

ORIGINAL ARTICLE

Positive Myocardial Uptake of Bone Scintigraphic Agents Associated with Cardiac Amyloidosis: Frequency of Positive Uptake Data Based on Daily Clinical Practice

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Abstract

Objective: The bone scan plays an important role for detecting number of conditions relating to bones, including: bone cancer or bone metastasis, bone inflammation. Extraosseous uptake, in particular, myocardial uptake, was observed in some patients examined with the bone scans. Positive uptake of ^{99m}Tc -labeled bone radiotracers is associated with cardiac amyloidosis. However, the frequency and cause of positive cardiac ^{99m}Tc -MDP uptake have not been fully studied. In this regard, the aim of this study was to assess the frequency and characteristics of patients with high myocardial uptake of bone scintigraphy in daily clinical practice setting.

Methods: We retrospectively analyzed 4180 bone scintigraphies performed in daily clinical practice during 7-years period. The intensity of the myocardial uptake was graded based on a visual scale ranging from 0 to 3 points. Score 0 indicates the absence of uptake. Score 1 defined uptake less than that of bone (referred to as the adjacent rib). Uptake similar to that of bone was classified score 2. Score 3 was defined as uptake greater than that of reference bone. Positive myocardial uptake included a visual score 2 or 3.

Result: Positive ^{99m}Tc -MDP myocardial uptake occurred in 12 patients among 4180 patients (0.3%). 7 of 12 positive scan patients were consistent with amyloidosis confirmed by biopsy. In these patients, the mean age was 75.6 ± 5.2 years old. Ten cases showed biventricular uptake and 2 showed LV uptake only.

Conclusion: Positive cardiac uptake of bone scintigraphic agents was present in 0.3% of bone scintigraphies in a clinical practice setting. This may be a sign of cardiac amyloidosis involvement which may give the presence of extraosseous bone tracer uptake its own importance and a new role.

Keywords: ^{99m}Tc -MDP, Bone scintigraphy, Cardiac amyloidosis, Daily clinical practice

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Amyloidosis is a systemic, progressive disease with multiple organ involvement. Deposits of misfolded proteins eventually form extracellular deposits of amyloid. Cardiac amyloidosis is an infiltrative-restrictive form of cardiomyopathy (1–4).

There are many types of amyloidosis based on the accumulating protein, but more than 90% of the cardiac involvement is light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) (1). ATTR has 2 sub-types. One is an acquired “wild-type” form ATTR and another one was

genetically transmitted form such as mutant ATTR (3, 4). The treatment and the prognosis of disease depend on disease the localization and the type of amyloid disease.

Cardiac amyloidosis was previously regarded a rare condition. AL cardiac amyloidosis is the most prevalent type responsible for $\pm 70\%$ of all newly diagnosed patients with cardiac amyloidosis. A limited number of epidemiologic studies have been reported, but the incidence of AL amyloidosis in the Western world is 8–12 per million persons per year. Data on ATTR amyloidosis are more sparse; a recent

Swedish study reported an incidence of 2.0 per million inhabitants per year, although the clinical relevance of amyloid depositions reported on autopsy remains unknown (3).

Diagnosis of cardiac amyloidosis is challenging due to unspecific clinical manifestations, such as low exercise tolerance and edema (5, 6). An early sign may be non-specific fatigue or weight loss. Some of the clinical findings indicate a specific type of cardiac amyloidosis. For ATTR, these include polyneuropathy, carpal tunnel syndrome, spinal stenosis in >50%. For AL, symptoms include macroglossia, periorbital purpura, or nephrotic range proteinuria.

The bone scan is primarily used to diagnose a number of conditions relating to bone diseases including: bone cancer, bone metastasis, and bone inflammation. Extraosseous uptake, such as myocardial uptake has been observed in a number of patients examined with bone scans. Additionally, in some reports, the uptake of ^{99m}Tc-labeled bone radiotracers in cardiac amyloidosis has been reported (7). Mohamed-Salem et al. reported that the frequency of positive cardiac uptake was 2.78% in >75 years old (8). However, the frequency and characteristics of myocardial ^{99m}Tc-labeled methylene diphosphonate (^{99m}Tc-MDP) uptake have not been fully evaluated in daily clinical setting. Therefore, the aim of this study was to assess the frequency and characteristics of patients with positive myocardial uptake of bone scintigraphy in daily practice in a regional center hospital.

Methods

Study population

We retrospectively analyzed 4180 bone scintigraphies performed at Funabashi Municipal Medical Center from January 2012 to December 2018. The study conformed with the principles addressed in the Declaration of Helsinki. The current analysis was approved by the institutional review board and ethics committees of Funabashi Municipal Medical Center. The requirement for informed consent was waived because of the low-risk nature of this retrospective study and the inability to obtain informed consent directly from all patients.

Bone scintigraphy

All 4180 patients received ^{99m}Tc-MDP (FUJIFILM Toyama Chemical Co. Ltd.) for examining suspected bone metastasis. All patients received 555 to 740 MBq of ^{99m}Tc-MDP intravenously. Images were acquired 3 hours after radiotracer administration (9). Whole body images were acquired at a scan speed of 16 cm/minute using low energy high resolution collimators (DISCOVERYTM NM, GE). We performed planar images and also performed SPECT images centered on the thorax if clinically indicated in some patients.

The intensity of the myocardial uptake was graded based on a visual scale ranging from 0 to 3 points. Score 0 indicates the absence of uptake. Score 1 defined uptake less than that of bone (referred to as the adjacent rib). Uptake similar to that of bone was classified score 2. Score 3 was defined as uptake greater than that of reference bone (Figure 1A). Positive myocardial uptake included a visual score 2 or 3. The distribution of the uptake in myocardium was defined as focal uptake, diffuse uptake, uptake in a segmental ventricular wall uptake, diffuse ventricular uptake, or diffuse biventricular uptake. Cardiac uptake was also assessed with quantitative analysis by drawing a region of interest (ROI) over the heart corrected for contralateral counts and calculating a heart-to-contralateral ratio (H/CL) (Figure 1B) (10).

Results

Patient characteristics

The original clinical diagnoses of the patients in all 4180 patients (48–84 years old, 48% male) are shown in Figure 2. Among the 4180 patients, 12 (0.3%, 8 male patients) exhibited myocardial uptake of ^{99m}Tc-MDP. Five of these patients had a visual score of 2 (0.1%). The remaining seven patients had a visual score of 3 (0.2%). The demographic, clinical, and image findings of these 12 patients are shown in Table 1. We found a significant interaction with age and gender on myocardial uptake. Patients with myocardial uptake were older (75.6 ± 5.2 years) than those with no uptake (67.6 ± 8.2 years). As regards gender, males represented 47% of subjects with no uptake, but 67% of those with positive uptake. The ratio of myocardial uptake was 0.4% in males and 0.18% in females. There was no free light chain detected in the plasma of these 12 patients.

Bone scintigraphy

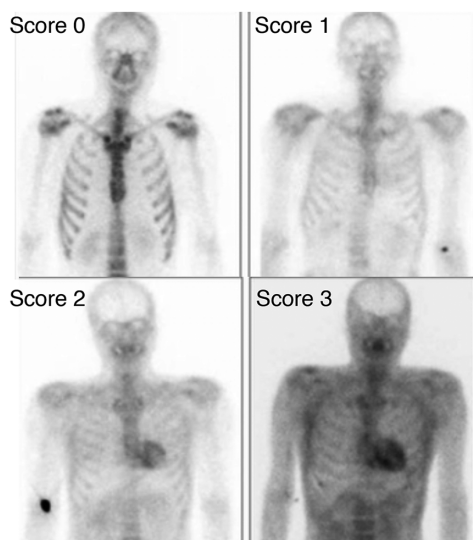
The current database revealed positive ^{99m}Tc-MDP myocardial uptake in 12 patients (0.3%). Of the 12 positive patients, 10 patients had concurrent ^{99m}Tc-MDP uptake in the right and left ventricle (LV). The remaining 2 patients only had LV uptake. In analyzing patients >75 years old in our study, myocardial deposition was 0.68%.

The H/CL ratio data is presented in Table 1. All of 12 patients had H/CL ratio >1.5; mean ratio was 1.84 ± 0.15 with visual score 2, and 2.77 ± 0.42 in visual score 3.

Cardiac function

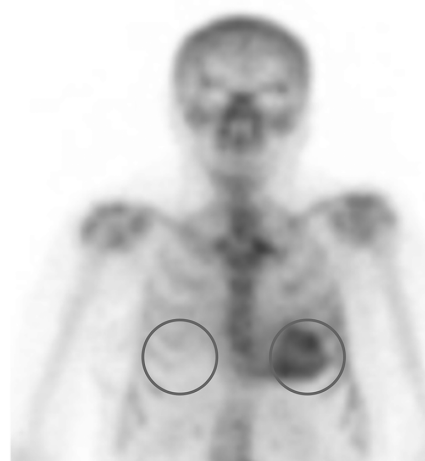
Three patients had atrial fibrillation. Echocardiography showed diastolic dysfunction in 9 patients with E/A <1.0 patterns, LV hypertrophy, or left atrial enlargement (11). Only one patient showed low LV ejection fraction (48%).

A. Visual Cardiac Score



Score 0: Absent Myocardial Uptake
 Score 1: Myocardial Uptake < Bone
 Score 2: Myocardial Uptake = Bone
 Score 3: Myocardial Uptake > Bone

B. Heart-to-Contralateral Ratio



$$\text{H/CL Ratio} = \frac{\text{Heart ROI mean counts per pixel}}{\text{Contralateral ROI mean counts per pixel}}$$

Figure 1 Semi-quantitative and quantitative interpretation: ^{99m}Tc -MDP uptake of myo-cardium.

A: The intensity of the myocardial uptake was graded according to a visual scale ranging from 0 to 3 points, in which the absence of uptake was assigned a score of 0 points; uptake less than that of bone (referred to as the adjacent rib), 1 point; uptake similar to that of bone, 2 points; and uptake greater than that of bone, 3 points.

B: Heart-to-contralateral ratio was calculated by drawing a region of interest over the heart, copying and mirroring it to the contralateral chest and calculating the ratio of heart ROI mean counts to contralateral ROI mean counts.

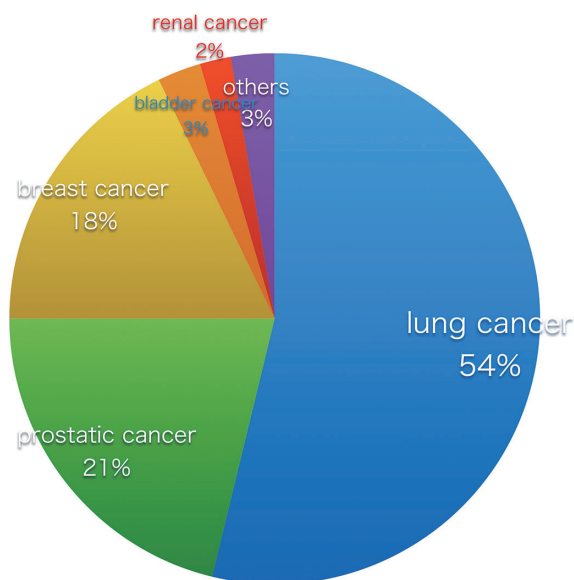


Figure 2 The original clinical diagnoses for ^{99m}Tc -MDP scintigraphy.

One-half of the patients in ^{99m}Tc -MDP bone scintigraphy had lung cancer (54%), and nearly one-fifth had prostatic cancer and breast cancer (21% and 18%).

Amyloid deposition

In 6 cases, amyloid deposits from the biopsy fragments of fat aspiration were observed with using standard Hematoxylin-Eosin and Congo red staining. Moreover, in subject No.2,

amyloid deposition was not detected from abdominal fatty aspiration biopsy, but recognized from skin biopsy.

Discussion

Detection of cardiac amyloidosis

The diagnosis of cardiac amyloidosis is often delayed due to the rarity of the disease and due to its' non-specific clinical manifestation. In fact, increasing clinical awareness and application of modern non-invasive diagnostic approaches have contributed to improve the detection of cardiac amyloidosis (1, 3).

Non-invasive methods in detection, such as nuclear imaging techniques, have made a fundamental change in the diagnosis of cardiac amyloidosis. Bone scintigraphy can facilitate early diagnosis and can differentiate between AL and ATTR types (7, 12). Score 0 and 1 cardiac uptake of radiotracer are associated with AL and Score 2 and 3 cardiac uptake are associated with ATTR. Gillmore et al. demonstrated that the diagnosis of ATTR can be made by a visual score of 2 or 3 at scintigraphy in the absence of free light chain in urine or plasma and there was no biopsy (7). In the current study, based on Gillmore et al. study, 12 patients (0.3%) were diagnosed with ATTR using bone scintigraphy with visual score of 2–3. There was no free light chain in plasma. These cases avoided myocardial invasive biopsy for diagnosis.

Table 1 The demographic, clinical, and imagistic findings of the 12 patients of positive myocardial deposition by ^{99m}Tc -MDP

Case	Age	Gender	Original disease	Score	H/CL	Distribution	UCG finding	Biopsy site
1	74	M	Prostatic cancer	2	2.0	LV, RV	af, LVH	abdominal fat
2	68	F	Breast cancer	3	2.9	LV, RV	LVH	skin
3	77	M	Prostatic cancer	2	1.9	LV, RV	E/A<1	—
4	68	F	Lung cancer	2	1.6	LV diffuse	E/A<1	abdominal fat
5	84	M	Lung cancer	3	3.2	LV, RV	LVH	abdominal fat
6	72	M	Prostatic cancer	3	2.5	LV, RV	wnl	—
7	78	M	Prostatic cancer	2	1.8	LV, RV	EF: 48%	abdominal fat
8	80	F	Lung cancer	3	2.9	LV diffuse	wnl	—
9	79	M	Lung cancer	2	1.9	LV, RV	wnl	—
10	76	M	Lung cancer	3	2.7	LV, RV	af	abdominal fat
11	81	M	Lung cancer	3	2.0	LV, RV	af	—
12	70	F	Lung cancer	3	3.2	LV, RV	LVH	abdominal fat

M: male, F: female, H/CL: heart-to-contralateral ratio, LV: left ventricle, RV: right ventricle, af: atrial fibrillation, LVH: left ventricular hypertrophy, E: early diastolic filling velocity, A: atrial filling velocity, EF: ejection fraction, wnl: within normal limit

In our analysis, bone scintigraphy with ^{99m}Tc -MDP managed to diagnose cardiac amyloidosis and was positive on 0.3% in daily practice. The previous Spanish study reported that the prevalence of moderate to severe bone scintigraphy uptake was 3.88% in males and 0.77% in females over 75 years old (8). In analyzing the cases of the over 75 years olds in our study, myocardial deposition was 0.68%. The differs slightly from the data acquired in Spain. Several reasons may explain this discrepancy. First, there is a difference in the average age. Just focusing on age greater than 75 years old in the current study, the average age was 77 years old compared to 81 years old in the Spanish cohort. Secondly, male sex was only 48% in the current study compared to 65% in the Spanish study. Further, racial differences may play a role.

All 12 patients had no heart failure symptoms at the time of bone scan. However, during the follow-up, 2 of the 12 patients in the current study died due to suspected heart failure. This reflects the poor prognosis of patients with cardiac amyloidosis. Some studies have reported a survival (5, 13), of 24 to 66 months in untreated patients with ATTR. Castano et al. reported in a multi center study that a greater H/CL ratio (>1.5) on ^{99m}Tc -PYP cardiac imaging in patients with ATTR cardiac amyloidosis is associated with lower survival (14). In our study, all of 12 patients had a H/CL ratio >1.5. From this point of view, we predicted that the cases which had myocardial uptake in our research would trend toward a worse cardiac survival.

Detection of cardiac amyloidosis using ^{99m}Tc -MDP

We retrospectively analyzed only ^{99m}Tc -MDP bone scintigrams. ^{99m}Tc -MDP was used as a tracer because this study was a retrospective analysis of bone scintigraphy which was the daily practical examination in our single hospital.

Three different bone complexing molecules have varying avidity for cardiac amyloid deposits including ^{99m}Tc technetium-labeled agents: pyrophosphate (^{99m}Tc -PYP), methylene diphosphonate (^{99m}Tc -MDP) and 3, 3-diphosphono-1, 2-propanodicarboxylic acid (^{99m}Tc -DPD). Although the binding mechanism is still under consideration, reports of bone scans with increased ^{99m}Tc -PYP uptake in the heart in patients with amyloid infiltration have dated from the early 1980's. Testing in small cohorts of amyloid patients has confirmed ^{99m}Tc -PYP uptake in amyloid hearts. However low intensity signal and false positive results in hypertensive, sarcoid, and dilated cardiomyopathies limit the use of this agent (15, 16). ^{99m}Tc -MDP binds preferentially to cardiac amyloid, although with less avidity and sensitivity than that of ^{99m}Tc -PYP. Data comparing ^{99m}Tc -MDP to ^{99m}Tc -PYP in 7 patients with biopsy-proven cardiac amyloidosis reported 100% versus 56% uptake respectively (17). Additionally, ^{99m}Tc -MDP uptake is less intense than that of ^{99m}Tc -PYP, diminishing its potential as the tracer of choice for cardiac amyloidosis. ^{99m}Tc -DPD, in contrast to the other bone avid molecules, shows preferential uptake in ATTR cardiomyopathy. In the first of two studies from Bolgona, 15 patients with ATTR and 10 patients with AL cardiomyopathy underwent ^{99m}Tc -DPD scanning. Positive uptake was reported in all ATTR and none of the AL hearts (18). A second study involving 79 patients with amyloid cardiomyopathy (45 ATTR and 34 AL) and 15 control individuals identified mild ^{99m}Tc -DPD signal in AL hearts, but less tracer selectivity for ATTR heart involvement (19). While not definitive, ^{99m}Tc -DPD uptake in the heart of a patient with systemic amyloidosis strongly suggests ATTR disease (20).

Study limitations

This study has some limitations. First, it is a retrospective

analysis and not all the cases had complete medical investigations. The diagnostic algorithm of cardiac amyloidosis could not be followed because there were no heart failure symptoms at the time of bone scan in those with positive scans. Only 7 cases had ^{99m}Tc -MDP scintigraphy plus biopsy for amyloid deposits. The limited number of patients and differing forms of cardiac amyloidosis included in the study require further investigation and additional series of cases to be evaluated in order to determine the role of imaging techniques in diagnosis, prognosis assessment and future response to appropriate treatment (21).

Secondly, SPECT images was not performed in all cases. SPECT imaging should be considered to avoid erroneous results due to blood pool uptake and to confirm myocardial radiotracer uptake. SPECT is also useful to assess the distribution of myocardial ^{99m}Tc -MDP uptake in individuals with positive planar scans, to identify ^{99m}Tc -MDP uptake in the interventricular septum (commonly involved in amyloidosis), and to quantify the degree of myocardial uptake by comparison to rib uptake.

Conclusion

Cardiac uptake of positive ^{99m}Tc -MDP was present in 0.3% of the bone scintigraphies in daily clinical practice settings. This may be a sign of cardiac involvement with amyloid associated with extraosseous bone tracer uptake. It may be important to evaluate myocardial uptake during bone scintigraphy so as not to miss the sign of cardiac involvement of amyloidosis.

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None.

Conflicts of interest

The authors have no financial conflicts of interest to disclose concerning this study.

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■ JSNC News

JSNC 2020 in Aichi



Dear Friends and Colleagues,

Welcome to the 30th Annual Meeting of the Japanese Society of Nuclear Cardiology (JSNC), which to be held on December 18-19, Friday and Saturday, 2020 at JP Tower, Nagoya in Japan. As the congress president of JSNC, I am very pleased to extend you a warm invitation to the conference.

First I apologize for the postponement of the congress due to the COVID-19. Basically the program will be set along the previous one with some changes related to overseas lectures. The main theme of the conference “Guiding the Clinical Pathways and Giving Insight into the Heart” is not changed. I would like for all participants to sense the movement and future direction of nuclear cardiology.

Sincerely yours,

Jun Hashimoto, M.D., Ph.D.

