in the damaged myocardium.

Most of the previous studies have been performed only in the acute stage of myocardial infarction. In the study by Johnson et al,¹³ in which 14 patients with recurrent myocardial infarction were included, 2 patients with positive antimyosin scans with recurrent infarction were described 7 or 9 days after the onset. However, ^{111}In antimyosin did not localize in areas of prior myocardial necrosis occurring more than 2 weeks before the current myocardial infarction. Other studies which included recurrent myocardial infarction, did not show positive antimyosin uptake in previous remote infarcts.^{14,15} Recent study showed the case of a coronary heart disease patient with a history of chest pain of more than 12 months.¹⁶ Recently, ^{111}In antimyosin monoclonal antibody imaging was performed in 28 patients, clinically suspected of having myocarditis. Antimyosin scans were positive in 9 patients who had evidence of myocarditis on right ventricular biopsy, and negative in 11 who had no evidence of myocarditis by biopsy. The remaining 8 had positive antimyosin scans but showed no evidence of myocarditis on right ventricular biopsy. On the basis of a right ventricular biopsy standard, the sensitivity of this method was 100% and the specificity 58%.⁸

In our previous study on an experimental model of coxsackievirus myocarditis,¹⁷ cardiac uptake of $^{99\text{m}}\text{Tc}$ -pyrophosphate (PYP) reached a maximum on the seventh day after virus infection but decreased significantly on the fourteenth day when myocardial lesions were most prominent. Thus, $^{99\text{m}}\text{Tc}$ -PYP may be useful only in the acute stage of viral myocarditis.

Our recent study demonstrated that measurement of ^{125}I antimyosin uptake of the heart is a sensitive technique for detecting acute viral myocarditis in the experimental animal.⁹ The antimyosin uptake ratio of the heart began to increase 3 days after virus inoculation when histologic abnormality had not yet appeared. On Day 14, the uptake ratio of the heart reached a maximum and histologically, myocardial lesions were most extensive and prominent at this stage.

On Day 28, when cellular infiltration had decreased and myocardial fibrosis was evident, the uptake ratio remained elevated. Thus, the increase in antimyosin uptake in the early stage of viral myocarditis, correlated well with histopathologic changes and persisted long after virus inoculation. These findings suggest that antimyosin scintigraphy is useful for diagnosing viral myocarditis in its subacute to chronic stage as well as in the acute stage. In this study, we found positive antimyosin scans in 2 patients with biopsy-proven myocarditis 2 or 4 weeks after the onset of the disease when CK, GOT or LDH had already normalized.

Although further studies are necessary to clarify the mechanism of persistent uptake of ^{111}In antimyosin, ^{111}In antimyosin imaging may be a useful noninvasive method for the diagnosis of myocardial infarction or myocarditis in the later stage as well as the acute stage of the diseases, and for evaluating the effect of therapeutic interventions, clinical course or prognosis.

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