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A case of cardiac amyloidosis incidentally detected by bone scintigraphy

Hiroki Tanaka[1*], Makoto Hosono[2], Mitsunori Kanagaki[1], Marina Shimizu[1], Naoko Matsubara[1], Kazuna Kawabata[1], Tadashi Miyamoto[3], Kazumi Itoi[4]

[1]Department of Diagnostic Radiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
[2]Department of Radiology, Kindai University Faculty of Medicine, Osaka, Japan
[3]Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Hyogo, Japan
[4]Department of Respiratory Surgery, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

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ABSTRACT

A 73-year-old man with lung cancer underwent bone scintigraphy for disease staging. Diffuse myocardial technetium hydroxymethylene diphosphonate (^{99m}Tc-HMDP) uptake was incidentally found. A diagnosis of amyloid transthyretin (ATTR) cardiac amyloidosis was suspected, although the patient had no symptoms at this time. Single-photon emission computed tomography (SPECT) showed particularly strong uptake in the ventricular septum. Cardiac magnetic resonance imaging (CMR) showed widespread subendocardial and partly transmural enhancement of the left ventricular myocardium on delayed postcontrast T1-weighted images. These findings were consistent with ATTR cardiac amyloidosis. ^{18}F-FDG uptake in the left ventricle wall was observed on PET/CT. He was finally diagnosed with ATTR by endomyocardial biopsy. There are two major subtypes of cardiac amyloidosis: ATTR amyloidosis and amyloid light-chain (AL) amyloidosis. Endomyocardial biopsy is the gold standard for diagnosis. Recently, however, several reports have shown that bone scintigraphy using a ^{99m}Tc-labelled bone-seeking agent can detect ATTR cardiac amyloidosis and differentiate it from AL amyloidosis. Bone scintigraphy may play an important role in the detection and differentiation of ATTR cardiac amyloidosis.

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Introduction

Cardiac amyloidosis is a rare condition in which amyloid fibrils are deposited in the interstitium of the heart and cause morphological and functional abnormalities. Cardiac amyloidosis is difficult to detect because the clinical manifestations are often varied and nonspecific (1). There are two major subtypes of cardiac amyloidosis: amyloid transthyretin (ATTR) amyloidosis and amyloid light-chain (AL) amyloidosis. Although clinical signs and laboratory findings have many similarities between the disease types, their distinction is important because their management and prognosis are different (2). Endomyocardial biopsy is the gold standard for diagnosis (3). Recently, however, several reports have shown that bone scintigraphy using a ^{99m}Tc-labelled bone-seeking agent can detect ATTR cardiac amyloidosis and differentiate it from AL amyloidosis (3-5). There are a few case reports of ATTR cardiac amyloidosis incidentally detected by bone scintigraphy (4, 5). We report a case of ATTR cardiac amyloidosis, with findings of various imaging modalities, incidentally detected by bone scintigraphy and confirmed pathologically.

Case Report

A 73-year-old male with lung cancer underwent bone scintigraphy for disease staging. Planar whole-body bone scintigraphy was performed in the anterior and posterior projections 3 hours

* *Corresponding author:* Hiroki Tanaka. Department of Diagnostic Radiology, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77 Higashi-Namba-cho, Amagasaki-shi, Hyogo 660-8550, Japan. Tel: +816-6480-7000; Fax: +816-6480-7001; E-mail: h18tanakahiroki@gmail.com

after the injection of 740 MBq (20 mCi) of 99m technetium hydroxymethylene diphosphonate (^{99m}Tc-HMDP). The bone scintigraphy images incidentally demonstrated diffuse myocardial tracer uptake (Figure 1A). A diagnosis of cardiac amyloidosis was suspected, although the patient had no symptoms at this time. Cardiac uptake on the planar image at 3 hours was evaluated using a semiquantitative visual scoring method in relation to bone (rib) uptake according to a previous report (3): grade 0 =no cardiac uptake and normal bone uptake; grade 1=cardiac uptake less than rib uptake; grade 2=cardiac uptake equal to rib uptake; and grade 3=cardiac uptake greater than rib uptake with mild/absent rib uptake. Grade 2 or 3 uptake strongly suggests ATTR cardiac amyloidosis (3). The cardiac uptake of this patient corresponded to grade 3 (uptake greater than rib uptake with mild rib uptake). Single-photon emission computed tomography (SPECT) showed particularly strong uptake in the ventricular septum (Figure 1B). Cardiac magnetic resonance imaging (CMR) showed widespread subendocardial and partly transmural enhancement of the left ventricular myocardium on delayed postcontrast T1-weighted images (Figure 2A).

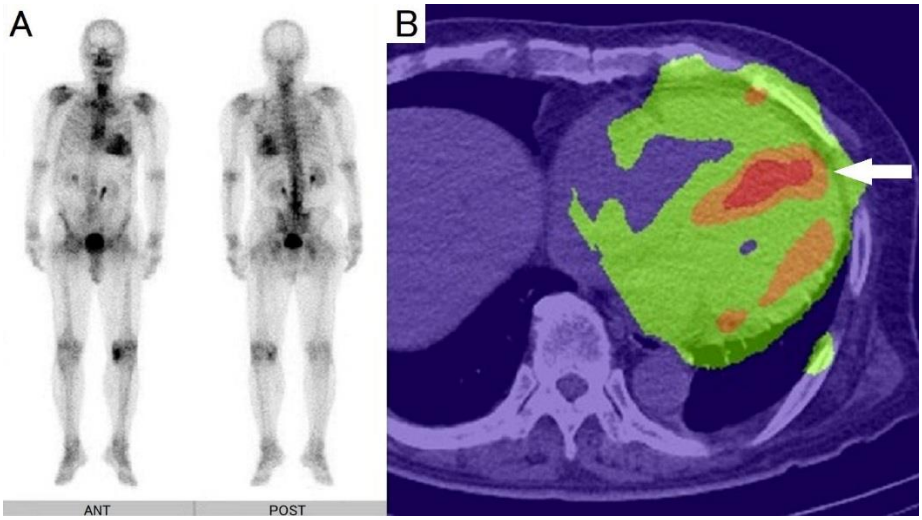

Figure 1. Planar whole-body bone scintigraphy showed myocardial tracer uptake, corresponding to grade 3 (A). SPECT showed particularly strong uptake in the ventricular septum (B) (arrow)

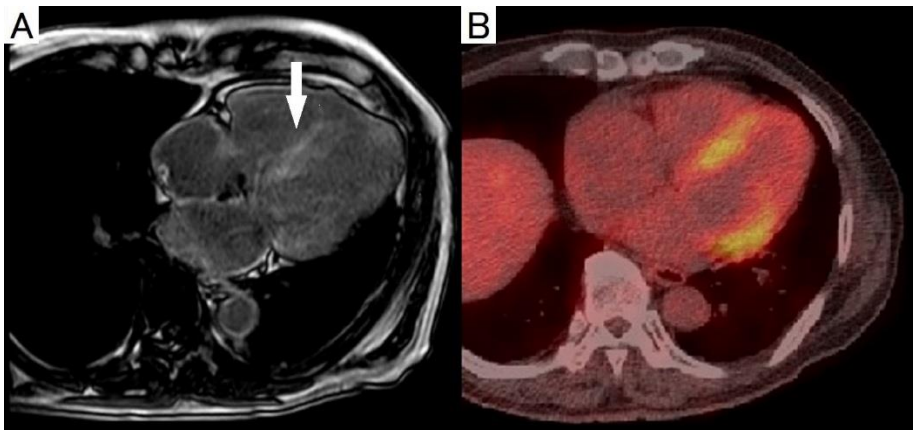

Figure 2. Widespread subendocardial and partly transmural enhancement of the left ventricular myocardium was detected in delayed postcontrast T1-weighted images (A) (arrow). ^{18}F-FDG PET/CT revealed tracer uptake (SUV_{max}=6.2) in the left ventricle wall (B)

The cardiac ultrasound showed a dilated left atrium and left ventricle diastolic dysfunction. The ejection fraction was estimated at 55%. The interventricular septum (IVS) and left ventricular posterior wall (LVPW) were slightly thicker (13 mm) than those in healthy subjects. These findings were consistent with cardiac amyloidosis.

^{18}F-FDG PET/CT imaging performed after 13 hours of fasting for the staging of lung cancer revealed tracer uptake (SUV_{max}=6.2) in the left ventricle wall (Figure 2B). No monoclonal protein was identified. Subsequent endomyocardial biopsy demonstrated diffuse amyloid deposition in the stroma of the myocardium.

Immunohistochemistry revealed positive transthyretin staining of the deposits, which is consistent with ATTR cardiac amyloidosis (Figure 3). Transthyretin gene mutation was not detected, and the patient was finally diagnosed with wild-type ATTR (ATTRwt).

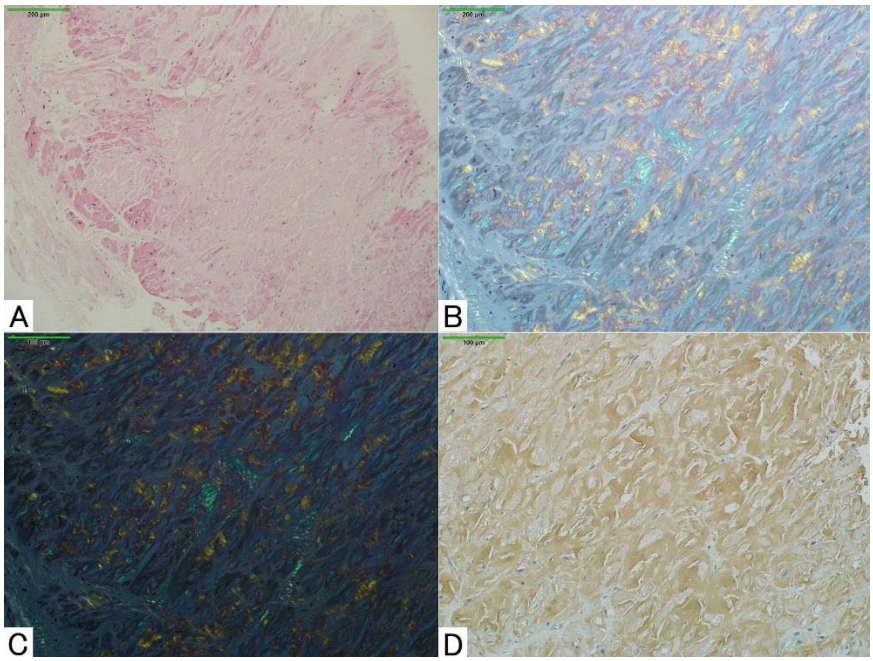

Figure 3. Endomyocardial biopsies demonstrated diffuse homogenous depositions in the stroma of the myocardium with haematoxylin-eosin staining (A). The deposits were positive for DFS (direct fast scarlet) staining (B, C). Immunohistochemistry revealed positive transthyretin staining of the deposits (D)

Discussion

Amyloidosis is a disease associated with deposits of amyloid fibrils formed by a misfolded precursor protein. More than 30 types of amyloid precursor proteins have been identified. Among them, amyloid fibrils formed by the immunoglobulin light chain, transthyretin, apolipoprotein A1, and amyloid A protein (AA) can deposit in the heart and cause cardiac dysfunction. ATTR amyloidosis is classified into hereditary transthyretin amyloidosis (ATTRv) with mutations in the transthyretin gene and ATTRwt with no mutation (6).

Cardiac amyloidosis often presents as a restrictive cardiomyopathy with heart failure and progressive exercise intolerance (7). AL and ATTR are common subtypes of cardiac amyloidosis (2). AL cardiac amyloidosis is associated with poor prognosis, with a median survival from diagnosis of <12 months. The prognosis of ATTR cardiac amyloidosis is typically 3-5 years (8, 9). The treatment options for these subtypes are also different (10). Therefore, the differentiation of AL and ATTR cardiac amyloidosis is important, although there are many similarities in the clinical signs and laboratory findings of these subtypes (2). Endomyocardial biopsy is the gold standard for diagnosis (3). However, this technique is invasive, and it is difficult to perform it in all cases in daily clinical practice.

The most common echocardiographic feature is a thickening of the left ventricle wall, particularly in the absence of hypertension, but this feature has poor specificity for the detection of cardiac amyloidosis. A granular sparkling hyperechogenic appearance, an echocardiographic feature of cardiac amyloidosis, can occur in other causes of left ventricular hypertrophy. Moreover, its sensitivity tends to be low, at 26% to 36% (11). A granular sparkling hyperechogenic appearance was not observed in our patient.

On CMR, cardiac amyloidosis shows widespread late gadolinium enhancement (LGE) of the myocardium, in addition to features of restrictive cardiomyopathy. Differences in LGE patterns in AL and ATTR cardiac amyloidosis have been shown, with subendocardial LGE being more prevalent in AL and transmural LGE more prevalent in ATTR cardiac amyloidosis (12). Transmural LGE was seen in our patient.

Recent studies have shown that bone scintigraphy using ^{99m}Tc-labelled bone-seeking agents, such as ^{99m}Tc-HMDP, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and ^{99m}Tc-pyrophosphate (PYP), is able to diagnose ATTR cardiac amyloidosis and differentiate it from AL amyloidosis (3, 13, 14),

although the mechanism remains unclear. These tracers seem to be used interchangeably (3).

The cardiac uptake of this patient corresponded to grade 3, strongly suggestive of ATTR cardiac amyloidosis (3). However, cardiac uptake may also be seen in a small proportion of patients with AL amyloidosis (3, 14). In a recent study of 857 patients with histologically proven amyloid, Gillmore et al. reported that cardiac ATTR amyloidosis can be reliably diagnosed in the absence of histology provided that all of the following criteria are met: a) heart failure with an echocardiogram or CMR that is consistent with or suggestive of amyloidosis; b) grade 2 or 3 cardiac uptake on a radionuclide scan with ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP; and c) the absence of a detectable monoclonal protein (14). Our patient met all of the criteria and was diagnosed with ATTR cardiac amyloidosis by endomyocardial biopsy.

SPECT imaging is particularly useful in positive or equivocal cases to differentiate myocardial uptake from blood pool uptake and to describe regional heterogeneity. The finding of diffuse uptake in the myocardium can lead to a presumptive diagnosis of cardiac amyloidosis, with the exclusion of more focal myocardial or pericardial diseases, such as myocardial infarction, pericarditis, sarcoidosis, or myocarditis (3, 15). In a previous study, most of the patients with ATTR cardiac amyloidosis had widespread ^{99m}Tc-DPD uptake in all myocardial segments, whereas uptake in the ventricular septum was detected in all of the patients (16). Pradel et al. reported that the ventricular septum showed greater ^{99m}Tc-HMDP uptake than the rest of the myocardium in a recent study of 50 patients with ATTR cardiac amyloidosis (17). Diffuse FDG uptake in the left ventricle wall was also detected in our patient. Although there is a limitation that we did not prepare for low carbohydrate diet or fasting for more than 18 hours, this finding might reflect cardiac amyloidosis (18).

In conclusion, bone scintigraphy may play an important role in the detection and differentiation of ATTR cardiac amyloidosis.

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