Original Article Re-evaluating the potentials and limitations of ^{99m}Tcaprotinin scintigraphy for amyloid imaging

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Abstract: The definitive diagnosis of amyloidosis is made histologically with Congo red stain. Noninvasive imaging techniques for amyloidosis are beneficial for early and definite diagnosis of amyloid deposition in the body. ^{99m}Tc-aprotinin has the benefit of detecting amyloid deposits mainly in the heart, but it can also detect a wide range of lesions in other locations. The usefulness and limitations of ^{99m}Tc-Aprotinin scintigraphy for amyloid imaging were re-evaluated based on results from 25 patients (15 men and 10 women; median age, 62.9 y; range, 34-83 y). In addition, other nuclear tracers for imaging amyloidosis are discussed. Of the 25 patients with suspected amyloidosis, 19 patients were proven to have amyloid deposits by histopathological diagnosis. Major ^{99m}Tc-Aprotinin images showed positive findings, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of existing amyloid deposits were 94.7, 33.3, 81.8, and 66.7%, respectively. For analysis based on biopsy region, the sensitivity, specificity, PPV, and NPV of existing amyloid deposition were 30.6, 82.6, 73.3, and 43.2%, respectively. ^{99m}Tc-Aprotinin has a high potential for diagnosis of amyloid deposition in body; however, due to its physiological uptake, its potential is limited for detection of amyloid deposits in the liver, kidney, and spleen.

Keywords: ^{99m}Tc-aprotinin, amyloidosis, SPECT/CT, SPECT, scintigraphy

Introduction

Amyloidosis is a disease that results from extracellular deposition of the protein amyloid. Amyloid deposition can occur in various tissues of the body, and can lead to cell toxicity, organ dysfunction, and death. Therefore, the clinical presentation and clinical course is quite variable, and depends on the amyloid-involved organ. In most cases, amyloidosis is proven through a biopsy from the gastrointestinal tract or kidney. The definitive diagnosis of amyloidosis is made with histopathology, primarily Congo red stain. Noninvasive imaging techniques for detecting amyloidosis are beneficial, because early and definite diagnosis can allow for early treatment and monitoring of treatment [1]. Several imaging modalities can be used to detect localization of amyloid deposits and to monitor their progression and regression. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can provide morphology and functional imaging, which are useful in diagnosis and follow-up of localized amyloidosis [1]. Nuclear imaging with amyloidspecific radiotracers such as ^{99m}Tc-aprotinin [2] and ¹²³I or ¹³¹I serum amyloid protein (SAP) [3], or nonspecific radiotracers such as ^{99m}Tc-(pyro) phosphate [4], ^{99m}Tc(V)DMSA [5], ⁶⁷Ga citrate [6], ¹¹¹In-metaiodobenzulguaidine [7], and ¹³¹Iβ₂ macroglobulin [8] have impacted identification of amyloid deposits in systematic amyloidosis. Recently, PET imaging with ¹²⁴I-mAb m11-1F4 [9] and ¹²⁴I-labeled peptide p5 [10] has been reported to have specific responses to amyloid deposition patterns.

99mTc-aprotinin has the benefit of detecting amyloid deposits mainly in the heart, but it can detect a wide range of lesions [11]. Several case reports have described the utility of 99mTcaprotinin for amyloid imaging [12, 13]. One advantage of 99mTc-Aprotinin is that it requires a simple labeling procedure. Also, the safety of ^{99m}Tc-Aprotinin is assured because Aprotinin (Trasylol) itself is a clinically licensed drug, and ^{99m}Tc-Aprotinin had been used for renal scintigraphy [14]. Moreover, the radiation dose is relatively low compared to other scintigraphic tech-[15]. Therefore, ^{99m}Tc-aprotinin niques scintigraphy has the potential to be a widespread technology that facilitates improvement in diagnosis of amyloidosis. The present report focused on re-evaluating the potentials and limitations of ^{99m}Tc-aprotinin scintigraphy.

Materials and methods

Patients

Use of ^{99m}Tc-aprotinin scintigraphy was approved by the institutional review board in our hospital, and written informed consent was obtained from all patients prior to testing. 99mTcaprotinin scintigraphy was confirmed for 32 patients with 35 scans during June 2010 -October 2012, and histopathological diagnosis of amyloid deposits was obtained from 25 patients with 59 lesions. No unexpected adverse events or side effects related to 99mTcaprotinin were confirmed in any of the study patients. Finally, these 25 patients (15 men and 10 women; median age, 62.9 y; range, 34-83 y) with suspected or known amyloidosis who underwent ^{99m}Tc-aprotinin scintigraphy diagnosed during those 3 years were analyzed in this study. Amyloidosis was histopathologically diagnosed in all patients by biopsy specimens stained with Congo red dye.

Preparation of 99m Tc-aprotinin

Labeling kits were prepared following the methods of Smyth [16]. 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 are performed by Fujifilm RI Parma (Tokyo, Japan), in order to maintain objectivity of the evaluation, and have revealed a radiochemical purity of 97.8% (range 90.7-99.8%).

Imaging protocol

Planar and tomographic imaging was performed 90 min after a 2-mL injection containing 740 MBq of 99mTc-aprotinin. The acquisition included anterior and posterior whole body scans (11-13 cm/min) and regional static images (acquisition time, 5-7 min per image) obtained with using a single photon emission computed tomography (SPECT) system (e-com signature; Siemens, Erlangen, Germany) or SPECT/CT system (Infinia3 Hawkeye4, General Electric Medical Systems, Milwaukee, WI). Both cameras were 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.

Image interpretation

The images were reviewed by our nuclear medicine board. Abnormal focal accumulation of the tracer was determined by visual interpretation. The reference image for visual interpretation referred to the image of a control subject presented in the article reported by Han et al. [15]. If the obtained image had a focal uptake which was not confirmed in reference image, it was regarded as positive ^{99m}Tc-aprotinin uptake. Thus, ^{99m}Tc-aprotinin uptake in the liver, spleen, kidney, and bladder, which were confirmed in all cases as physiological uptake, were regarded as negative. These findings were compared with the final clinical and histopathological diagnoses.

Results

Patient characteristics

Patient characteristics are shown in **Table 1**. Of the 19 patients with histopathologically proven amyloidosis, seven had primary AL amyloidosis, six had AA amyloidosis, and the other was undetermined. Major coexisting diseases were multiple myeloma (n=6) and rheumatoid arthri-

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Patient No	Age	Sex	Suspected or defined site for amyloid deposit	Coexisting disease and/or clinical symptom	Type of amy- loidosis	Biopsy site	Positive (+) or negative (-)	^{99m} Tc-Aprotinin positive site
1	79	F	Myocardium	Arrhythmia, hypertrophic cardiomyopathy	AL	Subcutaneous tissue	+	Myocardium, thyroid, colon, nasal cavity
2	75	Μ	Stomach	Multiple myeloma: IgG type	AL	Stomach	+	-
3	57	Μ	-	Systematic amyloidosis	AL	Myocardium, stom- ach, skin	Myocardium, stomach (+)	Myocardium, thyroid, large joint
4	54	F	-	Rheumatoid arthritis, system- atic amyloidosis, renal failure	AA	Colon, stomach, duo- denum	+	Colon, vertebra, pelvic bone, large joint, thyroid
5	64	F	Myocardium	Atrioventricular block	AL	Subcutaneous tissue	+	Thyroid, colon
6	84	F	Colon	Rheumatoid arthritis, chronic diarrhea	AA	Colon	+	Colon, large joint
7	64	Μ	Myocardium	Anemia, shortness of breath on exertion, Myocardium failure	AA	Kidney	+	Colon, Myocardium, vertebra, sternum, pelvic bone
8	82	Μ	Myocardium	Atrioventricular block	Unknown	Subcutaneous tissue	+	Myocardium
9	68	F	-	Systematic amyloidosis	AL	Kidney	+	Lung, Myocardium, vertebra, pelvic bone
10	65	М	Lung	Lung nodular lesion	AA	Lung, lip, colon, stomach	+	Lung nodule, Myocardium, colon, thyroid
11	61	F	Carpal tunnel	Multiple myeloma: IgA type/ capital tunnel syndrome	-	Bone marrow, stom- ach, duodenum	-	Large joint, vertebra, pelvic bone
12	62	F	Kidney	Bence-Jones protein positive, nephrosis syndrome	Unknown	Kidney, bone marrow, liver, stomach, colon	Kidney (+)	Vertebra, pelvic bone, scapula
13	57	F	-	Multiple myeloma: IgG type	-	Bone marrow, stomach, duodenum, subcutaneous tissue	Stomach, duodenum, subcutaneous tissue (+)	Myocardium, vertebra, pelvic bone, thyroid
14	83	Μ	-	Polyneuritis, monoclonal im- munoglobulinemia	-	Bone marrow, skin	-	-
15	57	F	Liver	Multiple myeloma: IgG type, polyneuritis, elevation of liver enzyme	Unknown	Colon, stomach, skin	+	Colon
16	34	М	Lower extremity	Leg swelling	AA	Stomach, duodenum	+	Large joint, nasal cavity, oral cavity, thyroid

Table 1. Patients' characteristics

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17	62	F	Pancreas head	Multiple myeloma: IgA type, jaundice	AL	Pancreas head	+	Pancreas head, Myocardium, large joint, thyroid
18	58	F	Capital tunnel	Capital tunnel syndrome, liver dysfunction	-	Bone marrow, stom- ach, colon, liver, skin	-	Lung, thyroid
19	39	F	-	Systematic amyloidosis	Unknown	Myocardium, kidney	+	Myocardium, lung, thyroid, breast, vertebra, pelvic bone, large joint, salivary grand
20	63	Μ	Myocardium	Myocardium failure	-	Stomach, duodenum	-	Large joint, nasal cavity, lung, vertebra, pelvic bone,
21	64	F	Myocardium	Multiple myeloma: IgG type, shortness of breath on exer- tion	Unknown	Lung, myocardium, bone marrow	Lung (+)	Lung
22	77	М	Myocardium	Myocardium failure	-	Myocardium, kidney	-	Myocardium (weak uptake)
23	56	F	Myocardium	Rheumatoid arthritis, system- atic amyloidosis	AA	Stomach, duodenum	+	Lung, thyroid, vertebra, pelvic bone, colon, salivary grand, thyroid
24	67	Μ	Muscle	Myopathy	AL	Myocardium, stom- ach, colon, muscle, subcutaneous tissue	+	Myocardium, skeletal muscles
25	40	М	Myocardium	Pericardial effusion	-	Myocardium	-	-



Figure 1. An 83-year-old man (Patient No. 14) with polyneuritis, monoclonal immunoglobulinemia, and elevated serum amyloid A underwent ^{99m}Tc-Aprotinin scintigraphy for suspicion of amyloidosis. ^{99m}Tc-Aprotinin image shows physiological Aprotinin uptake in the nasal cavity, liver, spleen, and kidney. In this case, amyloid deposition was not proven by histopathological diagnosis.

tis (n=3). Although seven patients had no symptoms at the time of ^{99m}Tc-Aprotinin scintigraphy, the scan was performed in order to survey the extent of amyloid deposition excepting the sites where amyloid deposition had already been proven. Two patients developed new myocardial symptoms (atrioventricular block and sick sinus syndrome, respectively) after ^{99m}Tc-Aprotinin scintigraphy with positive findings in the myocardium. The major biopsy site was the stomach (n=13), colon (n=7), and duodenum (n=6) through endoscopic examination, and the bone marrow (n=6), myocardium (n=6), kidney (n=5), subcutaneous tissue (n=6), and skin (n=4). Of the 25 patients, 19 patients were proven to have amyloid deposits by biopsy. The biopsy site was set as close to the 99mTc-aprotinin-positive site as possible; however, it was performed in a substitute organ when the positive site was thought to have huge risk for biopsy or was unreachable. Since these biopsy sites were not always defined by ^{99m}Tc-Aprotinin scintigraphy images but resulted in a careful study of the patient's status, it was the major limitation of handing this examination for screening for amyloid deposition.

^{99m}Tc-aprotinin image

High uptake at the kidney, bladder, and liver; middle to high uptake at the spleen; and middle to low uptake at the nasal cavity were common in all cases, in accordance with previously reported images [15]. The major ^{99m}Tc-aprotinin positive sites were in the myocardium (n=11), thyroid (n=11), large joints (n=9), vertebra (n=9), colon (n=8), and lung (n=7). Of the 12 patients with clinical symptoms and histopathologically proven amyloidosis, 42% (5/12) had a ^{99m}Tc-Aprotinin-positive site that matched the organs related to the symptoms. If 99mTc-Aprotinin image showed any positive findings, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of existing amyloid deposition were 94.7, 33.3, 81.8, and 66.7%, respectively. For the biopsy region-based analysis, the sensitivity, specificity, PPV, and NPV of existing amyloid deposition were 30.6, 82.6, 73.3, and 43.2%, respectively. Several ^{99m}Tc-aprotinin images are presented from cases with undetected amyloid deposition by biopsy (Figure 1), proven amyloid deposition in the kidney (Figure 2), proven amyloid deposition in the colon (Figure 3), proven amyloid deposition in the lung (Figure 4), and proven amyloid deposition in the myocardium and muscle (Figure 5). Amyloid deposit in tissues was pathologically proved by congo red staining and red-green birefringence by polarized light (Figure 6).

Discussion

Aprotinin is a low-molecular-weight polypeptide protease inhibitor. Aprotinin labeled with ^{99m}Tc accumulates in areas with amyloid deposits, especially with antiproteases that exist in amyloid deposits [17]. The usefulness of ^{99m}Tc-Aprotinin imaging was first reported by Aprile et al. In their study, ^{99m}Tc-Aprotinin uptake was confirmed in several regions (salivary glands, tongue, and thyroid) in eight patients, indicating that ^{99m}Tc-Aprotinin is a potential tracer that can be used for detection of extra abdominal



Figure 3. A 54-yearold woman (Patient No. 4) suffering from rheumatoid arthritis for six years. 99mTc-Aprotinin scintigraphy showed band-like uptake in the lower abdomen (white arrow) and high uptake in the thyroid (white arrow head). The uptake in large joints (black arrow head) and bone are frequently found in patients with rheumatoid arthritis.

Figure 2. A 62-year-old woman (Patient No. 12) with nephrosis syndrome and urine positive for Bence-Jones protein. Amyloid deposition in the kidney was proven, ^{99m}Tc-Aprotinin images are obscured due to physiological uptake in the kidney (white arrow).

and myocardial AL amyloid deposits [2]. 99mTcaprotinin imaging was used to diagnose cardiac amyloidosis with high sensitivity (95-97%), and at one point was compared to echocardiography [1]. Schaadt et al. reported ^{99m}Tc-aprotinin uptake in several regions, including the lungs, pleura, liver, spleen, intestines, myocardium, and tongue, which are common sites for amyloid deposits. The authors concluded that ^{99m}Tc-aprotinin scintigraphy is noninvasive and sensitive for detection of a wide range of extraabdominal amyloid deposits [11]. Similar results were obtained in the present study; amyloid deposits in the heart, lung, and colon were frequently visualized with 99mTc-aprotinin imaging.

^{99m}Tc-aprotinin can play a useful role in imaging of cardiac involvement of amyloidosis [2, 11, 15, 18, 19]. ^{99m}Tc-aprotinin scintigraphy might be able to detect amyloid deposits in an early stage of the disease, because it identified "silent" amyloid deposits in five patients preceding clinical symptoms [15]. Two cases with positive ^{99m}Tc-aprotinin in the heart that preceded the myocardial symptoms were experienced, which might support the potential use of ^{99m}Tc-aprotinin scintigraphy for early detection of amyloid deposits. However, ^{99m}Tc-Aprotinin accumulation in cardiac amyloid deposits was generally mild compared with renal uptake; therefore, diagnosis of cardiac amyloidosis should be carefully considered. Han et al. reported that assessment with the median heart to background uptake ratio was higher with cardiac amyloidosis than without cardiac amyloidosis, which can help with the diagnosis [15].

Physiological ^{99m}Tc Aprotinin uptake in the liver and kidney was definitely confirmed, and uptake in the spleen was also seen, and found to be slightly lower than in the liver. This indicated that detection of amyloid deposits in liver and spleen is not appropriate for ^{99m}Tc Aprotinin scintigraphy. Moreover, injected ^{99m}Tc Aprotinin is mainly excreted through the kidneys, and therefore it is very difficult to evaluate amyloid deposition in kidney [17]. Amyloid deposition was seen in the stomach for several patients in this study, but evaluation was not possible by



Figure 4. A 64-year-old woman (Patient No. 21) with multiple myeloma (A: planner whole body image, B: Chest CT, C: SPECT image, D: fused SPECT/CT image, E: Coronal image). The patient was suspected to have cardiac amyloidosis due to shortness of breath on exertion. ^{99m}Tc-Aprotinin image showed positive findings in both lungs but was negative in the myocardium. Finally, amyloid deposition in the lung was proven. SPECT/CT was helpful to identify the exact location of ^{99m}Tc-Aprotinin uptake in the lung.

^{99m}Tc Aprotinin due to physiological uptakes of the left liver lobe and the spleen that surround the signal from the stomach. In a similar way, the proximal side of duodenum (which can be accessed by gastric endoscopy) seems to be a difficult place for recognition of amyloid deposits because physiological liver uptake is so close by.

Non-specific intestinal uptake, which is considered to be excretion via the enterohepatic circulation or protein loss across the intestinal mucosa, has been reported [17]; however, it was not recognized in the present study. Another finding was a variety of ^{99m}Tc Aprotinin uptakes in the nasal cavity and thyroid. According to the control subject images and clinical data revealed by Han [15], slight 99mTc Aprotinin uptake at the nasal cavity has been reported and frequently confirmed. The occurrence of ^{99m}Tc Aprotinin uptake at the thyroid is not related to the radiochemical purity of 99mTc Aprotinin. Additionally, radio isotope uptake indicating isolation of ^{99m}TcO4⁻ such as uptake in the salivary gland was not confirmed. Therefore, ^{99m}Tc Aprotinin uptake at the thyroid appears to indicate amyloid deposition. According to the present results, ^{99m}Tc Aprotinin appears to have a quite low reliability for reflecting amyloid deposition at the skin and subcutaneous tissues. Moreover, amyloid deposition in brain is not expected for ^{99m}Tc-Aprotinin scintigraphy [12], since it does not cross the bloodbrain barrier [15].

Amyloid deposition is associated with chronic inflammatory conditions, inflammation, and neoplasias. Rheumatoid arthritis and multiple myeloma are major underlying diseases, and were frequently confirmed in the subjects in the present study. These diseases show diverse symptoms due to variable amyloid deposition, and are associated with poor prognosis [20, 21]. 99mTc Aprotinin images showed specific features of rheumatoid arthritis, with uptake in vertebra, pelvic bones, and large joints. These sites are not common sites for amyloid deposition related to rheumatoid arthritis; however, further evaluation is needed to clarify the relationship between features of rheumatoid arthritis and amyloid deposits, as the existence of amyloid deposition has generally relied on firstline biopsy sites.

Diagnosis of systemic amyloidosis still depends on biopsy and histopathological assessment.



Figure 5. A 67-year-old man (Patient No. 24) with myopathy (A: planner whole body image, B: axial image of SPECT/CT, C: coronal image of SPECT/CT, D: axial image of SPECT/CT). ^{99m}Tc-Aprotinin image shows positive findings in the myocardium (B and C: white arrow) and skeletal muscle (D). SPECT/CT contributed to the definition of myocardial uptake.

There are two main strategies for the biopsy. The first line is to obtain a specimen from an organ that is frequently associated with occurrence of amyloid deposits, even if it is a clinically uninvolved organ. The second line is to obtain a specimen from a clinically involved organ. Recent trends of biopsy sites in the firstline approach include the gastrointestinal tract, labia, salivary gland, and subcutaneous abdominal fat (aspiration) [1]. In the present study, biopsy was performed in these regions as well as the region that showed ^{99m}Tc Aprotinin uptake. It was expected that ^{99m}Tc Aprotinin would contribute to localization of the sites for biopsy. However, the uptake site was sometimes difficult to access for a biopsy, and the



Figure 6. Pathological specimen of the lung tissue obtained from a 64-year-old woman (Patient No. 21). The pathological specimen showed amyloid deposition (red-orange) with congo red staining (original magnification x 100). Congo-red-stained amyloid was also visualized as red-green birefringence under polarized light (original magnification x 100). Both micrographs are of the same section.

biopsy itself carries risk depending on the biopsy site and patients status. Even if 99mTc Aprotinin uptake is not confirmed in a first-line biopsy site, a case showing any positive 99mTc Aprotinin uptake tended to have amyloid deposition in the first-line biopsy site. Thus, first-line biopsy may be an option if any ^{99m}Tc Aprotininpositive sites are confirmed. The discrepancy between biopsy results and ^{99m}Tc Aprotinin images may depend on the amount of amyloid deposition. Histopathological diagnosis can be performed with a small sample specimen in a qualitative manner, but, considering the sensitivity of nuclear examination, some quantity of amyloid deposition is required in order to recognize positive findings in scintigraphy. The low reliability of ^{99m}Tc Aprotinin for skin and subcutaneous amyloid deposition could have been caused by this discrepancy.

¹²³I-serum amyloid P component (SAP) is a nuclear tracer that has been proven to detect amyloid and to determine the extent and distribution of amyloid deposits in systemic AL, AA, and ATTR amyloidosis [22]. ¹²³I-SAP can identify amyloid deposits in the liver, spleen, kidneys, bone, and adrenal glands [23]. ¹²³I-SAP fails to detect cardiac amyloid deposition due to blood pool content, increased uptake in the spleen, and insufficient fenestration in the endothelium of the myocardium [24].

Although many amyloid non-specific traces or specific traces can provide images identifying amyloid deposits, the major limitation of scintigraphy is the semi-quantitative method of

assessment of distribution of radioisotopes. This leads to low reliability for reproducibility and assessment of disease progression or therapeutic effect in follow- up studies. Compared to SPECT, PET can generally provide better quantification and resolution. PET imaging is beneficial for quantitative assessment, and it may therefore be able to provide more a detailed analysis for amyloidosis. Increased FDG uptake in amyloidosis has been shown in several articles [25-27]. However, it should be examined in greater detail because of reports showing negative findings of FDG-PET [13, 28]. The amyloid-specific PET tracer ¹¹C-Pittsburgh compound-B (PiB) showed good results for imaging brain amyloid [29], and it successfully visualized amyloid deposits in the heart [30]. However, imaging mismatch between ¹¹C-PiB and ^{99m}Tc Aprotinin for amyloid deposition in heart has been experienced [12]. Recently, amyloidolytic murine IgG1 mAb11-1F4 labeled with I-124 (¹²⁴I-mAb m11-1F4) has been expected to identify AL amyloidosis in human studies [9].

Conclusions

The usefulness and limitations of ^{99m}Tc-Aprotinin scintigraphy was re-evaluated for amyloid imaging, based on the results of 25 patients. ^{99m}Tc-aprotinin detected a wide range of lesions, but had limited detection of amyloid deposits in the liver, kidney, stomach, skin, and subcutaneous tissue. For the biopsy regionbased analysis, the sensitivity of existing amyloid deposition was low. However from the results of patient-based analysis, amyloid deposition might be suggested if ^{99m}Tc-Aprotinin images show any positive findings.

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