Indium 111–monoclonal antimyosin antibody imaging in the diagnosis of acute myocarditis

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ABSTRACT A definitive diagnosis of myocarditis requires right ventricular biopsy. Despite its specificity, however, right ventricular biopsy may lack sensitivity due to the focal nature of the disease. Because indium 111–monoclonal antimyosin antibody imaging can be used to detect myocardial necrosis, this procedure was performed on 28 patients clinically suspected of having myocarditis, 25 of whom had left ventricular ejection fractions of less than 45%, and the results were compared with those of right ventricular biopsy performed within 48 hr of the scan. Antimyosin scans were positive in nine patients who had evidence of myocarditis on right ventricular biopsy, and negative in 11 who had no evidence of myocarditis by biopsy. The remaining eight 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%, the specificity 58%. We conclude that antimyosin antibody imaging is a reliable screening method for the evaluation of patients suspected of having myocarditis, and that a positive antimyosin scan indicates the need for right ventricular biopsy to establish the histologic diagnosis.


ALTHOUGH A PRESumptive diagnosis of myocarditis can be made on the basis of clinical findings, the histologic demonstration of a cell infiltrate associated with necrotic or degenerative myocytes is necessary for a definitive diagnosis. Right ventricular endomyocardial biopsy is a widely used technique, but its sensitivity for myocarditis has not been established. Furthermore, because of the focal nature of the disease, right ventricular endomyocardial biopsy may lack sensitivity because it may fail to sample a sufficient number of myocardial sites.

Radiolabeled Fab of monoclonal antimyosin antibodies bind to cells that have lost the integrity of their plasma membranes; intracellular myosin is exposed to extracellular fluid when the membrane degenerates. Scintigraphic examinations with these antibodies have been used to localize and quantify regions of myocardial necrosis in myocardial infarction. Because myocardial necrosis is an obligatory component of myocarditis, the present study was performed to evaluate the applicability of this technique in the diagnosis of myocarditis.

Methods

Patient population. Twenty-eight patients were studied who presented at the Massachusetts General Hospital between 1984 and 1985 with histories and clinical findings suggestive of acute myocarditis (table 1). All patients underwent right and left heart catheterization, right ventricular endomyocardial biopsy, and imaging with monoclonal antimyosin Fab labeled with indium-111 (111In), and all were demonstrated to have normal coronary arteries by selective coronary artery cineangiography.

Three patients had left ventricular ejection fractions greater than 45% (two men, one woman). One patient presented with chest pain and electrocardiographic changes resembling an evolving myocardial infarction; normal coronary arteries and no evidence of spasm were demonstrated during emergency coronary cineangiography. Another presented with pericardial effusion, chest pain, and atrial fibrillation, and one had unexplained bisedis congestive heart failure, a normal left ventricular ejection fraction, and hemodynamic findings consistent with constrictive versus restrictive physiology. The pericardium appeared normal on two-dimensional echocardiography and computed body tomography.

Twenty-five patients presented with global left ventricular dysfunction demonstrated by cardiac catheterization or equilibrium-gated blood pool scanning (13 men, 12 women; mean age 50 ± 3 years, range 19 to 77; average left ventricular ejection fraction 27 ± 2%). Of these 25 patients, four (16%) presented with ventricular tachyarrhythmias and one (4%) with chest pain.
TABLE 1
Characteristics of 28 patients suspected of having myocarditis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Clinical score</th>
<th>Presentation</th>
<th>Biopsy results</th>
<th>AMAb scan</th>
<th>Initial LVEF</th>
<th>Six month follow-up LVEF</th>
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<td>20</td>
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<td>70^</td>
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AF = atrial fibrillation; AMAb = antimiysin antibody; CHF = congestive heart failure; CP = chest pain; eff = pericardial effusion; LVEF = left ventricular ejection fraction; Myoc = myocarditis; NSC = nonspecific change; VT = ventricular tachycardia; VF = ventricular fibrillation.

^aPrevious bout of biopsy-proven myocarditis.

^bPatients with abnormal left ventricular ejection fractions who showed an improvement of 10% or more.

The remaining 20 (80%) presented with acute onset of heart failure. Heart failure was present for less than 1 year in three of the 20 in this group, and for less than 6 months in 17. Four of the 20 had had a previous episode of biopsy-proven myocarditis, and presented with another episode of heart failure and symptoms suggestive of relapse.

Transvenous right ventricular endomyocardial biopsy and pathologic evaluation. Patients underwent right ventricular endomyocardial biopsy through the right jugular vein as previously described. Multiple biopsy specimens (usually six or seven, each measuring 1 to 3 mm in diameter) were obtained with a Caves-Schultz-Stanford biopsy. Three to four samples were immediately fixed by immersion in buffered 10% formalin for histologic study by light microscopy. One sample was placed in 2.5% buffered glutaraldehyde for electron microscopy, and one was snap-frozen for immunofluorescence studies. Paraffin sections were stained with hematoxylin and eosin, Masson trichrome, and Congo red. The frozen sample was sectioned and stained with hematoxylin and eosin, and with toluidine blue. Sections of 1 μm were cut from each of the specimens embedded in plastic and stained with toluidine blue.

Biopsy specimens were analyzed without knowledge of the scan results. Specimens were divided into three categories on the basis of light microscopic studies: specimens defined as showing myocarditis contained an inflammatory infiltrate adjacent to necrotic or degenerative myocytes, with or without interstitial fibrosis (figure 1); specimens showing myocyte hypertrophy, interstitial fibrosis and/or replacement fibrosis but no evidence of myocarditis were placed in the nonspecific change category; normal specimens showed no abnormalities.

Ventriculography and clinical evaluation. The initial left ventriculogram was recorded by the radionuclide technique in 24 patients and by the contrast technique in four. All patients were interviewed and examined by one of the investigators before cardiac catheterization. From a review of the clinical history and laboratory data, as previously reported, patients were scored according to the number (0 to 3) of clinical features at the onset of illness that were suggestive of myocarditis; a febrile, virus-like illness just before the development of cardiac symptoms; pericarditis; or laboratory abnormalities (elevation of the serum creatine kinase level, erythrocyte sedimentation rate, or white cell count).

All patients with heart failure due to dilated cardiomyopathy received digoxin and diuretics; in addition, 11 patients received...
afterload-reducing agents (captopril, 10; prazosin, one) at the
time of initial evaluation of ventricular function. Although the
medications were continued with minor adjustment throughout
the study, there were no patients in whom afterload-reducing
therapy was initiated during the course of the follow-up period.
Furthermore, none of the patients who were categorized as
having improved ventricular function at the time of follow-up
evaluation were receiving afterload-reducing agents. Only one
patient (table I, No. 6), who presented in cardiogenic shock,
received intravenous inotropic therapy with norepinephrine.
None of the patients received oral or intravenous phosphodies-
terase inhibitors.

Follow-up left ventriculograms were obtained at six months
by the radionuclide technique. Ventricular function was consid-
ered improved if all three of the following criteria were present:
(1) an increase in left ventricular ejection fraction of 10% or
more, (2) a decrease in the cardiothoracic ratio of the chest film,
and (3) a decrease in symptomatic heart failure by one or more
New York Heart Association classes.

Indium 111–monoclonal antimyosin Fab cardiac imaging. We used monoclonal antibody R11D10 (directed against
the heavy chain of cardiac myosin) coupled to DTPA\(^{7}\) for radio-
labeling with \(^{111}\)In (kits from Centocor, Malvern, PA). After
informed consent was obtained, the radiolabeled, pyrogen-free
conjugate was administered to all patients within 24 to 48 hr of
myocardial biopsy. To test for hypersensitivity, 0.05 ml of the
radioactive agent was administered intradermally. If no wheal
or flare was observed within 15 min, 500 \(\mu\text{g}\) of antimyosin Fab
labeled with 1.8 mCi (66.6 MBq) of \(^{111}\)In was administered
intravenously. Ungated planar and single photon–emission
computed tomography (SPECT) images were obtained at 24 and
48 hr after administration of the radioactive agents, as previously
described.\(^{7}\) Ungated images were recorded in the anterior and
40 to 50 degree left anterior oblique views with the use of a
medium-energy collimator with the pulse height analyzers set at
centerlines of 173 and 247 keV (20% window in each). For
SPECT imaging, patients were positioned so that the smallest
diameter circle could be inscribed by the detector of a rotating
gamma camera (Technicare Omega-500/560 AP, Solon, OH).
A series of 120 images was collected at 3 degree increments for
20 sec each into a 64/64 matrix and was stored for subsequent
analysis. The SPECT images were reconstructed with a filtered
backprojection algorithm into transverse, sagittal, and coronal

Results

Antimyosin Fab was administered without untoward
reaction in all subjects. The clinical scores and histo-
logic, ventriculographic, and antimyosin imaging
results are listed in table 1.

Endomyocardial biopsy findings. Right ventricular bi-
opsies were diagnostic for myocarditis in nine patients
(32%), showed nonspecific changes in 13 (47%), and
were normal in six (21%).

Results of antimyosin imaging. Table 2 shows the cor-
relation between results of right ventricular biopsy and
antimyosin imaging. Results of \(^{111}\)In-antimyosin imaging
were positive in 17 patients (61%) and negative in
11 (39%). In all 17 patients with positive antimyosin
scans, tracer uptake was heterogeneous within the left
ventricle. All patients with biopsy-proven myocarditis
had positive antimyosin scans. In addition, eight pa-
tients with no evidence of myocarditis on biopsy had
positive antimyosin scans. Of these eight patients, the
biopsy samples of five were classified as normal and
three showed nonspecific change. The changes con-
sisted of varying degrees of interstitial and/or replace-
ment fibrosis and myocyte hypertrophy, but no evi-
ence of inflammation. A negative antimyosin scan was obtained in 11 patients; none of them had evidence of myocarditis by biopsy, although most of them (10 patients) showed nonspecific change.

Follow-up. All six patients (left ventricular ejection fraction <45%) with biopsy-proven myocarditis and dilated cardiomyopathy received immunosuppressive therapy: four a combination of azathioprine and prednisone, one prednisone alone, and one cyclosporine and prednisone. Improvement occurred in four of these six patients (67%). No deaths have occurred in this group of patients with biopsy-proven myocarditis. Spontaneous improvement occurred in four of the eight patients with positive antimyosin scans and biopsy specimens showing no evidence of myocarditis (50%). Each of the four patients who showed improve-

FIGURE 2. A positive antimyosin image. Diffuse uptake in the cardiac region (arrow) is seen in the planar images (top) and in the coronal tomographic reconstruction (bottom). LAO = left anterior oblique projection.
ment had a clinical score equal to or greater than 2. No deaths have occurred in this group. Finally, improvement also occurred in three of the 11 patients (27%) with negative antimyosin scans.

Discussion

It would be highly desirable to have a noninvasive screening test for myocarditis that could identify those patients who should undergo endomyocardial biopsy.2 One noninvasive method, the gallium-67 scan, is helpful because an inflammatory cell infiltrate is a histopathologic feature of this disease. Antimyosin scanning provides an opportunity for monitoring the other obligatory abnormality associated with myocarditis, myocardial necrosis.7 Experimental and clinical studies previously demonstrated that antimyosin Fab was specific only for necrotic myocytes in which intracellular myosin was accessible to extracellular fluid.3,4 In this study, a positive antimyosin scan was present in all patients with biopsy-proven myocarditis. Of equal importance, all patients who had a negative antimyosin scan also had a negative biopsy result.

Of particular interest are those eight patients who had no evidence of myocarditis on biopsy but who had positive scans. Could normal myocardial biopsies be the result of focal disease with consequent sampling

FIGURE 3. A negative antimyosin image. No tracer uptake is seen in either the planar images (top) or the coronal tomographic reconstruction (bottom). LAO = left anterior oblique projection.
Comparison of results of right ventricular biopsy and of antimyosin imaging in 28 patients with histories suggestive of myocarditis

<table>
<thead>
<tr>
<th>Antimyosin scan result</th>
<th>Right ventricular biopsy result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>9</td>
</tr>
<tr>
<td>Negative</td>
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</table>

The probability that either the two columns or the two rows of this table were drawn from the same population is .004 by the Fisher test.

error? Spontaneous improvement is a feature of acute myocarditis. A spontaneous substantial improvement in ejection fraction occurred in four of these eight patients. The improvement in left ventricular ejection fraction at the time of follow-up radionuclide ventriculography must have been independent of loading changes due to medical therapy, because none of these improved patients required therapy for heart failure at that time. Although these findings suggest that an underlying diagnosis of myocarditis may have been missed because of a sampling error or a failure to identify early myocardial necrosis by histologic criteria, a definitive characterization of this group will require longer term follow-up.

Results more difficult to explain are those of three of the 11 patients with negative biopsies and negative scans who also showed improvement in their ejection fractions. It may be possible that during the course of myocarditis both necrosis and inflammation may have resolved at the time the patient was studied, yet improvement of ventricular function lagged behind the resolution of tissue injury. Another possibility is that there are other forms of transient depression of ventricular function that are still not characterized.

Thus, antimyosin scintigraphy appears to be a reliable screening method for the evaluation of patients suspected of having myocarditis. A positive antimyosin scan indicates the need for endomyocardial biopsy to establish the histologic diagnosis. If the present results are confirmed in studies of a larger number of patients, it may be possible to avoid biopsy in patients who present with a negative scan.

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