AL Amyloid

The Other Guys

Margot Davis, MD MSc FRCPC
Clinical Assistant Professor
University of British Columbia
Disclosures

- Consultancy/speaking fees: Janssen, Novartis, Boehringer-Ingelheim, Takeda, Pfizer, Akcea, Alnylam, Amgen, Ferring, TerSera
- Grant funding: Pfizer, Takeda, Boehringer-Ingelheim, Servier, Akcea
Objectives

- Review the presentation of AL amyloid including the conditions associated with it
- Differentiate the presentation & clinical course of AL amyloid from TTR-amyloid
- Discuss treatment options for AL amyloid
AL Amyloid: the Basics

- Annual incidence ~10/1,000,000
- Prevalence ~50/1,000,000 py
- Mean age Dx 63
- 55% men
- Risk factors:
  - MGUS
  - Genetic predisposition?
AL Amyloid: Clinical Presentation

Death in >1/2 due to HF or arrhythmia

Heart
- Heart failure with preserved ejection fraction
- Thickened ventricular walls and low voltages on electrocardiography
- Dyspnea at rest or exertion, fatigue
- Hypotension or syncope
- Peripheral oedema

Gastrointestinal tract
- Malabsorption and weight loss
- Bleeding (factor X)

Nervous system
- Peripheral
  - Symmetric lower extremity sensorimotor polynuropathy
  - Carpal tunnel syndrome (bilateral)
- Autonomic
  - Postural hypotension
  - Erectile dysfunction (males)
  - Gastrointestinal motility alterations

Liver
- Increased alkaline phosphatase
- Hepatomegaly

Kidney
- Nephrotic range proteinuria
- Renal failure
- Peripheral oedema

Periorbital purpura

Macroglossia

Clinical Clues Between Subtypes of Amyloid Cardiomyopathy

<table>
<thead>
<tr>
<th>Amyloid Type</th>
<th>Systemic Amyloidosis</th>
<th>Transthyretin (TTR) Amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype</td>
<td>AL</td>
<td>ATTRm</td>
</tr>
<tr>
<td>Age range, yrs</td>
<td>50+</td>
<td>40+ (V122I, 60-65 yrs)</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>55% male</td>
<td>Either, slight male dominance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked male predominance &gt;15:1</td>
</tr>
</tbody>
</table>

**Clinical cues**

- Multiorgan involvement
- Periorbital bruising or macroglossia are almost pathognomonic
- Severe hypotension with ACE inhibitors
- African-American/Caribbean origin (for V122I variant)
- Left ventricular hypertrophy without presence of prior history of hypertension
- History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement

ACE, angiotensin-converting enzyme; AL, light-chain amyloidosis; ATTRm, mutated transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ECHO, echocardiogram; MRI, magnetic resonance imaging.

# Comparison of Cardiac Amyloidoid Types

<table>
<thead>
<tr>
<th>Amyloid Type</th>
<th>Systemic Amyloidosis</th>
<th>Transthyretin (TTR) Amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype</strong></td>
<td><strong>AL</strong></td>
<td><strong>ATTRm</strong></td>
</tr>
<tr>
<td>Protein deposited</td>
<td>Light chain</td>
<td>Mutated TTR protein</td>
</tr>
<tr>
<td>Disease etiology</td>
<td>Plasma cell dyscrasia with ↑ light chains</td>
<td>Familial mutation of TTR</td>
</tr>
<tr>
<td>Specific features</td>
<td>Kidney, heart, nerves, GI tract, and liver affected</td>
<td>V122I common in African Americans</td>
</tr>
<tr>
<td>Median survival</td>
<td>1-3 years</td>
<td>2 years</td>
</tr>
<tr>
<td>Clinical course</td>
<td>HF can be fulminant, but may improve dramatically if rapid response to therapy</td>
<td>Similar to wt, but may be more rapid; may be dominated by neuropathy</td>
</tr>
</tbody>
</table>
Free Light Chains in AL

- Primary pathogenic mechanism
  - Tissue deposition
  - Direct myocardial toxicity
- Biomarker useful for diagnosis and monitoring response to therapy
- Treatment target
Diagnostic Pitfalls in AL

- Amyloidosis plus monoclonal protein does **not** necessarily equal AL amyloidosis unless immunofluorescence or mass spec demonstrates light chains in amyloid deposits.

- Conversely, nuclear scintigraphy **cannot** differentiate between AL and ATTR in the presence of a monoclonal protein (FLC or SPEP/UPEP).
Prognosis in AL Amyloidosis

- Burden of amyloid deposition – cardiac biomarkers
  - Predicts early deaths (<1 year)
- Size and biology of plasma cell clone – dFLC, %BMPC, t(11:14)
  - Predicts late deaths
- Response to therapy
Prognosis in AL: Revised Mayo Staging

- **Stage 1:** 0/3
  - 5 yr OS: 82%
  - Median survival: 94.1 mos

- **Stage 2:** 1/3
  - 5 yr OS: 62%
  - Median survival: 40.3 mos

- **Stage 3:** 2/3
  - 5 yr OS: 39%
  - Median survival: 14 mos

- **Stage 4:** 3/3
  - 5 yr OS: 20%
  - Median survival: 5.8 mos

- 
  - dFLC ≥ 18 mg/dL
  - TnT ≥ 0.025
  - NT-proBNP ≥ 1800
  - or
  - BNP ≥ 400

Prognosis in AL: Hematologic & Organ Responses

![Graph showing survival probabilities and response rates](image)

Leukemia (2012) 26, 2317–2325
AL: Light chain-suppressive therapy

Patient risk stratification

**Low risk and transplant eligible**
- ECOG performance status 0–2
- Left ventricular ejection fraction >40%
- NT-proBNP levels <3,000 ng per litre
- Cardiac troponin T <0.06 ng per ml
- NYHA class I–IV
- O2 saturation >95% on room air
- Total bilirubin <2 mg per dl
- Baseline systolic blood pressure >90 mmHg

**Intermediate risk**
- Ineligible for HDM–SCT (stages I–IIa)
- BMDex – decreases the effects of both gain 1q21 and t(11;14)
- CyborD – stem cell sparing is preferred in patients with renal failure but has a poor outcome in patients with t(11;14)
- M Dex – preferred in patients with neuropathy or fibrotic lung disease

**High risk**
- Stage IIIb NYHA class >III
- Low-dose combination regimens
- Standard regimens with intensive care support

**Refractory or relapse**
- Consider BDex if less than complete response after HDM–SCT
- Repeat frontline therapy in relapsing patients if possible (shorter time to third-line therapy)
- Bortezomib-naïve patients: bortezomib and ixazomib
- IMiDs (lenalidomide and pomalidomide)
- Bendamustine
- Daratumumab

Doxycycline improves survival in patients receiving chemo for AL amyloidosis
Symptom-Directed Management

**Congestive Symptoms**
- Loop diuretics and thiazides in combination with mineralocorticoid receptor antagonist

**Cardiomyopathy Medications**
- Avoid β-blockers, ACEi, and ARB
- Do not modify disease progression
- Can result in worsening fatigue and hypotension

**Atrial Arrhythmias**
- Amiodarone
- Catheter ablation
- Calcium channel blockers are contraindicated (bind to the amyloid fibrils)
- Digoxin can cause cardiac toxicity (progressive accumulation in amyloid-rich heart despite normal serum levels)
- Catheter ablation has high recurrence rate, necessitating AV ablation with permanent pacemaker placement in refractory cases

**Hypotension**
- α-1 blocker midodrine and compression stockings
Importance of early diagnosis and therapy

Conclusions

- AL is a rare disease associated with multiorgan dysfunction and a very poor prognosis if not promptly treated.
- Differentiation between AL, ATTR, and other causes of HFpEF is essential to ensure appropriate treatment.
- Free light chains are the pathologic basis of the disease, a valuable tool in its diagnosis, and the primary treatment target.
- Despite advances in therapy, advanced cardiac involvement is still associated with a poor prognosis.
- Novel and developing therapies will hopefully change this prognosis in the future.
Case Presentation
85 year old man referred for possible ATTR cardiac amyloidosis

- **PMHx:** HTN, DM2, CKD (GFR 30), Atrial fibrillation – diagnosed 2017, rate controlled
- **Meds:**
  - Ramipril 1.25 mg daily
  - Metoprolol 25 mg BID
  - Warfarin
  - Lasix 20 mg daily
  - Atorvastatin 20 mg daily
  - Trajenta

- **Admitted with ADHF September 2018**
  - Recently returned from trip, eating lots of salty food
  - Troponin 0.20 on presentation

- **MIBI normal**

- **Echo in hospital:**
  - Normal LV size, EF 39%
  - Dilated RV, normal function
  - Septum 15 mm, PW 11 mm, increased RV wall thickness
  - Biatrial enlargement
  - Mild-moderate MR and AR
  - Strain not reported
Tc-PYP scan

- Marked increased activity throughout the left ventricular myocardium, low grade activity within the right ventricle
- Diffuse activity typical of TTR cardiac amyloidosis
Clinic Evaluation

- NYHA 2
- No syncope
- No history CTS
- Numbness/paresthesias in arms/hands at night
- Intermittent foamy urine
- No macroglossia, change in taste, GI symptoms, weight loss. Bleeds but on OAC.

Exam
- 117/70; 81 bpm (irregular)
- JVP 4 cm ASA, AJR+
- No macroglossia
- S1S2 irregular, no murmurs
- Chest clear, trace edema
- BNP 364, TnI 0.07
- Cr 179, GFR 25, K 4.6, Na 142, Hb 139
Further Investigations

- SPEP: Normal pattern
- UPEP: Small band in gamma region
  - Immunofixation: small monoclonal free kappa light chain
- Serum free light chain assay
  - Kappa: 205
  - Lambda: 17.1
  - Ratio: 11.99
Audience response: What is the most appropriate next step?

- 1. Prescribe tafamidis 61 mg daily
- 2. Refer for liver transplant
- 3. Tissue biopsy
- 4. Refer for stem cell transplant
- 5. Suggest patient enroll in clinical trial of novel TTR-directed therapy
Abdominal fat pad biopsy:
- Negative for amyloid

Bone marrow biopsy:
- Mild increase (5-10%) in kappa restricted plasma cells. Histologic findings consistent with a diagnosis of a plasma cell neoplasm. No definite evidence of amyloid infiltrate by Congo red staining.

Next?
Case summary

- Overall most consistent with ATTR with concomitant MGUS
  - Older age, male
  - AF for 2 years
  - Rapid recovery after ADHF episode
- Cannot rule out AL, given abnormal FLC and marrow
  - History of unexplained renal disease and lack of CTS also concerning
- Needs EMBx with mass spec to differentiate, as management vastly different for 2 diseases