Cardiac Amyloid: it is not all AL

Stacey Shiovitz
October 26, 2012
Case

47yo man with new heart failure and atrial fibrillation
Case

• Presented with new SOB – diagnosed CHF, A-fib
  o TTE: EF 52% with diastolic dysfunction
  o Septal (15mm) and posterior (12mm) wall thickening

• Difficult to medically optimize his symptoms
  o TEE cardioversion; ablation for A-flutter

** 1 year later **

• Repeat TTE
  o EF 43% with significant diastolic dysfunction

• Cardiac MRI
  o Dilated chambers, thickened ventricular walls, thickened atrial septum, widespread delayed enhancement of the myocardium
  o Suspicious for cardiac amyloid
Case

- Admitted to UW for expedited work-up
  - NYHA class III-IV, anasarca

- PMH:
  - Exertional syncope x4 episodes
  - OSA on CPAP

- Family history
  - Father died in his 40’s from presumed cardiac disease
  - 2 brothers with cardiac disease NOS

- Social history
  - Remote alcohol, no significant tobacco or illicits
Case

• Exam: AF VSS
  - normoglossia, normal cardiopulmonary exam, no lymphadenopathy, no organomegaly, improving edema

• Labs:
  - WBC 8.6 with normal diff, Hgb 15, Hct 46, Plt 286
  - Lytes wnl, Cr 1.36; Prot 6.1, albumin 3.3, LFTs wnl
  - Troponin 1.38, BNP 2013
  - INR 1.9, PTT 49
  - SPEP: IgA-lambda (0.2 g/dL)
  - Serum light chains: lambda 32.5, kappa 1.05, ratio 1.03
  - UPEP: lambda Bence-Jones protein
  - 24-hour urine: protein 3.6g, BJ P 0.64g
Case

- Abdominal fat pad biopsy
  - Congo red stain positive for green birefringent material

- Bone marrow biopsy
  - Mildly hypercellular marrow (60-70%) with trilineage hematopoiesis
  - Increased plasma cells: aspirate 10-15%; core 15-20% (CD138 stain)
  - Congo red stain positive for green birefringent material
  - Flow: 0.16% population of atypical lambda-restricted plasma cells
  - Cytogenetics: 46,XY with iFISH positive for t(11;14) in 3% of cells
  - Molecular: positive for B-cell clonality

- Skeletal survey: no lytic lesions
Case

• Diagnosis:
  1) Multiple myeloma
  2) Amyloid, presumed AL
Amyloidosis
Pathophysiology

• Deposition of amyloid proteins into soft tissues leading to organ failure

• Can be the result of wild-type or mutated proteins

• Over 28 amyloidogenic proteins identified
  o Characteristic cross-beta sheet quaternary structure seen by X-ray crystallography: monomers → protofibrils
  o Protofibril structure is more resistant to degradation
  o 4–6 protofibrils weave together to make an amyloid fibril

Leung, Blood 2012
Cardiac involvement

- Part of systemic amyloid or isolated
  - Nodular deposits and branching filaments in the myocardium

- Spectrum of manifestations
  - Asymptomatic
  - Decreased exercise capacity / fatigue (56%) / SOB (63%)
  - Lower extremity edema (82%), anasarca
  - Angina (25%)
  - Hypotension (14%), syncope (20%)
  - Arrhythmias (14%)
  - Heart failure (25%)

Dubrey, QJM 1998; Selvanayagam, JACC 2007; Desai, Card Rev 2010
Leung, Blood 2012
Non-cardiac manifestations

- **Kidney**: most common
  - Proteinuria (73%)
  - Nephrotic syndrome (30%)

- **Nervous system**
  - Central or peripheral
  - Autonomic: syncope, ED, gastroparesis, diarrhea

- **Skin**
  - Plaques, fissures, nodules (amyloidomas)

- **GI**
  - Macroglossia (AL), nausea/vomiting, pseudo-obstruction
  - Hepatomegaly (AL)

- **Lung**
  - Restriction on PFTs

- **Heme**
  - Factor X deficiency
  - Vitamin K-dependent factor deficiency

- **Non-specific**
  - Fatigue
  - Weight loss (may be masked by edema)

- Comenzo, Blood 2009; Leung, Blood 2012
Diagnosing amyloid

- Biopsy the dysfunctional organ
  - Sensitivity: heart 100%; liver 97%; kidney 94%

- Or whatever is easiest to obtain
  - Sensitivity: fat pad 70-80%, rectum 75%, bone marrow 56%

- IHC diagnosis: Congo Red stain positive
  - Green birefringence in deposited tissues or in blood vessels

- Characteristic appearance on EM

- Leung, Blood 2012; Maceira, Circ 2005
Types of Amyloid
AL amyloid

• “Primary” amyloidosis

• Deposition of AL fibrils from immunoglobulin light chains
  - Seen with B-cell dyscrasias, including MGUS
  - 10-15% with concurrent multiple myeloma

• Clinical: multi-organ failure is common
  - Majority (90%) will have cardiac involvement

Desai, Card Rev 2010
AA amyloid

- “Secondary” amyloidosis

- Complication of chronic inflammatory condition or conditions with marked serum amyloid A (SAA) protein
  - Often seen with autoimmune conditions

- Clinical: present with renal failure +/- proteinuria
  - Dominate by renal disease
  - Rare cardiac involvement

- Treat the underlying condition
  - Organ failure may reverse over time
Maybe it’s not AL?

- Most common is AL amyloid, but ...

<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>Precursor protein</th>
<th>Clinical presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>kappa or lambda light chains</td>
<td>Cardiac, renal, hepatic/GI, PNS, soft tissues</td>
</tr>
<tr>
<td>ATTR</td>
<td>Mutant transthyretin</td>
<td>Cardiac, PNS</td>
</tr>
<tr>
<td>Senile systemic</td>
<td>Wild-type transthyretin</td>
<td>Cardiac, pulmonary, PNS</td>
</tr>
<tr>
<td>AA*</td>
<td>Serum amyloid A</td>
<td>Renal</td>
</tr>
</tbody>
</table>

- Approximately 10% of presumed AL amyloid may be another subtype
  - Consider testing for other mutations

References:
Transthyretin (TTR)

- Transporter for thyroxine and retinol-binding protein

- Chromosome 18; protein of 127 amino acids
  - Predominantly synthesized in the liver
  - Tetramer of 4 identical subunits

- >100 amyloidogenic mutations
  - Most are single AA substitutions, which destabilize the tetramer
  - Free monomers then form fibrils, which can deposit in tissues

Dungu, BMJ Heart 2012
TTR testing

- **Tissue staining for TTR expression**
  - Immunolabeled anti-TTR stain
  - Characteristic honeycomb pattern around individual myocytes

- **Serum testing for genetic mutations**
  - Wild-type: SSA
  - Variant: ATTR

---

Dungu, BMJ Heart 2012
Senile Systemic Amyloidosis (SSA)

- Wild-type TTR

- Clinical: older man with carpal tunnel syndrome, later followed by diagnosis of CHF
  - Male predominance; average age 70yo+ (25% of 80yo in autopsy series)
  - 34% of older adults undergoing CTS decompression found to have SSA

- Insidious onset of heart infiltration
  - Cause of death typically cardiac
  - Rare involvement of other systems

Selvanayagam, JACC 2007; Sekijima, Human Path 2011; Dungu, BMJ Heart 2012
ATTR Val 122 Ile

- Prevalence 4% in African-Americans
  - 23% of African-Americans with cardiac amyloid found to have variant TTR
  - May be higher in Afro-Cubans

- Clinical: similar phenotype to SSA
  - Frequent carpal tunnel syndrome, but rare neuropathy

- Isolated cardiac involvement

- Dungu, BMJ Heart 2012
ATTR
Thr 60 Ala

- Seen frequently in patients with Irish heritage

**Clinical: Familial Amyloid Polyneuropathy (FAP)**
  - Progressive polyneuropathy
  - Predominant autonomic dysfunction
    (ex. orthostasis without tachycardia; GI dysmotility)

- Majority have cardiac involvement
  - Portends worse prognosis

-Dungu, BMJ Heart 2012
ATTR Val 30 Met

- Clinical: FAP (Familial Amyloid Polyneuropathy)

- Rare cardiac involvement

- Most novel agents studied in patients with this mutation due to longer prognosis

- Desai, Card Rev 2010; Dungu, BMJ Heart 2012
Cardiac evaluation
# EKG

<table>
<thead>
<tr>
<th>Condition</th>
<th>AL</th>
<th>SSA</th>
<th>Val 122 Ile</th>
<th>Thr 60 Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low voltage</td>
<td>70%</td>
<td>29%</td>
<td>0</td>
<td>16%</td>
</tr>
<tr>
<td>1st degree AV block</td>
<td>18%</td>
<td></td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>2nd degree</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd degree</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L ant fascicular block</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- A-fib/flutter most common arrhythmia
- No correlation between EKG and survival

- Dubrey QJM 1998; Selvanayagam, JACC 2007; Desai, Card Rev 2010; Dungu, BMJ Heart 2012
TTE

- **Speckled myocardium** (specificity 70-80%)
  - Less commonly seen with newer harmonic imaging

- Findings increase with later disease stages:
  - Diastolic dysfunction
  - Thickened LV (not true LVH)
    - Especially in absence HTN
    - Thickened septum (spec. 100%)
  - Systolic dysfunction
  - Restrictive pattern

Selvanayagam, JACC 2007; Dungu, BMJ Heart 2012
EKG + TTE

Better in combination than alone

• Low voltage EKG + thickened LV on TTE:
  o Frequency 70%, Sens. 75%, Spec. 95%

• Low voltage EKG + IV septum >1.98 cm on TTE:
  o Sens. 72%, Spec. 91% (in a high-risk population)

Dubrey QJM 1998; Rahman, JACC 2004
Cardiac MRI

- Characteristic late gadolinium enhancement
  - seen in 2/3 of amyloid patients

- Degree correlates with myocardial amyloid load
  - Suggestive of more advanced disease

Maceira, Circulation 2005
Serum markers: Troponin

- Due to myonecrosis and small-vessel ischemia from amyloid deposition
- Disproportionate to degree of heart failure
- Best studied in AL amyloid
  - Detectable troponin associated with significantly worst prognosis: HR 3.1


mOS: 45 vs. 11 mos.
Serum markers: BNP

- Diastolic dysfunction and increased expression of natriuretic peptides in the amyloid infiltrated ventricles
- More useful in AL than ATTR
- Typically falls after treatment started
  - AL: 30% decrease with 3 cycles of chemotherapy
  - Not proportional to disease response

Selvanayagam, JACC 2007; Desai, Card Rev 2010
## AL vs. ATTR

<table>
<thead>
<tr>
<th></th>
<th>Cardiac AL</th>
<th>Cardiac ATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Plasma cell dyscrasia (paraprotein, elevated serum light chains, Bence Jones protein)</td>
<td>Carpal tunnel syndrome common</td>
</tr>
<tr>
<td></td>
<td>Multi-organ involvement</td>
<td>Older (&gt;55)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>6–12 months</td>
<td>Family history* Peripheral/autonomic neuropathy†</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>NT pro-BNP severely elevated</td>
<td>NT pro-BNP moderately elevated</td>
</tr>
<tr>
<td>Echo</td>
<td>Concentric wall thickening &lt;15 mm</td>
<td>Concentric wall thickening &gt;15 mm</td>
</tr>
<tr>
<td>Cardiovascular MRI</td>
<td>Circumferential subendocardial enhancement</td>
<td>Transmural enhancement, right ventricular involvement</td>
</tr>
<tr>
<td>SAP scintigraphy</td>
<td>Visceral uptake</td>
<td>Negative</td>
</tr>
<tr>
<td>$^{99m}$Tc-DPD scintigraphy</td>
<td>Often negative</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Not senile systemic amyloidosis (SSA).
†Not reported in SSA or ATTR V1221.
NT pro-BNP, N-terminal pro-brain natriuretic peptide; SAP, serum amyloid P component (SAP); $^{99m}$Tc-DPD, $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid.

Dungu, BMJ Heart 2012
Treatment
Symptom Control

OPTIONS:
• Diuretics
  o Risk of hypotension, decreased cardiac output
• Beta-blockers
  o Watch cardiac output, AV nodal blockade
• Pacemaker
  o Per regular protocols; no survival benefit

AVOID:
• Calcium-channel blockers
  o Strong negative inotropic effect
• ACE-inhibitors
  o Cause hypotension through restrictive physiology
• Digoxin
  o Increased toxicity due to binding of amyloid fibrils

• Selvanayagam, JACC 2007; Desai, Card Rev 2010; Dungu BJ M Heart 2012
Algorithm

Tissue diagnosis

Amyloid Typing
1) Evaluate for monoclonal gammopathy
2) TTR gene testing in African-Americans and neuropaths and patients without monoclonal gammopathies
3) Immunogold electron microscopy or proteomic studies if indicated
4) Additional genetic studies (e.g., Apo A1, A2, Lysozyme) if indicated

Light-chain (AL)
Hereditary
Senile (ATTR)

Consider Clinical Trial or Registry

SCT | MDex
---|---
CR or Stable organ disease | No CR, Progression or Relapse
Observe | Clinical Trial with Novel Agent(s)

If ATTR, consider trial of Diflunisal

Comenzo, Blood 2009
AL amyloid

- Prognosis: 6-12 months with cardiac involvement

- Treat similarly to plasma cell dyscrasias
  - High-dose melphalan followed by autologous stem cell transplant
    - Improved survival: 4.6 vs 1 year
    - Often not a candidate due to advanced cardiac disease
    - High peri-transplant mortality (13-30%)
  - Melphalan + prednisone/dexamethasone
    - Option for poor risk patients
    - Time to response >1 year
  - Bortezomib
  - Lenalidomide


ASCT:
- 5-year: 75% survival
TTR

- Prognosis:
  - SSA: 6 years
  - ATTR: 3-5 years

- Slower onset of cardiac dysfunction
  - But death still typically due to cardiac etiologies

- Supportive care / conservative management is key

- Selvanayagam, JACC 2007; Dubrey, QJM 2012
Targeted TTR therapies

• Diflunisal
  o NSAID-class; currently only used off-label
  o Bound by TTR in plasma, maintaining amyloid protein in less amyloidogenic form
  o RCT for neuropathy in FAP underway

• Tafamadis (Vyndaqel)
  o Approved in Europe, only for exceptional circumstances
  o Small molecule that binds TTR, stabilizing tetramer in vitro
  o RCT for V30M showed trend towards improved symptoms, disease stability

• Gene therapy: ALN-TTR01, ISIS-TTRRx
  o Phase 1 studies
  o RNA silencing agent, anti-sense nucleotide

• Castano, CHF 2012; Dungu, BMJ Heart 2012
Solid Organ Transplant: Liver

- Liver = source of mutant TTR
- First done in 1991; >1500 done to date
  - Often have been done as domino transplants
  - Case report of domino liver recipient developing amyloid at +8 yr
- More common for Val 30 Met
  - Longer prognosis; better survival post transplant
  - Autonomic > cardiac dysfunction
- Decreases variant TTR levels >95%
  - Deposited amyloid proteins can be a nidus for wild-type TTR deposition
  - Paradoxical acceleration of wt TTR deposition after OLT
    (even if not clinically apparent cardiac disease pre-transplant)

- Selvanayagam, JACC 2007; Dungu, BMJ Heart 2012; Dubrey, QJM 2012
Solid Organ Transplant: Heart

• Median recurrence: 11 months

• Few with durable long-term survival
  o AL: improved with post-transplant chemotherapy (1 year: 50→70%)
  o Better survival for non-AL types (1 year: 86%)
  o More often elected for older patients
  o Can consider in SSA patients that present early (<60yo)

• Combination
  o TTR: Heart/Liver
  o AL: OHT followed by melphalan-conditioned HSCT
    • “extended criteria” used for heart transplant
    • 1-year survival 80%

Selvanayagam, JACC 2007; Dungu, BMJ Heart 2012; Dubrey, QJM 2012
Back to the case
Case

- Diagnosed with amyloid and myeloma
  - Discharged to SCCA – plan to start bortezomib and dex

- Shortly thereafter admitted with decompensation
  - Found to have marked elevations in liver enzymes
  - >5 episodes of PEA arrest, eventually did not survive
  - Autopsy requested
Autopsy report

I. Cardiac amyloidosis (810g) with restrictive cardiac physiology (clinical).

A. Myocardium and endocardium with extensive amyloid deposits and patchy myocyte drop-out.
B. Stiff myocardium with left ventricle hypertrophy (1.6 cm thick) and small lumen of left ventricle.
C. Severe chronic passive liver congestion (2400 g).
D. Severe pulmonary congestion (right: 1400 g; left: 1470 g).
   1. Bilateral red, serous pleural effusions (1 L each side).
   2. Alveolar septa with amyloid deposits.
   4. Two foci of infarct (1.0 cm) with associated narrow vessels due to amyloid deposits.
II. Multiple myeloma.
   A. Plasma cell neoplasm (15-20% plasma cells, LM-12-339)
   B. Elevated monoclonal lambda light chain.
   C. Firm spleen with macroscopic amyloid deposits (290 g).
   D. No lytic lesions noted in spine or ribs.

III. Systemic AL amyloidosis, also involving:
   A. Blood vessels throughout the body, except brain.
   B. Bilateral kidneys (right: 290 g; left 250 g).
      1. Scarred cortex with severe vessel narrowing due to amyloidosis.
      2. Interstitial deposits in the pelvis with tubular atrophy.
   C. Interstitial amyloidosis of the thyroid, adipose, bowel and bladder wall, adrenal gland, and prostate.
Take home points

- Cardiac amyloid has a poor prognosis, especially in AL.

- Have a high suspicion for cardiac involvement:
  - EKG: Low voltage
  - TTE: LVH without HTN
  - MRI may be most helpful

- Always consider non-AL types of amyloid:
  - Especially high risk groups: African-American
    - Carpal tunnel syndrome in an older man
  - Beware of assuming MGUS is the cause

- Target treatment to particular type:
  - Better prognosis for non-AL despite fewer targeted therapies
References