Amyloidosis

1. What is Amyloidosis?

Amyloidosis refers to a diverse group of disorders which have in common the abnormal accumulation of protein in tissues, often resulting in derangement in organ function.

2. What are Amyloid proteins?

The protein constituents of amyloid are heterogeneous, and vary depending on the underlying disorder. However, all amyloid proteins share the following common characteristics:

- Non-branching fibrils 7.5-10 nm diameter composed of paired filaments which demonstrate a cross beta pleated sheet arrangement
- A P-component (5%), which may affect tissue deposition

3. How are Amyloid proteins produced?

This depends on the type of underlying disorder:

- In some settings there is protein production due to an abnormal (neoplastic) cellular proliferation
  
  Examples: multiple myeloma and excess light chain production
  medullary thyroid carcinoma and excess thyrocalcitonin production

- In some settings there is inflammatory stimulation of protein production:
  Example: secondary (AA) amyloidosis with serum amyloid protein production by liver

- In some settings there is a genetic defect leading to an abnormal protein
  Example: Familial amyloidotic neuropathy
4. What does Amyloid look like?

Characteristic deposits in vessel walls (glomeruli, arterioles etc) and interstitium

Routine H&E: pink, homogeneous

Congo Red: dark red

Polarized Congo Red: birefringent, yellow-green color

5. How can Amyloidosis be classified?

<table>
<thead>
<tr>
<th>Localized</th>
<th>Systemic</th>
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<tbody>
<tr>
<td>medullary carcinoma of thyroid</td>
<td>plasma cell dyscrasias</td>
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<tr>
<td>isolated organ involvement</td>
<td>inflammatory conditions</td>
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<tr>
<td>Alzheimer’s disease</td>
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<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Hereditary</th>
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<tbody>
<tr>
<td>Plasma cell dyscrasia (immunoglobulin:AA)</td>
<td>Inflammatory condition (serum amyloid protein: AA)</td>
<td>Familial Mediterranean</td>
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<td>Familial amyloidotic neuropathy</td>
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Type of Protein Involved:

**AL**: composed of immunoglobulin light chains, usually lambda, associated with plasma cell dyscrasia

**AA**: synthesized by liver in association with chronic inflammatory conditions (rheumatoid arthritis)

**AB2m**: composed of Beta 2 microglobulin associated with hemodialysis, renal failure

**AB2**: abnormal transmembrane protein associated with cerebral amyloid (Alzheimer’s)

**ATTR**: altered transthyretin in familial amyloidosis, normal transthyretin in age-associated amyloid

Special immunohistochemical stains are available to identify specific proteins, which may be helpful in distinguishing hereditary forms (and initiating followup with family members)
6. **What are the effects of Amyloid deposition?**

**Kidney:** may be enlarged, normal, or shrunken
  deposition in glomeruli leads to proteinuria, nephrosis, renal failure

**Liver:** deposits in space of Disse, often with minimal functional impairment

**Heart:** interstitial deposition
  may result in restrictive cardiomyopathy, conduction defects

**GI tract:** deposits in vessels, lamina propria, muscularis
  may lead to malabsorption, bleeding, diarrhea
  tongue often involved by nodular deposits

7. **How is Amyloidosis diagnosed?**

- Often a difficult diagnosis, because of vague, insidious onset of signs and symptoms
- Amyloidosis should always be somewhere in the list of differential diagnoses in the setting of multisystem organ dysfunction
- Diagnosis can be made by tissue biopsy, and appropriate staining, subcutaneous fat needle aspiration
- May require further work-up: bone marrow exam, protein electrophoresis, etc...

8. **How is Amyloidosis treated?**

- Treatment is usually aimed at correcting the underlying disorder, if identified, and supportive therapy of organ dysfunction
- In widespread systemic amyloidosis, disease is often fatal