Use of bone scintigraphy in the diagnosis of cardiac amyloidosis

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Abstract

Cardiac amyloidosis is a rare and progressive disease caused by the accumulation of amyloid in the heart. Since cardiac amyloidosis is a potentially treatable disease, early diagnosis is the key to improving patient survival and quality of life. There is no convincing evidence demonstrating that nuclear imaging has a fundamental role in the non-invasive diagnosis of TTR cardiac amyloidosis. Thanks to their high sensitivity and specificity, osteotropic radiocompounds are considered sufficient to establish the diagnosis, avoiding the use of endomyocardial biopsy. In this study, we analyzed the data obtained from the tests conducted on patients belonging to the Cardiology Operating Unit of the AOU "San Giovanni di Dio e Ruggi d'Aragona" who presented suspected cardiac amyloidosis.

These patients underwent scintigraphy with 99mTc-HMDP (hydroxymethylenediphosphonate), using a large-field computerized γ-camera with parallel hole collimator and SPET. All the acquired images were subsequently subjected to quantitative and qualitative analysis, allowing us, through radiomics, to extract a large number of parameters that reflect the morphological and predictive characteristics, using more or less automatic analysis algorithms. This analysis allowed us to obtain quantitative information that is hidden from a qualitative analysis of the image. The possibility of extracting hidden information from digital medical images is also of particular interest as it can enhance the predictive capabilities of existing automatic segmentation algorithms: the extraction of new, previously hidden information can be exploited for the automatic segmentation of images.

Introduction

Cardiac involvement, hence the name cardiac amyloidosis, is due to the accumulation of protein fragments in the myocardial extracellular matrix responsible in the long run for heart failure which, if untreated, can lead to death [1].

There are different forms of cardiac amyloidosis, but the two main ones are the light chain form (AL amyloidosis) and transthyretin (TTR). Light chain amyloidosis (AL) is not hereditary and is called this due to the accumulation of immunoglobulin light chains, produced in the bone marrow from plasma cells.

Less common than AL amyloidosis is a familial form associated with a point mutation in the TTR molecule.

TTR is a serum protein synthesized by the liver, responsible for the transport of RBP (a protein that binds retinol or vitamin A). Senile systemic amyloidosis or "wild type TTR" (ATTRwt) is a pathology that exclusively affects males aged > 65 years. The accumulation of TTRwt occurs mainly in the heart and this form of amyloidosis generally presents with symptoms of heart failure.

Given the intrinsic pathogenetic heterogeneity of ATTR amyloidosis, the diagnosis is not easy. Diagnostic suspicion varies depending on the predominant symptom. The greatest difficulties especially concern cases with exclusive cardiac involvement in the absence of a family history in which the clinical and instrumental picture is suggestive of hypertensive or hypertrophic heart disease [2].

The use of bisphosphonate scintigraphy has proven to be a safe and reliable method for the diagnosis of all cardiac forms of ATTR regardless of biopsy confirmation, as long as the intensity of cardiac uptake of the tracer is equal to or greater than that of the bone. If the presence of light chain amyloidosis is suspected, however, the only alternative remains, for the moment, the use of needle aspiration and bone marrow biopsy [3,4,5].

The attempt to carry out a diagnosis as close as possible to the pathological diagnosis represents the greatest aspiration for those who work in the field of diagnostic imaging. The differential diagnosis between the different types of cardiac amyloidosis is important for prognosis, therapy, and genetic investigation. Since cardiac amyloidosis is a potentially treatable disease, early diagnosis is the key to improving patient survival and quality of life. There is no convincing evidence that nuclear

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imaging has a fundamental role in the non-invasive diagnosis of cardiac TTR amyloidosis.
Thanks to their high sensitivity and specificity, osteotropic radiocompounds are considered sufficient to establish the diagnosis, avoiding the use of endomyocardial biopsy [6].
This study aims to define the methods with which the scintigraphic examination with bisphosphonates is carried out from a technical point of view, analyzing the various steps step by step and evaluating them from the point of view of the Medical Radiology Technician.
The data and the acquisition protocol described and analyzed derive from scintigraphic examinations with HMDP (hydroxymethylenediphosphonate) bone tracer carried out in selected patients presenting the clinical suspicion of cardiac amyloidosis, from 2019 to April 2023, belonging to the "San Giovanni di Dio e Ruggi d'Aragona".

Materials and methods

From June 2019 until April 2023, all those patients belonging to the Cardiology Operating Unit of the AOU "San Giovanni di Dio e Ruggi d'Aragona" were considered as potential candidates for enrollment in our study who, after a cardiological characterization, had the clinical suspicion of cardiac amyloidosis and were referred for an HMDP scintigraphy (Table 1).

DATA	
Total patients	44
Of which man	25
Of which woman	19
Positive patients	2
Negative patients	42

Table 1. *Description of enrolled patients.*

All patients underwent scintigraphy with Tc-99m HMDP (hydroxymethylenediphosphonate) [7]. The examination was carried out using a large-field computerized γ-camera, equipped with a parallel hole collimator and SPET. Whole-body planar acquisitions (10 cm/min) were performed both early at 5 minutes and late at 3 hours after i.v. administration. of ≈700 MBq of Tc-99m HMDP.
In the presence of cardiac uptake, targeted details and a tomographic study were performed at chest level (128x128 matrix, zoom 1, 120 projections, 20 s/projection).

Acquisition protocol

The scintigraphy protocol for cardiac amyloidosis is performed following clinical evaluation by the nuclear radiologist who justifies and authorizes the examination. The acquisition and archiving of images are instead managed by the radiographer. The main contraindication is the absence of pregnancy, furthermore since radioactive substances are excreted through breast milk, the test is strongly contraindicated even in breastfeeding women.
The radiopharmaceuticals used are all Technetium-based and three are the most favored nowadays: 99mTc-HMDP, 99mTc-PYP, 99mTc-DPD [8].
The activity administered is around 10 MBq per kg of the body, therefore approximately 700 MBq in a 70 kg patient.
After administration, during the waiting period, the patients must drink at least half a liter of water to facilitate the elimination of the radiopharmaceutical through the urinary system. Immediately before starting the exam, it is important that the patient empties their bladder and remove any metallic object, including from their pockets.
The test consists of two acquisition phases: an early one five minutes after administration and a late one three hours after administration.

In both phases the patients are in a supine position with the head straight, the chin slightly turned upwards, the arms placed along the sides with the hands resting on the table with the palm side, the legs are extended and the feet slightly internally rotated.

The two acquisition phases are in turn composed of the following subphases:
- Total-body: cranio-caudal acquisition of the entire body with the gamma camera as close as possible to the patient, with variable duration based on the set scanning speed and the scan length. Usually, the duration is around 18 min with an acquisition of 10cm/min. The collimators used are those for low energy high resolution (LEHR 3.3.1). The energy window must be set around 15-20% with photopeak at 140 KeV for 99mTc. The matrix for Whole Body acquisition is 256x1024 and the zoom is equal to one;
- Static: acquisition of detail at the thoracic level with a gamma camera centered on the cardiac area lasting approximately 10 minutes. Collimators and energy settings are the same as those used for Total-Body scanning. The matrix is 128x128 with zoom equal to one;
- SPET: tomographic acquisition with gamma camera centered on the heart with 360° rotation of 128 total projections and 20 seconds per projection. Collimators used and energy settings are the same as for Total-Body acquisition. The matrix is 128x128 with a zoom of one.

The evaluation of osteotropic radiopharmaceutical uptake, which is the key to the diagnosis of ATTR cardiac amyloidosis, was performed with both semi-quantitative and quantitative methods (Figure 2).
The semi-quantitative analysis is based on the visual comparison of the radiopharmaceutical uptake between the myocardium and the bone (ribs) 3 hours after the injection, as described by Perugini et al. [3], using a 4-grade scale (Figure 1): grade

0 (no cardiac uptake and normal bone uptake of the drug); grade 1 (mild cardiac uptake and less than bone uptake of the drug); grade 2 (moderate cardiac uptake associated with attenuated bone uptake); grade 3 (high cardiac uptake with reduced or absent bone uptake).

The threshold value is represented by score 2; a value equal to or greater than 2 indicates positivity for ATTR amyloidosis, while a value less than 2 is considered negative. The quantitative analysis uses the H/CL ratio (myocardial-to-contralateral lung ratio). A circular ROI is performed on the heart,

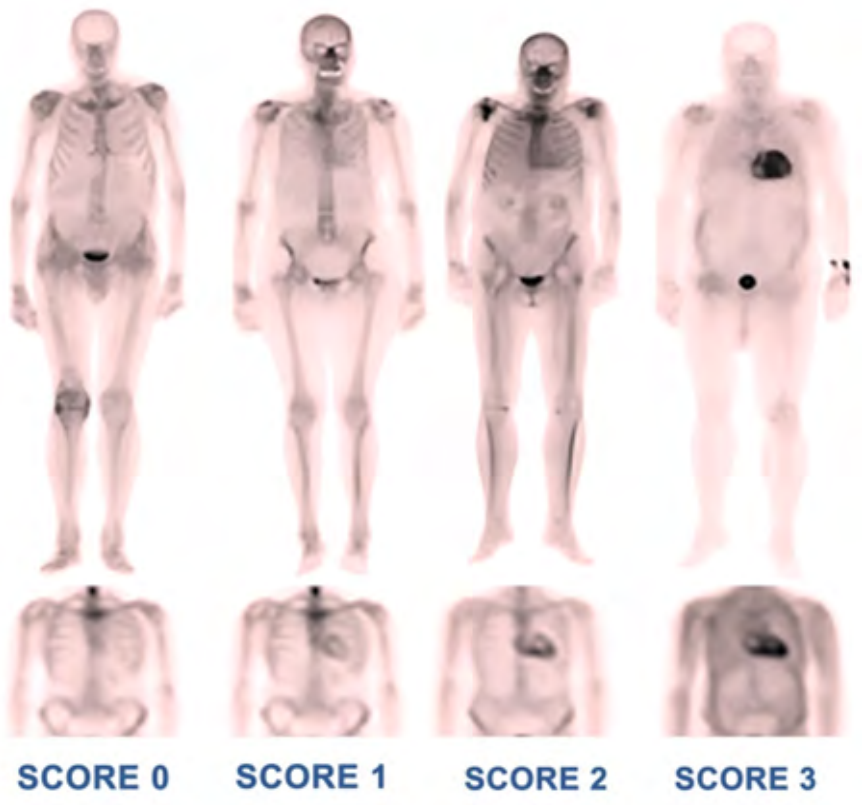

Figure 1. *Scintigraphy with diphosphonate (99mTc-HMDP) for the study of cardiac uptake during TTR amyloidosis. Semi-quantitative evaluation using the Perugini visual score* [3]. *Score* 0: *no cardiac uptake in the presence of normal bone uptake*; *Score* 1: *weak cardiac uptake, lower than bone uptake*; *Score* 2: *moderate cardiac uptake with attenuated bone uptake*; *Score* 3: *high cardiac uptake with reduced or absent bone uptake.*

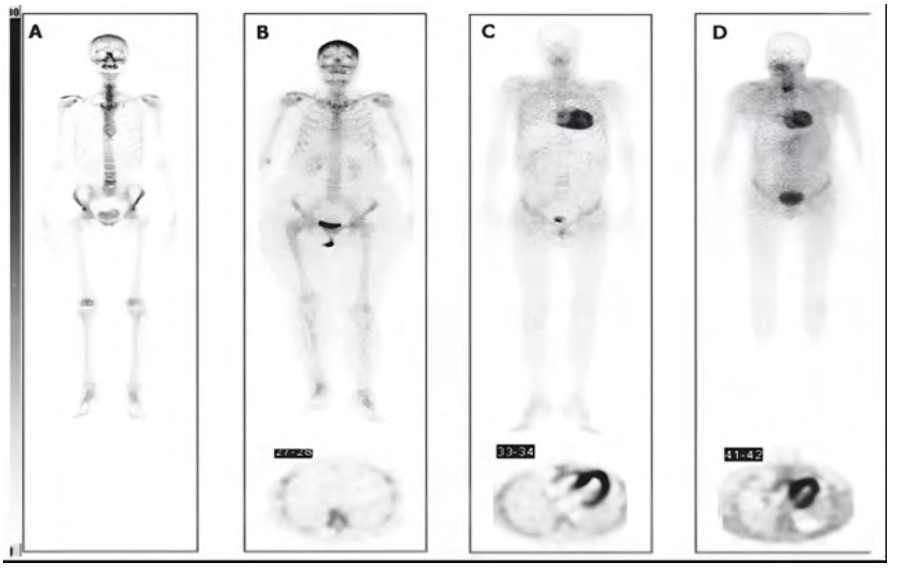

Figure 2. Cardiac uptake of 99mTc-DPD in patients with transthyretin (ATTR) or light chain (AL) cardiac amyloidosis. Total-body scans are shown above, and axial SPET scans of the myocardium are shown below. In Figure A, absence of visible cardiac uptake of the radiopharmaceutical. Figure B shows a patient with AL amyloidosis and echocardiographic documentation of cardiac involvement without detectable myocardial uptake of 99mTc-DPD; a weak uptake is visible only at the soft tissue level. Figures C and D depict two patients with full-blown transthyretin amyloidosis who show strong myocardial uptake of 99mTc-DPD (with reduced uptake at the bone level); in one of the patients (Figure D) splanchnic uptake is also appreciable) [3].

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in planar mode, and a second, mirror-image ROI is drawn on the contralateral hemithorax, considering the fundus and ribs. Total and absolute counts in each ROI are then measured. Subsequently, the H/CL ratio is calculated as the ratio between the counts detected in the cardiac ROI and the counts detected in the ROI of the contralateral hemithorax.
The HCL ratio was calculated on the acquisitions 3 hours after the radiopharmaceutical injection, and in this case, the limit value is equal to 1.3 to distinguish positive aTTR patients from negative ones [9].
The analysis of tomographic measurements (SPET) was performed using Bull's eye maps and calculating the segmental percentage uptake.

Results

During the study period, 44 patients were evaluated. In two patients the scintigraphic examination with Tc-HMDP was positive (Figures 3 and 4).
The same two patients underwent a further tomographic scan (Figures 5 and 6). On SPET scans the analysis was critical to selectively differentiate the visible cardiac uptake of the radioactive tracer from the uptake revealed in the planar images.

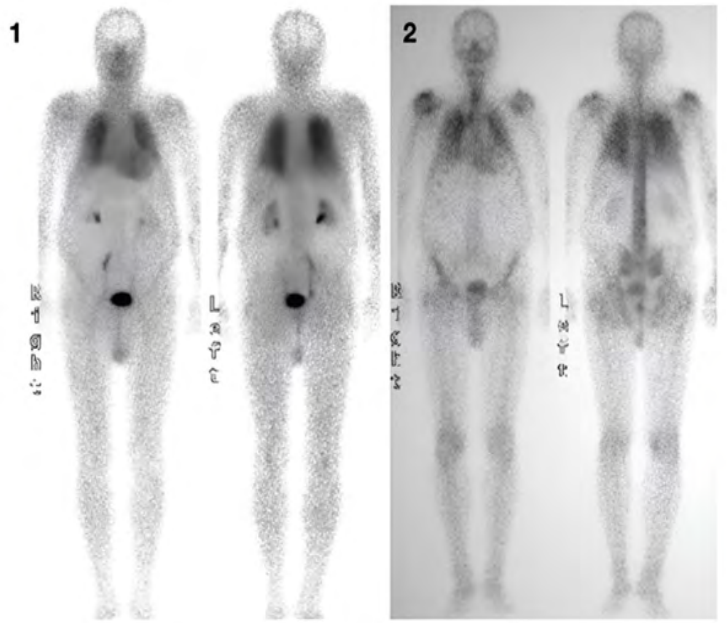

Figure 3. *Patient* 1: 1) *Early acquisition at* 5 *minutes*; 2) *Late acquisition at* 3 *hours.*

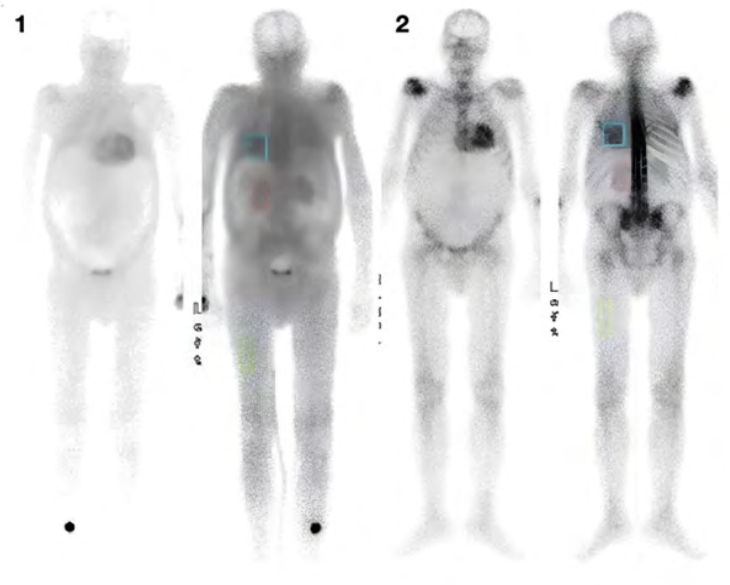

Figure 4. *Patient* 2: 1) *Early acquisition at* 5 *minutes*; 2) *Late acquisition at* 3 *hours.*

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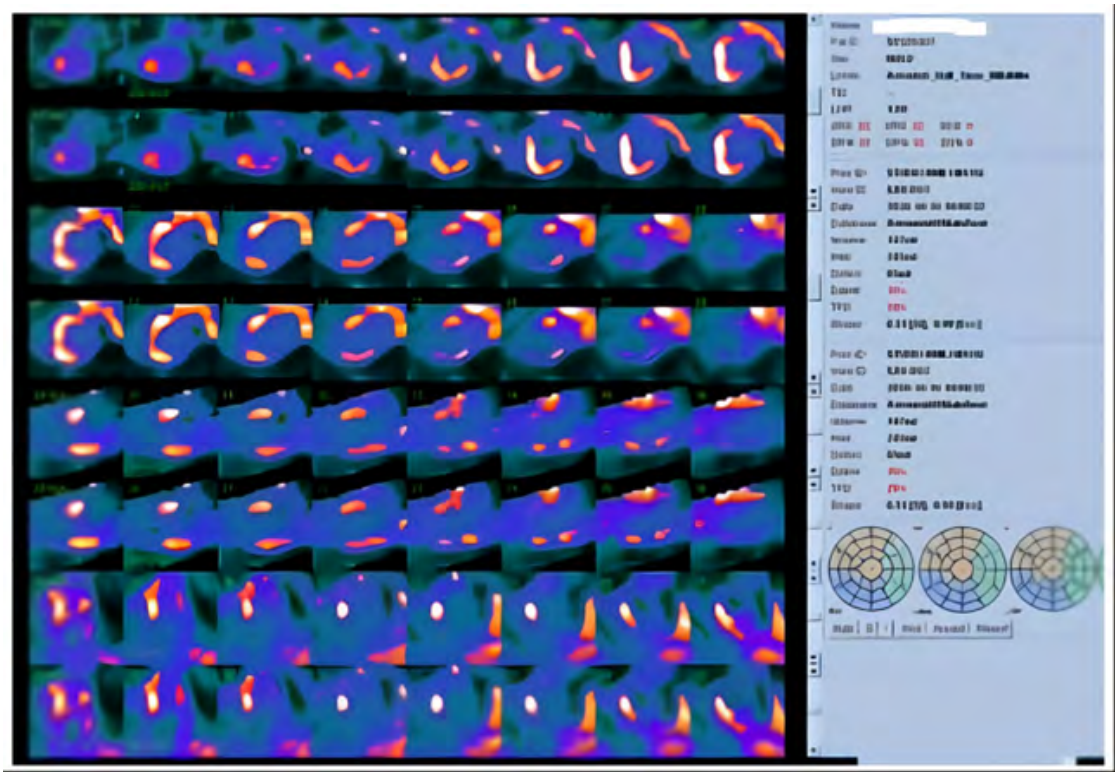

Figure 5. *SPET patient* 1

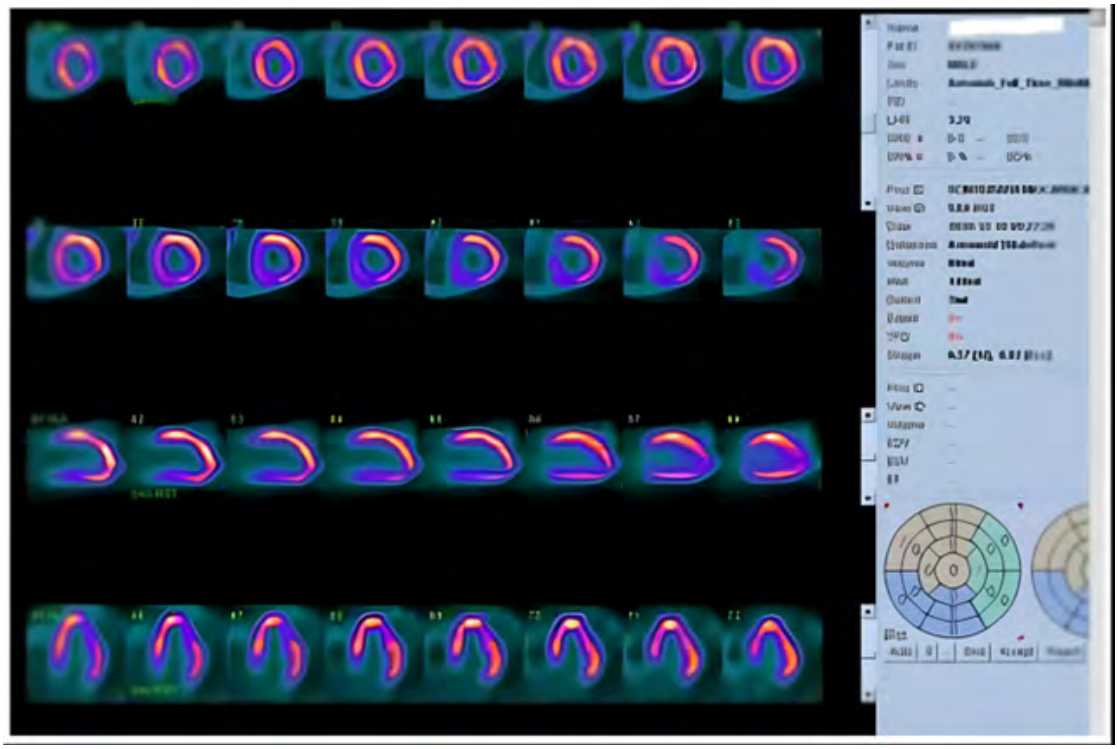

Figure 6. *SPET patient* 2

Discussion

In the population studied by us, only 2/44 (4%) patients tested positive for 99mTc-HMDP scintigraphy, a figure in agreement with what is reported in the literature [10]. Osteotropic radionuclide scintigraphy is the only modality that can allow accurate diagnosis of ATTR cardiomyopathy without the need for invasive endomyocardial biopsy in patients in whom monoclonal proteins are not present in serum and urine [11].

Conclusions

The differential diagnosis between the different types of cardiac amyloidosis is important for prognosis, therapy, and genetic investigation [12]. Since cardiac amyloidosis is a potentially treatable disease, early diagnosis is the key to improving pa-

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tient survival and quality of life. There is no convincing evidence that nuclear imaging has a fundamental role in the non-invasive diagnosis of cardiac TTR amyloidosis. Thanks to their high sensitivity and specificity, osteotropic radioactive compounds are considered sufficient to establish the diagnosis, avoiding the use of endomyocardial biopsy.
Planar images represent the most used method for the diagnosis of cardiac amyloidosis, the SPET method is not required by the guidelines for the identification of TTR cardiac amyloidosis [12]. However, in clinical practice, SPET is used in the case of positive planar images.
Therefore, validation protocols are needed for image acquisition and the analysis and identification of patients with cardiac amyloidosis. In this sense, it is hoped that with the progress and improvement of methods and the clinical validation of new radiopharmaceuticals, it will be possible to identify in a non-invasive way those patients affected by different types of cardiac amyloidosis.

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