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WHAT ARE THE SAFEST AND EASIEST EXTRA-CARDIAC BIOPSY SITES FOR THE DIAGNOSIS OF WILD-TYPE TRANSTHYRETIN CARDIAC AMYLOIDOSIS? CONFIRMATION OF THE DIAGNOSIS BY BIOPSY OF THE PECTORALIS MUSCLE DURING PACEMAKER INSERTION

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ABSTRACT

Background: The use of nonbiopsy diagnosis of wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) has grown worldwide. However, in specific scenarios, a biopsy of the myocardium or involved tissues must be conducted to confirm deposition of amyloid transthyretin (ATTR).

Case report: An 83-year-old woman was diagnosed with decompensated heart failure, sick sinus syndrome (SSS), and an atrial septal defect (ASD). Cardiac amyloidosis was also suspected. Technetium-99m-labelled pyrophosphate (Tc-99m-PYP) scintigraphy revealed that tracer uptake was greater in the right ventricular (RV) myocardium than in the left. Tc-99m-PYP uptake in many of the skeletal muscles, including the pectoralis major, was also observed. Permanent pacemaker implantation for SSS was performed without complications. A sample of the pectoralis major was resected while forming the pocket for the pacemaker and was used to confirm deposition of ATTR through Congo red staining and immunohistochemical analysis. No mutations were detected in the transthyretin gene. Therefore, the patient was diagnosed with ATTRwt-CA and treatment with tafamidis was initiated.

Conclusion: Histological confirmation of amyloid type is generally needed when a patient presents with suspected immunoglobulin light chain cardiac amyloidosis, visual grade 1 myocardial Tc-99m-bone-avid isotope uptake, visual grade 2–3 uptake with plasma cell dyscrasia, or suspected infrequent types of amyloidosis. In our patient, a rare Tc-99m-PYP uptake pattern due to RV overload from ASD was observed, and a biopsy was required to confirm amyloid type. A biopsy of the pectoralis major may be performed when a permanent pacemaker is implanted, and it can be useful for confirming deposition of ATTR.

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KEYWORDS

Bone-avid tracer, pectoralis major muscle, permanent pacemaker implantation, sick sinus syndrome, wild-type transthyretin amyloidosis

LEARNING POINTS

- Since 2016, wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) has been diagnosed without biopsy; however, biopsy is still required in some cases to detect deposition of amyloid transthyretin (ATTR).
- Biopsies to confirm ATTR deposition should be performed at sites where technetium-99m-labelled pyrophosphate uptake indicates deposition.
- The pectoralis major has a high rate of technetium-99m-labelled pyrophosphate uptake and biopsy of this muscle, which can be performed when creating a permanent pacemaker pocket, may be useful for confirming ATTR deposition in patients with suspected ATTRwt-CA.

INTRODUCTION

Wild-type amyloid transthyretin (ATTRwt) amyloidosis is a systemic disease in which ATTR is deposited in many organs, particularly the heart, lung, ligaments, and tenosynovium. ATTR deposition in the heart leads to wall thickening and conduction disturbances, resulting in cardiac amyloidosis (CA) associated with heart failure and tachy- and or bradyarrhythmias, such as atrioventricular block and sick sinus syndrome (SSS).

Diagnosing ATTRwt-CA without biopsy has increased since 2016[1], but biopsy of the myocardium or involved tissues must still be conducted in specific situations to confirm ATTR deposition[2]. To achieve a high positive detection rate for ATTR deposition in biopsies, collecting a sufficient amount of tissue from sites with significant ATTR deposits is essential. This is because the diagnostic sensitivity for detecting ATTR deposition varies depending on the amount of sample collected and the extent of deposition in the collected tissue[3,4]. Tissue samples are typically collected from affected organs or more accessible sites, depending on institutional practices[4]. In ATTRwt-CA, the heart is the most commonly affected organ; therefore, endomyocardial biopsy, which has nearly 100% specificity and sensitivity, is the gold standard for detecting ATTR. However, this test is highly invasive and requires technical expertise, and the need for it has been minimised by the collection of alternative tissues. Tracer uptake has been previously detected using technetium-99m-labelled pyrophosphate (Tc-99m-PYP) scintigraphy in some muscles of the skeletal trunk of patients with ATTRwt-CA[5]. Furthermore, Tc-99m-PYP imaging-based computed tomography (CT)-guided core needle biopsy of the internal oblique and gluteus medius muscles with high Tc-99m-PYP uptake rates of approximately 90%[5] has served as a screening biopsy to confirm the presence of ATTR [4,6].

Herein, we report the case of an 83-year-old woman with decompensated heart failure, SSS requiring implantation of a permanent pacemaker (PPM), and atrial septal defect (ASD). CA was suspected, although a rare pattern of myocardial Tc-99m-PYP uptake was observed. Tc-99m-PYP uptake was detected in multiple skeletal trunk muscles, including the pectoralis major. In this case, biopsy of the pectoralis major with a Tc-99m-PYP uptake rate of approximately 80%[5] was performed at the time of PPM implantation to confirm ATTR deposition.

CASE DESCRIPTION

An 83-year-old Japanese woman (height, 147.7 cm; weight, 48.7 kg) was admitted to our hospital due to exertional dyspnoea persisting for 2 weeks. She was assessed as New York Heart Association functional class III and reported multiple episodes of presyncope per day. Her medical history included surgery for right carpal tunnel syndrome at another hospital 5 years earlier.

The patient's vital signs were as follows: temperature, 36.6°C; pulse rate, 52 beats/min; systemic blood pressure, 110/61 mmHg; and oxygen saturation (measured on room air using a

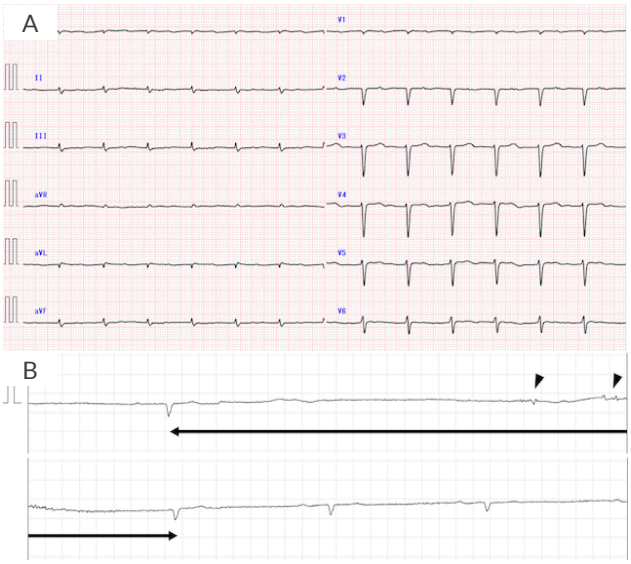


Figure 1. Electrocardiography findings. First-degree atrioventricular block with a PQ interval of 330 milliseconds, low voltage, and poor precordial R wave progression are shown on the electrocardiogram recorded on admission (A). A 24-hour ambulatory Holter electrocardiogram, recorded during an Adams–Stokes attack (B), shows a prolonged RR interval of 7 seconds (arrows) and subsequent sinus bradycardia (B). Arrowheads indicate artifacts.

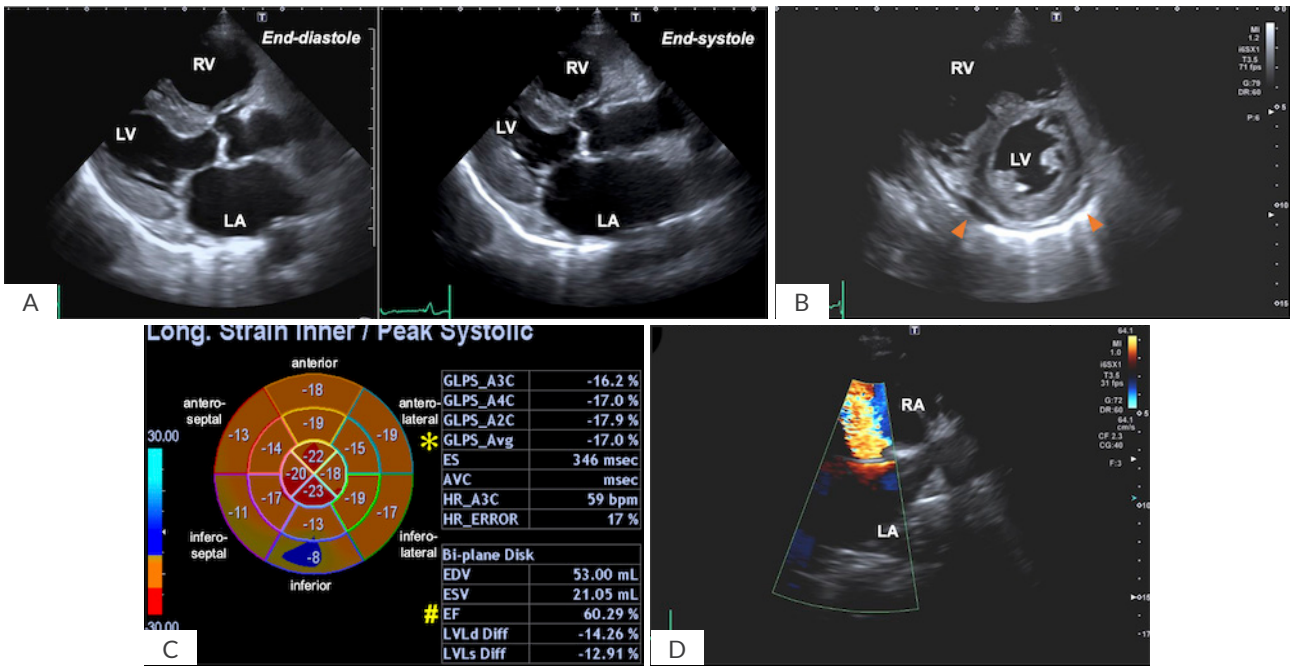


Figure 2. Transthoracic echocardiogram recorded on admission. A small left ventricle with an end-diastolic dimension of 33.5 mm and increases in the interventricular septum and left ventricular (LV) posterior wall of 12.4 mm and 12.6 mm, respectively, are shown (A and B). The right ventricle (RV; 36.5 mm) with an increase in the thickness of 6.0 mm and left atrium (LA; 42.5 mm) are dilated. The bull's eye map (with the apex at the center of the color-coding map) illustrates segmental longitudinal LV peak systolic strain values of the 16-segment model generated by speckle-tracking analysis of two-dimensional LV images acquired from the apical 2-, 3-, and 4-chamber views (A2C, A3C, and A4C, respectively). A normal LV ejection fraction (EF) of 60.3% (hash mark) is shown, as well as a normal LV global longitudinal peak systolic strain (GLPS) value—calculated as the mean of these 16 values—of −17.0% (asterisk) with an apical to basal strain ratio of 1.7, indicating no apical sparing (cutoff, >2.1) (C). Atrial septal defect with a pulmonary to systemic blood flow ratio of 1.4 is shown (D). Arrows indicate a small amount of pericardial effusion. RA, right atrium.

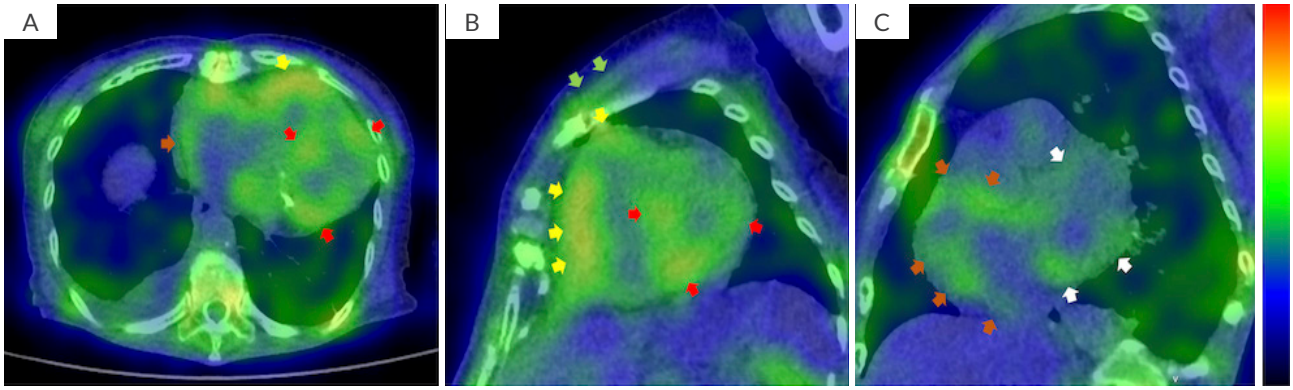


Figure 3. Single-photon emission computed tomography–computed tomography fusion images of technetium-99m-labeled pyrophosphate scintigraphy obtained 2 hours after injecting 20 mCi of the radiotracer. The horizontal (A) and short axial (B, C) planes of the heart. Accumulation of technetium-99m-labeled pyrophosphate in the left ventricular myocardium, including interventricular septum (red arrows); right ventricular myocardium (yellow arrows); left atrial myocardium (white arrows); right atrial myocardium (brown arrows); and pectoralis major (light green arrows) muscles is shown.

pulse oximeter), 95%. Upon auscultation, soft grade 2 heart murmurs were audible during mid-systole, and wet rales were audible in the lung. The liver was palpable for a width of two fingers along the right midclavicular line below the costal margin, and moderate pretibial oedema was observed. Blood tests revealed an elevated brain natriuretic peptide level of 173.2 pg/ml (reference range, ≤18.4 pg/ml), but a normal high-sensitivity cardiac troponin I level of 12.5 pg/ml (reference range, ≤18.4 pg/ml). Chest radiography revealed an enlarged cardiac silhouette with a cardiothoracic ratio of 62% and pulmonary congestion. Electrocardiogram findings revealed first degree atrioventricular block, low voltage, and poor precordial R wave progression *(Fig. 1A)*. A 24-h ambulatory Holter electrocardiogram revealed frequent prolongation of the RR interval, with the maximum being 7 seconds *(Fig. 1B)*. Echocardiographic findings revealed a mild increase in the wall thickness of the left and right ventricles, dilation of the right ventricle, preserved left ventricular ejection fraction, no apical sparing, and an ASD *(Fig. 2)*. The estimated peak systolic pressure of the pulmonary artery increased to 35 mmHg.

The patient was diagnosed with decompensated heart

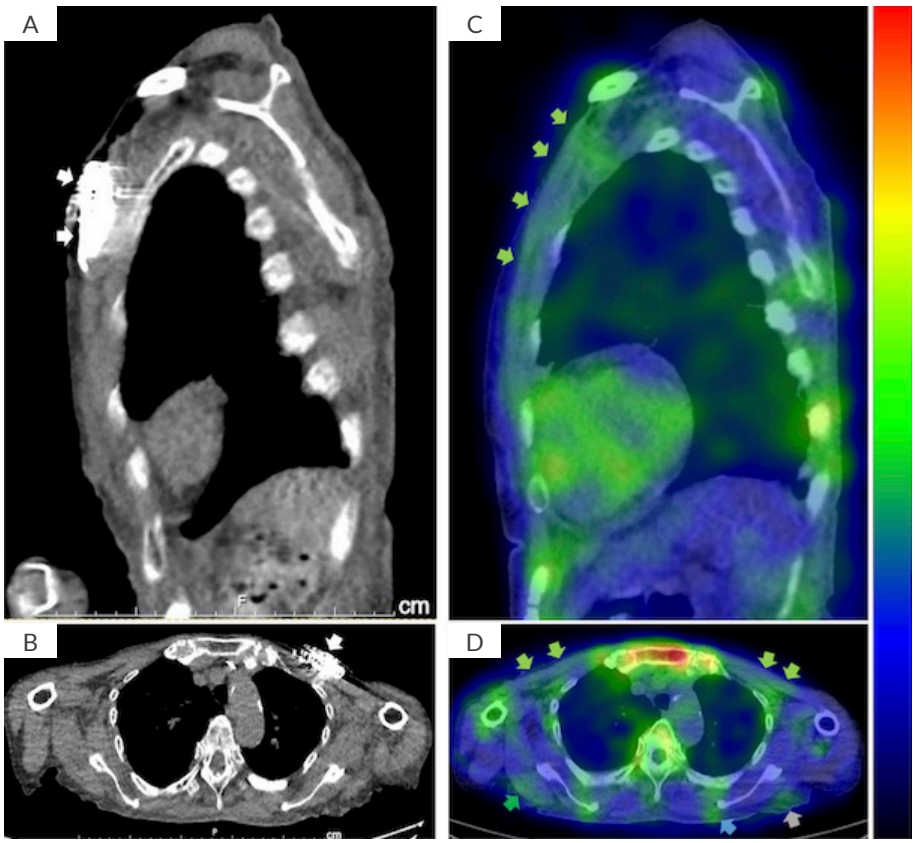


Figure 4. Single-photon emission computed tomography–computed tomography fusion images of technetium-99m-labeled pyrophosphate scintigraphy and computed tomography images obtained before and after permanent pacemaker implantation, respectively. The sagittal (A, C) and horizontal (B, D) planes. Accumulation of technetium-99m-labeled pyrophosphate is observed in the pectoralis major (light green arrows) directly beneath the implanted pulse generator (white arrows). Green, blue, and gray arrows indicate technetium-99m-labeled pyrophosphate uptake in the infraspinatus and trapezius muscles, and subcutaneous fat of the back, respectively.

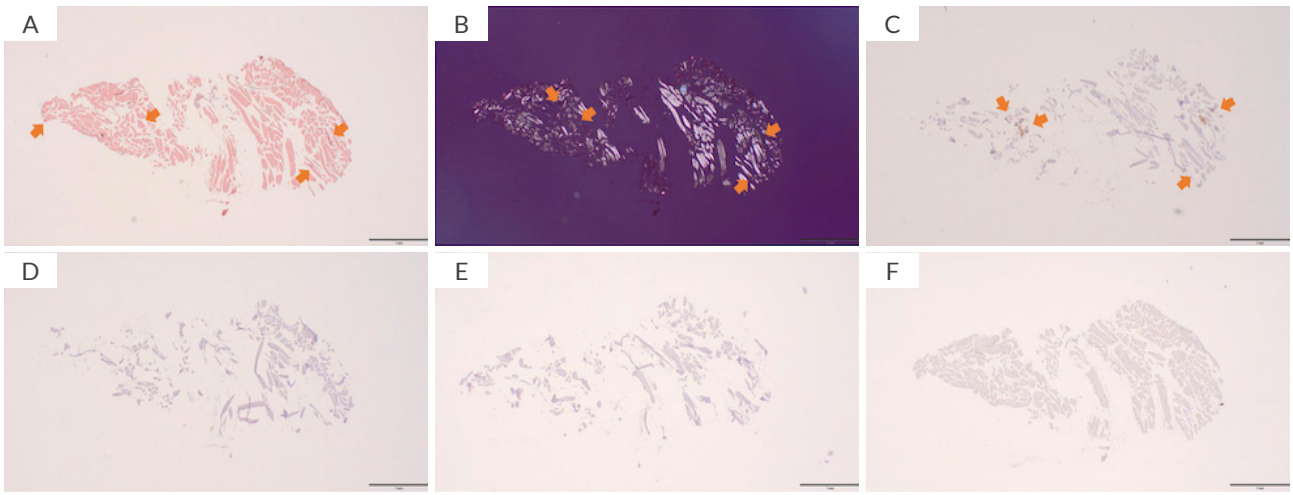


Figure 5. Histopathological staining of tissue samples obtained from the left pectoralis major when the permanent pacemaker was implanted. Congo red staining shows amyloid deposits (arrows) appearing as red–orange staining under a light microscope (A) and apple-green birefringence when visualized using a cross-polarized light microscope (B). Immunohistochemical staining using a panel of type-specific antibodies against the most common amyloidogenic proteins leading to cardiac amyloidosis are as follows: anti-transthyretin 115–124 (polyclonal rabbit anti-human prealbumin, custom) (C), anti-kappa light chain 116–133 (polyclonal rabbit anti-human kappa light chains, custom) (D), anti-lambda light chain 118–134 (polyclonal rabbit anti-human lambda light chains, custom) (E), and anti-amyloid A (monoclonal mouse anti-human amyloid A, DAKO, Carpinteria, CA, USA) (F). Only anti-transthyretin 115–124 stains amyloid deposits (arrows). The scale bars in all panels indicate 1 mm.

failure, SSS, and ASD. CA was also suspected. The patient therefore underwent Tc-99m-PYP imaging, with the scan showing a rare myocardial tracer uptake pattern in which uptake was prominent in the right ventricle, but slight in the left *(Fig. 3)*. Moreover, tracer uptake was noted in both atria and several skeletal trunk muscles—including the pectoralis major.

Loop diuretics (azosemide 30 mg) were administered for treating decompensated heart failure, and improvement in dyspnoea was observed. Subsequently, PPM implantation for managing SSS was performed without complications[7].

While creating the pocket for the pacemaker, a 3-mm^3 sample of the pectoralis major muscle was resected to examine amyloid deposition *(Fig. 4)*. Approximately 5 minutes were required to collect the sample. Congo red and immunohistochemical staining, performed at a specialised amyloidosis centre in Japan, confirmed the presence of ATTR deposits *(Fig. 5)*. Deoxyribonucleic acid sequencing of

the transthyretin gene showed no mutation. Therefore, the patient was diagnosed with ATTRwt-CA. Disease modifying therapy using 61 mg of tafamidis was initiated.

DISCUSSION

In this report, we describe the case of an older woman with SSS and suspected CA. Tc-99m-PYP uptake was observed in the myocardium and several skeletal trunk muscles, including the pectoralis major. A biopsy sample of the pectoralis major, obtained when the PPM was implanted to treat the SSS, was used to confirm the deposition of ATTR.

Typically, the amyloid type must be histologically confirmed in patients with suspected immunoglobulin light chain CA; visual grade 1 myocardial Tc-99m-bone-avid isotope uptake less than uptake in the rib; visual grades 2–3 myocardial tracer uptake equal to or greater than uptake in the rib, with plasma cell dyscrasias; and suspected infrequent types of amyloidosis[2]. In our patient, an unusual pattern of tracer uptake was observed, with greater uptake in the right than in the left ventricle. This necessitated a biopsy to confirm amyloid type. The reason for the development of this uptake pattern was unclear but may have resulted from long-standing overload of the right ventricle due to ASD.

Recently, some authors have reported cases in which ATTR accumulation was observed in the fat tissue at the site where the pulse generator pocket was created during PPM implantation[8,9]. However, the Tc-99m-PYP uptake, which indicates ATTR deposition in ATTRwt amyloidosis, in subcutaneous fat is lower than that in the myocardium and skeletal trunk muscles[3,5]. Therefore, even if a large amount of tissue is surgically removed from subcutaneous abdominal fat, the biopsy positivity rate remains approximately 60–70%[10]. In a 2025 report by Mvita Bakatubia et al. including 15 patients (3 cases of ATTRwt-CA, 8 cases of variant ATTR-CA, and 4 cases with no transthyretin gene sequence data) who underwent thoracic fat pad biopsy to diagnose ATTR-CA during cardiovascular treatment involving implantable electronic devices, ATTR accumulation was confirmed in only 4 cases (27%)[9].

When a biopsy is obtained from skeletal trunk muscles that have Tc-99m-PYP uptake, ATTR deposition is frequently confirmed[4]. Patients with ATTRwt-CA often have concomitant coronary artery disease or atrial fibrillation/flutter and are typically on antiplatelet or anticoagulant medications. In a study of these patients using Tc-99m-PYP imaging-based CT-guided core-needle biopsy, the ATTR detection rate in the biopsy of the internal oblique muscle was 88.9% (16 of 18 cases), with only one case of a haemorrhagic complication requiring no treatment[4]. However, a subsequent attempt resulted in considerable bleeding without sequelae in a patient taking two antiplatelet agents for post-coronary stent implantation and one anticoagulant for atrial flutter, despite the confirmation of ATTR deposition[11]. Furthermore, in 2 cases where Tc-99m-PYP uptake was more pronounced in the gluteus medius muscle than in the internal oblique muscle, biopsies of the former muscle were performed to confirm ATTR deposition without bleeding, although one case continued anticoagulant therapy[6].

In conclusion, the biopsy of the pectoralis major performed at implantation of a PPM confirmed ATTR deposition in our patient. The present study expands on the possible use of Tc-99m-PYP imaging-based biopsy of skeletal trunk muscles to confirm ATTR deposition. The best alternative biopsy site other than the myocardium, which would involve lower risk and greater ease of access, can be identified by a prior Tc-99m-PYP scan. However, more cases are required to strengthen these findings.

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