Cardiac Amyloidosis
Diagnosis and Management

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Somers Point Division

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Disclosures

◊ I have no relevant financial relationships or conflicts of interest to disclose.
Background

- Amyloidosis refers to a disease state in which there is extra cellular deposition of low molecular weight subunits of a variety of proteins in different organs. These proteins have a common “β-pleated sheet” which is highly insoluble and thus causes deposition throughout the body (4,5).
- Can be either the full fibril or fragments
- This may involve the kidneys, liver, heart, and nervous system.
- There are at least twenty five known subtypes of amyloid, the four major subtypes that typically have cardiac involvement are AA type, AL type, ATTR wild type /familial, ATTR mutant type / hereditary.

AL Cardiac Amyloidosis

- The most common form of amyloidosis and the most aggressive form affecting the heart.
- AL amyloidosis most commonly has cardiac involvement, while only approximately 5% of AA amyloid involves the just the myocardium alone.
- The myocardium and kidneys remain the most commonly affected organs.
  - Heavy proteinuria and nephrotic syndrome
  - Morbidity and mortality specifically related to the heart, include LV dysfunction, conduction system disease, pericardial disease, thromboembolism, stroke, and small vessel disease (6,7).
- This is mainly due to light chain deposition in the myocardium.
- Although systemic amyloidosis takes many forms, cardiac involvement is most common in primary (AL) amyloidosis, in which immunoglobulin light chains elaborated as a consequence of a plasma cell dyscrasia (e.g., multiple myeloma) are deposited within the myocardium.
ATTR Amyloid

- Mutant type/hereditary/familial ATTR
- Wild type /Senile
- Familial amyloidosis (an autosomal dominant disease related to elaboration of mutant forms of transthyretin [TTR]) commonly affects the peripheral nerves and kidneys, but may also be associated with significant cardiac involvement in roughly one-fourth of cases.
- Amyloid derived from wild-type TTR results in a restrictive cardiomyopathy, most commonly presenting in men in their early 70's onwards, but occasionally seen as young as age 60.
- (Wild type) Although almost 1 in 4 males > 80 years have some TTR-derived amyloid deposits at autopsy, the clinical significance of a mild degree of deposition is unknown; generally clinical manifestations of heart failure occur once enough amyloid has been deposited to cause LV wall thickening (1).
- Approximately 3 – 4% among US African Americans have a common inherited mutation of the TTR gene (Val122Ile), which produces a restrictive cardiomyopathy in a minority, but may contribute to heart failure in a higher proportion (1).

AA Amyloid

- Those with secondary (AA) amyloidosis as a consequence of chronic infections or inflammatory conditions typically do not develop myocardial disease.
- Rheumatologic disorders
- Chronic hemodialysis
- Spondoloarthropathy
**Physiology**

1. Amyloid fibril infiltration
2. Circulating free light chains
3. Cardiomyocyte apoptosis

### Table 1: Amyloid Subtypes and Clinical Characteristics

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Demographics</th>
<th>Organ Involvement</th>
<th>Left Ventricular Hypertrophy</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>M ≈ F</td>
<td>Any (heart, kidney, GI, tongue, nerves, liver, soft tissue)</td>
<td>+</td>
<td>Chemotherapy or Stem-cell transplant</td>
</tr>
<tr>
<td>Wild-Type ATTR</td>
<td>M&gt;&gt;&gt;F</td>
<td>Heart (&amp; carpal tunnel syndrome)</td>
<td>+++</td>
<td>Supportive &amp; Clinical trials</td>
</tr>
<tr>
<td>Mutant ATTR</td>
<td>M&gt;&gt;&gt;F</td>
<td>Heart &amp; nerves (&amp; carpal tunnel syndrome)</td>
<td>+++</td>
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</tr>
</tbody>
</table>

* In the United States, the most common mutation (V122I) is seen predominantly among individuals of African descent. In other countries, demographics differ.
Symptomatology

- Systolic CHF
- Diastolic CHF
- Non-ischemic Cardiomyopathy
- Restrictive CM
- Dyspnea on exertion
- Atrial fibrillation
- Peripheral Neuropathy
- Worsening CKD/nephrotic syn
- DVT/PE
- Carpal Tunnel
- Hepatomegaly
- Purpura/macroglossia

Consider the diagnosis

- Cardiac amyloidosis should be suspected in individuals with heart failure and thickened ventricles with grade 2 or greater diastolic dysfunction on echocardiography or typical findings on cardiac magnetic resonance imaging (CMR; diffuse late gadolinium enhancement.)
Testing to consider

- Lab /UA
- ECG
- Echocardiography
- MRI
- Tech 99 PYP Nuclear Imaging
- Genetic testing
- Fat pad biopsy
- RV biopsy

Laboratory analysis

- Elevated Cr.
- Renal involvement
- Proteinuria
- SPEP, UPEP- monoclonal antibodies and light chain
- LFTs
- Genetic testing
ECG and Echocardiography

- Low QRS voltage (limb leads) on the surface ECG in the face of increased ventricular wall thickness
- Bi-atrial enlargement on echocardiography
- A sparkling or granular texture to the myocardium
- Abnormal thickening of the cardiac valves
- Thickened RV
- Thickening of the interatrial septum
- Pericardial effusion
- Strain imaging with apical sparing
Diagnosis

- Although identification of amyloid deposition in alternative locations (e.g., liver, abdominal or rectal fat pad, kidney) may be useful to identify systemic disease.
- Definitive diagnosis of cardiac amyloidosis requires confirmation of amyloid deposition on endomyocardial biopsy specimens.
- The amyloid protein is typically identified as an amorphous pink material in the interstitium surrounding individual myocytes that stains turquoise green with sulfated Alcian blue or exhibits apple green birefringence under polarized light on staining with Congo red.
- Immunohistochemistry is particularly important to identify the specific type of amyloid involved and direct the appropriate pathway for treatment.
- The observation that bone-avid nuclear tracers (e.g., technetium-99m-pyrophosphate) bind TTR amyloid in the heart may facilitate noninvasive identification of non–light chain amyloid variants.
Technetium 99m Transthyretin pyrophosphate nuclear imaging

◊ The American Society of Nuclear Cardiology (ASNC) has specific recommendations for using 99mTc-Technetium-Pyrophosphate in the diagnosis of cardiac amyloidosis (ATTR type) with guidelines for patient selection, technetium dosing, imaging procedure, and interpretation to increase the pre-test probability of obtaining a positive diagnosis (3).

◊ Several studies have shown the utility of this radio pharmaceutical agent in diagnosing ATTR type amyloidosis due to its avid uptake in myocardium with transthyretin deposition as is seen in ATTR type cardiac amyloidosis (2,3).

◊ The majority of the literature shows that this testing can be used for the differentiation of AL type amyloid from ATTR type amyloid (2,3).
Figure 1. Quantitation of Cardiac $^{99m}$Tc-PYP Uptake Using Heart to Contralateral Lung (H/CL) Ratio

Biopsy proven ATTR with H/CL = 2.08

Figure 2. Grading $^{99m}$Tc-PYP Uptake on Planar and SPECT Images

Grade 0  Grade 1  Grade 2  Grade 3
Figure 7. Hematoxylin and eosin stain of fat pad biopsy showing amyloid involvement of the vasculature.
Treatment

- In most patients, cardiac amyloidosis is a progressive illness with poor long-term prognosis.
- Diuretics are the cornerstone of treatment and can help to improve symptoms.
- For those with atrial fibrillation, control of the ventricular rate may improve diastolic filling time.
- Calcium channel blockers should be avoided—negative ionotropic affect
- Digoxin (Avoid)—amyloid fibrils can bind to digoxin
  - Causing dig toxicity
- Beta blockers / ACE? Controversial
- Amiodarone
Standard Therapies

- Steroid Therapy - dexamethasone – AL, ATTR
- Cyclophosphamide - AL
- Bortezomib - protease inhibitor - AL
- Melphalan - AL
  - Alkylates and cross links DNA inhibiting protein synthesis
  - Immunomodulators (e.g., lenalidomide or pomalidomide) - AL

Anticoagulation

- DVT/PE
- Atrial fibrillation - High risk for CVA
Pacer and ICD?

- The conduction system is often affected in all forms of amyloid heart disease. Although the sinus node may be most often involved pathologically.
- Patients with AL amyloidosis may have progressive conduction disease, the severity of which may not be apparent from the surface electrocardiogram.
- ICD unclear benefit given that implantation often fails to prevent sudden cardiac death, which in many cases is probably due to electromechanical dissociation related to the severe myocardial dysfunction.

Newer agents on the market

- Patisaran-ATTR
- Inotersen-ATTR
  - Bind to TTR mRNA reducing serum TTR protein and tissue deposits

- Tefamidis-ATTR
  - Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis
Treatment

◊ Chemotherapy and/or autologous stem cell transplantation (ASCT) is an attempt to eradicate the underlying plasma cell clone responsible for AL amyloid formation.

◊ The goal of therapy is to achieve a 90 percent or greater reduction in serum free light chain levels, but not all patients may be able to attain this level of response.
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Figure 1. Randomization, Evaluation, and Outcomes.
The most common reasons that screened patients were not admitted to the trial were as follows: closure of enrollment (for patients with wild-type transthyretin protein), N-terminal pro-B-type natriuretic peptide level less than 600 pg per milliliter, clinical instability, and an estimated glomerular filtration rate lower than 25 ml per minute per 1.73 m² of body-surface area. Among patients assigned to receive tafamidis who did not complete the trial, 25 were no longer willing to participate, 17 had adverse events, 6 underwent organ transplantation, 2 had implantation of a cardiac mechanical assist device (CMAD), 1 was lost to follow-up, and 1 had a protocol violation. Among patients assigned to receive placebo, 17 were no longer willing to participate, 11 had an adverse event, 5 underwent organ transplantation, and 1 had a protocol violation. Vital status at 30 months was available and confirmed for all patients who underwent randomization. The numbers shown do not depict the death count for the purpose of primary analysis. Some reasons for discontinuation (i.e., heart transplantation and CMAD implantation) were treated as death in the primary analysis. The total number of actual deaths was 144.
Conclusions

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo.
Transplant

- Cardiac transplantation in patients with cardiac amyloidosis is associated with poor long-term outcomes, presumably due to recurrence of amyloid within the transplanted heart;
- However, improved outcomes may be possible with combined cardiac and stem cell transplantation in a small number of patients who are diagnosed early and do not have extracardiac disease. In patients with familial amyloidosis due to mutant TTR, liver transplantation may remove the source of the mutant protein.
- Liver transplantation — In ATTR amyloidosis, the source of the amyloidogenic protein is the liver. Transplantation of the liver removes the mutant amyloidogenic TTR in familial ATTR but in senile systemic amyloidosis the precursor protein is native TTR and thus liver transplantation is not indicated.
- Patients with advanced heart disease may be treated with combined heart and liver transplantation.

Take home points

- Cardiac amyloidosis continues to be an under recognized, and therefore undertreated disease; as it is an uncommon cause for acute and/or chronic heart failure in patients.
- In addition, the early recognition of cardiac amyloid is essential to preventing further cardiac deterioration in the form of cardiomyopathy, arrhythmia, and possible sudden cardiac death (6, 7).
- Consider amyloidosis and a diagnosis of heart failure in patients with worsening renal dysfunction, proteinuria, carpal tunnel syndrome, with echo characteristics that we spoke about.
- Begin treatment early and identify the correct form of amyloid.
- Consider referral to advanced heart failure for advanced treatment and possible transplant options.
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