Cardiac Amyloidosis: Unmasking the Great Masquerader
When to Suspect, How to Diagnose

2023 MSK Cardio-Oncology Symposium

Jennifer E. Liu, MD
Chief, Cardiology Service
Professor of Clinical Medicine
Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
Patient: JT

- 54F, PMH of controlled HTN, presenting with cough, DOE and decreased effort tolerance over 1 year.

- Extensive work-up:
  - Allergy, GI and ENT consultation. No clear etiology identified.
  - Exercise stress test showing reduced exercise capacity; unremarkable otherwise
  - Echo “mild LVH” c/w hypertensive heart disease

- Symptoms worsen → DOE after one block

- Syncope after getting out of the car. Admitted to the hospital.
  Cardiac work-up:
  - ECG: sinus rhythm with 1st degree AV block and low voltage
  - Echo: concentric LV hypertrophy (IVS 1.6 cm). LVEF 59%; GLS -13%. Normal wall motion.
  - Cardiac MRI: diffuse delayed enhancement suggestive of infiltrative cardiomyopathy → suspicion of cardiac amyloidosis
Patient JT

Labs:
- Abnormal kappa/lambda ratio 0.14; positive serum/urine IFE + lambda light chain
- NT-proBNP 1,200 ng/ml; cTnl 0.3 ng/ml

Tissue biopsy:
- Bone marrow biopsy → amyloid seen in a vessel wall
- Fat Pad biopsy → negative for amyloid
- Endomyocardial biopsy → positive for amyloid deposition; AL subtype confirmed on mass spectroscopy

Lambda light chain amyloidosis with cardiac involvement
Mayo Stage IIIa Disease

Early 2018
- symptoms onset/1st echo

Late 2019
- diagnosis
Objectives

• What is cardiac amyloidosis?
• How does one diagnose it?
• What are the clues to the diagnosis, when to suspect?
• Why is it important to make the diagnosis promptly?
Cardiac Amyloidosis

- Restrictive CM characterized by myocardial infiltration/deposition of amyloid fibrils (AL vs. ATTR)

- H & E stain: amyloid fibrils seen as light pink hyaline extracellular deposits displacing the cardiac myocytes, causing thick and stiff walls. Thick walls $\neq$ LVH.

- Congo red stain: yield pathognomonic apple-green birefringence under polarized light microscopy; gold standard for identifying amyloid deposits.

- After amyloid fibrils have been confirmed, mass spectroscopy is essential for typing amyloid: AL vs. TTR.
AL Amyloidosis: Multi-organ system involvement

- Renal: proteinuria/nephrotic syndrome, renal failure
- Neurologic: peripheral neuropathy, autonomic dysfunction
- GI: dysphagia, malabsorption, GI bleeding, liver dysfunction
- Soft tissue/ENT: macroglossia, periorbital purpura, carpal tunnel syndrome, nail changes.

Consider the diagnosis in patients presenting with HF associated with other systemic illnesses
Clinical Presentation:
Common Signs/Symptoms

- Fatigue
- Dizziness/syncope
- Weight loss
- Paresthesias
- Edema
- Dyspnea
- Carpal tunnel syndrome
- Hoarseness
- Mucocutaneous lesions
- Hepatomegaly
- Cardiac dysrhythmias
- Alternating constipation and diarrhea
- Orthostasis
- Bleeding tendency
- Frothy urine

Diagnosis elusive, often delayed due to multisystemic presentations, often mistaken for more common diagnoses

4 = average number of MDs seen before diagnosis

> 1/3 of patients are diagnosed >1 year after the onset of symptoms

In a survey of 443 patients
220 cardiologists missed the diagnosis

http://www.amyloidosis.org/facts
TTR Amyloidosis: Noncardiac Clues

- Neurologic: sensorimotor polyneuropathy; autonomic dysfunction
- Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, hip and knee arthroplasty
- Black race
- Family history of polyneuropathy

Prevalent in certain clinical contexts

- 13-17% patients with HFpEF
- 16% patients with severe AS undergoing TAVR

Gonzalez-Lopez et al, Eur Heart J 2015
Costano et al, Eur Heart J 2017
Cardiac Amyloidosis: Clinical Manifestations

• Heart failure
  – Restrictive cardiomyopathy with predominant right heart failure symptoms; diastolic dysfunction preceding systolic dysfunction

• Angina
  – Amyloid infiltration of intramyocardial and microvessels

• Syncope
  – Exertional syncope due to low and fixed cardiac output
  – Postural hypotension due to autonomic neuropathy
  – Tachyarrhythmias
    • Atrial fibrillation/cardioembolic stroke
    • Ventricular arrhythmia
  – Bradyarrhythmia/AV block

• Sudden death
  – Asystole, PEA, ventricular arrhythmia
Echo: First-line Screening Tool
Typical Echo Features

- Increased wall thicknesses with decreased LV end-diastolic volume
- Granular/sparkling appearance of the LV myocardium
- LVEF preserved; reduced in advanced stages
- Valve thickening; pericardial effusion
- Increased right and left atrial volumes; reduced atrial function due to amyloid involving the atrial walls; atrial septal thickening
- RV wall thickening and reduced function
- Diastolic dysfunction; vary from abnormal relaxation to a restrictive filling pattern with elevated filling pressures.

E/A = 2.6; DT 140 msec; E/e’ = 21.6
Early Stage of Phenotypic Expression: Mild/Moderate LV Wall Thickening

- Early stage of phenotypic expression → mild/moderate wall thickening
- Diagnostic challenge to differentiate the underlying pathology.
- Conventional echo parameters have limited diagnostic accuracy

IVS = 1.6 cm  \( \rightarrow \) Hypertrophic CM

IVS = 1.7 cm  \( \rightarrow \) Cardiac Amyloidosis

Basal IVS = 2.2 cm  \( \rightarrow \) Hypertensive Heart Disease
Conventional Echo Parameters to Differentiate Etiologic Diagnosis of Mild to Moderate “Hypertrophy”

**Table 1** Echocardiographic parameters presented at each review

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 24)</th>
<th>CA (n = 8)</th>
<th>HCM (n = 8)</th>
<th>HHD (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>61 ± 5</td>
<td>58 ± 6</td>
<td>62 ± 5</td>
<td>61 ± 4</td>
<td>.25</td>
</tr>
<tr>
<td>MWT (mm)</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
<td>.28</td>
</tr>
<tr>
<td>LVMi (g/m²)*</td>
<td>117 ± 17</td>
<td>113 ± 24</td>
<td>119 ± 16</td>
<td>117 ± 10</td>
<td>.79</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>33 ± 9</td>
<td>34 ± 7</td>
<td>35 ± 11</td>
<td>30 ± 8</td>
<td>.44</td>
</tr>
<tr>
<td>E (cm/sec)</td>
<td>83 ± 32</td>
<td>87 ± 22</td>
<td>85 ± 46</td>
<td>76 ± 26</td>
<td>.77</td>
</tr>
<tr>
<td>E/A ratio (cm/sec)</td>
<td>1.2 ± 0.7</td>
<td>1.6 ± 0.9</td>
<td>1.1 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>.11</td>
</tr>
<tr>
<td>DT (m/sec)</td>
<td>226 ± 51</td>
<td>211 ± 63</td>
<td>213 ± 44</td>
<td>253 ± 38</td>
<td>.19</td>
</tr>
<tr>
<td>e' (m/sec)</td>
<td>6 ± 2</td>
<td>6 ± 2</td>
<td>7 ± 2</td>
<td>6 ± 3</td>
<td>.67</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>15 ± 6</td>
<td>16 ± 7</td>
<td>16 ± 11</td>
<td>13 ± 8</td>
<td>.52</td>
</tr>
</tbody>
</table>

No difference in echo indices between the groups

JASE 2014;27:888-95
• CA manifest significantly lower GLS than HCM and LVH; but some overlap with HCM
Heart 2012;98:1442-1448

Apical Sparing or “Cherry On Top” Pattern

- More pronounced depression of the base and midventricular strain relative to apical strain
- Confer high degree of accuracy differentiating CA from other etiologies
  - 93% sensitive and 82% specific in identifying patients with CA
Impact of BE’s plot on improving the etiologic diagnosis of mild/mod LVH in 20 Level 3 echo readers
Addition of bull’s eye map improved accuracy with 22% of cases reclassified correctly
Largest improvement seen in cardiac amyloidosis.

Review the strain bull’s eye plot on echo studies with mild/mod LVH!
Mechanism of Apical Sparing

Ternacle et al (JACC Img 2016):

- 79 patients (AL, WT-TTR, M-TTR); compared echo GLS with LGE on CMR, and pathological assessment from 3 patients with cardiac transplant.

- Amyloid deposits more abundant in the basal and midcavity sections than the apex

- Amyloid burden correlated with impaired LS and LGE

- LGE correlated with regional LS reduction

- LS and LGE showed a basal to apical gradient in 3 types of CA (AL, M-TTR, WT-TTR); apical sparing pattern absent in 50% of patients

- Basal to apical gradient of amyloid deposition:
  - Higher wall stress at the base due to larger radius
  - Basal segments more prone to apoptosis and remodeling due to turbulence in the outflow tract
  - Myocyte and matrix orientation more diverse at the apex, which may influence amyloid deposition
Cardiac Structural and Functional Abnormalities Across A Spectrum of Amyloid Deposition

- 323 subjects (116 AL, 183 ATTR) → CMR and echocardiography.
  - Amyloid burden defined by CMR measured extracellular volume
  - Gradual worsening functional and structural metrics with increasing amyloid infiltration.
  - GLS more likely to become abnormal at low levels of cardiac infiltration, hence, an early marker of disease
  - LVEF preserved up until high disease burden

DS Knight, M Fontana, JACC Img 2019;12:823-33
Optimal Echo Parameter to Distinguish CA Among Thickened Hearts

• EF to GLS ratio (EFSR)
  – Best diagnostic accuracy
  – Outperforming GLS and RELAPS
  – Cut off 4.1 (when LVEF > 4X GLS) → dx CA likely (AUC 0.96; sensitivity (90%), specificity (92%))

• Increased EFSR explained by reduced longitudinal deformation in EF, in part compensated by preserved LV twist and smaller reduction of circumferential strain

• EFSR also performed well in detection of TTR amyloidosis

Pagorelias et al, Circ CV Imaging 2017
Clues to Diagnosis: Low Voltage on ECG

127 AL amyloid patents with biopsy proven cardiac involvement (Murgah B, AJC 2005):

- Low voltage - 45%
- Pseudoinfarct – 47%
- Atrial fibrillation – 10%
- LVH - 7%

➢ Low voltage on ECG less common in the TTR subtypes.
➢ Low sensitivity and specificity; helpful when interpreted in the context of clinical presentation and other imaging studies
Clues to Diagnosis: Red Flags on Echo; When to Suspect

- Unexplained hypertrophy, particularly in the presence of other classical echo features of CA. Don’t always assume HHD or HCM as the Dx

- Disconnect between “LVH” on echo and low voltage on ECG

- Depressed GLS with an apical sparing pattern

- Disassociation between EF and GLS (high accuracy w/ ratio > 4.1)
Cardiac MRI: Delayed Gadolinium Enhancement

- Pattern of enhancement
  - Diffuse to patchy
  - Subendocardial to transmural
- Diagnostic utility:
  - 90% sensitivity and specific
  - PPV, NPV ~ 90-93%
- Negative scan does not exclude the diagnosis

Ruberg F, Berk J. Circulation 2012
Boynton, JACC CV Imaging 2016
Tissue Diagnosis – Mandatory in AL amyloidosis
Prove presence of amyloid in an involved organ/tissue
- Fat aspirate
- Bone marrow
- Renal/Cardiac biopsy

Kittleson et al.. Circulation. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association, Volume: 142, Issue: 1, Pages: e7-e22,
Cardiac involvement is the major determinant of survival

- cTnI $< 0.1$ µg/L and NT-proBNP $< 332$ ng/L
- cTnI $> 0.1$ µg/L or NT-proBNP $> 332$ ng/L
- cTnI $> 0.1$ µg/L and NT-proBNP $> 332$ ng/L

➢ Early diagnosis and initiation of treatment is crucial to prevent irreversible damage; particularly now with advent of effective treatment

Staging of AL and ATTR Based on Serum Cardiac Biomarkers

Commonly used for risk stratification and prediction of survival.


Pregenzer-Wenzler et al. JACC HF 2020
# Prognostic Value of Echo Indices

## Multivariable Proportional-Hazard Model

<table>
<thead>
<tr>
<th>Metric</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial volume index (ml/m²)</td>
<td>0.9963</td>
<td>0.9807–1.0122</td>
<td>0.6471</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.9926</td>
<td>0.9686–1.0171</td>
<td>0.5516</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>1.0241</td>
<td>1.0018–1.0469</td>
<td>0.0349</td>
</tr>
<tr>
<td>Septal wall thickness (mm)</td>
<td>1.0579</td>
<td>0.9586–1.1675</td>
<td>0.2653</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>0.9945</td>
<td>0.9865–1.0025</td>
<td>0.1766</td>
</tr>
<tr>
<td>Pericardial effusion present*</td>
<td>0.9713</td>
<td>0.6029–1.5646</td>
<td>0.9051</td>
</tr>
<tr>
<td>MAPSE (cm)</td>
<td>0.5994</td>
<td>0.2708–1.3270</td>
<td>0.2092</td>
</tr>
<tr>
<td>2D-GLS (−%)</td>
<td>0.8151</td>
<td>0.7604–0.8737</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Buss, et al JACC 2012
Global Longitudinal Strain (GLS): Strong Predictor of Survival

Survival Based on GLS

Multivariate Model for Prediction of Mortality

Buss, et al  JACC 2012
A strong predictor of survival: GLS > 14.2% identified a 4-fold difference in survival

GLS provides incremental value over the standard cardiac biomarker based staging system
Predictor of Survival: Cardiac Response to Treatment

- NT-pro BNP Response: >30% and >300 ng/dl decrease
- BNP: ≥ 30% and ≥ 50 pg/ml decrease

Palladini et al, JCO 2012
Lilleness et al, Blood 2019
Predictor of Survival: Cardiac Response to Treatment

- Improvement in GLS is associated with better survival
- Pts with both NT-proBNP and GLS response showed best survival outcome
Advanced AL Cardiac Amyloidosis
Cardiac Response to Treatment

Pre-Treatment

Post-Treatment CR for 2 years

IVS = 1.5 cm
EF 33%
GLS = -6.1%

IVS = 1.3 cm
EF 50%
GLS = -14.1%
Summary

- Cardiac amyloidosis consists of misfolded proteins, AL vs. TTR in the myocardium, that leads to a restrictive cardiomyopathy.

- Diagnosis of CA remains elusive and relies on a high level of suspicion, often misdiagnosed for a more prevalent condition.

- Dyspnea or heart failure with unexplained hypertrophy, findings on imaging studies suggestive of CA, and other non-cardiac clues should raise suspicion of the diagnosis.

- Extent of cardiac involvement is the major determinant of survival.

- Imperative to make the diagnosis promptly so treatment can be initiated as soon as possible to minimize cardiac damage.
Thank You!