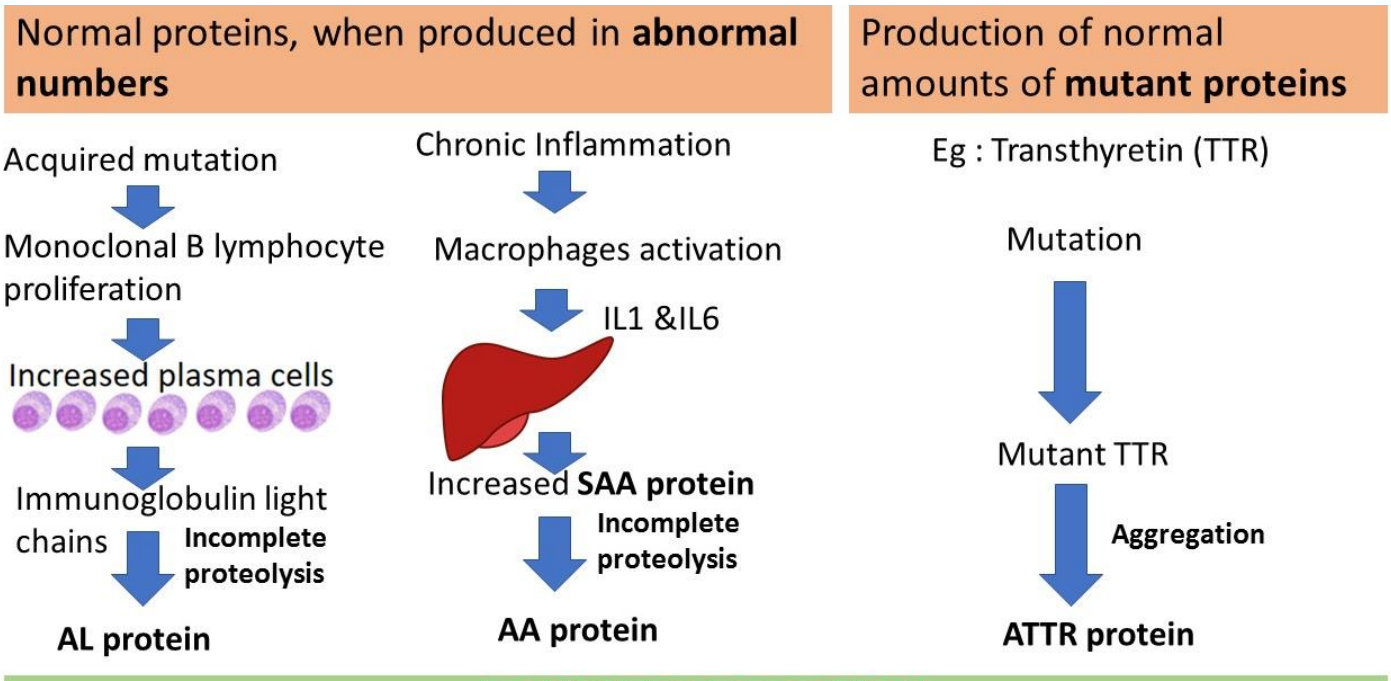
Amyloidosis

- Amyloidosis refers to a group of conditions characterized by extracellular accumulation of fibrillar proteins that are responsible for tissue damage and necrosis
- Amyloidosis includes both inherited and inflammatory disorders
- Amyloidosis is a disorder primarily of protein misfolding. Proteins which are soluble in their physiological forms become insoluble and accumulate when they are misfolded
- These extracellular accumulations bind to numerous glycosaminoglycans and phospholipids such as serum amyloid P component
- Though numerous proteins are misfolded, histologically they all look similar and resemble sucrose hence the name **"amyloid"**

Pathophysiology

- 23 proteins have been recognized to undergo amyloid like deposition
- These protein form individual filaments measuring **7.5 to 10 nm** in diameter which join to form a **β pleated sheet**
- These are detected by **Congo red stain** (red-green color birefringence)
- Misfolded proteins are phagocytosed my macrophages extracellularly and degraded by proteasomes intracellularly however, amyloid deposits evade these immune responses
- Amyloid can form by
    - Normal proteins with an inherent property to misfold
    - Mutated protein which cannot fold properly
- Amyloid proteins can be discussed as three major types and few minor types of proteins
    - **AL (Amyloid light chain proteins)**
        - These are produced by plasma cells and are associated with monoclonal B cell proliferation
        - These proteins are immunoglobulin light chains prone to misfolding
    - **AA (Amyloid associated proteins)**
        - Produced from serum amyloid-associate protein (SAA) as precursor
        - Non immunoglobulin protein which is large and weighs 12Kda and higher
        - Synthesized by liver cells under the influence of IL-6 and IL-1
        - Elevated levels of SAA with inherent enzymatic defect for its breakdown leads to amyloidosis
        - Mutated SAA does not undergo phagocytosis by macrophages
    - **Aβ amyloid**
        - Produced from amyloid precursor protein (APP)
        - Smaller protein weighing 4Kda associated with Alzheimer's disease
    - **Transthyretin (TTR)**
        - Transports thyroxin and retinol physiologically
        - TTR deposits are seen in aged patients due to misfolding (senile systemic amyloidosis)
        - In familial cases it deposits due to defects in lysosome
    - **β_2 microglobulin**
        - seen in patients on long term dialysis
        - Amyloid variant develops due to misfolding and renal disease, with deposits in synovium, joints and tendon sheets
        - Most commonly seen in carpal ligaments of wrist leading to compression of median nerve (carpal tunnel syndrome)



Classification of amyloidosis

- Amyloidosis can be classified as
  - Primary amyloidosis: amyloidosis associated with defective plasma cell proliferation
  - Secondary amyloidosis: amyloidosis resulting from chronic inflammatory reaction
  - Systemic amyloidosis: involving multiple organs
  - Localized amyloidosis: involves single organ

Type of amyloidosis	Type of amyloid protein	Site	Example
Primary amyloidosis: immunocyte dyscrasias with amyloidosis	AL	Multifocal sites in skeletal system	Multiple myeloma
Reactive systemic amyloidosis	AA	Systemic involvement	Tuberculosis, bronchiectasis, chronic osteomyelitis, RA ankylosing spondylitis, inflammatory bowel disease
Familial amyloidosis	ATTRs	Systemic involvement, CNS	Mediterranean fever Familial polyneuropathies
Localized amyloidosis	AL	Lung, larynx, skin, urinary bladder, tongue	Grossly detectable nodular masses
Endocrine amyloid	Unique proteins	Thyroid, pancreas, stomach	Medullary carcinoma of thyroid, pheochromocytoma, undifferentiated carcinomas of stomach

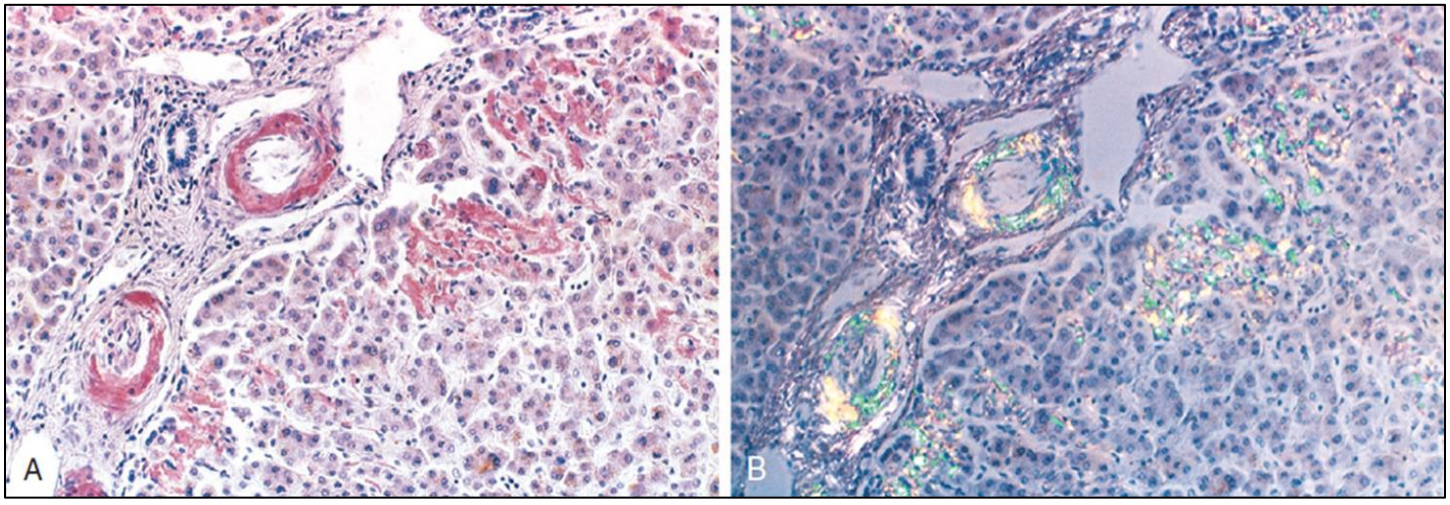
- In multiple myeloma, plasma cells produce increased quantities of abnormal immunoglobulin (monoclonal gammopathy) leading to M protein (myeloma protein) formation
- Plasma cells also produce abnormal ƙ and λ chains known as Bence jones proteins

- In familial amyloidosis there is a gain of function mutation in gene pyrin which codes for inflammasome resulting in overproduction of inflammatory cytokine IL-1

Morphology of amyloidosis

- On gross examination, application of iodine and sulphuric acid to the cut surface of effected organ yields mahogany brown areas
- Minor deposits are unrecognizable and larger deposits show pale, gray areas with firm, waxy consistency
- On histopathologic examination, amyloid is always seen in between cells and in AL forms perivascular accumulation is common
- Most commonly used dye is Congo red which gives red or pink color to deposits under light microscope and bright apple green birefringence under polarized light microscope

Organ	Macroscopically	Microscopically
Kidney	• Cut surface shows large, pale gray, firm areas • Long standing cases show reduction in size	• Glomeruli are affected with thickening of basement membrane and capillary loops
Spleen	• Enlargement (200 to 800 grams) • Sago spleen: splenic follicles produce tapioca like granules • Lardaceous spleen: splenic pulp forms large sheet like deposits • Blood in sinuses imparts reddish color to the waxy, friable deposits	• Engorgement of blood vessels surrounding splenic follicles
Liver	• Enlargement (up to 9000 grams)	• First appears in spaces of Disse • Advanced cases involve hepatocytes causing compression atrophy of cells
Heart	• Grey pink, dew drop like, subendocardial elevations	• Deposits are seen between the myocardial fibers



Liver affected with amyloidosis, Congo red staining under light microscope and polarization microscope respectively

Clinical course of amyloidosis

- Clinically amyloidosis can be asymptomatic or even lead to death
- Presenting symptoms are non-specific ones such as weakness, fatigue and weight loss
- Advanced cases show
    - Renal disease: severe proteinuria leading to renal failure and death
    - Hepatosplenomegaly
    - Cardiac amyloidosis: development of arrythmias (death in 40% of cases), conduction disturbances and restrictive cardiomyopathy
- Biopsy of involved organs followed by Congo red staining is the most important diagnostic tool
- Serum and urine electrophoresis and immunoelectrophoresis can be performed in suspected AL cases
- Proteomic analysis is used for detection of small quantities of amyloid (from fat aspirates)
- Systemic amyloidosis shows poor prognosis with death in 1 to 3 years
- Depending on the location AA prognosis varies but usually better than AL type

Miscellaneous points

- Amyloid shows β pleated structure in X ray crystallography and under electron microscope non branching fibrils of indefinite length are seen
- Proliferation of smooth muscle cells is important for neo intimal hyperplastic response
- Other stains used for amyloid are crystal violet, Thioflavin T
- Most common site for a biopsy for amyloidosis is from kidney
- Amyloidosis is associated with type 2 DM as replacement of islets of Langerhans cells will produce insufficient insulinemia