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^{99m}Tc-DPD scintigraphy and SPECT/CT in patients with AL and ATTR type amyloidosis

Potential clinical implications

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Abstract

Although pathological confirmation is the gold standard for diagnosis of amyloidosis, there is a need for a relevant imaging modality to identify involved organs and evaluate disease extent. Thus, we prospectively investigated imaging findings of ^{99m}Tc-DPD scintigraphy in AL and ATTR amyloidosis.

A total of 21 subjects with pathologically confirmed AL or ATTR amyloidosis were included. Pretreatment whole body ^{99m}Tc-DPD planar scanning and regional SPECT/CT were performed in all subjects. For allegedly involved organs, ^{99m}Tc-DPD uptake was visually and semi-quantitatively evaluated on a 4-point scale (grade 0: no uptake, 1: uptake less than spine, 2: uptake similar to spine, and 3: uptake greater than spine).

There were 29 organs involved in AL and 12 in ATTR. Significant ^{99m}Tc-DPD uptake was found in 24 organs (sensitivity = 82.8%) in AL and 9 organs (sensitivity = 75.0%) in ATTR. Additional SPECT/CT was helpful to ensure abnormal DPD uptake in the involved organs, which was uncertain by attenuation in planar imaging. Degree of ^{99m}Tc-DPD uptake was significantly higher in ATTR compared with AL amyloidosis ($P = .017$). Diffuse soft tissue uptake with photon defects in the liver area was found only in ATTR amyloidosis.

This study showed that ^{99m}Tc-DPD scintigraphy might have capacity to differentiate between AL and ATTR subtypes with good sensitivity in various organs involving primary systemic AL and ATTR amyloidosis. Additional SPECT/CT significantly improved the diagnostic efficacy of ^{99m}Tc-DPD scintigraphy.

Abbreviations: ^{99m}Tc-DPD = ^{99m}Tc-3,3-diphosphono-1,2-pyrophosphate, AA = amyloid A, AL = amyloid light-chain, ATTR = transthyretin, SPECT/CT = single-photon emission computed tomography/computed tomography.

Keywords: amyloidosis, SPECT/CT, ^{99m}Tc-DPD, whole body scintigraphy

1. Introduction

Amyloidosis refers to a group of diseases characterized by deposition of proteinaceous fibrils composed of low-molecular weight subunits of a variety of serum proteins (i.e., amyloid), which causes harm and loss of function to affected tissues or organs.[1–3] The disease can be systemic or organ-specific [3–6] and is divided into various subtypes based on the precursor protein, majority of deposits, tissue distribution, and extent of deposition.[1,7–9] Among these, precursor protein is the most importantly used characteristic because it is directly related to treatment and prognosis.[1,10]

Accurate characterization of amyloidosis is essential because the clinical course, process of diagnostic work up, treatment and prognosis vary by subtype.[2–4] For that, tissue biopsy provides precise information regarding subtypes of amyloidosis, there is also a need for a noninvasive imaging modality that can screen the whole body to evaluate disease extent and treatment response. Imaging studies including nuclear medicine have played an important role in amyloidosis, especially in identifying the type of amyloidosis, extent of disease, and response to treatment.[1,2,11]

Several radiotracers for nuclear medicine images have been tested and utilized for amyloidosis.[3]^{123}I-Serum amyloid P component (SAP) scintigraphy has been used for non-invasive diagnosis, monitoring, and treatment response in patients with amyloid light-chain (*AL*), amyloid A (*AA*), and cases of transthyretin (*ATTR*) amyloidosis.[12–16] However, low-quality cardiac visualization, high cost, and limited availability of purified SAP and ^{123}I are major disadvantages to its use.[6,12,17–19] There are several articles for ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), which has established its usefulness in the field of oncology, while clinical

Editor: Nagabhushan Seshadri.

JL and KK contributed equally to this work.

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120175).

The authors declare that they have no conflicts of interest.

Supplemental Digital Content is available for this article.

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How to cite this article: Lee J, Kim K, Choi JO, Kim SJ, Jeon ES, Choi JY. 99mTc-DPD scintigraphy and SPECT/CT in patients with AL and ATTR Type Amyloidosis: Potential clinical implications. Medicine 2020;99:4(e18905).

Received: 28 July 2019 / Received in final form: 20 December 2019 / Accepted: 24 December 2019

http://dx.doi.org/10.1097/MD.0000000000018905

value have not been proven in amyloidosis. Technetium-labeled radiotracers have been regarded as useful tools with advantages of convenient use and lower price, and notable previous studies using technetium-labeled agents such as ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-hydroxymethylene diphosphate (^{99m}Tc-HDP), and ^{99m}Tc-3,3-diphosphono-1,2-pyrophosphate (^{99m}Tc-DPD) have distinguishing ability of the subtypes of cardiac amyloidosis.[2,6,10,20–24] However, studies showing disease extent throughout the whole body using scintigraphy are scarce, even though amyloidosis is a systemic disease.

One of the major advantages of nuclear medicine is that it enables the evaluation of the whole body at once. A comprehensive understanding of the precise scintigraphy findings could help identify involved organs, assess disease burden, and select methods for further evaluation. Therefore, we prospectively investigated the imaging findings of ^{99m}Tc-DPD scintigraphy in patients with primary systemic AL or ATTR amyloidosis.

2. Methods

2.1. Study subjects

From December 2012 to December 2014, 31 subjects with suspected or alleged amyloidosis prospectively underwent ^{99m}Tc-DPD scintigraphy. Among these patients, 10 were excluded because of other pathological subtype (2, AA subtype), no pathological report (3), or previous treatment before the scan (5). Thus, a total of 21 subjects with pathologically confirmed primary systemic AL or ATTR amyloidosis were finally enrolled for analysis, and medical records were reviewed. Our institutional review board approved the study protocol of this prospective study, and informed consent was acquired from all subjects.

2.2. ^{99m}Tc-DPD scintigraphy and SPECT/CT

Anterior and posterior whole body scans were performed 3 to 4 hours after intravenous administration of 740 MBq ^{99m}Tc-DPD using a dual-headed gamma camera equipped with low-energy, high-resolution collimators at a scan speed of 21 cm/min. If there was suspicious abnormal soft tissue ^{99m}Tc-DPD uptake, regional single-photon emission computed tomography/computed tomography (SPECT/CT) was performed for that radioactive lesion using a hybrid SPECT/CT gamma camera (Siemens, SYMBIA T-16). SPECT acquisition settings were matrix size 128 × 128 and time per view of 25 seconds. The equipment had a dual detector with 180 degrees of rotation and step and shoot modes. The data was reconstructed using iterative reconstruction with a Gaussian filter applying scatter correction. Regional CT was performed by a continuous spiral technique after SPECT, using a section width of 0.5 mm, flexible scan time, 130 kV voltage, and matrix size of 128 × 128. No intravenous or oral contrast material was used. Attenuation correction was based on CT-acquired attenuation maps.

2.3. Image analysis

Whole body planar and regional SPECT/CT images were acquired in all subjects. Two nuclear medicine physicians interpreted the planar and regional SPECT/CT images in consensus. For involved organs, ^{99m}Tc-DPD uptake was visually and semi-quantitatively evaluated with a 4-point scale (grade 0: no significant uptake or no difference from physiologic uptake, grade 1: uptake less than spine, grade 2: uptake similar to spine, and grade 3: uptake greater than spine). In addition, the presence of diffusely increased soft tissue uptake was evaluated.

2.4. Statistical analysis

Comparison of continuous variables with known normal values in 1 group was performed with a one-sample T-test. Comparison of continuous variables between 2 groups was performed with the Mann-Whitney *U* test. For comparison between 3 or more groups, the Kruskall–Wallis test was used for continuous variables and Pearson's chi-square tests for nominal variables. A P value $\leq .05$ was regarded as significant. Statistical analysis was performed using SPSS Statistics 19.0.0 for Windows (IBM Corporation, Somers, NY).

3. Results

3.1. Clinical and laboratory characteristics

The clinical and laboratory characteristics of our study subjects were summarized in Table 1. A total of 21 subjects (mean age 62.1 ± 11.1 years, and 66.6% males) were all pathologically diagnosed with amyloidosis: AL in 16 and ATTR in 5. The proportion of males was slightly higher, though the difference was not statistically significant. Allowing multiple responses, the most frequent symptom in both subtypes was dyspnea (n = 11), followed by generalized edema (n = 8), discomfort or pain in the lower extremities (n = 5), and foamy urine (n = 2).

In AL amyloidosis, most patients had nonspecific symptoms including dyspnea, fatigue, general weakness/edema, or foamy urine. Serologic results showed significantly elevated N-terminal pro brain natriuretic peptide (NT-proBNP) level ($P = .024$) with a variable degree of diastolic cardiac dysfunction. Serum albumin level had lower tendency than group of ATTR, although without statistical significance ($P = .056$). For echocardiographic parameters, intraventricular septal width measured during diastole was significantly thicker than normal reference ($P < .0001$). Fourteen patients had been diagnosed with combined multiple myeloma (87.5%) in cases of systemic AL amyloidosis without any other simultaneous malignancy.

In the ATTR group, most patients complained about dyspnea and edema. Serologic results also showed elevated creatinine, β_2-macroglobulin, and NT-proBNP, also with a variable degree of diastolic dysfunction. For echocardiographic parameters, intraventricular septal width measured during diastole showed a thicker than normal value.

In comparison of the 2 subtypes, there was no significant difference in age (63.9 ± 10.9 vs 56.6 ± 11.1 y, $P = .171$), sex (male, 68.8% vs 60.0%, $P = .131$), or any serologic test. In echocardiographic findings, patients with ATTR subtype had a significantly thicker intraventricular septal width than those with AL subtype (11.6 ± 2.2 vs 15.8 ± 2.8 mm, $P = .012$) (Table 1).

3.2. ^{99m}Tc-DPD scintigraphy and SPECT/CT findings

There were a total of 41 organs from 21 patients diagnosed with amyloidosis pathologically and clinically. All patients had at least 1 involved organ confirmed histopathologically. There were 29 involved organs in patients with AL amyloidosis: 11 hearts, 11 kidneys, 4 livers, and 1 skin. Among the above organs, 18 were histopathologically confirmed. In the remaining 11 organs, involvement was diagnosed by chest/abdominopelvic CT, heart MR, or ultrasonography; this showed involvement of 4 kidneys,

Table 1

Clinical and Laboratory Characteristics of Patients with AL or ATTR Amylodosis.

Characteristics	AL (n = 16)	ATTR (n = 5)	*P* value
Mean age (years)	63.9 (range, 43.0 – 78.0)	56.6 (range, 41.0 – 69.0)	.171
Sex (male)	11 (68.8%)	3 (60.0%)	.131
Renal function			
Creatinine (mg/dl)	1.008 ± 0.453 (0.38 - 2.00)	1.29 ± 0.64 (0.76 - 2.36)	.408
Estimated GFR (mL/min)	82.98 ± 36.58 (32.9 - 186.6)	61.72 ± 27.31 (29.5 - 99.8)	.186
β_2-Microglobulin (mg/l)	3.09 ± 1.59 (1.28–7.54)	2.99 ± 1.64 (1.41–4.93)	.934
Hepatic function			
AST (U/l)	28.4 ± 10.5 (18.0 – 56.0)	28.2 ± 4.15 (23.0 – 33.0)	.406
ALT (U/l)	22.1 ± 10.1 (10.0 – 46.0)	21.0 ± 7.97 (14.0 – 33.0)	1.000
ALP (U/l)	163.9 ± 206.6 (53.0 – 689.0)	65.2 ± 21.0 (33.0 – 90.0)	.409
Albumin (g/dl)	3.1 ± 0.7 (1.7–3.9)	3.54 ± 0.96 (2.1 - 4.5)	.313
Heart enzyme			
NT-proBNP (pg/ml)	5942.0 ± 9084.5 (77.7 - 33498.0)	3873.0 ± 1318.5 (2061.0 - 5925.0)	.680
Troponin I (ng/ml)	0.1545 ± 0.237 (0.006 - 0.804)	0.13 ± 0.06 (0.19 - 0.59)	.436
Echocardiography			
IVSd width	11.6 ± 2.2 (8.0 – 14.0)	15.8 ± 2.8 (13.0 – 19.0)	.012
Ejection fraction	56.0 ± 15.0 (28.7 – 74.0)	53.2 ± 7.3 (45.0 – 63.0)	.386
Diastolic dysfunction grade (1/2/3/4)	7 (53.8%)/2 (15.4%)/4 (30.8%)/0 (n = 13; within normal limit in 3)	3 (60%)/0/0/1 (20%) (n = 4; within normal limit in 1)	.790

Reference ranges: creatinine (mg/dl), 0.6–1.1; estimated GFR (mL/min), 60–150; β_2-macroglobulin (mg/l), 1–2.4; AST (U/l), 0–40; ALT (U/l), 0–40; ALP (U/l), 53–128; albumin (g/dl), 3.5–5.2; NT-proBNP (pg/mL), 0–222; Troponin I (ng/mL), 0–0.78; IVSd width (mm), 6.0–11.0; ejection fraction (%, Simpson's), 50–85.

AL = amyloid light-chain amyloidosis, ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate aminotransferase, ATTR = transthyretin-related amyloidosis, GFR = glomerular filtration rate, IVSd = interventricular septal width measured during diastole, NT-proBNP = N-terminal pro brain natriuretic peptide, RV = right ventricle.

3 hearts, 2 livers, 1 bowel, and 1 lung. There were 12 involved organs in patients with ATTR amyloidosis: five 5 hearts, 4 bowels, 2 kidneys, and 1 lung (Table 2). Among them, 6 organs were histopathologically confirmed. In the remaining 6 organs, involvement was diagnosed by the same imaging modalities as used for AL amyloidosis; 4 bowels, 1 kidney, and 1 lung. Details on each case are showed in Supplementary Table, http://links.lww.com/MD/D656.

Significant ^{99m}Tc-DPD uptake was shown in 33 involved organs of all 41 organs independent subtype (sensitivity = 80.5%); 82.8% in AL and 75.0% in ATTR (Table 2). For the pathologically proven affected organs, significant ^{99m}Tc-DPD uptake was found in 19/24 organs (sensitivity = 79.2%); 84.6% in the heart (11/13), 62.5% in the kidney (5/8), 100% in the liver (2/2), and 100% in the skin (1/1). For the clinically diagnosed organs, 14/17 showed significant ^{99m}Tc-DPD uptake (sensitivity = 82.4%); 100% in the heart (3/3), 80.0% in the kidney (4/5), 100% in the liver (2/2), 100% in the bowel (5/5), and 0% in the lung (0/2). There was no significant difference in sensitivity between cardiac involvement and that in other organs (87.5%, 14/16 vs 76.0%, 19/25; $P = .365$).

Table 2

Sensitivity of ^{99m}Tc-DPD scintigraphy to detect involved organs before treatment in patients with AL or ATTR amyloidosis.

Involved organs	AL amyloidosis (n = 29)	ATTR amyloidosis (n = 12)
Heart	10/11 (90.9%)	4/5 (80.0%)
Kidney	8/11 (72.7%)	1/2 (50.0%)
Bowel	1/1 (100%)	4/4 (100%)
Liver	4/4 (100%)	-
Others	1/2 (skin in 1 and lung in 1) (50.0%)	0/1 (lung) (0%)
Overall	24/29 (82.8%)	9/12 (75.0%)

^{99m}Tc-DPD, Technetium-99m-3,3-diphosphono-1,2-pyrophosphate.

AL = amyloid light-chain amyloidosis, ATTR = transthyretin-related amyloidosis.

In AL amyloidosis, significant ^{99m}Tc-DPD uptake was found in 15 of the pathologically-proven 18 affected organs (sensitivity = 83.3%); 87.5% in the heart (7/8; grade 1 in 6, grade 2 in 1), 71.4% in the kidney (5/7; grade 1 in 3, grade 2 in 1, and grade 3 in 1), 100% in the liver (2/2; grade 1 in 1 and grade 3 in 1), and 100% in the skin (1/1; grade 1 in 1). Although pathological study was not performed, 9 of 11 additional organs clinically suspected of AL amyloidosis involvement revealed ^{99m}Tc-DPD uptake (81.1%; 3/4 in the kidney with grade 1 in 2 and grade 2 in 1, 3/3 in the heart all with grade 3, 2/2 in the liver with grade 1 in 1 and 3 in 1, 1/1 in the bowel with grade 3, and 0/1 in the lung) (Table 3). The sensitivity for detecting cardiac involvement (10/11, 90.9%) was higher than that for detecting other organ involvement (14/18, 77.8%), though without statistical difference ($P = .364$).

In ATTR, significant ^{99m}Tc-DPD uptake was found in 4 of 6 pathologically-proven affected organs (sensitivity = 66.7%); 80.0% in the heart (4/5; grade 3 in 4) and 0% in the kidney (0/1). Although pathological study was not performed, 5 of 6 additional organs clinically suspected of ATTR amyloidosis involvement revealed ^{99m}Tc-DPD uptake (83.3%, 4/4 in the bowel with grade 1 in 1, grade 2 in 2, and grade 3 in 1; 1/1 in the kidney with grade 1; and 0/1 in the lung) (Table 3). The uptake grade of involved heart was higher than that of other involved organs with borderline statistical significance (3.0 ± 0 vs 1.8 ± 0.8; $P = .113$). There was no significant difference in sensitivity between involved organs (80.0% and 4/5 for the heart vs 71.4%, 5/7 for other organs; $P = .735$). In addition, diffusely increased soft tissue uptake, except in the liver area, was found in all patients with ATTR subtype, but not in those with AL subtype (Figs. 1–3).

In comparing the 2 subtypes in ^{99m}Tc-DPD uptake grading, grade 2 (59.3%) had the highest percentage of AL subtypes for involved organs. On the other hand, grade 4 (41.7%) had a greater percentage of ATTR subtype ($P = .036$, Table 3). In other words, the uptake grade of the ATTR subtype was significantly

Table 3

DPD uptake grades of involved organs with AL or ATTR amyloidosis.

	DPD uptake grade				
	0	1	2	3	*P* value
AL	5 (17.2%)	16 (59.3%)	4 (14.8%)	4 (14.8%)	.036*
ATTR	3 (25.0%)	2 (16.7%)	2 (16.7%)	5 (41.7%)	

DPD, 3,3-diphosphono-1,2-pyrophosphate; AL = amyloid light-chain amyloidosis, ATTR = transthyretin-related amyloidosis.
* Pearson's Chi-square test.

higher than that of the AL subtype (1.24 ± 0.91 vs 1.75 ± 1.28; $P = .017$).

In 20 of the 41 involved organs (48.8%; 9 hearts, 6 kidneys, 4 livers, and 1 bowel), additional SPECT/CT images were helpful to determine whether there was abnormal soft tissue ^{99m}Tc-DPD uptake related to amyloidosis on planar imaging. 18 organs (9 hearts, 6 kidneys, 2 livers, and 1 bowel) with equivocal or no definite DPD uptake in planar imaging, eventually were confirmed with mild DPD uptake by SPECT/CT (Fig. 3). In the remaining 2 organs, SPECT/CT was also helpful to ensure abnormal DPD uptake in involved organs, which were uncertain by attenuation in planar imaging (Fig. 2).

4. Discussion

Amyloidosis is a systemic disease with various subtypes that have different treatments and prognoses. Tissue confirmation is essential for diagnosis but is not only imperfect for overall evaluation of this systemic disease, but also limited for patients who are intolerable to invasive procedures. Since amyloidosis is a systemic disease, and organ-related symptoms appear only after affected organ dysfunction has started, identifying involved organs in subclinical status is important for timely proper treatment before organ failure. However, because there are poor choices of imaging modalities for suspicious organs, even after pathologic confirmation, sometimes an additional biopsy of suspected involved organs is required to confirm amyloidosis involvement. In the present study, whole body ^{99m}Tc-DPD scintigraphy with additional SPECT/CT for patients with pathologically-proven AL or ATTR amyloidosis showed good sensitivity for identifying involved organs and helped to characterize the subtype of amyloidosis. Especially, additional SPECT/CT images were helpful to determine the presence of abnormal ^{99m}Tc-DPD uptake suggesting amyloidosis and improved the sensitivity for detecting the involved organs over planar images.

Because the major cause of death in amyloidosis is related to heart involvement, early and accurate diagnosis of cardiac amyloidosis followed by appropriate therapy is clinically important.[25–28] Although echocardiography or magnetic resonance imaging are choice of image modalities for cardiac amyloidosis, precise diagnosis of cardiac involvement and differentiating subtypes with non-invasive diagnostic tools remain difficult, with limited ability in the early phase.[2,6,29–31] In the present study, ^{99m}Tc-DPD scintigraphy with regional SPECT/CT showed a high sensitivity of 87.5% of cardiac involvement in both of AL and ATTR patients with preserved left ventricular ejection fraction and normal or mild diastolic

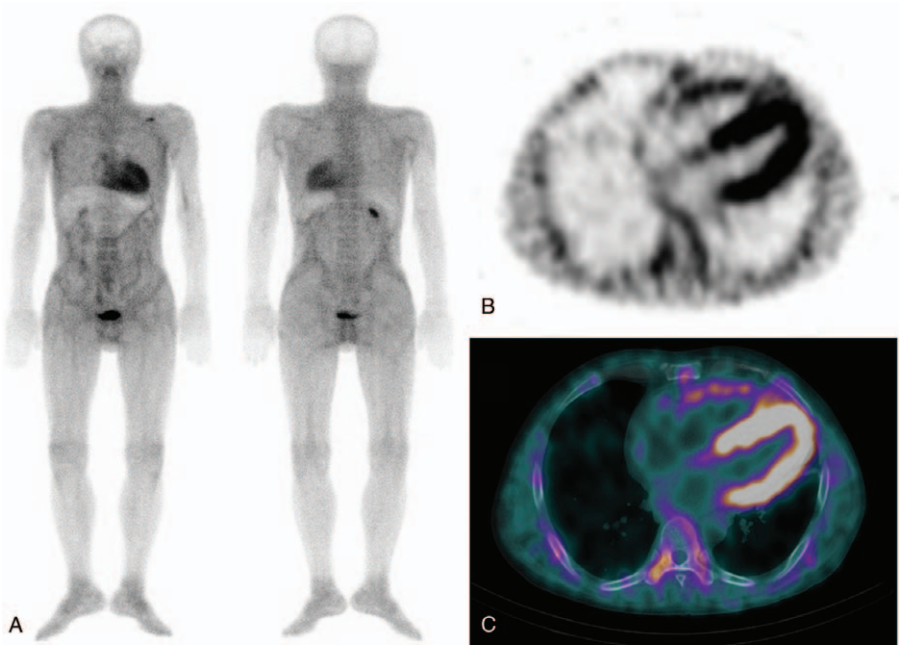

Figure 1. (A) Anterior and posterior whole body ^{99m}Tc-DPD scan images of a 50-year-old male patient with ATTR subtype of cardiac amyloidosis show diffusely increased soft tissue and cardiac uptake with a photon defect in the liver. Skeletal uptake is relatively decreased compared to the usual bone scans. (B and C) Additional SPECT/CT image is helpful to validate that cardiac uptake corresponded to the myocardium, suggesting amyloidosis.

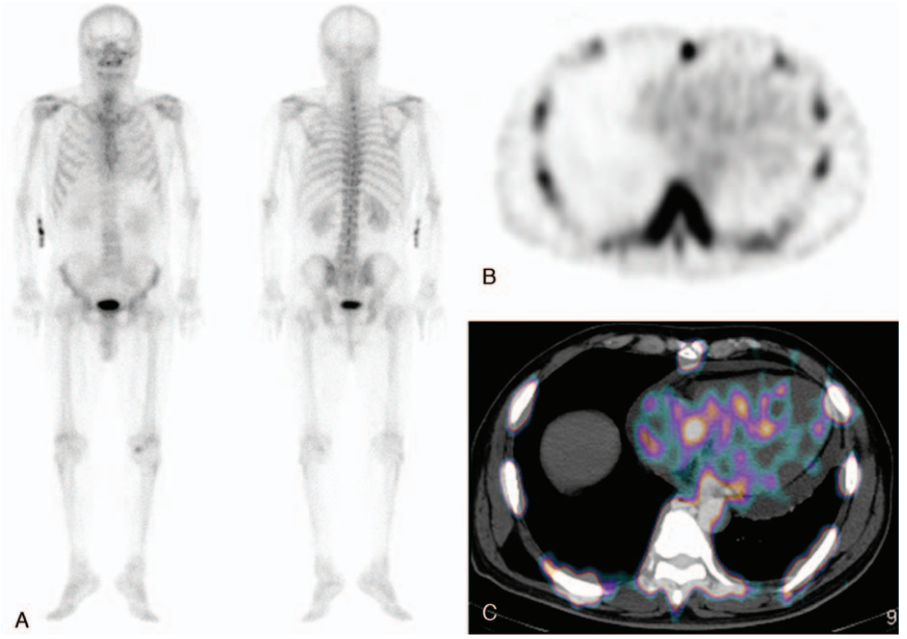

Figure 2. (A) Anterior and posterior whole body ^{99m}Tc-DPD scan images of a 64-year-old male patient with AL subtype of cardiac amyloidosis show equivocal mild ^{99m}Tc-DPD uptake in the cardiac area. It is unclear whether that uptake is related to cardiac amyloidosis because there was pericardial effusion on chest X-ray and echocardiography. (B and C) On the additional SPECT/CT image, the ^{99m}Tc-DPD uptake does correspond to the myocardium, suggesting cardiac amyloidosis. On the contrary, there is no significant ^{99m}Tc-DPD uptake in the pericardial effusion on the SPECT/CT image.

dysfunction. Our results were different from those of previous studies showing no significant ^{99m}Tc-DPD uptake in hearts with AL amyloidosis, even by regional SPECT.[6,19,32] This difference may be explained by the use of regional SPECT/CT in our study; the first is precise attenuation correction of heart, which is deep anatomic location of the chest, and second is accurate anatomic correlation to myocardial uptake, especially in cases of combined pericardial effusion. These advantages may contribute to the relative higher sensitivity of our study.

Except in cardiac amyloidosis, ^{99m}Tc-DPD uptake in extra-cardiac amyloid deposits is not fully described. In the present study, extra-cardiac ^{99m}Tc-DPD uptake was observed in various

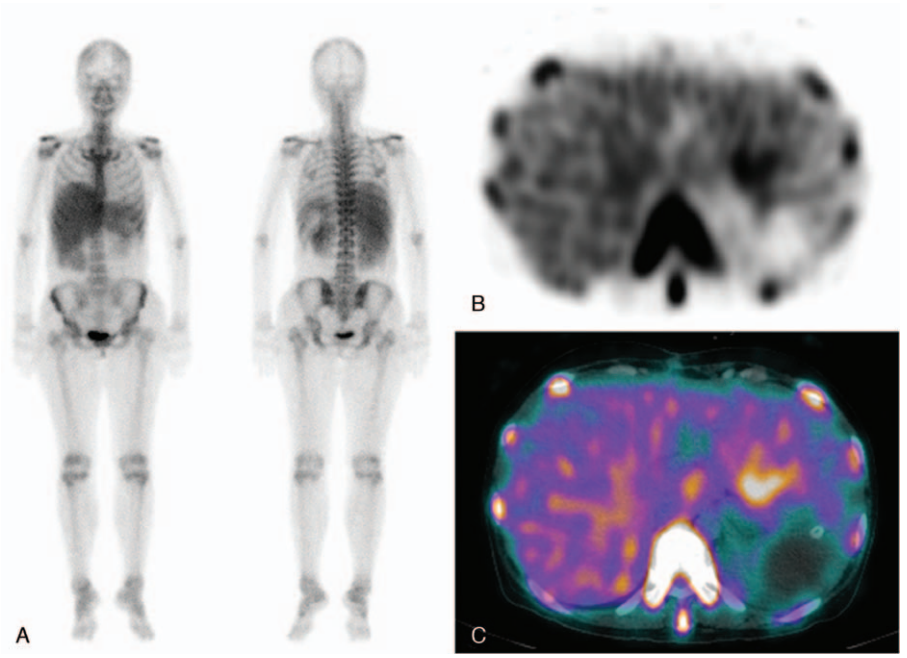

Figure 3. (A) Anterior and posterior whole body ^{99m}Tc-DPD scan images of a 42-year-old female patient with AL subtype amyloidosis involving the liver and kidneys show diffusely increased ^{99m}Tc-DPD uptake in the liver and both kidneys. However, it is not clear whether there is increased splenic uptake because of hepatomegaly. (B and C) Additional SPECT/CT image is helpful to clarify that the ^{99m}Tc-DPD uptake is confined to the enlarged liver.

organs with clinically suspected amyloidosis including the kidney, bowel, liver, and skin, showing moderately high sensitivity in both AL and ATTR amyloidosis (77.8% for AL and 71.4% for ATTR). In particular, there was high uptake in hepatic AL amyloidosis and bowel amyloidosis in both AL and ATTR types. Like cardiac amyloidosis, SPECT/CT was helpful to identify abnormal ^{99m}Tc-DPD uptake based on accurate anatomic localization and attenuation correction.

Extraosseous accumulation of ^{99m}Tc-phosphate derivatives, including ^{99m}Tc-DPD, is related to expanded interstitial volume, hyperemia, and a high local concentration of metals such as iron or calcium. However, the precise uptake mechanism for amyloidosis is still unclear. Since amyloidosis is characterized by abnormal deposition of amyloid in the interstitium of affected tissues or organs, it may cause increased interstitial volume and passive localization of ^{99m}Tc-phosphate derivatives as a consequence of dynamic equilibrium with blood.[33] Also, because the kidney is the most commonly affected organ and the major excretory route of ^{99m}Tc-DPD, blood concentration of ^{99m}Tc-phosphate derivatives might remain high in patients with renal impairment. This is another strong hypothesis for the well-visualized extraosseous uptake of involved organs in patients with amyloidosis. Moral et al. have suggested that cardiac uptake of ^{99m}Tc-DPD in AL amyloidosis could be related to radiotracer in the bloodstream secondary to reduced clearance by heart failure rather than true specific deposition in the myocardium.[6] Another possible mechanism is dystrophic calcification that could occur in degenerated or necrotic tissue, resulting in breakage of cell membranes, allowing influx of calcium into cells and accumulation of ^{99m}Tc-phosphate derivatives in the affected organs.[33] This possible mechanism was also supported by the normal serum calcium levels in all patients in our study (serum calcium = 8.6 ± 1.0 mg/dl, reference range = 8.4–10.2 mg/dl). However, these are general hypotheses for the extraosseous accumulation of ^{99m}Tc-phosphate derivatives, which may not explain the different ^{99m}Tc-DPD uptake patterns between AL and ATTR amyloidosis.

There was a higher cardiac uptake in ATTR than AL amyloidosis in the present study, and these findings are consistent with previous studies.[2,19] An additional noteworthy feature of ^{99m}Tc-DPD scintigraphy in our study was higher soft tissue uptake in only ATTR amyloidosis. In all 5 cases with ATTR subtype, ^{99m}Tc-DPD scans showed not only strong cardiac uptake, but also diffusely increased soft tissue uptake with a photon defect in the liver. These findings were not seen in AL amyloidosis. These findings may be used as key diagnostic criteria for differentiating between ATTR and AL, along with cardiac uptake grade in ^{99m}Tc-DPD scintigraphy. Previous studies have shown that the TTR mutation has high affinity for serum HDL, and this affinity causes conglomeration and deposition of the TTR protein in tissues organs.[34] Andersson et al have shown that these lipophilic depositions of TTR molecules can passively bind to the cell membrane, may have oxidative toxic effects by interfering with cytoplasmic signaling pathways, and induce cell apoptosis in a neuroblastoma cell line.[35] Further, this deposition could cause high concentrations of calcium in affected sites due to damaged cells and transchelation of ^{99m}Tc-phosphate derivatives.[33] Also, abnormal deposition of TTR molecules could activate scavenger systems and cause secondary hyperemia. Perugini et al. have suggested another hypothesis that ^{99m}Tc-DPD has a direct affinity for specific fragments of TTR protein, since there was strong ^{99m}Tc-DPD uptake in only ATTR cardiac amyloidosis,[19] although this has not been demonstrated at the cellular level. We consider that multiple mechanisms might be involved in the higher ^{99m}Tc-DPD uptake in ATTR.

This study has several limitations. First, this was a single institutional study with a relatively small number of subjects. Second, pathologic confirmation was not performed in all clinically involved organs, which might produce bias regarding the sensitivity of ^{99m}Tc-DPD scanning. Further study with a larger subject pool is warranted.

5. Conclusion

The results of this study confirmed that significant ^{99m}Tc-DPD uptake was observed in various organs with primary systemic AL or ATTR amyloidosis with good sensitivity in whole body scintigraphy with additional SPECT/CT. Additional SPECT/CT significantly improved the diagnostic efficacy of ^{99m}Tc-DPD scintigraphy. Uptake grade of involved organs and degree of background activity might help to differentiate between AL and ATTR subtypes.

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