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Performance of ^{99m}Tc-aprotinin scintigraphy for diagnosing light chain (AL) cardiac amyloidosis confirmed by endomyocardial biopsy

Toru Awaya[1,2], MD/ Ryogo Minamimoto[3], MD, PhD/ Kentaro Iwama[4], MD/ Shuji Kubota[1], MD / Masatoshi Hotta[3], MD / Risen Hirai[5], MD / Masaya Yamamoto[1], MD/ Osamu Okazaki[1], MD, PhD/ Hisao Hara[1], MD, PhD/ Yukio Hiroi[1], MD, PhD/ Michiaki Hiroe[1], MD, PhD / Masao Moroi[2], MD, PhD

[1]Department of Cardiovascular Medicine, National Center for Global Health and Medicine, Tokyo, Japan

[2]Division of Cardiovascular Medicine, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

[3]Division of Nuclear Medicine, National Center for Global Health and Medicine, Tokyo, Japan

[4]Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan

[5]Department of Hematology, Internal medicine Tokyo-Kita Medical Center, Tokyo, Japan

Corresponding author: Toru Awaya, MD, Division of Cardiovascular Medicine,

National Center for Global Health and Medicine

1-21-1, Toyama Shinjuku-ku Tokyo 162-8655, Japan

Phone: +81-3-3202-7181

Fax: +81-3-3207-1038

E-mail: tooru.awaya@med.toho-u.ac.jp

Keywords: AL (light chain) cardiac amyloidosis; ^{99m}Tc-aprotinin scintigraphy; Nuclear imaging

National Center for Global Health and Medicine

1-21-1, Toyama Shinjuku-ku Tokyo 162-8655, Japan

Abstract

Background: Light chain (AL) cardiac amyloidosis is associated with a poor prognosis. Diagnosing at an early stage is critical for treatment and the management of cardiac complication.

Purpose: We aimed to evaluate the diagnostic performance of ^{99m}Tc-aprotinin images in patients with AL cardiac amyloidosis.

Methods and Results:

^{99m}Tc -aprotinin scintigraphy and endomyocardial biopsy were performed in 10 patients with suspected amyloidosis. Endomyocardial biopsy showed amyloid deposits in 5 of 10 patients. ^{99m}Tc-aprotinin (planer image) was positive in 4 of 5 patients who had amyloid deposits in endomyocardial biopsy. On the other hand, all 5 patients without amyloid deposits were negative in planer image. ^{99m}Tc-aprotinin (SPECT/CT image) was positive in all 5 patients who had amyloid deposits.

Conclusions: ^{99m}Tc-aprotinin scintigraphy is valuable for the noninvasive diagnosis of AL cardiac amyloidosis.

AL, light chain; PYP, pyrophosphate; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; BJP, bence jones protein; λ, lambda; κ, kappa; ICD, implantable cardioverter defibrillation.

Introduction

Cardiac amyloidosis may lead to refractory heart failure due to loss of diastolic function and carries an increased risk for sudden death due to fatal arrhythmias. Among the subtypes, AL amyloidosis has the worst prognosis (1). However recent studies have shown that chemotherapy and peripheral blood stem transplantation treatment can be effective during the early stages and the prognosis of AL cardiac amyloidosis has been improving (2-4). Therefore, diagnosing at an early stage is critical. The diagnosis is confirmed histologically by endomyocardial biopsy. However, cardiac invasive procedures need solid justification, requiring clinicians to apply the most accurate non-invasive test available, before recommending it to the patient.

Late gadolinium-enhanced (LGE) cardiac magnetic resonance (CMR) imaging and nuclear

imaging have been shown to be important noninvasive diagnostic tools (5, 6). However, the subendocardial enhancement on LGE-CMR that has been associated with cardiac amyloidosis was reported to be caused by subendocardial fibrosis due to micro-vessel ischemia resulting from amyloid plugging, rather than amyloid deposition itself (7). This means that LGE-CMR may not accurately distinguish between different causes of cardiac micro-vessel disease. Furthermore, the use of gadolinium is limited by the high prevalence of chronic kidney disease (CKD) among AL amyloidosis patients, which puts them at risk for nephrogenic systemic fibrosis.

Nuclear imaging with amyloid specific radiotracers such as ^{99m}Tc-aprotinin and ^{123}I-serum amyloid protein (SAP), or a nonspecific radiotracer such as ^{99m}Tc-pyrophosphate (PYP) have been studied in the past (8-10) . Among these, particularly ^{99m}Tc-aprotinin has been shown to best detect amyloid deposits in the heart (8, 11, 12). While physiological ^{99m}Tc-aprotinin uptake is seen in the liver, kidney, spleen, and urinary tract, this was not the case in the myocardium. Therefore, it stands to reason that ^{99m}Tc-aprotinin is useful for identifying cardiac lesions (8, 11).

The extracellular deposits in various types of amyloidosis, including AL amyloidosis,

contain proteases and their inhibitors. Therefore, ^{99m}Tc-aprotinin (aprotinin; a serine protease inhibitor) scintigraphy can detect amyloid deposits by binding to proteases located within (8, 13).

The accuracy of ^{99m}Tc-aprotinin scintigraphy has been reported for systemic amyloidosis, but not specifically for cardiac AL amyloidosis. Here, we studied the diagnostic performance of ^{99m}Tc-aprotinin scintigraphy for AL cardiac amyloidosis by comparing the results with tissue yielded from endomyocardial biopsy.

Methods

Patients

This prospective study was conducted according to the principles outlined within the Declaration of Helsinki, and approved by the ethics review board of National Center for Global Health and Medicine (NCGM-G-00839-01, NCGM-G-00839-02).

Both ^{99m}Tc-aprotinin scintigraphy and endomyocardial biopsy were performed in patients with suspected amyloidosis from September 2012 to October 2016. ^{99m}Tc-aprotinin scintigraphy and

endomyocardial biopsy were completed within 6 months of each other. Endomyocardial biopsy site were right ventricular septum in 8 patients and from left ventricular posterior wall in 2 patients. Amyloid deposits in the endomyocardial biopsy specimen were identified using Congo red staining.

Preparation of ^{99m}Tc-aprotinin

Labeling kits were prepared following the methods of Smyth (14). Pyrophosphate kits were used to produce kits for ^{99m}Tc labeling of aprotinin (as addition of ^{99m}Tc at the time of use is enough for labeling). Production was carried out by sterile manipulation on a clean bench. Quality assessments of the kits produced in our hot laboratory were performed by pharmacists of our facility, to maintain objectivity of the evaluation, and have revealed a radiochemical purity of 98.7% (range 95.6 to 99.8%).

Imaging protocol

Planar and tomographic imaging was performed 90 min after a 2-mL injection containing 740 MBq of ^{99m}Tc-aprotinin. The acquisition included anterior and posterior whole body scans (11 to 13

cm/min) and regional static images (acquisition time, 5 to 7 min per image) obtained with using a single photon emission computed tomography (SPECT)/CT system (Infinia3 Hawkeye4, General Electric Health Care, Milwaukee, WI). Camera was equipped with a low-energy, high-resolution (LEHR) parallel-hole collimator. SPECT tomograms of the chest and the abdomen were also obtained for all patients. Images were taken on a 512 x 512 matrix for the static views and on a 128 x 128 matrix for the SPECT images. The ordered subset expectation maximization method (OSEM) was used for image reconstruction. We estimated dose for the exposition to ionizing radiation (both SPECT and CT). Sojan (15) reported that the mean for the females was 0.0079 mSv MBq^{-1} and for the males was 0.0056 mSv MBq^{-1}. Therefore, for a dose of 740 MBq of ^{99m}Tc-aprotinin, the dose would be between 4.1 and 5.8mSv. CT dose in our SPECT/CT system was estimated 1.3mSv. In summary, the estimated dose for the exposition to ionizing radiation (both SPECT and CT) were between 5.4 and 7.1mSv.

Image interpretation

The images were reviewed by our nuclear medicine board. Abnormal focal accumulation of

the tracer was determined by visual interpretation. For image interpretation we compared to a reference image from a control patient as previously described by Han et al (11). If the obtained image had a focal uptake in myocardium which was not confirmed in reference image, it was regarded as positive ^{99m}Tc-aprotinin uptake. These findings were compared with the final clinical and histopathological diagnoses.

Results

A total of 10 patients (7 men and 3 women, mean age: 61±12 years) were enrolled in this study. Amyloid deposits were histologically confirmed in 5 of 10 patients (Table1). ^{99m}Tc-aprotinin uptake was noted in all 5 patients who were diagnosed with AL cardiac amyloidosis histologically (primary amyloidosis in 2 patients, multiple myeloma in 2 patients, and primary macroglobulinemia in 1 patient). All patients suffered from heart failure (Table 1). Significant coronary stenosis were ruled out by coronary angiography. An Implantable Cardioverter Defibrillator (ICD) was inserted in 2 patients, and 3 of 5 patients deceased from these cardiac complications.

^{99m}Tc-aprotinin (planer image) was positive in 4 out of 5 patients who had amyloid deposits

in endomyocardial biopsy. On the other hand, all 5 patients without amyloid deposits were negative in planer image (Table 2). ^{99m}Tc-aprotinin (SPECT/CT image) was positive in all 5 patients who had amyloid deposits (Fig 1. upper row), whereas 3 out of 5 patients without amyloid deposits were false positive in SPECT/CT image (Table 2).

Discussion

All 5 patients who were diagnosed with AL cardiac amyloidosis (Fig 1. upper row) on histology showed positive findings in ^{99m}Tc-aprotinin (SPECT/CT image) (Table 1). On the other hand, all 5 patients without AL cardiac amyloidosis were negative in ^{99m}Tc-aprotinin (planer image) (Table 2).

Other imaging methods, such as ^{99m}Tc-PYP scintigraphy are useful to detect amyloidosis due to transthyretin deposition (ATTR) but are less common in AL amyloidosis (9). In our study, only 1 out of 3 patients with AL cardiac amyloidosis showed positive finding using ^{99m}Tc-PYP (Table 1). Increased FDG uptake in amyloidosis has been reported in several articles. However, there are also unneglectable numbers of reports showing negative findings of ^{18}F-FDG PET in amyloidosis

(16). On the other hand, ^{11}C-Pittsburgh B (PIB) and ^{18}F-florbetapir PET imaging may present a promising option for the diagnosis of cardiac amyloidosis including AL. PIB PET has been reported that sensitivity and specificity are 87 and 100%(10, 17, 18).

Other diagnostic modalities in the diagnostic workup for cardiac amyloidosis, such as electrocardiogram (ECG), transthoracic echocardiography (TTE) and CMR are also valuable, partly due to easy availability. They can provide clues like low voltage and pseudo-infarct pattern (poor R wave progression or abnormal Q waves) on ECG, and concentric ventricular thickening, diastolic dysfunction and granular sparkling on TTE (Table 1), however neither findings are specific (19), requiring a tool to confirm the diagnosis.

Several studies have reported that CMR could be used to detect cardiac amyloidosis (5, 6). Typical cardiac amyloidosis finding on LGE-CMR are subendocardial ring enhancement, and a dark blood pool that result from a faster washout of gadolinium from the myocardium (Fig 2). Figure 2 shows similar findings in both, ^{99m}Tc-aprotinin SPECT/CT and LGE-CMR.

The problem with LGE-CMR that it can be difficult to perform on patients with pacemakers (PM),

ICD, or CKD. Recently MR conditional PM and ICD have become available and native T1 mapping has been reported that it may have a higher sensitivity for detecting early stage in cardiac amyloidosis and can be used in CKD (20). In our study, we point out another problem that might arise from the use of LGE-CMR: Using only LGE-CMR would have led to a misdiagnosis in patient No 3 (Fig 3), who showed focal patchy enhancement in the right ventricular septum and and the left ventricular inferolateral region, which was not typical finding. The LGE finding was not used to diagnose cardiac amyloidosis. ^{99m}Tc-aprotinin scintigraphy and tissue biopsy could correct this problem. LGE shows not only amyloid deposition itself but also subendocardial fibrosis due to ischemia by small vessel amyloid deposition. It has been reported that LGE correspond to subendocardial fibrosis mainly (6, 7). Therefore, it may not exhibit typical finding in cases with less subendocardial fibrosis.

There were three false positive cases (patient No 6-8) (Fig 1. lower row) using ^{99m}Tc-aprotinin (SPECT/CT image) (Table 1, 2). These cases showed a subtle aprotinin uptake compared to the true positive cases and ^{99m}Tc-aprotinin (planar image) showed no positive finding (Fig 1, 4). The

mechanism of this subtle aprotinin uptake remains unclear.

Elevated levels of NT-proBNP, high-sensitivity cardiac troponin T (cTnT) and free light chain difference (dFLC) is a marker of poor prognosis of AL amyloidosis. Therefore, the severity of AL amyloidosis is assessed by three criteria (revised Mayo stage). Patients were assigned a score of 1 for each of NT-ProBNP ≥ 1,800 pg/mL (or BNP ≥ 400 pg/ml), cTnT ≥ 0.025 ng/mL, and dFLC ≥ 180 mg/l), creating stages I to IV with scores of 0 to 3 points, respectively. Their median overall survival from diagnosis was 94.1, 40.3, 14.0, and 5.8 months, respectively (3).

Chemotherapy and peripheral blood stem transplantation treatment can be effective during the early stages and the prognosis of AL cardiac amyloidosis has been improving (2-4). Therefore, it is also important to judge the effect of chemotherapy and transplantation treatment. It is reported that change in NT-proBNP and dFLC predicted survival after treatment (21). After chemotherapy, Patient 1 showed that all these criteria (NT-ProBNP, cTnT, and dFLC) decreased (Fig 5). ^{99m}Tc-aprotinin scintigraphy was also performed and aprotinin uptake decreased after chemotherapy. Aprotinin, which is a serine protease inhibitor, binds to amyloid deposits which contain proteases (8).

Therefore, we hypothesize that aprotinin uptake may be associated with the protease activity. Our results suggest that if chemotherapy treatment makes the amyloid deposit slow or to stop the amyloid deposits, ^{99m}Tc-aprotinin could not come to the active lesions. Not only can ^{99m}Tc-aprotinin scintigraphy be used for the diagnosis of amyloidosis, it may be useful for monitoring response to therapy. However, the limitations of our study include small sample size.

Patients with AL amyloidosis and heart failure symptoms face a median survival of less than one year (1). As consensus guidelines recommend against ICD placement for the primary prevention of sudden cardiac death (SCD) in patients with a life expectancy of less than 1 year. However, the prognosis of cardiac amyloidosis has been improving over the past decade (2). Therefore, primary prophylactic ICD implantation for cardiac amyloidosis is controversial. In cardiac amyloidosis patients, 3 of 15 patients of primary prophylactic ICD implantation and 3 of 4 patients of secondary prophylactic ICD implantation were received appropriate ICD shock or ATP (22). In our study, ICD implantation was 2 of 5 cases (Table 1). Patient 2 was secondary prophylactic ICD implantation because of ventricular fibrillation. Although Patient 4 was primary prophylactic ICD implantation,

ICD shock was recorded against VT approximately 3 months after ICD implantation. It is reported that multiform ventricular beats, couplets, nonsustained ventricular tachycardia (NSVT), and sustained VT are risk factor arrhythmic SCD, on the other hand NT-proBNP level was no significant correlation with NSVT compared to without NSVT in cardiac amyloidosis (22, 23).

New Knowledge Gained

Our findings suggest that ^{99m}Tc-aprotinin scintigraphy is valuable for the noninvasive diagnosis of AL cardiac amyloidosis by comparing the results with tissue yielded from endomyocardial biopsy.

Conclusion

^{99m}Tc-aprotinin scintigraphy has potential for the diagnosis of AL cardiac amyloidosis. However, there are small sample size in our study. Further research is needed to confirm whether ^{9m}Tc-aprotinin scintigraphy is useful for AL cardiac amyloidosis.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Figure legends

Figure 1. ^{99m}Tc-aprotinin SPECT/CT image (axial)

Upper row: All patients (No.1-5) are AL amyloidosis and ^{99m}Tc-Aprotinin uptake in myocardium .

^{99m}Tc-Aprotinin uptake is taken in the bone marrow and the left lung at No.3, 4. These might suggest accumulation of amyloid.

Lower row: All patients (No.6-10) are not AL amyloidosis, but ^{99m}Tc-Aprotinin subtle uptake in myocardium at No.6-8.

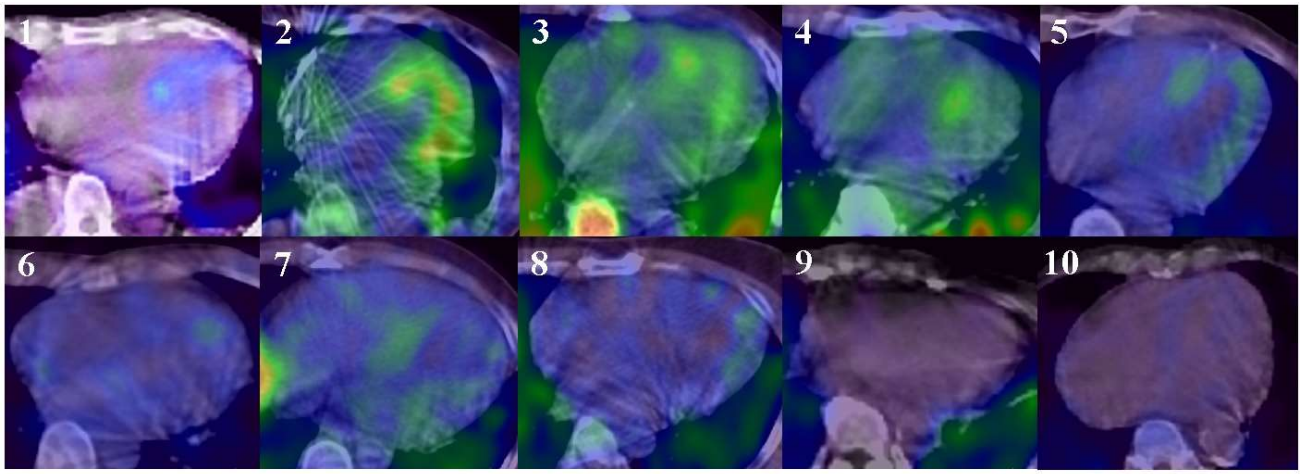


Figure 2. Cardiac scintigraphy, CMR and histology of a patient (No.5) with AL amyloidosis (BJP-λ). (Good correlation between the two imaging methods)

(A) ^{99m}Tc-aprotinin SPECT/CT image (short axis and vertical long axis) revealed diffuse uptake in

the left ventricular myocardium (white arrowheads). (B) LGE-CMR imaging (short axis and vertical long axis) showed increased signal in similar areas (global subendocardial ring enhancement) (white arrowheads). The intraventricular blood pool is dark.

(C, D, E, F) Different histological assessments of the same tissue-section obtained from endomyocardial biopsy specimen (original magnification x 200). (C) Congo-red staining shows amyloid-deposition in blood vessel walls (white arrow). (D) Under polarized light the congo-red-stained amyloid was visualized as apple-green birefringence. Immunochemistry detected lambda light chain (E), but not kappa light chain (F) in blood vessel walls.

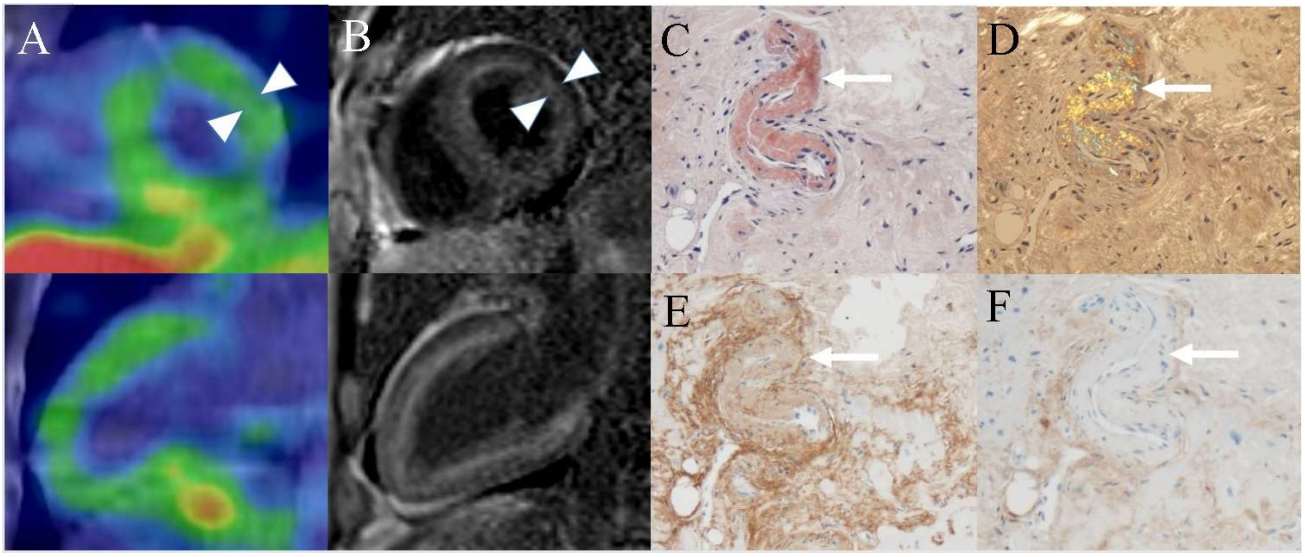


Figure 3. Cardiac scintigraphy and CMR of a patient (No.3) with AL amyloidosis (IgG-λ)

(Atypical finding of late-gadolinium enhancement in cardiac amyloidosis)

(A) ^{99m}Tc-aprotinin SPECT/CT image (axial) revealed uptake in lung, bone marrow (white arrowheads) and myocardium (especially septum, left ventricular inferolateral region) (white arrows). (B) Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging (four chamber image) showed increased signal in similar areas (subtle focal patchy enhancements in the right ventricular apical septum and in the left ventricular inferolateral region) (white arrows). Because the LGE was atypical finding that would be expected in cardiac amyloidosis, the possibility of endocardial infarction was considered, however rule out by coronary angiography. The LGE finding was not used to diagnose cardiac amyloidosis.

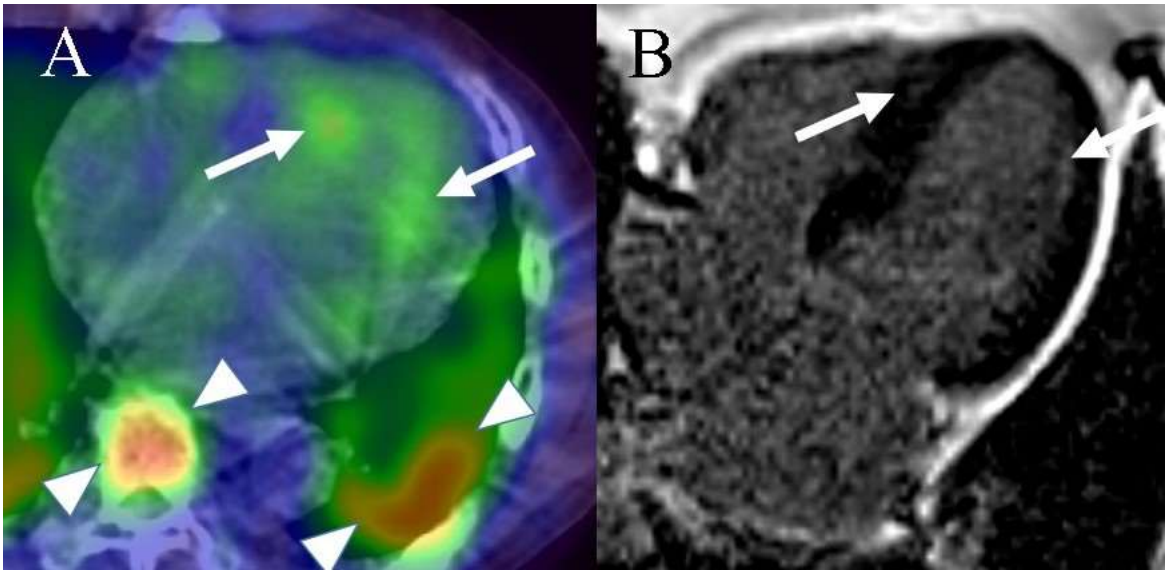


Figure 4. Cardiac scintigraphy and CMR of a patient (No. 7) with cardiac hypertrophy, but was not diagnosed with amyloidosis.

(False-positive case of ^{99m}Tc-aprotinin SPECT/CT image)

^{99m}Tc-aprotinin planar image (coronal) showed uptake in both lungs, but no uptake in the myocardium (top row). ^{99m}Tc-aprotinin SPECT/CT image (axial) revealed subtle uptake in the left ventricular basal septum (middle row, white arrow). Similarly, LGE-CMR (four chamber axis) showed increased signal in global subendocardium (especially basal septum) (bottom row). However, histological assessment of myocardial, skin, and intestinal tissue did not reveal amyloid deposition. One year later, LGE-CMR showed no clear change. However, SPECT/CT imaging revealed no uptake in the left ventricle and a radiochemical purity did not change (95.6% vs 95.6%). Taken together, the initial date SPECT/CT image was false positive.

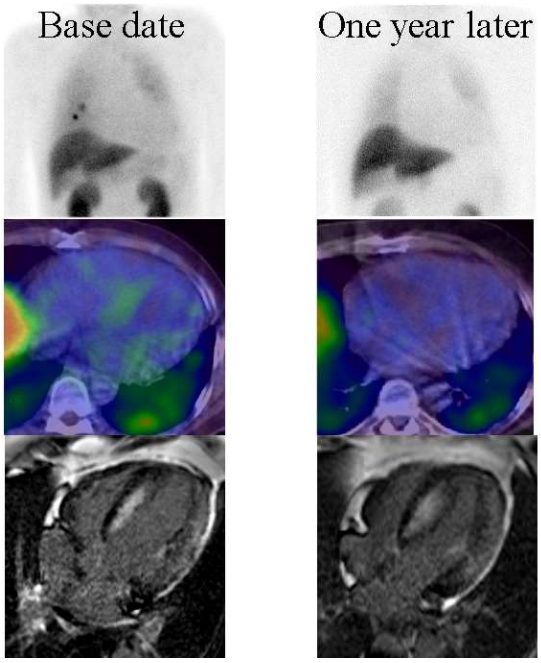


Figure 5. Very good partial response in a patient (No.1) with AL amyloidosis (BJP-λ) after Melphalan+Dexamethasone (MD) therapy.

(A) ^{99m}Tc-aprotinin SPECT/CT image (axial) before chemotherapy revealed uptake in the ventricular septum (white arrow). (B) Follow up ^{99m}Tc-aprotinin SPECT/CT image (one year after chemotherapy) showed a decrease in septal uptake (white arrow). The severity of AL amyloidosis is assessed by three laboratory markers (NT-proBNP, high-sensitivity cardiac troponin T, and free light chain difference). One year after chemotherapy, all these criteria decreased.

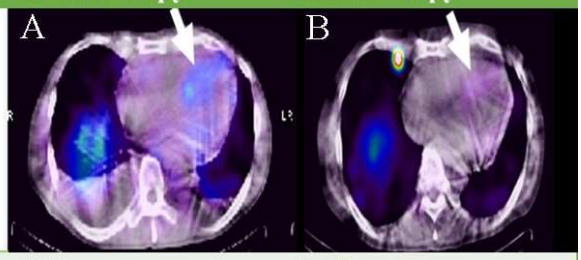
	Before chemotherapy	One year after chemotherapy
^{99m}Tc-aprotinin SPECT/CT image		
NT-proBNP (pg/mL)	5769	1155 ↓
High-sensitivity cardiac troponin T (ng/ml)	0.179	0.136↓
Free light chain (mg/L) 【difference】	κ 2.1, λ 1230 【1228】	K 5.8, λ 25.8 【20】↓

Table 1. Patients characteristic

No	Age	Sex	Type of amyloidosis	Primary illness	Cardiovascular complication	Outcome	^{99m}Tc-Aprotinin positive site	ECG	TTE	^{99m}Tc-PYP scintigraphy	LGE-CMR	Biopsy site in the heart	Biopsy positive(+) or negative(-)
1	67	M	AL(BJP-λ)	Multiple myeloma	Heart failure	Deceased	Myocardium, skeletal muscles, lung	CRBBB	EF70%, LVH, Diastolic dysfunction(E/A2.2)	-	Positive	Right ventricular septum	+
2	72	F	AL(BJP-λ)	Primary amyloidosis	VF(ICD) Heart failure	Deceased	Myocardium, lung	Pseudo-infarct pattern (abnormal Q waves)	EF54%, LVH, Diastolic dysfunction(E/A1.4)	Negative	Positive	Right ventricular septum	+
3	69	M	AL(IgG-λ)	Multiple myeloma	Heart failure		Myocardium, bone marrow, thyroid, nasal cavity, lung	CRBBB	EF70%, LVH, Diastolic dysfunction(E/A1.4)	-	Positive	Right ventricular septum	+
4	67	M	AL(IgM-κ)	Primary macroglobulinemia	VF(ICD) Heart failure	Deceased	Myocardium (planer image negative, SPECT/CT image positive) , lung	Low voltage, Pseudo-infarct pattern (poor R wave progression)	EF70%, LVH, Diastolic dysfunction(E/A3.2)	Positive	Positive	Right ventricular septum	+
5	58	M	AL(BJP-λ)	Primary amyloidosis	Heart failure		Myocardium	Low voltage, Pseudo-infarct pattern (poor R wave progression) Atrioventricular block	EF34%, LVH, Diastolic dysfunction(E/A2.2)	Negative	Positive	Right ventricular septum	+
6	47	F	-	HCM	VF(ICD) Heart failure		Myocardium (planer image negative, SPECT/CT image positive)	-	EF60%, LVH	-	Positive	Right ventricular septum	-
7	45	M	-	HHD	Heart failure		Myocardium (planer image negative, SPECT/CT image positive)	CRBBB	EF25%, LVH, Diastolic dysfunction (E/A2.5)	Positive	Positive	Right ventricular septum	-
8	43	M	-	DCM	VT Heart failure	Deceased	Myocardium (planer image negative, SPECT/CT image positive)	AF	EF50%	-	Positive	Right ventricular septum	-
9	64	F	-	Multiple myeloma	Heart failure		Negative	-	EF67%, LVH,	-	Negative	Left ventricular posterior wall	-
10	77	M	-	Multiple myeloma	Heart failure		Negative	-	EF70%, LVH,	-	Positive	Left ventricular posterior wall	-

ECG, electrocardiogram; TTE, transthoracic echocardiography; PYP, pyrophosphate; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; BJP, bence jones protein; λ, lambda; κ, kappa; CRBBB, complete right bundle branch block; EF, ejection fraction; LVH, left ventricular hypertrophy; E, early mitral inflow velocity; A, late mitral inflow velocity; E/A, the ratio of E to A; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillation; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; DCM, dilated cardiomyopathy; VT, ventricular tachycardia; AF, atrial fibrillation.

Table 2. Diagnostic performance of ^{99m}Tc-aprotinin imaging in patients with biopsy-proven cardiac amyloidosis.

		Biopsy positive	Biopsy negative
Planer image	**positive**	**4**	**0**
	negative	**1**	**5**
SPECT-CT image	**positive**	**5**	**3**
	negative	**0**	**2**