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Review

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Clinical application of cardiac scintigraphy with bone tracers: controversies and pitfalls in cardiac amyloidosis

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Abstract

Cardiac amyloidosis (CA) is a life-threatening disease caused by extracellular deposition of amyloidogenic proteins in the heart tissue; it could be associated with a poor prognosis and remains underdiagnosed and underestimated. During the last years, bone scintigraphy has been widely used to facilitate the diagnosis of CA, avoid endomyocardial biopsy, and differentiate amyloid light-chain amyloidosis from transthyretin amyloidosis. Technetium-99m pyrophosphate (^{99m}Tc-PYP) is the most used tracer in the United States, but a standardized and shared acquisition protocol is still lacking; technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) is widely used in Europe and can count on a more grounded data than ^{99m}Tc-PYP. Both tracers suffer from some diagnostic limitations (due to their biochemical characteristics) and pitfalls that can lead to a misdiagnosis of CA. We aim to briefly describe the main differences between ^{99m}Tc-PYP and ^{99m}Tc-DPD, analyzing the data available in the literature and highlighting the most frequent causes of misdiagnosis and pitfalls. Both ^{99m}Tc-DPD and ^{99m}Tc-PYP show good accuracy for the diagnosis of CA with high specificity and sensibility. Nevertheless, to achieve this accuracy, the correct acquisition protocols must be followed for each tracer, as suggested in the latest recommendation. Proper diagnosis of CA has a crucial role in patient management; therefore, it is important for

nuclear physicians to have the most specific approaches in acquiring and interpreting bone scintigraphy for transthyretin cardiac amyloidosis.

Keywords: Cardiac amyloidosis, ^{99m}Tc-PYP, ^{99m}Tc-DPD, bone scintigraphy, nuclear medicine

INTRODUCTION

Amyloidosis is a systemic disease with different clinical presentation depending on the tissues and organs involved. Cardiac amyloidosis (CA) is a restrictive infiltrative cardiomyopathy and is associated with the worst prognosis among the amyloidotic pathologies. CA remains underdiagnosed and underestimated because it can occur with non-specific symptoms and is correlated with considerable mortality[1]. CA is caused by extracellular deposition of amyloidogenic proteins in the heart tissue; the most common amyloid proteins involved are amyloid light-chain (in AL amyloidosis) and transthyretin (TTR) in TTR amyloidosis (ATTR). While the AL form is most frequently associated with hematologic disease (myeloma and monoclonal gammopathies), the TTR forms can be due to a mutated form of TTR (TTRv) or a wild-type form (TTRwt), the latter responsible for senile amyloidosis[2]. Another systemic form of amyloidosis is the AA type, which is related to the deposition of the Serum Amyloid A protein in the organs involved[3]; the most frequent clinical presentation is a chronic inflammatory condition associated with renal insufficiency. The liver and gastrointestinal tract can also be involved, while myocardial, skin, and soft tissue involvement is extremely uncommon. The AA form can be evaluated with labeled-SAP scintigraphy, while bone tracer scintigraphy is useless in this type of amyloidosis.

In 50%-80% of patients with clinically suspected AL amyloidosis, a biopsy of subcutaneous fat, salivary gland, or rectum is needed to confirm the diagnosis[4,5]; in patients with suspected TTR cardiac amyloidosis (TTR-CA), an endomyocardial biopsy (EMB) is frequently necessary to confirm the diagnosis[5], but myocardial perforation and tamponade are among the risks of complications associated with EMB and require a good level of expertise to avoid diagnostic delay[6] and procedure-related complications.

Nowadays, it is widely recognized that EMB could be avoided thanks to a diagnostic algorithm derived from a multicenter consensus paper that underlines the role of bone scintigraphy for the evaluation of the TTR-CA[7]. Even if echocardiography is a valuable and widely accessible tool for investigating heart failure, it is neither sensitive nor specific for CA[8]. Cardiac magnetic resonance (CMR) imaging can offer a much greater diagnostic value in CA, but it is costly, contraindicated in a substantial proportion of patients. and suffers from false-positive and -negative results. Furthermore, both echocardiography and CMR have the limit to not allow distinguishing different types of amyloid. During the last years, radionuclide imaging has increasingly been used to facilitate the diagnosis of CA, avoiding EMB and overcoming the limitation of echocardiography and CMR[7] because it can be considered a non-invasive diagnostic tool for the presence of amyloid with the advantage of accurately differentiating the two main forms (AL and TTR, which have completely different therapies, clinical evolution, and prognosis). In comparison to CMR and echocardiography, another potential role of radionuclide imaging could be the ability to early diagnose CA [Figure 1], especially in patients with proved genetic mutation without symptoms (carriers) since new specific drugs have been developed.

Technetium-99m pyrophosphate (^{99m}Tc-PYP) and technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) tracers, initially developed for bone nuclear imaging, have been increasingly used to evaluate the presence of CA. For both tracers [Figures 2 and 3], a visual evaluation following the scoring system proposed by Perugini can be performed[9]. This score compares the heart tracer

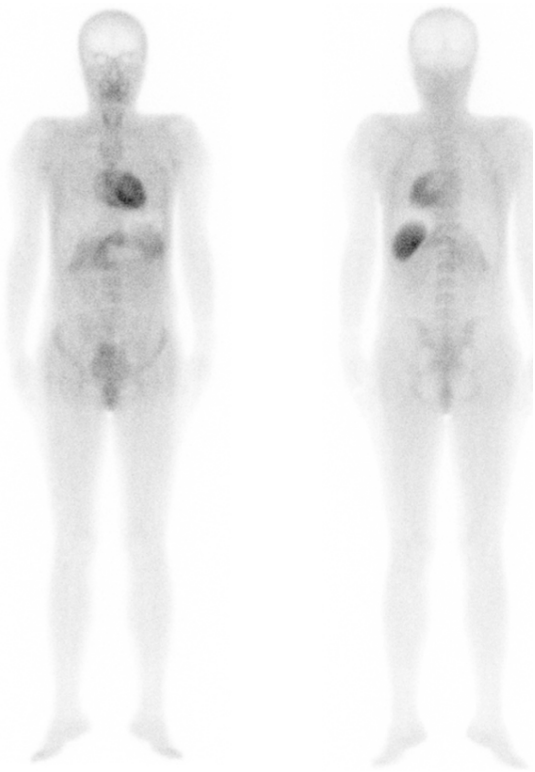

Figure 1. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid bone scan shows a carrier patient with Ala36Pro, visual score 3 with spleen uptake in 2014. After five years, the patient developed cardiac amyloidosis (hATTR CA).

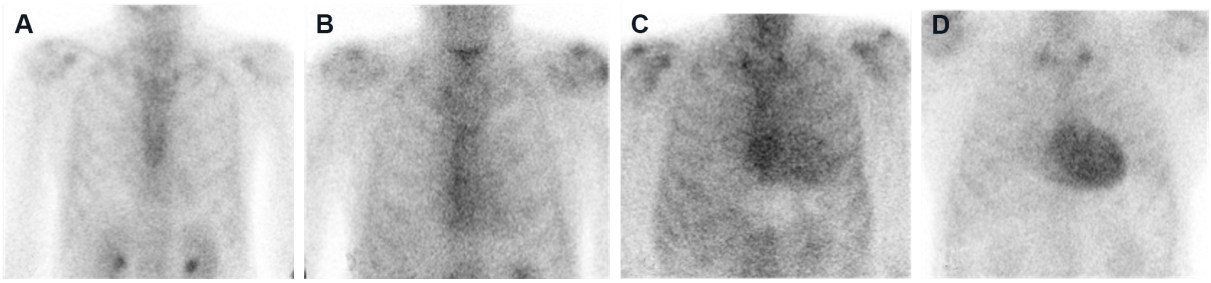

Figure 2. Technetium-99m pyrophosphate bone scan at 1 h: (A) visual score 0; (B) visual score 1; (C) visual score 2; and (D) visual score 3.

uptake to the bone tracer uptake on the 3 h planar images (0: absent cardiac uptake; 1: mild cardiac uptake less than bone; 2: moderate cardiac uptake equal to bone; 3: high cardiac uptake greater than bone): a positive planar scan is considered when there is Grade 2 or 3 uptake. The mechanism of myocardial uptake in CA is still unclear, but some authors reported that it is possibly related to the binding of the radiotracer to micro-calcifications, in correlation with the different calcium concentration in the amyloid fibrils (Subtype A showed higher uptake than Subtype B)[10].

The diagnostic accuracy of bone tracer scintigraphy has been widely described for both ^{99m}Tc-DPD[9,11-15] and ^{99m}Tc-PYP[16-19]. Nevertheless, not all bone tracers have been shown to be useful for the diagnosis of ATTR cardiomyopathy (ATTR-CM): ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP), also commonly used for bone scintigraphy, showed low sensitivity for diagnosis of ATTR-CM and is not recommended for this aim[9].

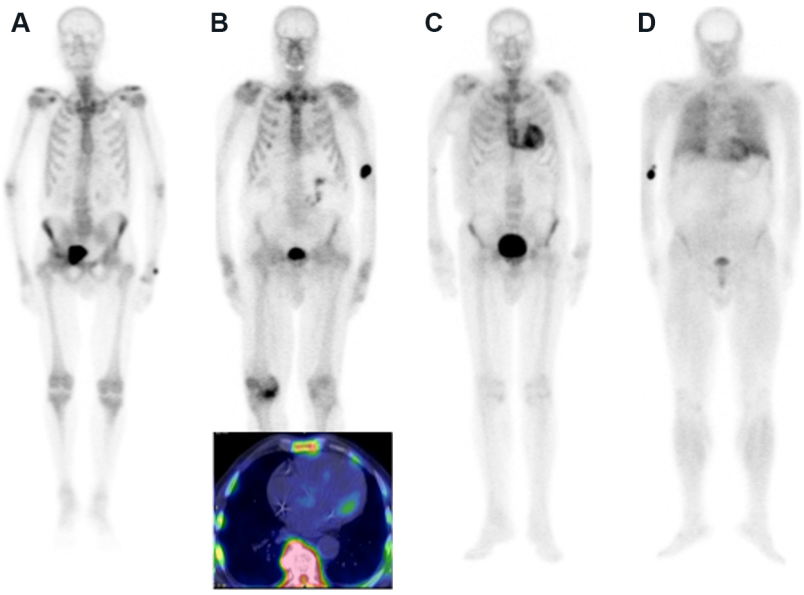

Figure 3. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid bone scan, 3 h acquisition: (A) visual score 0; (B) visual score 1 and corresponding single photon emission computed tomography/computed tomography image; (C) visual score 2; and (D) visual score 3.

Despite the high diagnostic accuracy reported in the literature, CA remains underdiagnosed and sometimes misdiagnosed. The most common and important cause of misdiagnosis is the failure to exclude AL cardiomyopathy (AL-CM) in patients with high tracer uptake (Grade 2 or 3 on planar images). Although in the literature myocardial uptake in AL-CM is usually described as Grade 1 or less, larger cohorts reported that 22% of patients showing Grade 2 or 3 uptakes on ^{99m}Tc-DPD or ^{99m}Tc-PYP scans have AL-CM on the EMB. Other cases of misdiagnosis can be related to some pitfalls due to a wrong imaging interpretation and/or an uncorrected acquisition protocol.

Despite the emphasis in published guidelines, failure or incomplete screening for AL amyloidosis has been reported in up to 24% of patients undergoing ^{99m}Tc-PYP[20]; in addition, many centers only perform planar imaging acquisition (without SPECT imaging to confirm myocardial uptake), with the high risk of misinterpreting the blood pool uptake as myocardial uptake. In this paper, we aim to briefly describe the main differences between ^{99m}Tc-PYP and ^{99m}Tc-DPD, analyzing the data available in the literature and highlighting the most frequent causes of misdiagnosis and pitfalls.

ACQUISITION PROTOCOLS AND DIAGNOSTIC CRITERIA

^{99m}Tc-PYP

This tracer is the only used tracer in the United States. Nevertheless, a standardized and shared acquisition protocol is still lacking[21] so it is difficult to correctly compare and analyze the data from the different studies. The American Society of Nuclear Cardiology (ASNC) released the latest Practice Points in 2019[22], suggesting to standardize the ^{99m}Tc-PYP acquisition protocol. The writing committee recommended planar imaging followed by the single-photon emission computerized tomography (SPECT) imaging or SPECT/CT imaging at 1 h; an optional SPECT imaging at 3 h can be used when a high blood pool activity has been observed in the 1 h SPECT images. The semi-quantitative analysis criteria reckon on a heart to contralateral lung ratio (H/CL) > 1.5 on 1 h imaging to accurately identify ATTR cardiac amyloidosis if systemic AL amyloidosis has been excluded. A similar recommendation was reported in a multi-societal expert consensus on imaging CA[23].

Most of the studies in the literature describe a good accuracy for the 1 h acquisition when a chest SPECT/CT is performed[7], because the planar images alone could not allow differentiating the blood pool, ribs uptake, or possible metastatic focal lesion on the heart area. In a single-center study, Bokhari *et al.*[17] identified a very high diagnostic accuracy (area under the curve of 0.992, $P > 0.0001$) for visual Grade ≥ 2 and a H/CL ratio ≥ 1.5 on 1 h images confirming that planar imaging could correctly distinguish ATTR-CA from AL-CA.

As reported above, guidelines recommend a 1 h time interval between injection and image acquisition. A 3 h post-injection imaging is considered optional unless there is evidence of excessive blood pool activity.

On 3 h images, a visual evaluation can be performed according to the Perugini visual score, comparing the heart tracer uptake with the bone tracer uptake: Grade 2 and 3 is consistent with ATTR-CA if a monoclonal plasma cell dyscrasia has been excluded, while Grades 0 and 1 are more suggestive for AL-CA.

The high diagnostic performance for ATTR-CA using ^{99m}Tc-PYP bone scintigraphy is derived from centers with expertise in this field and from a highly selected patient population. To reach the same diagnostic performance, it is crucial to follow the recommended diagnostic criteria. Unfortunately, Harb SC[21] described that at least 30% of responding hospitals perform ^{99m}Tc-PYP imaging to screen for CA, often times without light-chain measurement to exclude AL-CA and only 21% of institutions performed SPECT/CT imaging in addition to planar images despite the expert recommendation.

^{99m}Tc-DPD

This tracer is widely used in Europe and showed high sensitivity and specificity in the diagnosis of CA. The acquisition protocol is more standardized among centers than those of ^{99m}Tc-PYP and the diagnostic criteria reckon on a visual score analysis at 3 h: Grades 2 and 3 are considered positive for the presence of ATTR-CA when the presence of AL serum protein has been excluded. In the case of Grade 1, a SPECT or a SPECT/CT should be performed to exclude blood pool from myocardial wall uptake. In 2005, Perugini *et al.*[9] suggested using an early acquisition at 5 min for the semi-quantitative analysis of heart retention, whole body retention, and heart/whole body ratio in addition to the Perugini Score on late acquisition at 3 h. Other authors suggested to use only early phase at 10 min after injection of ^{99m}Tc-DPD or ^{99m}Tc-HMDP instead of the 3 h acquisition with a heart/mediastinum ratio > 1.28[24,25] considered suggestive for ATTR-CA. These two studies were conducted on a small population, therefore the 3 h acquisition protocol remains the most used acquisition protocol for ^{99m}Tc-DPD tracer in nuclear medicine centers.

Subsequent studies reported that mild uptake of ^{99m}Tc-DPD (Grade 1) may be noted in patients with other subtypes of CA (i.e., AL, amyloid A amyloidosis, and apolipoprotein A1). Rapezzi *et al.*[12] evaluated the ratio of heart-to-whole-body (H/WB) retention of ^{99m}Tc-DPD on the 3 h images in patients with TTR mutation and demonstrated that individuals with increased left ventricular myocardial wall thickness (1.2 cm) had much higher H/WB retention ratio compared to individuals with normal left ventricular myocardial wall thickness.

EXTRACARDIAC UPTAKE

The presence of extracardiac uptake (ECU) has been better studied for ^{99m}Tc-DPD than ^{99m}Tc-PYP because the whole-body acquisition protocol, widely used with ^{99m}Tc-DPD, allowed more consistent data regarding ECU. For ^{99m}Tc-PYP, the ECU has been reported in lung, but, considering that the most used acquisition protocol for this tracer includes only the chest, we can suppose that these data could be underestimated. Sperry *et al.*[26] suggested that ^{99m}Tc-PYP cannot be used to image extracardiac uptake in comparison to

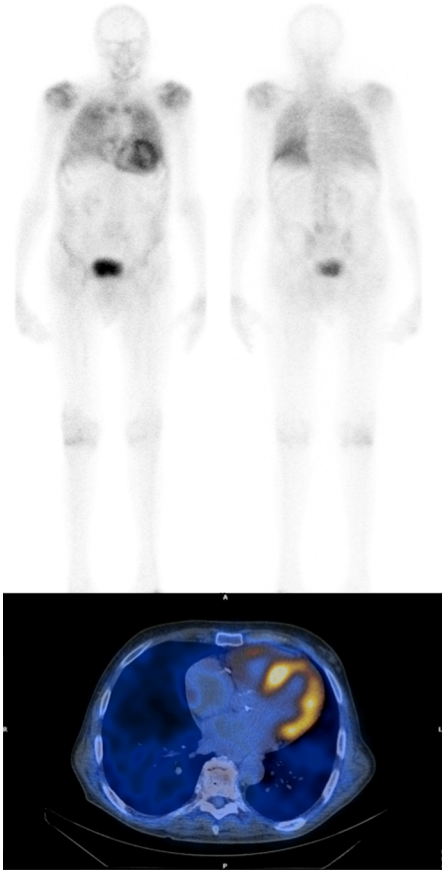

Figure 4. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid bone scan shows planar image positive for cardiac uptake (Perugini score 2) with diffuse uptake in the lung and in abdominal soft tissue, confirmed at single photon emission computed tomography/computed tomography image.

^{99m}Tc-DPD: in a retrospective study of 57 patients with advanced ATTR-CA who underwent 99mTc-PYP scintigraphy with whole-body acquisition protocol, the skeletal muscle uptake of the tracer was minimal with no significant difference between patients with Grade 2 and 3 myocardial uptake. It is well known that many extracardiac tissues and organs (lung, peripheral muscles, carpal ligament, tendon muscles, and abdominal fat) can be involved by ATTR; ECU of ^{99m}Tc-DPD has been widely described in the literature and has been considered a possible consequence of multiorgan transthyretin involvement, even though skeletal muscle has even been considered a potential source of attenuation of the bone uptake influencing the visual score system [Figure 4]. Since the consequences can be relevant in some patients, the availability of non-invasive imaging techniques able to detect this phenomenon is clinically relevant. Hutt *et al.*[27] firstly noted in 2014 a consistent and unusual pattern of ^{99m}Tc-DPD uptake involving the gluteal, shoulder, chest, and abdominal wall regions in 70/77 patients with cardiac ATTR (both wild-type TTR and mutant TTR). In a more recent and larger study[28] (563 patients with ATTR-CA), the same group demonstrated the progressive increase of the soft tissue-to-femur counts ratio from patients with Grade 0 to those with Grade 3 (overall from Grade 2 to 3) on 3 h whole-body planar images followed by chest SPECT/CT. It is important to underline that the difference between Grades 2 and 3 in the Perugini classification provides little prognostic information[28] in ATTR because it does not necessarily reflect a more advanced cardiac involvement.

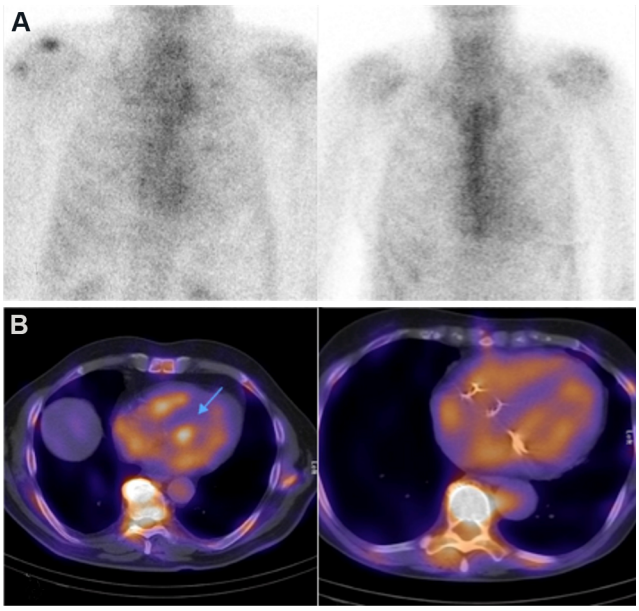

Figure 5. Technetium-99m pyrophosphate bone scan (A) 1 h planar images show mild tracer uptake on the cardiac area in two different patients; and (B) single photon emission computed tomography/computed tomography shows tracer uptake only in the cardiac chambers consistent for blood pool.

It is widely recognized that ^{99m}Tc-DPD and ^{99m}Tc-HMDP tracers show quite similar biochemical structure[29]. Cappelli *et al.*[30] reported their retrospective experience in the visualization of lung deposition of amyloid using ^{99m}Tc-HMDP scintigraphy: in a small cohort of 82 patients, lung uptake was present in 60% of ATTR cases but only in 6% patients with AL disease. Another study by Malka *et al.*[31] on 247 patients with CA (75 ATTRv, 107 ATTRwt, and 65 AL) described the presence of extracardiac uptake (lung, digestive tract, subcutaneous tissues, spleen, liver, thyroid, kidneys, and lymph nodes) in 29% of patients (33% ATTRv, 20% ATTRwt, and 40% AL) on an early-phase (10 min after injection) planar acquisition with ^{99m}Tc-HMDP. The most frequent site was the lung, mostly in ATTR (18%) compared to AL (11%) without significant difference between groups, suggesting that the soft-tissue uptake seems to be independent from the CU.

Therefore, two of the three bone tracers (^{99m}Tc-DPD/HMDP) currently used to detect ATTR-CM have been shown to also image extracardiac ATTR deposits, whereas ^{99m}Tc-PYP would not be able to recognize non-cardiac localizations of ATTR. It appears reasonable to state that the varying ability to image non-cardiac ATTR deposition among bone tracers is due to different properties of the single compounds more than to methodological aspects or different patients' characteristics.

PITFALLS

On ^{99m}Tc-PYP/DPD/HMDP planar images, the visualization of tracer uptake in the heart region related to blood pool [Figures 5 and 6] can be falsely attributed to myocardial uptake (i.e., in patients with enlarged right side cavities or reduced cardiac output), thus it is mandatory that, in all cases with mild tracer uptake on heart area, a chest SPECT or SPECT/CT be performed to clarify the true myocardial uptake, as discussed above. SPECT/CT images can also differentiate myocardial uptake from overlying bone [Figures 7 and 8], rib fracture, or a focal uptake due to a metastatic bone lesion overlapping the heart area. Other cases of possible false-positive findings at planar scan can be observed in patients with pleural effusions, obesity, presence of mitral or aortic calcification, and hydroxychloroquine toxicity[32,33].

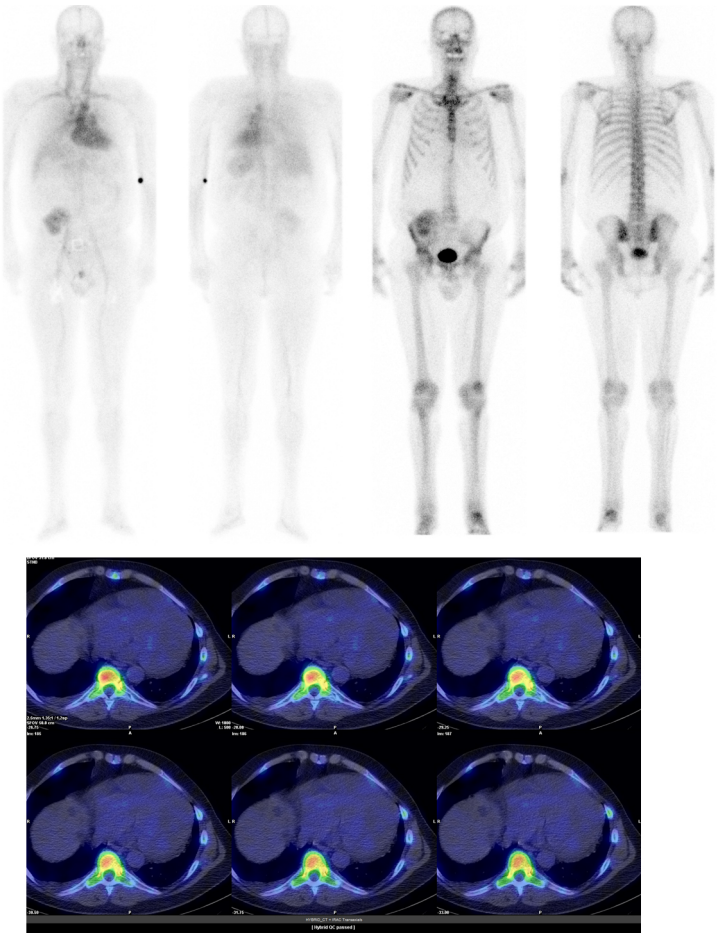

Figure 6. Case of a 60-year-old male with echocardiography consistent to hypertrophic cardiomyopathy, preserved ejection fraction. Pericardial effusion. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid bone scan performed for clinical suspicion of cardiac amyloidosis revealed mild uptake in heart area, but single photon emission computed tomography/computed tomography demonstrated that it is due to blood pool activity: visual score 0.

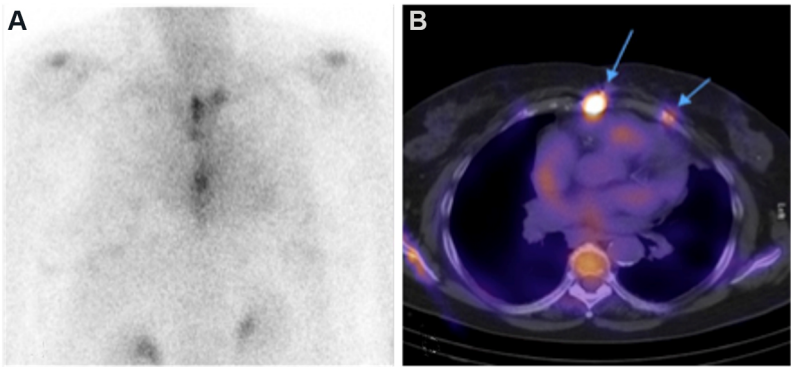

Figure 7. Technetium-99m pyrophosphate bone scan: (A) focal tracer uptake on planar images that overlaps the cardiac area; and (B) single photon emission computed tomography/computed tomography images show bone uptake.

For the ^{99m}Tc-PYP tracer only, another potential diagnostic limitation on 1 h planar images could be related to acute or sub-acute myocardial infarction because tracer uptake can also be observed in infarcted areas[34]. On the other hand, a case series describes that amyloid deposition and myocardial uptake may occur only in

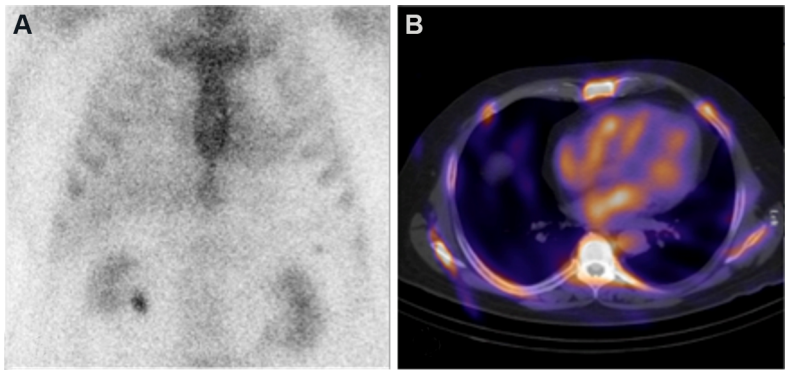

Figure 8. Technetium-99m pyrophosphate bone scan: (A) mild tracer uptake that overlaps the cardiac area on planar images; and (B) single photon emission computed tomography/computed tomography images show no uptake on heart walls.

the non-infarcted segments. In this scenario, the degree of uptake and the ratio on planar imaging may be below the threshold reported for definite diagnosis; however, SPECT imaging can help detect amyloid cardiac involvement[35].

We must remember that myocardial infiltration could be minimal, especially in the early stage of disease, resulting in false-negative scan even in patients with proved ATTR-CA. Patients with certain pathogenic TTR mutations, including Phe64Leu, Glu81Ala, and Val30Met, resulting positive for cardiac involvement on echocardiography could have negative cardiac bone scan[36,37], while patients with hereditary apolipoprotein A1 could present a positive bone scan[5]. The role of SPECT/CT images is even more relevant in the population with a low prevalence of CA to avoid false-positive results at planar scan.

CONCLUSION

Both ^{99m}Tc-DPD and ^{99m}Tc-PYP showed good accuracy for the diagnosis of CA with high specificity and sensibility, but, to achieve this accuracy, the correct acquisition protocols for each tracer suggested in the latest recommendation must be followed. The advantage of radionuclide images is that it allows a non-invasive diagnosis of CA and to differentiate the two main forms, AL and TTR-CA. This issue has a paramount clinical role because the two forms have different prognosis and treatment. The presence of new specific disease-modifying therapies underlines the importance of an early detection of CA even before the clinical presentation or when the echocardiography diagnostic criteria are not satisfied. The lack of head-to-head studies of ^{99m}Tc-DPD *vs.* ^{99m}Tc-PYP and the differences in the acquisition protocol does not allow comparing the performance of the two tracers. The ECU is better described with ^{99m}Tc-DPD, but its diagnostic role and prognostic value need to be better investigated with multicenter studies.

It seems reasonable to assume that this increased utilization of bone tracer scintigraphy for the detection of CA will continue to expand in the future into even lower-risk populations that include screening of asymptomatic "at risk" patients. It will therefore be crucial for nuclear physicians to have the most specific approaches in acquiring and interpreting bone scintigraphy for ATTR-CA.

DECLARATIONS

Authors' contributions

Conception and design of the study: Mattana F, Muraglia L, Girardi F, Cerio I, Porcari A, Dore F, Bonfiglioli R, Fanti S

Drafting the article and revising it critically for important intellectual content: Mattana F, Muraglia L, Girardi F, Cerio I, Porcari A, Dore F, Bonfiglioli R, Fanti S
Final approval of the version to be submitted: Mattana F, Muraglia L, Girardi F, Cerio I, Porcari A, Dore F, Bonfiglioli R, Fanti S

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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