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Case Report

A case report of an uncommon presentation of ^{99m}technetium pyrophosphate scintigraphy in transthyretin cardiac amyloidosis: A potential diagnostic pitfall, pseudo-positive or pseudo-negative?

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ABSTRACT

^{99m}Technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy has shown utility for diagnosis of transthyretin (ATTR) cardiac amyloidosis with a high sensitivity and specificity. However, in clinical practice, a protocol and a method of analysis of this modality are not yet unified. We present a case of ATTR cardiac amyloidosis showing a positive cardiac uptake in planar imaging but no myocardial uptake in single-photon emission computed tomography/computed tomography (SPECT/CT) fusion imaging on ^{99m}Tc-PYP scintigraphy. We considered this tracer accumulation in the cardiac blood pool to be an inconclusive study. In this report, we focus on an inconclusive study case as a potential pitfall of ^{99m}Tc-PYP scintigraphy and discuss the interpretation of ^{99m}Tc-PYP scintigraphy findings with using both planar and SPECT/CT imaging for improvement of diagnostic accuracy for ATTR cardiac amyloidosis.

<**Learning objective:** The present report describes the importance of distinguishing myocardial uptake from the cardiac blood pool by both planar and single-photon emission computed tomography/computed tomography fusion imaging on ^{99m}technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy for diagnosis of transthyretin cardiac amyloidosis. To improve diagnostic accuracy, the ^{99m}Tc-PYP scintigraphy protocol including the method of evaluation and interpretation of the findings should be unified.>

Introduction

Wild-type transthyretin cardiac amyloidosis (ATTRwt) is emerging as one of the major causes of heart failure (HF) especially in older adults [1]. In recent years, there has been increasing interest in the utility of cardiac scintigraphy for detection of ATTR cardiac amyloidosis [2–4]. Technetium ^{99m} labeled scintigraphy including ^{99m}technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy has shown high sensitivity and specificity for differentiating patients with ATTR cardiac amyloidosis, and noninvasive diagnostic criteria for ATTR amyloidosis have been proposed [4].

We present a case of ATTR cardiac amyloidosis with an inconclusive study of ^{99m}Tc-PYP scintigraphy showing cardiac blood pool uptake. We discuss the difficulties in correctly interpreting ^{99m}Tc-PYP scintigraphy and the importance of both planar and single-photon emission computed tomography/computed tomography (SPECT/CT) imaging for accurate diagnosis of ATTR amyloidosis.

Case report

An 80-year-old man who had mitral regurgitation with mitral valve prolapse and chronic atrial fibrillation for the previous 10 years presented with HF in New York Heart Association class III. He had a medical history of an operation for bilateral carpal tunnel syndrome in his 70 s. TTR amyloid deposition was proven by carpal ligament obtained at surgery. His electrocardiogram showed a tendency for low QRS voltage and poor precordial R wave progression (Fig. 1A). Transthoracic echocardiography showed left ventricular (LV) ejection fraction of 51%, increased septal wall thickness of 13 mm and moderate mitral regurgitation (Fig. 1C,D).

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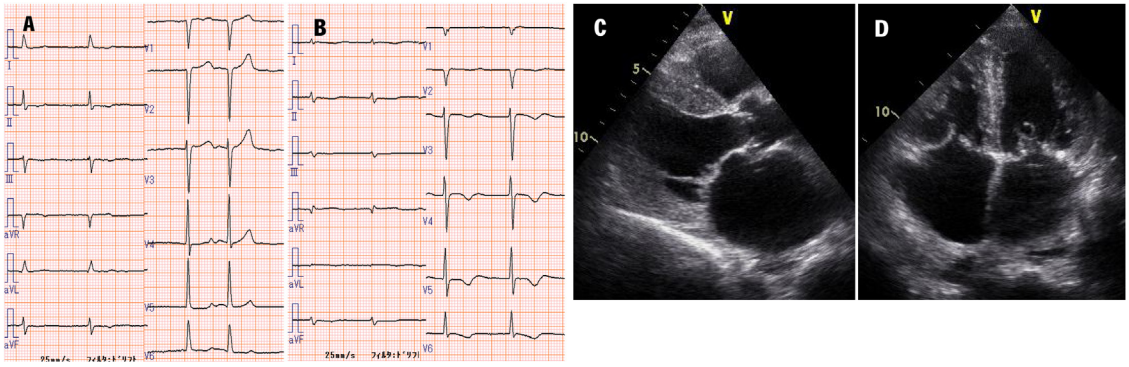

Fig. 1. An electrocardiogram showed atrial fibrillation, low voltage in limb leads, and poor R-wave progression in leads V1–V2 at the initial evaluation (A). The low voltage in limb leads progressed and T inversion in leads V3–V6 appeared 8 months later (B). A transthoracic echocardiogram showed left ventricular hypertrophy and severe biatrial dilatation (C, D).

At that time, we suspected cardiac amyloidosis and performed ^{99m}Tc-PYP scintigraphy. Planar imaging showed grade 1 uptake according to visual score by Perugini et al. [3] in the heart (Fig. 2A1), but SPECT/CT fusion imaging showed cardiac uptake in the blood pool (Fig. 2A2–A5). Therefore, we considered that ^{99m}Tc-PYP scintigraphy was an inconclusive study. Unfortunately, cardiac magnetic resonance (CMR) imaging was not performed because of declined renal function (estimated glomerular filtration rate = 29.8 ml/min/1.73m^2).

Afterward, his HF symptoms gradually worsened without any apparent trigger. He suffered from a gastric ulcer 8 months after the first ^{99m}Tc-PYP scintigraphy, upper gastrointestinal tract endoscopy was performed, and TTR amyloid deposition was revealed by biopsy of the stomach mucosa. We re-examined ^{99m}Tc-PYP scintigraphy and planar imaging showed grade 1 uptake as in the first inspection (Fig. 2B1). SPECT/CT fusion imaging showed cardiac blood pool uptake, but there was also local patchy intense tracer uptake in the myocardium of the LV septal wall (Fig. 2B2–B5). Endomyocardial biopsy was performed and revealed TTR amyloid deposition in the LV. Finally, a diagnosis of ATTR cardiac amyloidosis was made.

Discussion

^{99m}Technetium-labeled scintigraphy is a sensitive and specific modality for diagnosing ATTR cardiac amyloidosis [2–4]. Although several bone tracers and different methods of ^{99m}Tc-labeled scintigraphy have been used to assess ATTR cardiac amyloidosis, ^{99m}Tc-PYP scintigraphy is performed for screening of ATTR cardiac amyloidosis in the diagnostic work-up of patients with HF in Japan. In the past 6 years, ^{99m}Tc-PYP scintigraphy was performed for a total of 133 patients who were suspected of having a possibility of cardiac amyloidosis in our hospital.

All of the patients were administered 740 MBq of ^{99m}Tc-PYP (FUJIFILM, RI, Pharma, Tokyo, Japan) intravenously and imaged 3 h later by Siemens Symbia T2 or T6 (Siemens Medical, Munich, Germany) SPECT/CT cameras based on prior published data [3,5]. The scan was evaluated on planar imaging using the established semiquantitative visual score by Perugini (0 = absence of cardiac uptake, 1 = mild uptake less than that in bone, 2 = moderate uptake equal to that in bone, 3 = high uptake greater than that in bone) and was considered to be positive when there was moderate-to-severe ^{99m}Tc-PYP uptake (semiquantitative visual score: grades 2–3) in the ventricle [3]. SPECT/CT fusion imaging can provide better and more useful images for anatomical localization of the radiotracer to distinguish myocardial uptake or cardiac blood pool during assessment of ATTR cardiac amyloidosis, and false-positive results can be easily recognized using SPECT/CT fusion imaging [6,7]. We also confirmed both planar and SPECT/CT fusion imaging in our hospital.

In this report, we focus on inconclusive cases showing positive cardiac uptake on planar imaging but no myocardial uptake in SPECT/CT fusion imaging (resulting in cardiac blood pool). Fig. 3 shows our patient cohort. Fifty-six cases (42%) had positive cardiac uptake and 60 cases (45%) had negative cardiac uptake. The remaining 17 cases (13%) had grades 1–2 cardiac uptake on planar

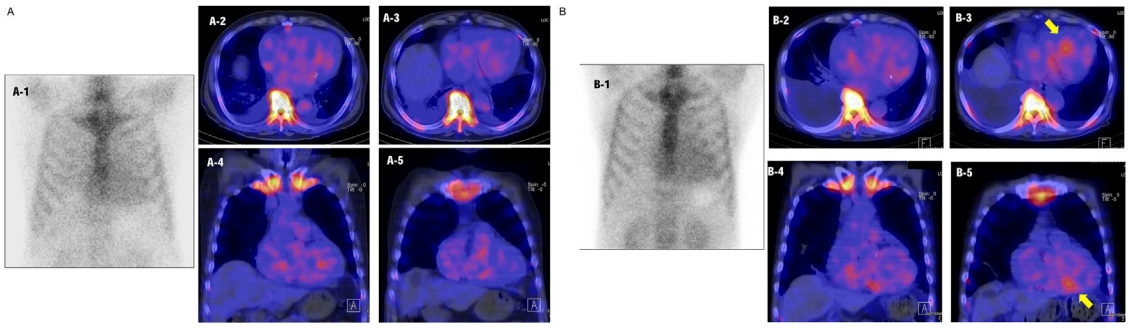

Fig. 2. ^{99m}Technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy and semiquantitative analysis on planar images using heart retention (done 3 h after injection of ^{99m}Tc-PYP) showed grade 1 uptake in the heart (A-1, B-1). Single-photon emission computed tomography/computed tomography fusion imaging showed cardiac blood pool uptake (A-2,3,4, B-2,3,4) on the first and second examinations, but local patchy uptake in the myocardium of left ventricle septal wall was also revealed in the second examination (B-2, 4; yellow arrows).

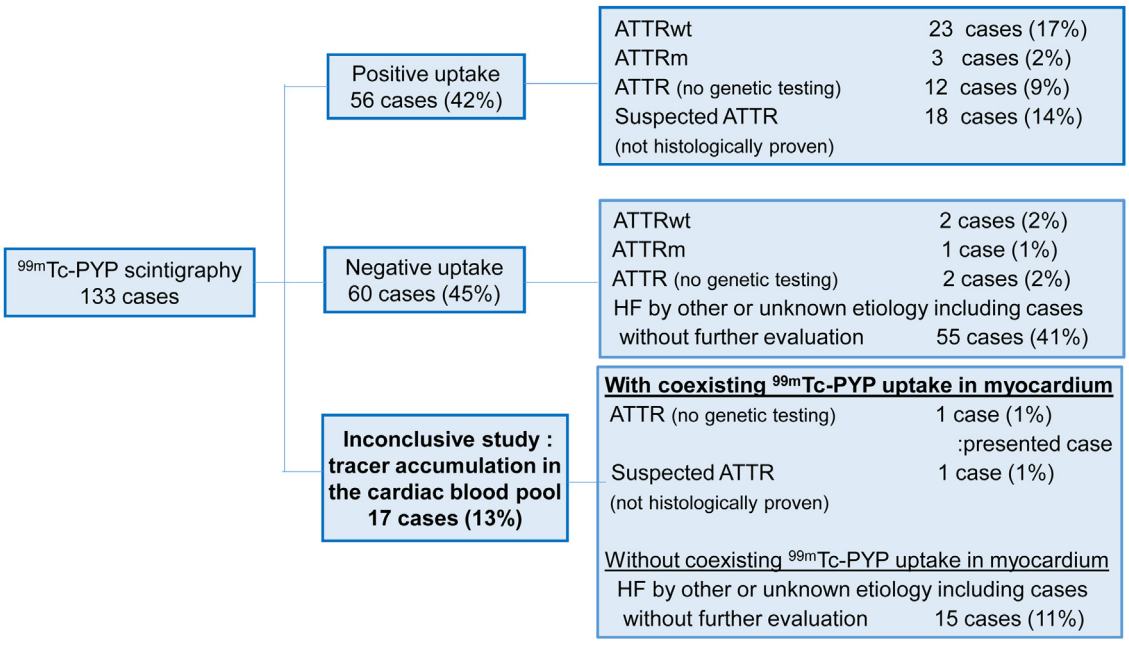

Fig. 3. Results of ^{99m}Tc-PYP scintigraphy in our 133 patients suspected of having ATTR cardiac amyloidosis.
^{99m}Tc-PYP, technetium pyrophosphate; ATTRwt, wild-type transthyretin cardiac amyloidosis (biopsy-proven TTR amyloid deposition and negative genetic testing); ATTRm, mutated transthyretin amyloidosis (biopsy-proven TTR amyloid deposition and positive genetic testing); HF, heart failure.

imaging but this mild-moderate uptake could be explained by the existence of the radiotracer in the cardiac blood pool on SPECT/CT imaging.

The cause of remaining mild-moderate ^{99m}Tc-PYP tracer accumulation in the cardiac blood pool after 3 -h incubation is not clear. According to the previous reports about ^{99m}technetium 3,3-diphosphono-1,2propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy, tracer accumulation in the cardiac blood pool may be caused by characteristics of the patient such as limited clearance by HF or fluid retention [8]. However, in our patients, there was no significant difference in estimated glomerular filtration rate or left ventricular ejection fraction among the three groups of positive cardiac uptake cases, negative cardiac uptake cases, and inconclusive study cases (data not shown). Additionally, on ^{99m}Tc-PYP scintigraphy in patients with ATTR cardiac amyloidosis, it is unknown whether myocardium uptake may be relatively reduced by acquisition at the timing of tracer accumulation remaining in the cardiac blood pool. There are only few reports about this point as far as we know. About ^{99m}Tc-DPD scintigraphy, retention of tracers in extracardiac tissues may reduce cardiac retention even in the presence of significant cardiac ATTR amyloidosis [9]. In our cohort, the prevalence of this pattern (tracer accumulation in in the cardiac blood pool) was relatively high (Fig. 3). This presented case had both patchy ^{99m}Tc-PYP uptake in the LV wall and cardiac blood pool accumulation, and a definitive diagnosis of ATTR cardiac amyloidosis was finally made by biopsy-proven TTR amyloid deposition. Therefore, in patients with ATTR amyloidosis, ^{99m}Tc-PYP uptake in the myocardium may not be completely suppressed even if tracer accumulation remains in the cardiac blood pool.

Moreover, the fact that protocols of ^{99m}Tc-PYP scintigraphy vary among facilities may be a problem. Our study protocol of ^{99m}Tc-PYP scintigraphy is based on the original literature for myocardial infarction [5] and the ^{99m}Tc-DPD scintigraphy protocol [3]. Recently, standardization of ^{99m}Tc-PYP scintigraphy methodology for diagnosis of ATTR amyloidosis has been proposed [10]. To improve diagnostic accuracy, the ^{99m}Tc-PYP scintigraphy protocol should be unified.

CMR imaging (including cine MR imaging, late gadolinium enhancement imaging, and native T1 mapping) has emerged as a noninvasive diagnostic modality for ATTR cardiac amyloidosis [11] although it cannot be performed in some cases because of renal dysfunction or cardiac implantable electronic devices. It can be useful to perform CMR for differential diagnosis in those patients with an inconclusive study by cardiac blood pool accumulation on PYP scintigraphy.

In conclusion, this report indicates the importance of two points. First, cardiac retention of ^{99m}Tc-PYP on planar images and anatomical localization of the tracer on SPECT/CT fusion imaging should be checked to distinguish myocardial uptake or the cardiac blood pool. Second, even if there is ^{99m}Tc-PYP tracer accumulation in the cardiac blood pool, it is necessary to confirm whether there is accumulation in the myocardium. Cardiac blood pool accumulation should be considered as an inconclusive study and cannot be considered as indicating negative ^{99m}Tc-PYP uptake.

Conflict of interest

None of the authors have conflict of interest to disclose in connection with our manuscript.

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