Amyloidosis

Intracellular accumulations

- There are four main pathways of abnormal intracellular accumulations:
- Inadequate removal of a normal substance secondary to defects in mechanisms of packaging and transport, as in fatty change in the liver
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion.
- Failure to degrade a metabolite due to inherited enzyme deficiencies. The resulting disorders are called *storage diseases*.
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example of this type of alteration.

Definition of amyloidosis

Amyloidosis is a disorder of protein misfolding.

Amyloid is beta pleated anything.

Amyloidosis is a condition in which extracellular deposits of fibrillar proteins are responsible for tissue damage.

These abnormal fibrils are produced by the aggregation of misfolded proteins.

The presence of abundant charged sugar groups in these adsorbed proteins gives the deposits staining characteristics that were thought to **resemble starch** (amylose). Therefore, the deposits were called "amyloid".

Pathogenesis of amyloidosis

- Normally, misfolded proteins are degraded intracellularly in proteasomes, or extracellularly by macrophages.
- Misfolded proteins are unstable and self-associate, leading to the formation of oligomers and fibrils that are deposited in tissues.
- Amyloid is deposited as fibrils in extracellular tissues and disrupt normal function.
- Amyloid deposits are composed of nonbranching fibrils, each formed of β-sheets.
- The dye Congo red binds to these fibrils and produces a red–green dichroism (birefringence) in polarisation light, which is commonly used to identify amyloid deposits in tissues.
- The proteins that form amyloid fall into two general categories:
  (1) normal proteins that have a tendency to fold improperly
  (2) mutant proteins that are prone to misfolding and subsequent aggregation.

Types of amyloid

The **AL (amyloid light chain) protein** is produced by plasma cells and is made up of immunoglobulin light chains.

- The AL type is associated with some form of monoclonal B cell proliferation.

The **AA (amyloid-associated) fibril** is a protein derived from a larger serum precursor called SAA (serum amyloid-associated) protein.

SAA is synthesized by liver cells under the influence of cytokines during inflammation.

- Long-standing inflammation leads to the AA form of amyloid deposits.

Aβ amyloid is found in the cerebral lesions of Alzheimer disease.

- The Aβ protein is derived from a much larger transmembrane glycoprotein called amyloid precursor protein (APP).

Other proteins in amyloid plaques

Transthyretin is a normal serum protein that binds carries thyroxin and retinol.

Common in senile systemic/cardiac amyloidosis.

Beta 2 microglobulin is a protein present in high concentrations in chronic renal failure patients' serum.

Classification of amyloidosis

Amyloid may be

1. **systemic** (generalized), involving several organ systems, or it may be
2. **localized**, when deposits are limited to a single organ.

The systemic pattern is subclassified into

1. **primary** amyloidosis when associated with a monoclonal plasma cell proliferation and
2. **secondary** amyloidosis when it occurs as a complication of an underlying process.

Hereditary or **familial** amyloidosis constitutes a separate with several distinctive patterns of organ involvement.

Primary Amyloidosis: AL amyloidosis

Amyloid in this category usually is **systemic** in distribution and is of the **AL** type.

This is the most common form of amyloidosis.

In 10% of cases of multiple myeloma there is systemic amyloidosis peresent.

The malignant plasma cells synthesize abnormal amounts of a single specific immunoglobulin (monoclonal gammopathy), producing an M (myeloma) protein spike on serum electrophoresis.

In addition, plasma cells also may synthesize and secrete either the λ or κ light chain.

Reactive Systemic Amyloidosis

The amyloid deposits in this pattern are systemic in distribution and are composed of AA protein.

Etiology is sustained chronic inflammation.

Classically, tuberculosis, bronchiectasis, and chronic osteomyelitis were the most common causes.

Today it is autoimmune disease. (rheumatoid arthritis for example).

Familial (Hereditary) Amyloidosis

The best-characterized is an **autosomal recessive condition called familial Mediterranean fever**. It is rare.

This is a febrile disorder characterized uncontrolled inflammasome formation.

Bouts of fever accompanied by inflammation of serosal surfaces, including peritoneum, pleura, and synovial membrane.

The amyloid fibril proteins are made up of AA proteins.

Inflammasomes form when an infection, injury or other disturbance is detected by the immune system, and they send messages to immune cells to respond.

Endocrine Amyloid
Amyloid of Aging

- Microscopic deposits of localized amyloid may be found in certain endocrine tumors.
- Also localized amyloid may be found in the islets of Langerhans in patients with type 2 diabetes mellitus.
- Senile (related to aging) systemic amyloidosis refers to the systemic deposition of amyloid in elderly persons. This form also is called senile cardiac amyloidosis.

Morphology

When amyloid accumulates in larger amounts, the organ frequently is enlarged and the tissue typically appears gray with a waxy, firm consistency.

On histologic examination, the amyloid deposition is always extracellular and begins between cells.

As the amyloid accumulates, it encroaches on the cells, in time surrounding and destroying them.

Histomorphology

- The histologic diagnosis of amyloid is based on its staining characteristics.
- With HE stain it is bland, hyalin like substance.
- With the dye Congo red, which under ordinary light imparts a pink or red color to amyloid deposits. Under polarized light the Congo red–stained amyloid shows so-called apple-green birefringence.
- This reaction is shared by all forms of amyloid and is caused by the crossed β-pleated configuration of amyloid fibrils.

Polarized light microscope

In order to detect amyloid we use our ordinary light microscopes with added or built in polarization filters.

Kidney

Histology notes: we always examine four kompartments in kidney samples: glomeruli, tubuli, vessels and interstititum.

Amyloidosis of the kidney is the most common and most serious feature of the disease.
Grossly, the kidney appears large, pale, gray, and firm.
Microscopically, the **amyloid deposits are found in the glomeruli.**
At first we see focal deposits in the mesangium. With progression, the deposition encroaches on the capillaries and leads to total obliteration of the capillaries.

The interstitial peritubular deposits frequently are associated with the appearance of amorphous pink casts within the tubular lumens, presumably of a proteinaceous nature.

Spleen

Enlargement (200 to 800 gm): splenomegaly.

- deposits may be in the splenic *follicles*, producing tapioca-like granules on gross examination "**sago spleen**"
- or the amyloidosis may principally involve the splenic *sinuses*, eventually extending to the splenic pulp, with formation of large, sheetlike deposits "**lardaceous spleen**".

In both patterns, the spleen is **firm** in consistency.

Liver

Enlargement of the liver: hepatomegaly

- Macroscopy: pale, gray vaxy liver.
- Microscopy: amyloid appears in Disse spaces and sinusoids. Entrapped hepatocytes eventually undergo pressure atrophy.

Heart

Amyloidosis of the heart may occur either as isolated organ involvement or as part of a systemic distribution.

When accompanied by systemic involvement, it is usually of the AL form.

The isolated form (senile amyloidosis) usually is confined to older persons.

The deposits may not be evident on gross examination, or they may cause minimal to moderate cardiac enlargement. The most characteristic gross findings are gray-pink, dewdrop-like subendocardial elevations, particularly evident in the atrial chambers. On histologic examination, deposits typically are found throughout the myocardium, beginning **between myocardial fibers** and eventually causing their pressure atrophy.

Other organs

In systemic amyloidosis deposits appears in

- Adrenals
- Thyroid
- Hypophysis
- GI tract
- Tongue
- Carpal tunnel syndrome

Clinical manifestations

Amyloidosis may be an unsuspected finding or it may be responsible for the patient's death. The clinical course depends on the particular sites or organs affected and the severity of the involvement.

- Most common symptoms and signs in systemic amyloidosis: renal disease, hepatosplenomegaly, cardiac disease.
- Most common cause of death in amyloidosis: renal failure or cardiac arrhytmias.
- Cardiac symptoms (cardiac amyloidosis) include: conduction disturbances, arrhytmias.

Diagnosis

Biopsy and subsequent Congo red staining is the most important tool in the diagnosis of amyloidosis.

In general, biopsy is taken from the organ suspected to be involved.

For example, renal biopsy is useful in the presence of urinary abnormalities. Rectal and gingival biopsy specimens contain amyloid in as many as 75% of cases with generalized amyloidosis.

Bone marrow examination in such cases usually shows plasmacytosis, even if skeletal lesions of multiple myeloma are not present.

Proteomic analysis of affected tissue is now being widely used for detection of small amounts of amyloid (from fat aspirates) and for definitive identification of the type of amyloid.

Prognosis

The prognosis depends to some extent on the control of the underlying condition. Patients with myeloma-associated amyloidosis have a poorer prognosis, although they may respond to cytotoxic drugs used to treat the underlying disorder.

Resorption of amyloid after treatment of the associated condition has been reported, but this is a rare occurrence.