Utility of Indium-111-Antimyosin Scintigraphy for Diagnosis of Myocardial Damage in Systemic Sclerosis

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The diagnosis of myocardial disease related to systemic sclerosis is often difficult, but it is clinically relevant since the occurrence of a specific ventricular dysfunction is of poor prognosis. This article reports a case of systemic sclerosis with a subacute episode of myocardial disease assessed by ^{111}In-antimyosin antibody, a specific marker of the necrotic myocardial fiber.

Key Words: antimyosin antibodies; myocardium; systemic sclerosis
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Monoclonal ^{111}In-DTPA antimyosin antibodies (AMA) bind specifically to exposed myosin when the myocyte membranes are disrupted (*1*). Specific myocardial uptake, evidenced by AMA scintigraphy, is observed in several conditions of myocardial necrosis such as acute myocardial infarction, acute myocarditis of viral or immune origin (systemic disorders), idiopathic dilated cardiomyopathy, cardiac rejection of transplanted hearts and chemotherapy toxicity (*2–5*).

Systemic sclerosis (SSc) is a generalized connective tissue disorder consisting of diffuse fibrosis and atrophy with multiple target organs. For example, the skin, kidneys, lungs, digestive tract and heart (pericardium and/or myocardium). Heart failure in SSc may be of several origins, including specific myocardial involvement, but this diagnosis is difficult in the absence of specific markers (*6*). This case reports the use of AMA scintigraphy for the diagnosis of evolutive myocardial damage in SSc.

CASE REPORT

A 28-yr-old man was admitted for exertional dyspnea and palpitations leading to syncopes related to transient atrial fibrillation and flutter. The patient had a history of severe digital arteritis (Raynaud's syndrome) since the age of 15, which was investigated twice, once in 1987 and once in 1988. Diagnosis of beginning collagenosis was suspected on the results of capillaroscopy. The patient was treated with calcium channel blockers and nursing of episodic necrosis of the fingers' pulp. On admission, he was apyretic with an irregular pulse at 120/mn, normal arterial blood pressure and neither gallop nor congestive signs. Bilateral sclerodactyly of every finger, with subcutaneous calcifications and necrosis scars on the fingers' pulp were found. There was no skeletal muscle pain or weakness. Atrial flutter with 2/1 conduction was found on the ECG. The chest radiograph showed an enlarged heart and apical lung accentuated vascular marking. After atrial electrostimulation, the heart rate returned to sinusal rhythm with a left bundle branch block on the ECG. Two-dimensional echography showed enlargement and global hypokinesia of the left ventricle, 64 mm end-diastolic left ventricular diameter, 21% fractional shortening with marked hypokinesia of the anterior and septal walls, and basal akinetic aneurism. Creatine kinase was normal: 53 IU/liter (normal value < 195). The mean pulmonary artery pressure was 17 mmHg, pulmonary capillary wedge pressure was 12 mmHg, cardiac output was 4.5 liter/min and cardiac index was decreased 2.4 liter/m (*2*). The angiographic left ventricular ejection fraction (LVEF) was 40%, and the coronary angiograms were normal. The patient was then treated with amiodarone, acetyl salycylic acid, calcic nadroparine and angiotensin-converting enzyme inhibitors, with a diagnosis of dilated cardiomyopathy related to SSc. Biological investigations showed no inflammatory syndrome, a moderate increase in creatinemia (124 μmol/liter), but neither proteinuria nor hemoglobinuria. Antinuclear factors, antidesoxyribonucleic acid, antinuclear and anticardiolipid antibodies and cryoglobulin were negative, as were syphilitic serologies. CH50, C3 and C4 were normal. Oesogastric fibroscopy and manometry and functional pulmonary studies were normal.

To detect potential evolutive myocardial damage, ^{201}Tl and ^{111}In-AMA imaging was performed 6 days after catheterization and initiation of pharmacological treatment. First, 74 MBq ^{111}In-AMA were intravenously injected. Forty-eight hours later, planar thoracic images (anterior, 40° and 70° oblique anterior views) were acquired, with a 20% window centered on the 173 and 247 KeV photopeaks of ^{111}In, matrix 128 × 128, and a preset time of 10 min. On the ^{111}In anterior planar image, a cardiac/pulmonary ratio (CPR) was calculated using two circular ROIs, one on the cardiac area and the other on the right lung. Then, 111 MBq ^{201}Tl were injected, and a dual-isotope SPECT acquisition was performed with a dual-head gamma camera, at right angle, fitted with medium-energy collimators. Tomographic acquisition parameters were as follows: 180°, circular orbit, 32 projections, matrix 64 × 64, 40 sec per projection. The two datasets (^{201}Tl-SPECT and ^{111}In-SPECT) were simultaneously, identically and automatically processed as follows: filtered (hamming), backprojection, centered and reoriented along the three axes with the help of the ^{201}Tl acquisition as a landmark. Neither background subtraction nor attenuation correction were performed. Corresponding short-axis, vertical long-axis and horizontal long-axis slices for each SPECT acquisition were displayed simultaneously. If needed, corresponding slices could be superimposed for better ^{111}In-AMA uptake localization. Left ventricular myocardium was divided in 21 segments to quantify the extent of ^{201}Tl defects.

Planar and SPECT ^{111}In-AMA images showed diffuse myocardial uptake of AMA over the whole left ventricular myocardium and significant, but lower, AMA uptake on the right ventricular myocardium (Figs. 1A and 2B). The CPR was 2.3. Normal values of our laboratory have previously been determined as inferior to 1.8 (*7*). Rest ^{201}Tl images showed a small posterior-lateral defect involving 1 of 21 segments (Fig. 2A). A radionuclide angioscintigraphy (^{99m}Tc-pyrophosphate) was performed, which demonstrated enlargement and global hypokinesia of both ventricles. The isotopic LVEF was 35% (normal values: 65 ± 10). A right ventricular endomyocardial biopsy showed only dystrophy of the

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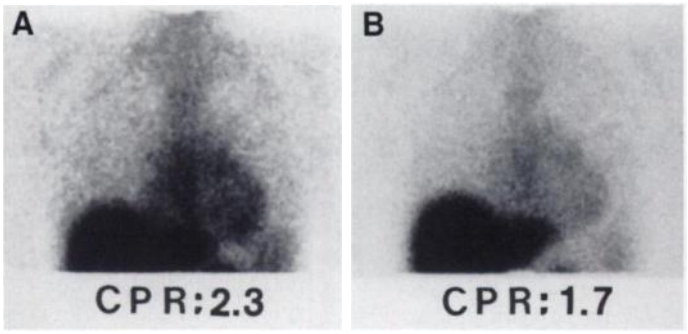

FIGURE 1. Indium-111-AMA planar imaging (anterior views). (A) Initial image during the acute cardiac episode showing abnormal myocardial AMA uptake. Cardiopulmonary ratio (CPR): 2.3 (normal < 1.8). (B) Second scan, 3 mo after the start of treatment: no more myocardial AMA uptake. CPR: 1.7.

myofibrillas, without inflammatory cells or fibrosis. Calcium channel blockers and D-penicillamine were added to the treatment previously mentioned.

Three months later, follow-up revealed no more dyspnea on exercise, normal heart auscultation and improved isotopic LVEF (50%) despite persistent segmental wall motion abnormalities (akinetic posterior and lateral walls), persistent enlargement of both ventricles and global hypokinesia of the right ventricle. A new ^{111}In-AMA and ^{201}Tl scintigraphy was performed. Thallium-201 images showed a clear defect of the posterior and lateral walls involving 4 of 21 segments, more extensive than the former observed 3 mo earlier (Fig. 3A). The ^{111}In-AMA scintigraphy was negative, showing only circulant antibody activity (Figs. 1B and 3B). The CPR was normal, evaluated at 1.7.

DISCUSSION

This case demonstrates transient evolutive diffuse myocyte necrosis, concomitant with arrhythmia and severe cardiac dysfunction, in a sclerodermic patient with no evidence of skeletal myopathy or pulmonary, renal or digestive specific injury. The purpose of AMA scintigraphy in this case was the confirmation of cardiac SSc involvement, the demonstration of the evolutivity of the disease and follow-up. Demonstration of subacute myocyte necrosis as one of the phenomena involved in this disease also may be of physiopathological interest.

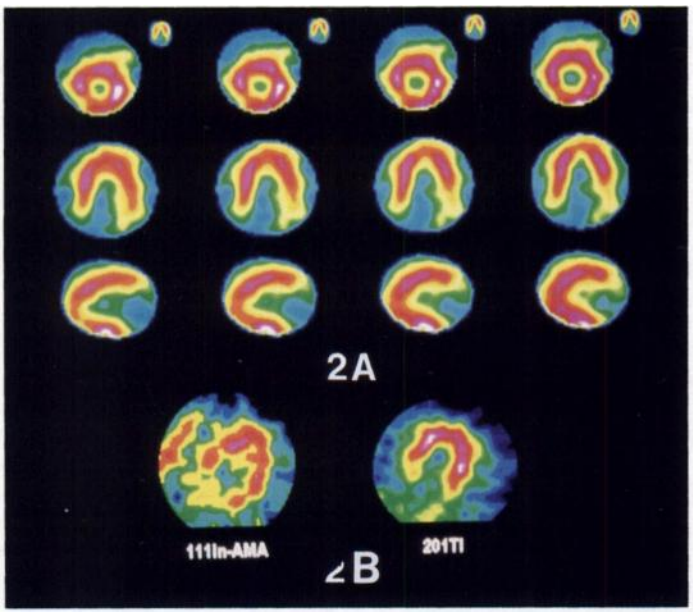

FIGURE 2. Initial dual-isotope ^{111}In-AMA and ^{201}Tl SPECT at rest during the acute cardiac episode. (A) Thallium-201 images showing a mild posterior-lateral defect. (B) Indium-111-AMA and corresponding ^{201}Tl transverse slice showing diffuse AMA uptake on both ventricles.

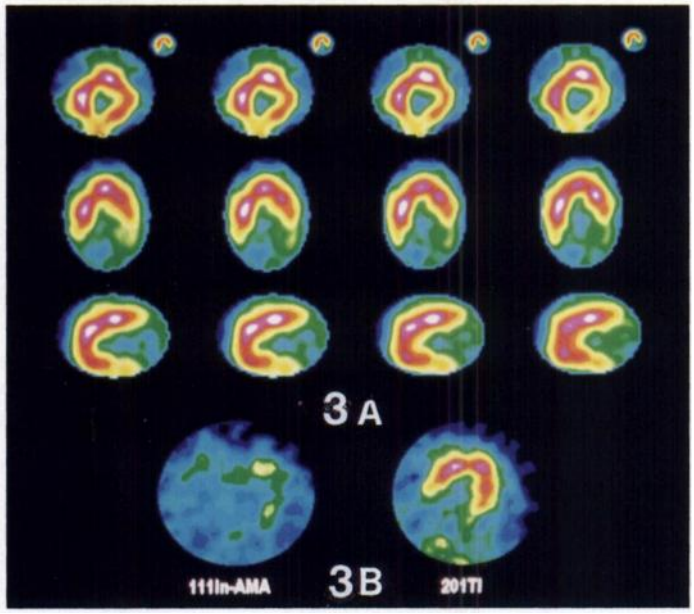

FIGURE 3. Dual ^{111}In-AMA and ^{201}Tl SPECT at rest 3 mo after the start of treatment. (A) Thallium-201 three-axis slices showing a clear posterior-lateral defect. (B) Negative ^{111}In-AMA and corresponding ^{201}Tl transverse slice.

Sclerodermic myocardial injury is histologically characterized by focal fibrosis distributed throughout the myocardium, muscle cell necrosis with contraction band formation (14/23 cases in Bulkey's autopsic series) and focal standard inflammation (*8*). The mechanisms that lead to fibrosis in SSc myocardial injury are not well established. One possible explanation is transient ischemia caused by vasospasms, alone or associated with fixed abnormalities of the microvasculature, or transient coronary occlusions, which result in contraction band necrosis and then replacement fibrosis (*6,8*). Other mechanisms also suggested are cellular immune activation and immune mediator release (growth factors, interleukines, interferon), resulting in fibroblast proliferation and collagen synthesis (*9*).

SSc myocardial involvement is usually diagnosed at a clinical stage. Clinical presentation (left and/or right ventricle failure, syncopes, tachycardias, acute myocardial infarction) is not specific, especially in the presence of other systemic sclerodermic injuries such as systemic hypertension consecutive to renal failure, pulmonary fibrosis with chronically increased pulmonary capillary pressure and pericardial involvement. Moreover, clinical symptoms are usually late, after a long clinically silent evolution. Consequently, only 7%–16% of SSc myocardial injuries are detected, although they affect a high proportion of SSc patients (up to 89% according to postmortem histopathologic studies). Although diagnosis is important, so treatment may be started as early as possible, symptomatic SSc myocardial injury is of poor prognosis. Survival after diagnosis is 18–24 mo, and 25% of the deaths associated with SSc are caused by specific myocardial disease (*6*).

Currently, the positive diagnosis of SSc myocardial injury is based on endomyocardial biopsy. As reported by many authors (*10–12*), this invasive technique suffers from a lack of sensitivity because it may not sample enough myocardial sites to detect a disease that may have a patchy distribution. Mason et al. (*12*) found less than 10% of positive biopsies in patients with typical clinical history of acute myocarditis; Dec et al. (*3*) found 22%. Electrical, echocardiographic, electrophysiological and angiographic abnormalities (ventricle enlargement and dysfunc-

tion, conduction abnormalities, atrial or ventricular arrhythmias) are frequently observed, but are not specific. Recently, several studies have shown the diagnostic interest of ^{201}Tl scintigraphy such as perfusion defects at rest, after exercise or after cold exposure are common findings in symptomatic or asymptomatic SSc patients, and even in patients with no ventricular dysfunction (*13,14*). These defects are reversible, at least in part, in the short term after administration of vasodilators such as dipyridamole or nifedipine (*15,16*). Thallium-201 imaging, however, has several limitations in this indication. Exercise or cold exposure defects can be observed in epicardial coronary artery disease. The reversibility of rest thallium abnormalities after administration of vasodilators is more specific for microvasculature injury, but rest defects are not always reversible because they may correspond to sequellar fibrosis. Moreover, a normal rest ^{201}Tl-SPECT does not exclude SSc myocardial injury (*13*). The presence of diffuse equilibrated injury of the microvasculature and/or of diffuse mild fibrosis may result in a diffuse decreased uptake leading to homogeneous images. Finally, ^{201}Tl abnormalities do not indicate the evolution of the disease since they may be sequellar from previous resolutive episodes of myocyte necrosis.

In this observation, ^{111}In-AMA imaging detected SSc myocardial injury earlier than rest ^{201}Tl-SPECT. There was initially a great discordance between rest thallium near-normal images and intense diffuse ^{111}In-AMA myocardial uptake on both ventricles. This pattern excluded myocardial infarction in relation with epicardial coronary artery occlusion (actually, coronary arteriogram was normal), but specifically evoked diffuse equilibrated perfusion abnormalities (microvessel injury) responsible for diffuse myocyte necrosis. Such diagnostic interest was previously demonstrated in symptomatic patients with other systemic pathologies: polymyositis, systemic lupus erythematosus and sarcoidosis (*7,17,18*). It may also be useful for the early detection of clinically silent cardiac involvement (*18*).

This also demonstrates the limits of rest ^{201}Tl-SPECT and the complementary use of ^{111}In-AMA scintigraphy to differentiate evolutionary (a few days after the arrythmia episode) from nonactive myocardial disease (3 mo later, no more ^{111}In-AMA uptake). This was previously shown in myocardial involvement of polymyositis, and was discussed in systemic sarcoidosis (*7,18*). The second scintigraphy also showed the myocardial scar (more extensive inferior-lateral defect on thallium images) resulting from this subacute episode, which was consistent with the persistent segmental akinesia.

The treatment the patient received may have played a role in the resolution of this episode, as it included calcium channel blockers and angiotensin-converting enzyme inhibitors, whose efficency in SSc myocardial injury has been suggested by several authors. Kahan et al. (*19*) demonstrated a short-term (90 min) improvement in left ventricular function and a durable increase in myocardial perfusion (evaluated with PET and ^{201}Tl-SPECT) after administration of nifedipine (*20*). A long-term role of angiotensin-converting enzyme inhibitors was also suggested. Improvement of left ventricular function indices and of myocardial perfusion (^{201}Tl-SPECT) was demonstrated in SSc patients after captopril treatment for a mean of 1 yr (*21,22*). Indium-111-AMA scintigraphy could be a marker of the evolution of the disease for pharmacological studies and could provide evidence of the benefits of these vasodilators on the active short-term process of myocardial damage and of therapeutic management of patients.

The results of these two scintigraphic investigations are of pathogenic interest since they confirm that myocyte necrosis may be involved in sclerodermic myocardial damage, with a subacute evolution in this case leading to a subsequent definitive myocardial fibrotic scar (^{201}Tl rest defect).

CONCLUSION

This observation demonstrates that ^{111}In-AMA scintigraphy may be a complementary, useful, noninvasive tool for myocardial investigations in SSc patients. The combination of rest ^{201}Tl and ^{111}In-AMA imaging may be more accurate and may allow earlier detection of SSc myocardial injury than ^{201}Tl imaging alone. This is of great interest in diagnosis and in the follow-up of the disease, as reported in many other systemic pathologies. Moreover, ^{111}In-AMA uptake may be a marker of the evolution of the disease, with interesting potential applications for therapeutic evaluation and management. Finally, with regard to its high sensitivity, ^{111}In-AMA scintigraphy may be useful for early detection of clinically silent SSc myocardial injury, which could lead to earlier treatment and better prognosis.

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