Incidental Myocardial Uptake in Patients with Prostate Cancer: A Challenging Subject

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ABSTRACT

Background: Countless confounding factors have been described in the interpretation of incidental myocardial uptakes. Among them, prostate cancer is probably the most important. While some authors may defend the benign etiology of these uptakes, others propose a further study to rule out amyloid cardiomyopathy.

Objective: Our aim is to investigate the clinical relevance of incidental myocardial uptakes in bone scans requested to evaluate prostatic neoplasia, assessing the possibility that the described uptakes correspond to cardiac amyloidosis (CA).

Methods: Retrospective revision of 997 patients, 20 of which showed incidental myocardial uptake. We performed a cardiological study in these 20 patients in order to indicate whether the myocardial uptake is just attributable to prostate cancer or data suggesting CA.

Results: By analysing clinical, biochemical and imaging data, 11 out of 20 of the patients had two or more Red-Flags of transthyretin amyloid cardiomyopathy (ATTR-c). In the other four cases, there was one Red-Flag suggestive of ATTR-c.

Conclusions: When myocardial uptake is detected incidentally in patients with prostate cancer, it cannot be attributed to the neoplasm itself before ruling out cardiac amyloidosis. Therefore, a cardiological study must be carried out following current protocols for the diagnosis of transthyretin amyloid heart disease.

Keywords: Amyloidosis, Cardiomyopathies, Incidental uptake, Prostatic neoplasms.

1. Introduction

Parkey et al. described in 1974 the usefulness of ⁹⁹mTc-pyrophosphate scintigraphy (⁹⁹mTc-PYP) for the detection of acute myocardial infarction. Since then, an increasing number of nuclear medicine applications for the diagnosis of cardiovascular diseases have been developed [1].

One of its latest applications in recent years is the non-invasive diagnosis of cardiac amyloidosis described by Gilmore et al. in which the utility of scintigraphy with different bone tracers is currently considered unquestionable [2].
For the classification of myocardial uptake grade, we employ a semi-quantitative score proposed by Perugini et al. in 2005, already used in the 1970s by authors such as Soin et al. [3], [4].

Most cardiac amyloidosis (CA) is caused by primary amyloidosis or transthyretin amyloidosis (ATTR), both in its genetic form (ATTR-v) and in the wild type variant (ATTR-wt). Interestingly, myocardial uptake of bone tracers is mainly evident in patients with transthyretin amyloidosis.

CA has classically been considered a rare disease. However, the implementation of non-invasive algorithms based on scintigraphy has led to an increasing prevalence of CA in recent years. Moreover, the appearance of specific treatments, which have been shown to improve the prognosis of these patients, has raised interest in this disease. Altogether, this demonstrates that CA has been underdiagnosed until now.

However, in the last few years, a great number of confounding factors in the interpretation of incidental myocardial uptakes detected in bone scans performed for other reasons have been described. Among them, prostate cancer is probably the most cited factor of misinterpretation. Interestingly, although some authors defend a benign etiology of these uptakes, others, more recently, believe the opposite to be true and propose a further study of these uptakes in search of amyloid cardiomyopathy [5]–[7].

Given that both prostate cancer and ATTR-wt are relatively frequent pathologies in men over 60 years old, it is logical to think that both pathologies will coexist in a significant number of patients. Therefore, in clinical practice, it is foreseeable to encounter cardiac uptakes in patients with prostate cancer, and it is necessary to decide whether to attribute this uptake to the tumor itself or perform an additional study to rule out amyloid heart disease.

### 2. Methods

We have retrospectively reviewed the bone scans requested for prostate neoplasia extension study in our hospital from 2017 to 2020. Those which showed incidental myocardial uptake of any intensity were included in this study.

740 MBq (20 mCi) of 99mTc-diphosphonate (hidroximetilen-diphosphonate [HDP], hydroxymethylene diphosphonate [HMDP] or dicarboxypropane diphosphonate [DPD]) were administered intravenously. A hybrid double-head camera was used, either Infinia Hawkeye 3 (General Electric Healthcare, Chicago, Illinois, United States) or Millenium VG (General Electric Healthcare, Chicago, Illinois, United States), equipped with collimators of low energy and high resolution.

Scintigraphies were independently evaluated by two nuclear physicians, determining the Perugini Score. In case of discordant scores after evaluation, both nuclear physicians discussed the results until a consensus was reached.

Once the bone scans were evaluated, the clinical history and imaging tests (echocardiography and other bone scans) of each patient were reviewed exhaustively, both prior to the performance of the scan and in subsequent evolution. All clinical, echocardiographic or other data supporting the diagnosis of amyloid heart disease (Red-Flags) were collected [8]. Moreover, data related to prostate cancer was also collected: Gleason, prostate-specific antigen (PSA) at diagnosis and PSA at the time of the performance of bone scan (Table I). Additionally, the causes of death of those patients who died during follow-up were reviewed.

The study was purely observational with no direct intervention in the management of patients, other than the review of their medical records. The design of this study has been approved by the local ethics committee. An informed consent was obtained for each patient’s data processing.

All statistical analysis was performed using R Statistical Software (version 4.0.1; R Foundation for Statistical Computing, Vienna, Austria). Spearman rank correlation was used to measure the degree of association between the score of Perugini and PSA levels, as well as between the score of Perugini and the presence/absence of bone metastases in the bone scan.

### 3. Results

977 scintigraphies were requested for the extension study of prostate neoplasia, but only 20 patients met the inclusion criteria. 8 patients presented a Perugini Score grade 1, 4 patients a Perugini Score grade 2 and 8 patients a Perugini Score grade 3 (Fig. 1). Patients’ ages range between 66 and 92 years at the time of diagnosis of prostate neoplasm.

Only in four of the explorations performed (20%), bone metastases were detected, in addition to myocardial uptake (Fig. 2). A Spearman coefficient of 0.14 was obtained, showing a weak positive correlation between the degree of Perugini uptake and the presence of bone metastases.

Table II shows the urological and scintigraphic data, as well as the Red-Flags for transthyretin amyloid cardiomyopathy (ATTR-c) identified in each patient. In 11 out of 20 patients (55%) identified two or more Red-Flags prior to the bone scan that, united to myocardial uptake in scintigraphy, make highly probable the diagnosis of transthyretin amyloid cardiomyopathy following the algorithms proposed by Gillmore et al. or other authors. In four cases (20%), there was one Red-Flag suggestive data of ATTR-c.

Regarding urological data, twelve patients underwent prostate biopsy, identifying four cases with low-risk (<6 Gleason), four with intermediate-risk (7) and four with high-risk (≥8). Similarly, the PSA of the patients at diagnosis ranged from 0.4 to 606 mg/l. PSA levels at bone scan performance range from 0.3 to 87.8 mg/l. A Spearman coefficient of −0.53 was obtained, which indicated that there was no positive correlation between the degree of Perugini uptake and the levels of PSA at the moment of bone scan performance.

Eight patients (40%) had died at the time of this review; three from heart failure, one from pulmonary origin sepsis, one from stroke, one from respiratory failure and two attributed to prostate cancer.
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TABLE I: Cardiac and Extracardiac Manifestations of Transthyretin Amyloidosis [8]

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Heart failure (biventricular) with preserved LVEF, atrial fibrillation, conduction system disease, ventricular arrhythmia, aortic stenosis (low-flow low-gradient)</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal insufficiency (mainly due to heart failure)</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Orthostatic hypotension, gastroparesis, sexual dysfunction, sweating abnormalities</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Carpal tunnel syndrome (bilateral), spinal stenosis (predominantly lumbar), peripheral sensorimotor neuropathy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle weakness, arthropathy, fatigue, cachexia/weight loss, biceps tendon rupture</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Elevated liver enzymes, nausea, constipation, early satiety, abdominal bloating</td>
</tr>
<tr>
<td>Ocular</td>
<td>Vitreous opacities</td>
</tr>
</tbody>
</table>

Fig. 1. A 79-year-old man diagnosed with prostate cancer (biopsy not performed, prostate-specific antigen 10.3) in 2009. Bone scan scintigraphy in 2018 revealed bone metastasis and incidental cardiac amyloidosis (Perugini Score 3). Clinical history of heart failure, pacemaker, restrictive cardiomyopathy, septum > 24 mm and Dupuytren.

4. Discussion

Amyloid cardiomyopathy is emerging as an increasingly common diagnosis in heart failure patients, particularly in preserved ejection fraction patients. This is due to the aging of the population, but also to the improvement of diagnostic techniques based on non-invasive protocols and to the growing interest in this disease as specific treatments have become available. In this context, scientific societies have developed guidelines, recommendations or protocols for the management of the disease, and in all of them nuclear medicine techniques play a major role [8]–[11].

The role of bone scintigraphy in the diagnosis of CA has been studied for decades. Already in 1983, Lee et al. published a study comparing the use of 99mTc-pyrophosphate (99mTc-PYP) versus 99mTc-methylene diphosphonate (99mTc-MDP) in the diagnosis of a pathology that was then considered very rare [12]. Although different tracers and image acquisition protocols have been studied since then, it is now accepted that 99mTc-PYP and 99mTc-DPD scans are the most reliable for the diagnosis and the recommended radiotracers in the different diagnostic algorithms [8]–[11].

Despite the high specificity of these techniques, different confounding factors have been described in the literature. Prostate cancer is one of the most important, mainly because of its high prevalence in the elderly. However, it is necessary to emphasize the importance of a correct CA diagnosis in these patients, because of its current prognostic implication.

Different authors have presented cases of incidental myocardial uptake when performing a bone scan for the extension study of prostate cancer. In agreement with those, our results suggest that the revision of each case with
TABLE II: Urologic Data, Bone Scan Data and Red Flags

<table>
<thead>
<tr>
<th>Age</th>
<th>Date</th>
<th>Gleason</th>
<th>PSA</th>
<th>BoneScan1</th>
<th>PSA1</th>
<th>BoneScan2</th>
<th>PSA2</th>
<th>Bone metastases</th>
<th>Perugini Score</th>
<th>Red-Flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>2018 NB</td>
<td>37.3</td>
<td>HDP-2018</td>
<td>37.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>HF LVEFp, CTS, Pacemaker-AV block*</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>2009 7</td>
<td>50</td>
<td>HDP-2018</td>
<td>43.9</td>
<td>MDP-2009</td>
<td>50</td>
<td>–</td>
<td>3</td>
<td>HF, Pacemaker-AV block, CTS*</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>2019 NB</td>
<td>99.5</td>
<td>HDP-2019</td>
<td>1.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>HF LVEFp, Septum &gt; 12 mm*</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>2010 6</td>
<td>12.8</td>
<td>HDP-2017</td>
<td>6.04</td>
<td>HDP-2009</td>
<td>NA</td>
<td>Yes</td>
<td>2</td>
<td>HF LVEFp, CTS*</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>2017 8</td>
<td>13.1</td>
<td>HDP-2018</td>
<td>0.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>CTS</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>2018 NB</td>
<td>143</td>
<td>HMDP-2019</td>
<td>12.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>CTS</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
<td>2019 NB</td>
<td>22.3</td>
<td>HMDP-2019</td>
<td>22.3</td>
<td>DPD-2020</td>
<td>7.55</td>
<td>–</td>
<td>1</td>
<td>CTS, HF LVEFp, Septum 13 mm*</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>2006 NB</td>
<td>606</td>
<td>HMDP-2020</td>
<td>7.7</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>2012 6</td>
<td>29.3</td>
<td>HDP 2018</td>
<td>28.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>CTS</td>
</tr>
<tr>
<td>10</td>
<td>79</td>
<td>2009 NB</td>
<td>10.3</td>
<td>HDP-2018</td>
<td>87.8</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>2013 8</td>
<td>12</td>
<td>HDP-2017</td>
<td>6.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>HF LVEFp, Pacemaker-AV block*</td>
</tr>
<tr>
<td>12</td>
<td>79</td>
<td>2015 9</td>
<td>60.3</td>
<td>HDP-2018</td>
<td>13</td>
<td>HMDP-2019</td>
<td>25.1</td>
<td>–</td>
<td>1</td>
<td>AV block, aortic stenosis, HF LVEFp, Septum 12 mm*</td>
</tr>
<tr>
<td>13</td>
<td>92</td>
<td>2020 9</td>
<td>15</td>
<td>HMDP-2020</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>67</td>
<td>2015 5</td>
<td>10.2</td>
<td>HDP-2017</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>HF LVEFp, dysautonomia, Septum 12 mm*</td>
</tr>
<tr>
<td>15</td>
<td>87</td>
<td>2012 NB</td>
<td>99.7</td>
<td>HDP-2018</td>
<td>14.8</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>1</td>
<td>AF, CTS, HF*</td>
</tr>
<tr>
<td>16</td>
<td>85</td>
<td>2018 7</td>
<td>10.5</td>
<td>HDP-2018</td>
<td>10.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>83</td>
<td>2018 7</td>
<td>7</td>
<td>HMDP-2020</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>HF LVEFp</td>
</tr>
<tr>
<td>18</td>
<td>85</td>
<td>2017 5</td>
<td>0.4</td>
<td>HMDP-2020</td>
<td>2.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>AF</td>
</tr>
<tr>
<td>19</td>
<td>81</td>
<td>2016 7</td>
<td>29.8</td>
<td>HDP-2017</td>
<td>0.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>CTS, HF LVEFp, Septum 12 mm*</td>
</tr>
<tr>
<td>20</td>
<td>91</td>
<td>2017 NB</td>
<td>46.2</td>
<td>MDP-2017</td>
<td>26.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: Age, date, Gleason Score and PSA (mg/l) at the diagnosis of prostatic cancer. BoneScan1 and PSA1: bone scan and PSA levels (mg/l) at that date. BoneScan2 and PSA2: other (previous or following) bone scan and PSA levels (mg/l) at that date.
PSSA—prostate-specific antigen; HF—heart failure; HF LVEFp—heart failure with preserved left ventricular ejection fraction; CTS—carpal tunnel syndrome; Pacemaker-AV block—pacemaker for atrioventricular block; AF—atrial fibrillation; NA—not available; NB—non-biopsied; HDP-hidroximetilen-diphosphonate; HMDP—hydroxymethylene diphosphonate; MDP—methylene diphosphonate.

Sufficient data for the diagnosis of cardiac amyloidosis.

the current criteria for CA will likely lead to the diagnosis of ATTR-wt in a very high percentage of the cases.

In 1983 Boedecker et al. presented a case of an 86-year-old male with prostate cancer and myocardial uptake in the 99mTc-MDP scan and no uptake in the 99mTc-HDP scan. Subsequently, the patient presented a clinical picture of acute heart failure. Although this event is not sufficient to establish a certain diagnosis, it could be considered a highly suspicious case of CA [12].

Other authors, such as Jones, have described case series with 99mTc-HDP myocardial uptake and without 99mTc-MDP uptake during follow-ups of more than three years. These findings were interpreted as chronic and probably benign myocardial uptake, which did not need further study. However, there is no data on whether these patients presented any cardiac clinical manifestation or not. At present, it is well known that amyloid deposits can be detected on the bone scan even years before the clinical onset. Therefore, it would be very interesting to be able to review this series of cases and to determine whether the patients presented with heart failure after the bone scan was performed [5], [13].

More recently, Fathala et al. presented a case of an 86-year-old male with incidental uptake on 99mTc-MDP scan, afterwards confirmed with 99mTc-DPD, who was eventually diagnosed with ATTR by using non-invasive criteria and referred for specific treatment. Accordingly, this author recommends considering cardiologic studies in all patients where myocardial uptake of the tracer is demonstrated [7].

The present review serves to illustrate the evolution of the current interpretation of myocardial uptake in bone
scans and the importance of nuclear medicine in the non-invasive diagnosis of CA.

In our series, 11 of the 20 patients studied had Red-Flags that make suspect the diagnosis of ATTR-c following the current diagnostic algorithms. Four of the remaining patients have a history of bilateral carpal tunnel syndrome (CTS) or heart failure with left ventricular ejection fraction preserved. In our opinion, the coexistence of a bilateral CTS and the presence of myocardial uptake in bone scans suggest that those cases would require further study, considering the frequent association of this syndrome with ATTR-c [14].

Even considering the limited number of patients reviewed in this revision, we find some very interesting findings: first, among the eight deaths during the follow-up, only two were attributable to prostate cancer. Nevertheless, four of them (50%) died from cardiovascular causes that could be related to cardiac amyloidosis. In the literature, it has been described that the majority of patients with prostate cancer die due to other reasons, being consistent with our results [3, 6]. Performing an appropriate cardiologic study of patients with incidental myocardial uptakes would allow us to set up the specific treatment and improve the prognosis of these patients.

Another interesting fact in our study is that only four (20%) patients had bone metastases on the bone scan, which could suggest that the myocardial uptake, if attributed to the cancer itself as some authors suggest, would be non-neoplastic in nature [3, 6]. Although this opinion cannot be contrasted at present, it suggests that a study with positron emission tomography techniques on these patients could help to differentiate whether it is indeed a paraneoplastic uptake. In any case, we consider that the term ‘benign’ uptake should be avoided at least as long as the presence of a CA is not conclusively ruled out. Furthermore, it should be noted that our results did not show any trend between the PSA values or the presence of bone metastases and the degree of myocardial uptake on scintigraphy.

In summary, in 75% of the patients studied there was sufficient data to highly suspect the existence of transthyretin cardiac amyloidosis. In addition, in our study the cause of death of several patients was not the cancer itself, but cardiovascular causes, suggesting that CA could have played an important role. Nowadays, CA has specific treatment and management of patients with cardiac amyloidosis. Can J Cardiol. 2020;Mar;36(3):322–34. doi: 10.1016/j.cjca.2019.12.034. PMID: 32145682.


5. LIMITATIONS

This is a descriptive, retrospective study conducted at a single center and subject to selection and survival biases. Although we have a large sample of prostate patients, there is heterogeneity in the follow-up and in the cardiological evaluation of these patients, and it does not allow us to reach more detailed conclusions. Finally, the retrospective nature of this study does not allow interventions (such as performing an echocardiography) on those doubtful aspects in the patient’s clinical history that could allow us to precise the nature of myocardial diphosphonate uptake.

6. CONCLUSIONS

Most patients with incidental myocardial uptake have clinical, echocardiographic or analytic data suggesting Cardiac Amyloidosis. Therefore, we cannot consider these uptakes as benign before ruling out this disease. It should be mandatory to perform a cardiologic study on these patients since it implies specific management with new treatments improving the prognosis of these patients.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES


