Cardiac Amyloidosis

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Disclosures

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New Referral

Diagnosis of ATTR made on basis of Positive PYP Scan

*Three Key Questions you ask?*

1. Septal Thickness?
2. H/CL ratio?
3. Echo Strain Value + Pattern?
66 Year-Old Male with Exertional Dyspnea

- CAD: previous stents; No HTN
- 1 yr. ago - Dyspnea while hiking
cath: mild CAD
- 6 mo. ago: progressive dyspnea,
  NT BNP ~2200 pg/ml ↓ to 500 after lasix (20 mg)
- 3 mo. ago - Renal infarct
  30 day monitor – no AF
- Echo: severe increase wall thickness (18 mm), EF 55%, strain -11%, RVSP 60 mmHg; MRI c/w amyloid, +LAA thrombus
- Serum protein electrophoresis: no monoclonal protein
- PYP scan: *markedly positive*
  H/CL ratio 2.4 at 1 hr, (positive . 1.3)
  SPECT + uptake in myocardium
- Creatinine 1.4 mg/dl
- NT BNP = 7257 pg/ml
- Trop T = 119 ng/l
- Peak V02 = 12.5 ml/kg-min (42% predicted)
66 Year-Old Male with Echo and MRI c/w amyloid

You recommend:

1. Tafamidis
2. Diflunisal
3. Patisiran
4. Heart transplant
5. Something else
66 Year-Old Male with Echo and MRI c/w amyloid

You recommend:

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5. **Something else**

- Serum free light chain assay
  - Kappa = 2.83 mg/dl (normal 0.33-1.94)
  - Lambda = 41.8 mg/dl (nl 0.57-2.63)
  - Ratio = 0.07 (normal 0.25-1.65)

- Serum protein **electrophoresis with immunofixation**: lambda monoclonal protein; same in urine

- Fat aspirate – negative for amyloid

- Bone marrow – 8% plasma cells, no definite amyloid

- EMB: + for AL
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- Diagnosis: ATTRwt,
- Prescribed tafamidis
AL Amyloidosis
A Race Against Time

• AL is a medical emergency
  • 20% die in first 6 months

• Once amyloid suspected – consider it AL until proven otherwise

• Once the diagnosis considered – give yourself *one week* to get the answer; amyloid yes/no

  Amyloid typing will take a little longer, but by then you should be referring the patient to an amyloid specialist
Amyloidosis
Two Main Types

**AL**
Light Chain Amyloid Protein Factory
Plasma Cells in Bone Marrow

**ATTR**
Transthyretin Amyloid Protein Factory
Liver

**ATTRm (hereditary)**-mutation-unstable
**ATTRwt (wild type*)** no mutation

*previously known as Senile

*Nomenclature: A = amyloid X = precursor protein; AL = light chain, ATTR = transthyretin*
Amyloidosis
Two Main Types

AL*

ATTR*

*Nomenclature: A = amyloid, X = precursor protein; AL = light chain, ATTR = transthyretin
Understanding *Pathophysiology* is key to Imaging

AL Amyloid – Direct light chain toxicity

Amyloid is:
- “Atypical”
- “Heterogeneous”
- “Complex”

Classic cardiac amyloid is pretty easy to diagnose

Variation in amyloid extent and distribution and in circulating toxic components is the *challenge*

Amyloid: “Infiltrative-Toxic” Myocardial Disease

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# Amyloidosis – Clinical Features of Different Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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| **AL (light chain)** | Multi-organ involvement common, *Heart Failure*  
Clues: hepatomegaly, peripheral and autonomic neuropathy, nephrotic syndrome, pulmonary nodules, *macroGLOSSIA*, *periOrBital purpura*, carpal tunnel. |
| **ATTRm (hereditary)** | *Heart Failure* and/or *peripheral or autonomic neuropathy*,  
Only 50% positive family history, heterogeneous penetrance. |
| **ATTRwt (wild type)** | *Heart Failure* - Carpal tunnel syndrome, biceps tendon rupture, spinal stenosis,  
Atrial fibrillation – common – often several years before HF. |
Wild-Type Transthyretin Amyloid* - Not Rare

- Men >55-60, increases with age
  - Youngest case diagnosed age 48
  - Women – ? Different phenotype
- Common features (currently recognized)
  - Hx of spinal stenosis – 10 years before diagnosis?
  - Biceps tendon rupture
  - Bilateral carpal tunnel syndrome – 5-10 years
  - Atrial arrhythmias – 3-5 years
  - Conduction system disease requiring pacemaker
- Heart Failure

*Previously termed “senile systemic amyloid”
Wild type transthyretin amyloid*(ATTRwt) cases hiding in plain sight

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<tr>
<th>Population</th>
<th>N</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Autopsy series, age ≥85 years¹</td>
<td>256</td>
<td>25%</td>
</tr>
<tr>
<td>Carpal tunnel release pts: men ≥50 years; women ≥60 yrs²</td>
<td>98</td>
<td>10% any amyloid*</td>
</tr>
<tr>
<td>Hospitalized HFpEF, &gt;60 yr., IVS &gt;12 mm, DPD scan³</td>
<td>120</td>
<td>13% positive DPD</td>
</tr>
<tr>
<td>Severe calcific AS⁴</td>
<td>112</td>
<td>5%</td>
</tr>
<tr>
<td>TAVR⁵</td>
<td>151</td>
<td>16%</td>
</tr>
<tr>
<td>Spinal Stenosis⁶</td>
<td>95</td>
<td>Unknown % amyloid</td>
</tr>
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²Sperry J Am Coll Cardiol 2018;72:2040-50
⁵Casteno et al: Eur Heart J. 2017; 35:2379-2887
⁶Yanagisawa Mod Pathol. 2015 Feb;28(2):201-7

All cardiologists need to know about ATTRwt. Develop a network of local, regional, national experts.

One study 100%!
Wild type transthyretin amyloid*(ATTRwt) cases hiding in plain sight

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*5 ATTRwt; 2 ATTRmt, 2 AL, 1 untyped
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“Bone scintigraphy enables the diagnosis of cardiac ATTR amyloidosis to be made reliably without the need for histology in patients who do not have a monoclonal gammopathy”
Nuclear Bone Scintigraphy – Back to the Future

- DPD, PYP, HDMP
- May replace biopsy in the right clinical setting
  - Heart failure with typical echo/MRI findings of amyloid
  - No monoclonal protein
- No monoclonal protein means
  1. Normal free light chain ratio
  2. No monoclonal protein in serum or urine by immunofixation electrophoresis (IFE)

Caution:
- Does not rule out AL!
- Make sure uptake is in Myocardium – SPECT/CT

Gertz et al Arch Intern Med. 1987;147:1039–1044
Bokhari Circ: Cardiovascular Imaging.2013; 6: 195-201
Gillmore JD at al. Circulation, 2016
Limitation of PYP for diagnosis of TTR amyloid

30-40% of patients with ATTRwt have unrelated monoclonal protein (“MGUS”) and cannot use PYP alone to diagnose amyloid.

M = Must
G = Go
U = Under
S = Skin (get tissue from somewhere)*

* MGUS Acronym - Courtesy of Dr. Dan Judge
Grade 2-3 \( ^{99m} \text{TcPYP} \) uptake may occur in AL!

"Bone scintigraphy enables the diagnosis of cardiac ATTR amyloidosis to be made reliably without the need for histology in patients who do not have a monoclonal gammopathy"
**CENTRAL ILLUSTRATION:** Accurate Use of Cardiac Scintigraphy for the Diagnosis of Transthyretin Amyloid Cardiomyopathy Contrasted With Key Causes of Misdiagnosis

- Positive PYP ≠ ATTR; Diagnosis = AL
  - Always screen for AL
- Positive PYP = blood pool uptake, no amyloid
  - Always perform SPECT

- ✓ Heart Failure with typical echo and/or CMR
- ✓ Negative sFLC, serum/urine IFE
- ✓ Positive PYP with SPECT

**Accurate Diagnosis = ATTR-CM**
- Perform TTR DNA sequence

- Negative PYP, Clinical suspicion persists

**Cardiac biopsy: Diagnosis = ATTRv**
- Perform biopsy if strong clinical suspicion


Mazen Hanna et al. J Am Coll Cardiol 2020;75:2851-2862
New Referral

Diagnosis of ATTR made on basis of Positive PYP Scan

*Three Key Questions you ask?*

1. Echo and/or MRI consistent with amyloid?
2. Has AL been excluded?
3. Does SPECT show myocardial uptake?
Diagnosis of Cardiac Amyloidosis

Clinical Suspicion with typical Echo/CMR Findings

Protein Electrophoresis with immunofixation, Serum Free Light Chain (sFLC) Assay

Monoclonal Protein Present or abnormal sFLC ratio?

Yes - Hematology Consult

Fat Aspirate, Pad

Bone Marrow Biopsy

Amyloid Present?

Yes

Cardiac Amyloid Confirmed

Amyloid Typing

No

Clinical Suspicion Remains

Cardiac Biopsy

Amyloid Present

Yes

No

Cardiac Amyloid Excluded

No

Cardiac Scintigraphy (99 TC-PYP, DPD, HMDP)

Grade 2, 3 uptake

H/CL > 1.5 at 1 hr (1.3 at 1 hr)

Yes = ATTR amyloid

TTR Sequencing

Wild Type TTR (ATTRwt)

Hereditary TTR (ATTRv)

1Current guidelines require typical echo and/or CMR findings (Table 2) to establish a diagnosis of ATTR without tissue biopsy. For AL (light chain) amyloid, if definite cardiac involvement will change management then endomyocardial biopsy is necessary to assess for cardiac involvement in those without typical echo/CMR findings

2SFLC by The Binding Site (Freelite) assay; K/L ratio 1.65 - 3.1 with renal dysfunction, collaboration with hematologist suggested

3Fat aspirate if local expertise in acquisition and interpretation. Fat pad biopsy is an alternative

4Depending on availability, some centers will go directly to cardiac biopsy

5Grade 2 – moderate myocardial uptake (equal to bone); grade 3 – severe uptake (greater than bone)

6Rare other amyloid types, such as Apolipoprotein AI, may demonstrate uptake with technetium labeled cardiac scintigraphy, clinical correlation required

7Protein precursor identification with laser micro-dissection mass spectrometry
Cardiac Amyloid - Treatment

• Directed at the underlying protein disorder
• Very different for AL compared with ATTR
• AL: control of the plasma cell disorder: chemotherapy and/or autologous stem cell transplant
• ATTR: reduce or stabilize TTR
• Supportive care – diuretics, control rate/rhythm
Cardiac Amyloidosis
Heart Failure Treatment

Beta-blockers
ACE-I and ARB
Entresto

Standard medical therapy often prescribed, usually poorly tolerated especially beta-blockers

Hypotension, autonomic neuropathy, low/fixed stroke volume
High risk of Atrial Thrombus in Amyloid. even in sinus rhythm

TEE cardioversion (AL and ATTR)

- 28% cancel due to thrombus
  46% of those on therapeutic AC or duration < 48 hr.
- 14% complications
  - VT/VF
  - Bradycardia requiring pacing
  - Stroke

Controls: 7% cancel; 2% complications (brief bradycardia)

- Thrombus often persists despite A/C
- Thrombus resolved in only 43% of amyloid pts at six months vs. 83% controls \(p=0.003\)

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Cardioversion in cardiac amyloid: Caution and TEE recommended, even if anticoagulation therapeutic

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\(^2\) J Am Coll Cardiol 2019;73:589–97
Clinical course of ATTRwt
Probably a long lead time – How long, we don’t know
TTR Amyloid Treatment Options

Liver – Stop production*

RNA interfering therapy
- Inotersen (Tegsedi)\(^1\)
- Patisiran (Onpattro)\(^1\)

Stabilize protein

Transthyretin stabilizers
- Tafamidis\(^2\)
- Diflunisal\(^3\)
- AG10\(^4\)

Fibril disrupter

Amyloid disrupters
- Doxycycline + TUDCA
- Monoclonal antibody (PRX0004\(^4\))

* Liver Transplant – hereditary only, may become obsolete

Heart Transplant – highly selected patients

\(^1\) FDA approved, ATTRm neuropathy
\(^2\) FDA approved for ATTR-cardiac
\(^3\) RCT data-neuropathy
\(^4\) Clinical trials
Both RNA interfering therapy

Phase III Neuropathy Trials
Hereditary (ATTRv) only
NYHA Class III, IV excluded

Endpoints
  Neuropathy Impairment Score and QOL

Not designed to assess mortality or cardiac efficacy

Both: slowed progression of neuropathy, improved quality of life in hereditary ATTR

Cardiac trials in progress!

Both cost $345,000-450,000 year, but there are programs for coverage
Tafamidis for Transthyretin Cardiac Amyloid ATTRwt and ATTRm

Maurer M et al: N Engl J Med, 2018

30% reduction in the risk of all-cause mortality with tafamidis compared with placebo (P=0.0259)*

The NNT for all-cause mortality = 7.5

FDA approved: 5/6/19, $225,000 year – assistance programs available
Take Home Points

1. Cardiac ATTR - not rare - look + you will find it!

2. PYP - Exclude monoclonal protein and do SPECT

3. Cardiac ATTR - transformed from universally fatal to a chronic cardiovascular condition
THANK YOU
Patient and Provider Resources

• Mayo Clinic Amyloid YouTube channel: http://bit.ly/1YuV19m

• Amyloidosis Support Group: http://www.amyloidosisupport.org/

• Amyloidosis Foundation http://amyloidosis.org/
QUESTIONS & ANSWERS