Diagnostic Approach to Cardiac Amyloidosis – The Great Masquerader

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Disclosure Information

Consultant/advisory board:
- Pfizer
- Alnylam

• Speakers bureau:
- Pfizer
- Astellas
- Alnylam
Main Types of Cardiac Amyloidosis

- Immunoglobulin light chain amyloidosis (AL)\(^1\)\(^-\)\(^3\)
- Transthyretin amyloidosis (ATTR)\(^1\)\(^-\)\(^4\)

Account for more than 95% of all cardiac amyloidosis diagnoses\(^1\)

Others including\(^1\)\(^-\)\(^3\)
- Serum amyloid A
- Apolipoprotein A1 (AApoA1)
- Immunoglobulin heavy chain
- Fibrinogen alpha chain
- Gelsolin

ATTR-CM Has 2 Subtypes: Wild-Type and Hereditary\textsuperscript{1,2}

- **Wild-type**
  - ATTR cardiomyopathy\textsuperscript{1,3,4}
  - Transthyretin amyloid cardiomyopathy

- **Hereditary\textsuperscript{†}**
  - ATTR cardiomyopathy\textsuperscript{2,4}
    - i.e., V122I
    - T60A
  - Mixed ATTR cardiomyopathy/polyneuropathy\textsuperscript{2}
    - i.e., V30M (late onset)
  - ATTR polyneuropathy\textsuperscript{2,4}
    - i.e., V30M (early onset)
  - Transthyretin amyloid polyneuropathy

\textsuperscript{*}The clinical presentation in ATTR differs according to the underlying mutation.

\textsuperscript{†}The mutations shown above are the most common mutations in ATTR.\textsuperscript{5}

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Raising Clinical Suspicion

- Clinical Presentation
- Biomarkers
- Electrocardiogram (ECG)
- Transthoracic Echocardiography (TTE)
- Cardiac MRI
Clinical Presentation
Signs and Symptoms That May Present in Patients With ATTR-CM

**Cardiovascular**
- Heart failure
- Intolerance to standard HF therapies
- Low voltage relative to LV thickness
- Echocardiography showing increased LV wall thickness
- Cardiac arrhythmia
- Aortic stenosis

**Nervous System**
- Autonomic
  - Autonomic neuropathy
  - Gastrointestinal complaints
  - Unexplained weight loss
  - Orthostatic hypotension
  - Sexual impotence
- Peripheral
  - Peripheral sensory motor dysfunction
  - Peripheral neuropathy

**Ocular**
- Vitreous opacity
- Glaucoma

**Musculoskeletal/Orthopedic**
- Biceps tendon rupture
- Lumbar spinal stenosis
- Carpal tunnel syndrome
- Hip/knee arthroplasty

**Renal**
- Renal impairment
- Cardiorenal syndrome

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Prevalence of wtATTR-CA among patients with severe AS undergoing TAVR

16% undergoing TAVR
6% undergoing SAVR

Cardiac Amyloid Screening Pre TAVR

Age >65y  Severe AS  IVSd ≥14 mm  BP <140/90 mmHg

+ ≥1 major criteria

Carpal tunnel syndrome  Ruptured biceps tendon  Spinal stenosis  NT-proBNP >1000 pg/ml  Troponin I >99th %ile URL

or ≥2 minor criteria

Diastolic dysfunction ≥2 grade or e’ < 10 cm/s  Atrial fibrillation  AV block or implanted pacemaker

Amyloidosis screening

99m Tc-DPD SPECT/CT

Immunofixation + free light chain assay
Biomarkers
Laboratory/Biomarker Clues

**Cardiac biomarkers**
- Low-grade persistent troponin elevation
- NT-proBNP level elevation
- Prealbumin & Albumin (mBMI)
- eGFR

**Laboratory tests**
- Abnormal free light-chain ratio
- Abnormal clone by serum + urine immunofixation (not SPEP)

Electrocardiogram
Discordance between LV wall thickness and QRS voltage

Pseudoinfarct patterns in up to 70% of cases

Conduction disease

Atrioventricular block in up to 22% of cases

Atrial fibrillation

ECG showing low voltage throughout, pseudoinfarcts in the anterior and inferior leads, and poor R-wave progression.

Figure used with permission from Edwards et al.4

Prevalence of low QRS voltage varies: ATTR-CM (20%) and AL amyloidosis (60%)

Echocardiogram
Echocardiographic Images in Cardiac Amyloidosis

Apical 4-Chamber View

Subcostal View

Speckled Pattern

Doppler flow

Longitudinal Strain
Increased Wall Thickness Score for the diagnosis of TTR-CM
The septal reflectivity ratio

**ATTR-CA Septal Microcalcifications**

- Microcalcifications
- Septal Reflectivity Ratio
- Anterior Septal Wall: Mean Peak Intensity
- Posterior Lateral Wall: Mean Peak Intensity

**ATTR-CA**

- SRR = 1.5
- SRR = 1.0
- SRR = 1.0
- SRR = 1.0

**Optimal Image**

- Anterior and Posterior Walls Well Visualized
- Excellent Endocardial Border Definition
- Uniform Gain Throughout All Image Decks
- >75% of Walls Visualized

**Suboptimal Image**

- Anterior and Posterior Walls Poorly Visualized
- Poor Endocardial Border Definition
- Over-exposed in the Nearfield
- Rib Shadow with >75% of Walls Visualized

**Septal Reflectivity Ratio**

- $1.62 (108.5/66.8)$

Mean pixel intensity of entire anterior septal wall = 108.5

Mean pixel intensity of entire posterior lateral wall = 66.8
Cardiac MRI
Magnetic Resonance Imaging in Cardiac Amyloidosis

Maceria A. Circulation 2005
Extracellular volume fraction in amyloidosis
Clinical Applications of $^{99m}$Tc-PYP Imaging in Suspected Cardiac Amyloidosis
Nuclear Imaging Modalities

Bone Seeking Tracers

• $^{99m}$Tc-pyrophosphate (PYP)
• $^{99m}$Tc-hydroxymethylene diphosphonate (HMDP)
• $^{99m}$Tc-3,3-diphosphono-1,2-propanodcarboxylic acid (DPD)
• PET tracers: $^{18}$F-NaF

Sympathetic Innervation

• $^{123}$I-$m$IBG

Amyloid Deposits

• $^{99m}$Tc-aprotinin and $^{123}$I-SAP
• PET tracers: $^{18}$F-florbetapir, $^{18}$F-florbetaben, F-18 flutemetamol and $^{11}$C-PIB (Pittsburgh Compound B)

Other Tracers

• $^{68}$Ga, $^{111}$In-antimyosin, $^{11}$C-choline

$^{99m}$Tc-DPD Scintigraphy in Transthyretin-Related Familial Amyloidotic Polyneuropathy (FAP)

- 8 pts with ATTR-FAP (4 M, mean 54 +/- 8 years) and 10 control oncological out-pts
- WB tracer retention at 3 hour and heart-to-whole body uptake ratio
- The 3 FAP patients with highest uptake had CM & arrhythmia

$^{99m}$Tc-DPD scintigraphy is proposed as a simple and valuable diagnostic aid to evaluate the severity of the disease and the risk of concomitant heart problems

Diagnostic Value of $^{99m}$Tc-DPD

Resurrecting $^{99m}$Tc-PYP

An old test gains new purpose

PYP is readily available in US and approved for the following indications:

- Blood pool imaging
  - GI bleed
  - Gated blood pool studies
- Cardiac imaging
  - Detection of acute MI
- Bone imaging
Comparison of $^{99m}$Tc-DPD and $^{99m}$Tc-PYP Scan Timelines

$^{99m}$Tc-DPD 25-30 mCi
- Study Time: 220 min
- Imaging Time: 64 min

$^{99m}$Tc-PYP 10 mCi
- Study Time: 60 to 80 min
- Imaging Time: 5 to 20 min


**Quantitative Score**

- Circular ROI over heart, copied, mirrored CL chest
- Mean counts/pixel corrected for background counts
- Heart-to-contralateral ratio (H/CL)

Both Planar and SPECT Imaging should be reviewed and Interpreted using visual and quantitative approaches.

SPECT imaging is necessary for studies that show planar cardiac uptake because it can help differentiate myocardial uptake from blood pool.

Positive SPECT with no blood pool.

Top row is 1 hour incubation, SPECT revealing blood pool. Bottom row is 3- hour delayed imaging revealing clearance of blood pool.

SPECT/CT fusion images reveal myocardial uptake and no blood pool.
Expert Consensus Recommendations for the Suspicion and Diagnosis of ATTR-CM

Maurer, Bokhari et al; Circulation Heart Failure, 2019.
GENETIC TESTING AND COUNSELING ARE RECOMMENDED TO DISTINGUISH BETWEEN HEREDITARY AND WILD-TYPE ATTR-CM

- wtATTR-CM and hATTR cannot be distinguished by clinical profile alone
- Genetic counseling and TTR gene sequencing are both recommended in all forms of confirmed ATTR-CM
- In healthy relatives of patients with hATTR, pre-and post-genetic test counseling may be offered
Biopsy: Where should you biopsy?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>ATTR-CM</th>
<th>AL-CM</th>
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</thead>
<tbody>
<tr>
<td>Abdominal fat pad</td>
<td>14-16%</td>
<td>73-84%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>30-38%</td>
<td>60%</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>100%</td>
<td>100%</td>
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</tbody>
</table>

CARDIAC TISSUE BIOPSY IS AN INVASIVE TECHNIQUE USED TO HELP DIAGNOSE ATTR-CM

- Documents the extent of amyloid infiltration
- Provides definitive etiologic classification of the amyloidogenic protein
- Achieves a definitive classification to help rule out AL amyloidosis
TISSUE TYPING AFTER BIOPSY CAN PROVIDE ETIOLOGIC CLASSIFICATION OF THE AMYLOIDOGENIC PROTEIN

**IMMUNOHISTOCHEMISTRY**

![Immunohistochemistry images](Image)

- A. TTR
- B. AA
- C. Kaposi
- D. Lambda


**MASS SPECTROMETRY**

![Mass spectrometry graph](Image)

This research was originally published In Molecular and Cellular Proteomics. Lavarello F, et al. Amyloidogenic and Associated Proteins in Systemic Amyloidosis Proteome of Adipose Tissue, Mol Cell Proteomics, 2008;7:1570-1583.

A negative biopsy may not necessarily rule out cardiac amyloidosis

The sensitivity of the biopsy depends on tissue location, pathologist tissue sample technique, tissue staining technique, and the varied distribution of amyloid deposits in the organ biopsied.
A Simple Score to Predict ATTR-CM

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60-69</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>or 70-79</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>or ≥ 80</td>
<td>4</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
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<tr>
<td>Ejection Fraction</td>
<td>&lt; 60%</td>
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<tr>
<td>Posterior Wall Thickness</td>
<td>≥ 12 mm</td>
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<tr>
<td>Relative Wall Thickness</td>
<td>&gt; 0.57</td>
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<tr>
<td>Hypertension Hx</td>
<td>Present</td>
<td>-1</td>
</tr>
</tbody>
</table>

Davies et al, JACC 2021
Thank you for listening!