Tips and Pitfalls in Nuclear Imaging for Cardiac Amyloidosis

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Radiologist and nuclear medicine physicians knew that amyloidosis is one of the causes of extraosseous myocardial bone scan agent uptake.

- But we considered it is RARE!
- As you know, it is not “rare”, rather “common”.

From Datz F.L ed. “Gamuts in Nuclear Medicine, 3rd edition”
Game was changed with Perugini article (2005)

Perugini et al. JACC 2005; 46: p1076-1084

- Classify uptake into 4 grade system.
  - In the original article used Tc-99m DPD. However, this scoring is called “Perugini score” and used in many articles.

  Grade 0: No myocardial uptake. Normal rib uptake
  Grade 1: myocardia uptake < rib uptake.
  Grade 2: myocardial uptake = rib uptake
  Grade 3: myocardial uptake > rib uptake. rib is faint or not visible.

From ASNC cardiac amyloidosis practice point (ver2.0) 2019
... and

Bokhari article (2013)

Bokhari S. et al.

- PYP uptake ratio between heart and contralateral lung showed very strong discriminator for ATTR CA.
Pit-fall: Sensitivity and Specificity.
Q: Is this the case of....

- 1) Definitely ATTR amyloidosis. No need for further test.
- 2) Possible ATTR amyloidosis, however need another test.
- 3) Definitely not amyloidosis. No need for further test.

H/CL = 1.9 (1hr),
    1.7 (3hr)

Pergini Score
probably 2 (1hr)
1 or 2 (3hr)
A: Case presentation.

- A case of Myeloma.
- We suspect the AL, but PYP finding was as you see.
- Myocardium biopsy proved AL amyloid.

2) is right answer.

- Even H/CL is quite positive for ATTR, blood test to exclude AL amyloidosis is mandatory.

A clue:
On the SPECT image, U shape of LV wall is not visible.
Pit fall: not all the positive case are ATTR.

<table>
<thead>
<tr>
<th>EMB Findings</th>
<th>Perugini 0</th>
<th>Perugini 1</th>
<th>Perugini 2</th>
<th>Perugini 3</th>
<th>n</th>
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<tr>
<td>No cardiac amyloid</td>
<td>31</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>35</td>
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<tr>
<td>Cardiac ATTR amyloid deposits</td>
<td>1</td>
<td>8</td>
<td>130</td>
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<td>Cardiac AL amyloid deposits</td>
<td>21</td>
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<td>Cardiac ApoAl amyloid deposits</td>
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<td>2</td>
<td>0</td>
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<tr>
<td>Cardiac amyloid deposits of unknown type</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>54</td>
<td>27</td>
<td>137</td>
<td>26</td>
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</table>

<table>
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<tr>
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<th>Grade 3</th>
<th>n</th>
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<tr>
<td>No cardiac amyloid</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>9</td>
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<tr>
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<td>1</td>
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<tr>
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<td>3</td>
<td>4</td>
<td>7</td>
<td>14</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>68</td>
<td>109</td>
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</tbody>
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<td>0</td>
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<td>3</td>
</tr>
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<td>3</td>
<td>4</td>
<td>7</td>
<td>14</td>
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<tr>
<td>Cardiac AL amyloid deposits</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

Gillmore J.D. et al. Circulation 2016; 133: 2404-2412

- Some AL amyloidosis shows positive findings.


Even PYP positive case, blood test to exclude AL CM have to be performed.
Pit fall: not all the ATTR CM is positive.

- Only 2 out of 19 cases of Phe64Leu mutation ATTR cardiac amyloidosis showed positive finding.

Musmeci MB et al. JACC imaging 2020 13: 1314-21
Not all the positive cases are CA.

- Bone scan for detect bone lesion in Myeloma patients.
- History of parathyroid operation.
- Clear myocardial uptake, but Myeloma >> AL?
- High density myocardium on CT
- Abnormal lung uptake.

Specimen from Lung proved metastatic calcification.

There is reason of myocardial bone scan uptake other than CA.

_Datz F.L ed. “Gamuts in Nuclear Medicine, 3rd_

**BONE IMAGING**

**COMMON:**
- Breast uptake — normal
- Cartilage calcification (e.g., costal, thyroid, cricoid)
- Cellulitis
- Chronic renal failure
- Electrical burn
- Infarct — myocardial, cerebral, splenic

**UNCOMMON:**
- Abscess
- Adriamycin cardiotoxicity
- Aneurysm
- Any cause of metastatic calcification
  - Breast — benign disease (e.g., fibrocystic disease)
  - Breast — malignant
  - Calcific tendinitis
Tip:
Use SPECT, and
SPECT/CT.
Q: Which one is ATTR-CA?

1) A is ATTR-CA
2) B is ATTR-CA
3) Both are ATTR-CA
4) Both are NOT.
Do not rely on numbers too much.

80yo female. A case of cancer with mild heart failure EF=48%. Diffuse/mild hypertrophy of LV

H/CL=317.60/228.75=1.39

ATTR amyloidosis was **proved** from operative (non cancer area) specimen

70yo female. A case of HT, Dyslipidemia and mild heart failure EF=52%. Diffuse/mild hypertrophy of LV

H/CL = 222.79/161.64.75=1.38

**Amyloid was not found** from myocardial biopsy

Ans: 1) A was ATTR-CA (B was not)
SPECT is essential for diagnosis. I prefer coronal SPECT.

- With coronal view, LV wall is easy to differentiate from blood pool.
SPECT/CT, Fusion is very helpful

- Sometimes, you cannot be confident only with SPECT.
- In such case, SPECT/CT fusion might be helpful.
Tips: When to image??
1hr or 3hr injection?

- In most cases, H/CL decline with time.
- However, blood pool activity also decline with time, thus contrast between heart to blood seems to be better on 3hr.
**Pitfall: 3hr H/CL is less proven.**

- Study from Columbia univ. Boston univ. & Mayo clinic
  - 3hr image tend to be low sensitivity than 1hr.
    - For H/CL, specificity is also less in 3hr.
    - For visual score, false positive cases are less in 3hr.

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**In this article, for 3 hr image, threshold was set to 1.3 rather than 1.5**

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**Castano A. et al. JAMA Cardiol. 2016 Nov 1;1(8):880-889**
Tips: when the myocardial uptake becomes max.

- For DPD, bone uptake increased with time, but myocardial uptake is highest on 1hr and then declined.

Hutt DF et al. Eur Heart J Cardiovasc Imaging 15; 1289-1298

- H/CL is always higher in 1hr than 3hr.

For H/CL measurement, 1hr should be better.

However, for the visual assessment, contrast is also very important, and it becomes better at 3hr.
**ATTR amyloidosis diagnosis criteria.**

**Table 2. Semi-quantitative Visual Grading of Myocardial $^{99m}$Tc-PYP Uptake by Comparison to Bone(rib) Uptake**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Myocardial $^{99m}$Tc-PYP Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>no uptake and normal bone uptake</td>
</tr>
<tr>
<td>Grade 1</td>
<td>uptake less than rib uptake</td>
</tr>
<tr>
<td>Grade 2</td>
<td>uptake equal to rib uptake</td>
</tr>
<tr>
<td>Grade 3</td>
<td>uptake greater than rib uptake with mild/absent rib uptake</td>
</tr>
</tbody>
</table>

- Visually: Grade 2-3 (equal or higher than ribs) is positive
  - Using 3 hr after injection image should be recommended.
- Quantitatively: H/CL ratio over 1.5 is positive.
  - Using 1 hr after injection has many evidences.

*ASNC cardiac amyloidosis practice point (ver2.0) 2019*
Pit fall:
Are all the bone seekers the same?
Are all the Bone tracers same?

• Not all the bone seekers are same.
• There is different character according to the tracers.
• MDP may be not useful for CA.

DPD

HMDP

with solid-state camera.
CA positive case showed high muscle activity.

Bellevre D al.
J Nucl Cardiol 2020 epub

PYP

SPECT

No correlation between myocardial and muscle uptake.

Bellevre D al.
J Nucl Cardiol 2020 epub

MDP do not show good accumulation to ATTR CA.

Cases from Yang JC, J Nucl Cardiol 25; p1879-1984
11 cases who showed high uptake on DPD did not show uptake on MDP
Perugini et al. JACC 2005; 46: p1076-1084

Hutt DF et al.
Eur Heart J Cardiovasc Imaging 15; 1289-1298

DPD sometimes show high soft tissue uptake with diminished bone uptake
What is the Next step?
They found H/CL=1.6 as the threshold to separate patient prognosis. But….

Castano A. et al. *JAMA Cardiol.* 2016;1:880-889


range of H/CL 1.5~1.6

only few cases distributed in this range. This threshold(=1.6) may not so useful in daily practice.

Nagasaki University data.
Quantification using SPECT.

Quantitative $^{99m}$Tc-DPD SPECT/CT in patients with suspected ATTR cardiac amyloidosis: Feasibility and correlation with visual scores

Caobelli F. et al J Nucl Cardiol 2020; 27: 1456-1463

Analysis with SPECT/CT
Pergini score and SUV correlates well.

Quantitation of myocardial $^{99m}$Tc-HMDP uptake with new SPECT/CT cadmium zinc telluride (CZT) camera in patients with transthyretin-related cardiac amyloidosis: Ready for clinical use?

Bellevre D. et al J Nucl Cardiol 2020 epub

Analysis using CZT camera.
ATTR patient showed high SUV in heart, but bone SUV is similar to normal subject.

• Quantitative analysis is a frontier.
Take home message.

• Tc-99m PYP is very useful tool for diagnose ATTR-CA.
  – However, there could be false negative, false positive case.
  – Even positive finding, blood test to exclude AL is necessary.

• H/CL ratio is useful tool, but do not rely on it too much.
  – Sometimes, visual interpretation is more important than measuring H/CL

• Planar is not enough.
  – In some cases, SPECT is required to differentiate blood pool activity and wall uptake.
  – SPECT/CT is very helpful