Amyloidosis
A Heterogeneous Disease

Toni Roberts, MD, PhD
Hematology Oncology Fellow
University of Washington

Faculty Discussant:
Edward Libby, MD
University of Washington/FHCRC
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

Case 2:
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

Case 3:
56 year old female with chronic normocytic anemia and diffuse pulmonary nodules identified during a COPD exacerbation.
Amyloidosis
A Heterogeneous Disease

- A protein misfolding disease in which peptides are converted from their soluble functional state into insoluble, highly organized fibrillar aggregates
- At least 30 different proteins have been identified as causative agents
- Despite diversity of amyloidogenic proteins, all adopt a common cross-β-sheet conformation which results in accumulation of insoluble fibrils in tissue leading to organ dysfunction

**Diagram:**
- Serum amyloid P component (SAP) binds protofibrils and prevents proteolysis
- Cross-seeding can occur with oligomer formation by one amyloidogenic peptide attracting other amyloidogenic peptides
- Hydrophobic surfaces, pH, ion strength, peptide mutations
- Once nucleus is formed, kinetic barrier for polymerization is overcome

**Legend:**
- Normal amyloid precursor protein
- Native (random structure)
- Misfolded Intermediate
- β-Sheet Intermediate
- Oligomer
- Protofibril
- Fibril
- Harmful amyloid plaques
Amyloidosis

Plaque Formation

Protofilaments

Protofibrils

Mature fibrils

Plaque Formation

Protofilaments

Protofibrils

Mature fibrils
Amyloidosis
Clinical Manifestations
<table>
<thead>
<tr>
<th>Disease</th>
<th>Precursor Protein</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Chain Amyloidosis (AL)</td>
<td>Immunoglobulin Light Chain</td>
<td>Myeloma, B cell neoplasm</td>
</tr>
<tr>
<td>Heavy Chain Amyloidosis (AH)</td>
<td>Immunoglobulin Heavy Chain</td>
<td>Myeloma</td>
</tr>
<tr>
<td>Amyloid A Amyloidosis (AA)</td>
<td>Serum Amyloid A Protein</td>
<td>Chronic Inflammation</td>
</tr>
<tr>
<td>Senile Systemic Amyloidosis (SSA)</td>
<td>Transthyretin Protein</td>
<td>Accumulation of Wild Type TTR</td>
</tr>
<tr>
<td>Familial Amyloid Polyneuropathy (ATTR)</td>
<td>Transthyretin Protein</td>
<td>Hereditary Mutation of TTR</td>
</tr>
<tr>
<td>Familial Amyloid Cardiomyopathy (ATTR)</td>
<td>Transthyretin Protein</td>
<td>Hereditary Mutation of TTR</td>
</tr>
<tr>
<td>Familial Oculoleptomeningeal Amyloidosis (ATTR)</td>
<td>Transthyretin Protein</td>
<td>Hereditary Mutation of TTR</td>
</tr>
<tr>
<td>Dialysis Related Amyloidosis (Aβ2M)</td>
<td>β2 Microglobulin</td>
<td>Copper Triggers Oligomerization</td>
</tr>
<tr>
<td>Lysozyme Amyloidosis (ALys)</td>
<td>Lysozyme</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Apo AI Amyloidosis (AApo AI)</td>
<td>Fragments of Apolipoprotein AI</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Apo AII Amyloidosis (AApo AII)</td>
<td>Fragments of Apolipoprotein AII</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Apo AIV Amyloidosis (AApo AIV)</td>
<td>Fragments of Apolipoprotein AIV</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Hereditary Fibrinogen Amyloidosis (AFib)</td>
<td>Fibrinogen Aα Chain</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Finnish Hereditary Amyloidosis (AGel)</td>
<td>Fragments of Gelsolin</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Cystatin Amyloidosis (ACys)</td>
<td>Cystatin C</td>
<td>Hereditary Mutation</td>
</tr>
<tr>
<td>Disease</td>
<td>Precursor Protein</td>
<td>Organ Affected</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Alzheimer Disease (Aβ)</td>
<td>Aβ Protein Precursor</td>
<td>Brain</td>
</tr>
<tr>
<td>Hereditary and Transmissible Spongiform Encephalopathies (APrP)</td>
<td>Prion Protein</td>
<td>Brain</td>
</tr>
<tr>
<td>Danish Hereditary Amyloidosis (ADanPP)</td>
<td>ADan Precursor Protein</td>
<td>Cerebral Vessels</td>
</tr>
<tr>
<td>British Hereditary Amyloidosis (ABriPP)</td>
<td>Abri Precursor Protein</td>
<td>Cerebral Vessels</td>
</tr>
<tr>
<td>Familial Subepithelial Corneal Amyloidosis (ALac)</td>
<td>Lactoferrin</td>
<td>Cornea</td>
</tr>
<tr>
<td>Familial Lattice Corneal Amyloidosis (AKer)</td>
<td>Keratoepithelin</td>
<td>Cornea</td>
</tr>
<tr>
<td>Age Related Pituitary Amyloidosis (APro)</td>
<td>Prolactin</td>
<td>Pituitary Gland</td>
</tr>
<tr>
<td>Medullary Carcinoma of the Thyroid (ACal)</td>
<td>Calcitonin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Type II Diabetes, Insulinoma (AIAPP)</td>
<td>Islet Amyloid Polypeptide (amylin)</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Type II Diabetes (Alns)</td>
<td>Insulin</td>
<td>Site of Repeated Insulin Injections</td>
</tr>
<tr>
<td>Senile Seminal Vesicle Amyloidosis (ASgl)</td>
<td>Semenogelin I</td>
<td>Seminal Vesicle</td>
</tr>
<tr>
<td>Senile Aortic Amyloidosis (AMed)</td>
<td>Lactadherin (medin)</td>
<td>Aorta</td>
</tr>
<tr>
<td>Isolated Atrial Amyloidosis (AANF)</td>
<td>Atrial Natriuretic Factor</td>
<td>Heart</td>
</tr>
<tr>
<td>Calcifying Epithelial Odontogenic Tumors (AOAAP)</td>
<td>Odontogenic Ameloblast Associated Protein</td>
<td>Jaw</td>
</tr>
<tr>
<td>Nodular Pulmonary Amyloidosis</td>
<td>Primary and Secondary Amyloidosis</td>
<td>Lung</td>
</tr>
</tbody>
</table>
Amyloidosis
Diagnosis

- Tissue Biopsy
  - affected tissue (neuronal, cardiac, renal)
  - fat pad aspirate (>90% sensitivity)
  - buccal salivary gland aspirate (86% sensitivity)
  - duodenal, colonic, rectal biopsy (70-80% sensitivity)
  - bone marrow (positive in >60% AL amyloidosis)

- Histochemistry
  - Congo red stain and polarized light
  - immunostaining
  - electron microscopy

- Extraction or Microdissection of Amyloid Plaque
  - amino acid sequence analysis
  - mass spectroscopy
**Case 1:**
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

**Case 2:**
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

**Case 3:**
56 year old female with chronic normocytic anemia and diffuse pulmonary nodules identified during a COPD exacerbation.
• **Incidence:**
  1275-3200 new US cases per year

• **Etiology:**
  neoplastic plasma cell or B-cell clone
  • high association with amino acid substitutions in light chain variable region
  • often no M spike with little intact monoclonal Ig (50% missed on SPEP/UPEP)
  • 40% of patients have light chains only
  • κ:λ ratio 1:3, whereas κ:λ ratio in multiple myeloma 3:2
  • combination of SPEP + UPEP + immunofixation + free light chain analysis approaches 100% sensitivity for detecting monoclonal protein in AL amyloidosis
• **Prognosis:**
  - median overall survival 3.8 years
  - 27% die within 1 year of diagnosis (75% from cardiac manifestations)
  - major prognostic factor is degree of cardiac involvement
    - cardiac MRI very sensitive for cardiac amyloidosis
  - cardiac amyloidosis staging:
    - **Stage 1:** normal troponin and BNP
    - **Stage 2:** troponin or BNP elevated
    - **Stage 3:** both troponin + BNP elevated

<table>
<thead>
<tr>
<th>Stage</th>
<th>Troponin/BNP</th>
<th>Deaths</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-t</td>
<td></td>
<td>80</td>
<td>26.4</td>
</tr>
<tr>
<td>II-t</td>
<td></td>
<td>73</td>
<td>10.5</td>
</tr>
<tr>
<td>III-t</td>
<td></td>
<td>89</td>
<td>3.5</td>
</tr>
</tbody>
</table>

P < 0.0001
There are insufficient data to indicate the optimal treatment of amyloidosis, therefore, all patients should be treated in the context of a clinical trial when possible.

Options include:
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib ± dexamethasone
- Bortezomib/melphalan/dexamethasone
- Cyclophosphamide/thalidomide/dexamethasone
- Dexamethasone/alpha-interferon
- High-dose melphalan with stem cell transplant
- Lenalidomide/cyclophosphamide/dexamethasone
- Lenalidomide/dexamethasone
- Oral melphalan/dexamethasone
- Pomalidomide/dexamethasone
- Thalidomide/dexamethasone
- Best supportive care

Organ involvement based on amyloidosis consensus criteria
Amyloidosis
AL Amyloidosis Management: mSMART Guidelines

Newly Diagnosed AL Amyloidosis

- Transplant Eligible
  - Mel 200 HSCT
  - Not wanting transplant

- Transplant Ineligible
  - Mel-Dex or CyBorD

Hematologic VGPR
- Observation
- < PR
- ≥ PR
  - Low risk
  - Observation
  - More chemotherapy

No Hematologic VGPR
- Observation
- < PR
- ≥ PR
  - Low risk
  - Observation
  - No
  - Yes

Treatment of AL

Transplant Eligibility
- Physiologic: Age ≤ 70 years
- Performance Score ≤ 2
- CrCl ≥ 30 ml/min* (unless on chronic dialysis)
- NYHA Class I/II

Transplant Ineligibility
- TnT ≥ 0.06 ng/ml
- NT-proBNP ≥ 5000
- more than 2 organs† significantly involved
Serum AA Amyloidosis

SAA

- acute phase reactant HDL apolipoprotein
- synthesized in liver under transcriptional regulation of IL-1, IL-6, TNFα
- sustained elevated levels of SAA prerequisite for AA amyloidosis
- GAGs serve as scaffold for polymerization
- kidneys, liver, spleen, heart, lungs, GI tract preferentially affected with ESRD in 85% and heart failure in 26%

Amyloidosis

Serum AA Amyloidosis

CHRONIC INFLAMMATION

Generates cytokines cascade (TNFα / IL-1 / IL-6)

Rheumatoid Conditions
Inflammatory Bowel Disease
Chronic Infections
Familial Mediterranean Fever

SAA (Serum amyloid A precursor protein)

Increases SAA levels

AA PROTEIN + SULFATED GAGS (Glycosaminoglycans)

Converts to AA Protein

SYSTEMIC AMYLOID A FIBRIL FORMATION & DEPOSITION WITH PRINCIPAL DAMAGE TO KIDNEY
# Amyloidosis

Serum AA Amyloidosis

## Table 1: Inflammatory diseases associated with AA amyloidosis.

<table>
<thead>
<tr>
<th>Inflammatory arthritis</th>
<th>Neoplastic diseases</th>
<th>Hereditary autoinflammatory diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Castleman's disease</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Hodgkin's lymphoma</td>
<td>TNF receptor-associated periodic syndrome (TRAPS)</td>
</tr>
<tr>
<td>Adult Still's disease</td>
<td>Waldenstrom's macroglobulinaemia</td>
<td>Muckle-Wells syndrome</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Hairy cell leukaemia</td>
<td>NOMID/CINCA syndrome</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Hepatic adenoma</td>
<td>Hyper-IgD syndrome</td>
</tr>
<tr>
<td>Gout</td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory bowel diseases</th>
<th></th>
<th>Hereditary autoinflammatory diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's disease</td>
<td>Chronic infections</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Bronchiectasis</td>
<td>TNF receptor-associated periodic syndrome (TRAPS)</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
<td>Muckle-Wells syndrome</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>NOMID/CINCA syndrome</td>
</tr>
<tr>
<td></td>
<td>Chronic pyelonephritis</td>
<td>Hyper-IgD syndrome</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whipple's disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic cutaneous ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B (?)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hereditary and acquired immunodeficiencies</th>
<th></th>
<th>Systemic vasculitides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common variable immunodeficiency</td>
<td>Behcet's disease</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinaemia</td>
<td>Polyarteritis nodosa</td>
<td></td>
</tr>
<tr>
<td>X-linked agammaglobulinaemia</td>
<td>Giant cell arteritis</td>
<td></td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>Takayasu's arteritis</td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Polymyalgia rheumatica</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th>Chronic infections</th>
<th>Conditions predisposing to chronic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (?)</td>
<td>Cystic fibrosis</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Sarcoidiosis</td>
<td>Epidermolysis bullosa</td>
<td></td>
</tr>
<tr>
<td>SAPHO syndrome</td>
<td>Injected-drug use</td>
<td></td>
</tr>
<tr>
<td>Schnitzler syndrome</td>
<td>Jejuno-ileal bypass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraplegia</td>
<td></td>
</tr>
</tbody>
</table>
Serum AA Amyloidosis

- Prognosis dictated by control of underlying inflammatory disease and production of SAA.
- In patients with renal disease, increase in SAA by 2 fold increases risk of death by 5 fold.
- If cardiac involvement, 5 year survival is 31%.
- SAA monitoring and surveillance fat pad aspirates are recommended.

Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*

<table>
<thead>
<tr>
<th>SAA Octile (mg/liter)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥4 to &lt;9</td>
<td>3.9 (1.5–10.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥9 to &lt;16.7</td>
<td>5.1 (2.7–9.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥16.7 to &lt;28</td>
<td>7.0 (3.7–13.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥28 to &lt;45.6</td>
<td>9.1 (4.8–17.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>≥45.6 to &lt;87</td>
<td>12.1 (6.9–21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥87 to &lt;155</td>
<td>17.0 (8.6–33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥155</td>
<td>17.7 (8.7–36.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
• prognosis dictated by control of underlying inflammatory disease and production of SAA
• in patients with renal disease, increase in SAA by 2 fold increases risk of death by 5 fold
• if cardiac involvement, 5 year survival is 31%
• SAA monitoring and surveillance fat pad aspirates are recommended

<table>
<thead>
<tr>
<th>Anti-TNF drugs</th>
<th>Characteristic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (IFX)</td>
<td>Chimeric (mouse/human)mAb IgG1</td>
<td>div. once 8 weekly 3-10mg/kg</td>
</tr>
<tr>
<td>Adalimumab (ADA)</td>
<td>Human mAb, IgG1</td>
<td>s.c. once biweekly 40-80mg/body</td>
</tr>
<tr>
<td>Etanercept (ETN)</td>
<td>Fusion protein of TNF receptor 2 and IgG1 Fc component</td>
<td>s.c. once weekly 25-50mg/body</td>
</tr>
<tr>
<td>Golisumab (GLM)</td>
<td>Human mAb, IgG1</td>
<td>s.c. once monthly 50-100mg/body</td>
</tr>
<tr>
<td>Certolizumab (CZP)</td>
<td>Humanized Fab’ fragment conjugated to a polyethylene glycol</td>
<td>s.c. once monthly 400 mg /body</td>
</tr>
<tr>
<td>IL-1 receptor antagonist</td>
<td>Non-glycosylated version of human IL-1RA</td>
<td>s.c. once or twice daily 100mg /body</td>
</tr>
<tr>
<td>Anti-IL-6 receptor antibody</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Serum AA Amyloidosis

- **Investigational Therapies:**
  
  **Eprodisate:**
  negatively charged sulfonated molecule that interrupts binding of SAA with GAGs
  
  HR for progression of renal disease 0.58 in phase III study
Investigators Therapies:

**Eprodisate:**
negatively charged sulfonated molecule that interrupts
binding of SAA with GAGs
HR for progression of renal disease 0.58 in phase III study

**CPHPC:** (R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]
pyrrolidine-2-carboxylic acid)
high affinity ligand for SAP which binds and promotes
clearance of SAP by 95% in phase I studies
Amyloidosis
Serum AA Amyloidosis

• Investigational Therapies:

  **Eprodisate:**
  negatively charged sulfonated molecule that interrupts binding of SAA with GAGs
  HR for progression of renal disease 0.58 in phase III study

  **CPHPC:** (R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid)
  high affinity ligand for SAP which binds and promotes clearance of SAP by 95% in phase I studies

  **AntiSense Oligonucleotides:**
  reduced SAA levels and amyloid deposits in mouse model
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

- IgG lambda paraproteinemia:
  SPEP with M spike too small to quantify
  serum free light chains elevated with normal ratio
  immunofixation with lambda restriction
  UPEP positive for Bence Jones protein

- Bone Marrow Biopsy:
  1) Normocellular marrow with normal trilineage hematopoiesis.
  2) Small monoclonal plasma cell population characterized by lambda light chain restriction by flow cytometry comprising 0.28% of bone marrow WBC with 10% bearing 11;14 translocation by FISH.
  3) Congo red stain negative for amyloid.

- Skeletal Survey: Scattered lucencies within calvarium. No additional evidence of myelomatous involvement within remainder of the axial or appendicular skeleton. CT head negative for lytic calvarial lesions.

- BNP 1041; troponin-I 0.4

- Renal Biopsy: Advanced diabetic nephropathy with arteriolar hyalinosis. Negative for light chain deposition and amyloid.
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

Case 2:
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

Case 3:
56 year old female with chronic normocytic anemia and diffuse pulmonary nodules identified during a COPD exacerbation.
Hereditary Amyloidosis

- orphan disease: prevalence 1.1/100,000
- autosomal dominant inheritance with variable penetrance
- 130 known mutations in transthyretin gene (TTR)
- endemic regions in Portugal, Sweden, Japan

- transthyretin primarily synthesized in liver, with 5% produced in retinal pigment epithelial cells, choroid plexus, and alpha cells of pancreatic islets

- mutations destabilize TTR tetramer

<table>
<thead>
<tr>
<th>TTR variant</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>V30M</td>
<td>most common TTR-FAP-associated variant</td>
</tr>
<tr>
<td></td>
<td>first described by Andrade in Portugal 1952, later in Sweden and Japan (endemic areas)</td>
</tr>
<tr>
<td></td>
<td>autosomal dominant inherited</td>
</tr>
<tr>
<td></td>
<td>typically affects peripheral nerves and autonomic nerves; later heart and other organs</td>
</tr>
<tr>
<td></td>
<td>onset of disease between 20 and 35 years</td>
</tr>
<tr>
<td>T60A</td>
<td>first identified in North-West Ireland, now found in Irish and Irish-American patients</td>
</tr>
<tr>
<td></td>
<td>typically causes late-onset systemic amyloidosis (&gt;50 years) with cardiac, and sometimes neuropathic involvement</td>
</tr>
<tr>
<td>L58H</td>
<td>first identified in Germany, later spread throughout the United States</td>
</tr>
<tr>
<td></td>
<td>typical clinical manifestation: carpal ligament deposition and involvement nerves of the upper extremities</td>
</tr>
<tr>
<td>G6S</td>
<td>carried by about 10% of people of white European descent</td>
</tr>
<tr>
<td></td>
<td>seems to be a neutral polymorphism not associated with amyloidosis</td>
</tr>
<tr>
<td>V122I</td>
<td>3.9% of African Americans and over 5% of the population in some areas of West Africa carry this mutation; therefore, it seems to be the most common amyloid-associated TTR variant worldwide</td>
</tr>
<tr>
<td></td>
<td>variant is associated with the risk of late-onset cardiac amyloidosis</td>
</tr>
<tr>
<td></td>
<td>no neurological symptoms</td>
</tr>
</tbody>
</table>
• bimodal symptom onset: 3\textsuperscript{rd} decade + 5\textsuperscript{th} decade

• most common symptoms:
  length dependent ascending neuropathy
  autonomic neuropathy
  cardiac arrhythmia
  cardiomyopathy
  dysphagia
  constipation/diarrhea/cachexia
  nephropathy
  subarachnoid hemorrhage
  spinal cord compression
  blindness
  carpal tunnel syndrome

• uniformly progressive and fatal; median overall survival 7.3–10.1 years
Hereditary Amyloidosis Diagnosis

A: Congo Red Staining - orange
B: Polarized Light - apple green
C: IHC with Anti-TTR Ab
D: Sequence Analysis of TTR Gene
E: Mass Spectroscopy of Serum TTR - mutant TTR has different molecular weight from wild type TTR
Orthotopic Liver Transplantation:
- first liver transplant in 1990 in Sweden; 120 are performed worldwide each year
- 1,917 total liver transplants have been performed in 19 different countries
- recommend transplantation at symptom onset / diagnosis
- slows disease progression and prolongs life
- eliminates 95% of variant TTR
- standard of care

Domino Liver Transplantation:
- takes 20-30 years for symptoms to develop in domino recipients
- offered to patients > 60 years old
- several reports of DLT recipients developing symptoms in 8-10 years
**Hereditary Amyloidosis: Therapeutic Approaches**

**Liver, eye, brain**
- Production, secretion
- Suppression of amyloidogenic TTR

**TTR tetramer**
- Stabilizers of TTR tetramers

**TTR monomer**
- Dissociation
- Misfolding
- Inhibition of amyloid deposits

**Pre-amyloid state**
- Polymization

**Amyloid fibril**

**Symptomatic treatments**
- Cardiac pacemaker, cardiac transplantation, dialysis, kidney transplantation, vitreous surgery, decompression for carpal tunnel syndrome, etc.

**Liver transplantation**
- ASO, siRNA

**Retinal laser photocoagulation**

**Gene conversion therapy**
- (single-stranded oligonucleotides)

**Tafamidis, Diflunisal**

**IDOX, doxycycline, TUDCA**

**Immunotherapy**
- (vaccine, antibody)

**Muscle Weakness**

(b) 
- Tafamidis
- Placebo

**Baseline**
- Month 6
- Month 12
- Month 18
- Month 24
- Month 30
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

Case 2:
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

- B12, methylmalonic acid, TSH, SPEP/UPEP/immunofixation/free light chains, syphilis IgG, HIV screen, HCV IgG, ESR/CRP negative
- TTE normal
- Sural nerve biopsy positive for amyloidosis with IHC demonstrating positive anti-TTR staining
- TTR mutational analysis demonstrated deleterious c223 T->A substitution in exon 3 resulting in Leucine78Histidine substitution
- Patient opting for clinical trial over liver transplant
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

Case 2:
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

Case 3:
56 year old female with chronic normocytic anemia and diffuse pulmonary nodules identified during a COPD exacerbation.
**Tracheobronchial Amyloidosis:**
- plaque variant or tumor variant
- may cause bronchial obstruction → recurrent pneumonia, respiratory failure
- management: observation, intermittent bronchoscopic resection, surgical resection, laser ablation

**Diffuse Interstitial Amyloidosis:**
- alveolar septal distribution → appears similar to pulmonary fibrosis on imaging
- progressive dyspnea

**Nodular Pulmonary Amyloidosis:**
- rare (case reports)
- single or multifocal, bilateral and asymmetrical
- nodules range from 0.4 – 5 cm with average size 3 cm and greatest reported size 15 cm
- may calcify or develop metaplastic bone or cartilage formation
- generally incidental findings on imaging or at autopsy
- indolent and benign course
Nodular Pulmonary Amyloidosis (NPA):

- localized form of Ig-associated (AL type) amyloidosis
- amyloid results from localized production of clonal or polyclonal Igs
- incidence of Ig kappa-derived amyloid 3:1 in contrast to lambda predominance in systemic AL amyloidosis
- codeposition of heavy chains (mixed AL/AH type) which is rare in systemic AL

- focal aggregates of lymphocytes and monotypic CD19+ plasma cells are present within and at the periphery of the nodules

- etiologies: lymphoplasmacytic lymphoma
  - MALT lymphoma
  - chronic inflammation (33% associated with autoimmune disorder)

- average age at detection 6th decade
- prognosis excellent with asymptomatic, indolent course
Nodular Pulmonary Amyloidosis
Case 1:
60 year old male with chronic hepatitis B and C, rheumatoid arthritis, poorly controlled diabetes mellitus, chronic hypertension, peripheral vascular disease, peripheral neuropathy, chronic kidney disease with nephrotic range proteinuria, and restrictive cardiomyopathy.

Case 2:
67 year old male with carpal tunnel syndrome, progressive severe bilateral sensorimotor polyneuropathy resulting in disability, and strong family history of severe polyneuropathy.

Case 3:
56 year old female with chronic normocytic anemia and diffuse pulmonary nodules identified during a COPD exacerbation.
- VATS middle right lobe wedge resection demonstrated nodular amyloid deposition with classic peripheral plasma cells and lymphocytes; IHC negative for kappa and lambda light chains, heavy chain, and SAA
- Laser dissection of plaque with mass spectroscopy demonstrated kappa light chain deposition
- SPEP, UPEP, immunofixation, serum free light chains negative; skeletal survey negative
- Bone marrow biopsy negative for clonal plasma cell population and for amyloid
- B12 levels low with negative anti-intrinsic factor Ab screen (anti-parietal cell Ab screen pending)
Conclusions:

1. Amyloidosis is a heterogeneous disease with more than 30 known causative proteins
   - AL most common with systemic manifestations and underlying plasma cell or B cell disorder
   - SAA second most common with systemic manifestations and underlying inflammatory disorder
   - ATTR third most common with neuropathy and restrictive cardiomyopathy dominating symptom complex

2. Obtain tissue for diagnosis
   - congo red stain \(\rightarrow\) polarized light \(\rightarrow\) IHC for Ig, kappa/lambda light chains, SAA, TTR
   - mass spectroscopy can identify amyloidogenic protein if IHC nondiagnostic

3. Clinical trials are underway for disease modifying therapies in ATTR, however the only therapy with demonstrated survival benefit is orthotopic liver transplant

4. Nodular pulmonary amyloidosis is a generally benign condition that may be incidentally identified radiographically and generally does not require treatment