Amyloidosis

Amyloidosis

- Def: deposition of Insoluble amyloid fibrils in Extracellular spaces of tissues
- Amyloid fibrils: β-pleated sheets of serum amyloid P (SAP) & aminoglycans
- Can be inconsequential or with severe patho-physiologic changes

Classification

- As per distribution:

1. Systemic Amyloidosis… Inflammatory, Genetic, Neoplastic, Iatrogenic
2. Localized/Organ-limited: Aging, DM

Classification

- As per biochem composition of precursor protein:

1. AL (Ig Light chain).....Pr./ Multiple myeloma
2. AH (Ig Heavy chain).....-do-
3. ATTR (Transthyretin).....Familial, Senile
4. Aβ2M (β2 Microglob)....Hemodialysis
5. AA (Apo-A).....Sec/Reactive
6. AIAAP (Islet Amyloid Polypeptide) .....Insulinoma

Etiopathigenesis

- Systemic Amyloidosis

1. AL

i. MC form of Amyloidosis

ii. Either Pr. Idiopathic or asso with MM

iii. Precursor protein = Ig light chains

iv. λ : k = 2 : 1

v. Overproduction of fragmented light chains or abn processing of Ig by macrophage enzymes

Etiopathigenesis

2. AA
   i. Sec/Reactive/Acqiured Amyloidosis
   ii. Most frequently a complication of Chr. Infxns (TB, Leprosy, Osteomyelitis, FMF)
   iii. Chr. Infl. states→ IL-1,6 & TNF-œ stimulate hepatic synthesis of Serum Amyloid A

Etiopathigenesis

3. Heredofamilial Amyloidosis:

e.g. ATTR, Aβ2M, AApoAI etc.

i. Dominantly inhereted
ii. Genetic mutations enhancing protein misfolding and fibril formation
iii. Delayed onset of ds symptoms (3-7decade)
iv. S/s...Polyneurolpathy, Nephropathy, CMP, Hepatomegaly, Dementia

Etiopathigenesis

- Localized Amyloidosis

1. Aß (AßPP): Alzheimer's ds, Aging
2. APrP (Prion Protein): Spongiform encephalitis
3. Acal (Procalcitonin): C-cell thyroid tumor
4. AIAPP (Islet Amyloid Polypeptide)
5. Apro (prolactin): Prolactinoma

Clinical Manifestations

- Depend on biochem nature n site of deposition of fibril protein
- For systemic amyloidosis....Proteinuria in AA n AL; Neuropathies in Familial Amyloidosis

Clinical Manifestations

- Kidneys:

i. Proteinuria---→Azotemia--→ESRD
ii. HTN (late feature, not so common)
iii. RTA
iv. No active urinary sediments

- Liver n Spleen

i. HSM without abn LFTs or cytopenia (hypersplenism)

Clinical Manifestations

- Heart:

i. Conduction blocks n Arrhythmias
ii. CMP (restrictive)---→ intractable CHF
iii. "Granular Sparkling"...hyperrefractile pattern on 2-D echo

- Skin:

i. Commonly involv in Pr. AL
ii. Waxy papules---axillary, inguinal n perineal
iii. Raccoon eyes---periorbital echymosis

Clinical Manifestations

- GIT:

➢ Results from direct involv of GI Tract or infilt of autonomic N. Syst. (neuropathy)

i. Diarrhoea
ii. Protein loosing enteropathy
iii. Malabsorption synd
iv. GI bleed, ulcerations
v. Macroglossia
vi. Esophageal dysmotility

Clinical Manifestations

- Nervous System:

i. Peripheral neuropathy
ii. OH
iii. Sphincter incompetence
iv. Carpal tunnel synd
v. Adie's pupils

- Cranial Nerve involvment is Rare

Clinical Manifestations

- Endocrine: Clinical dysfunction rare

i. Thyroid (with medullary Ca thyroid)
ii. Pancreas (with DM)

- Musculoskeletal:

i. Direct involv of joints (synovium, synovial fluid, articular cartilage) is rare
ii. Carpal tunnel synd from cystic bone lesions
iii. Pseudomyopathy (infiltration of muscles)

Clinical Manifestations

- Hematologic:

- Bleeding tendencies from…

i. Vessel wall (tunica media) involv

ii. Clotting factor (esp. factor X) def. from polyanionic amyloid fibril n clotting factor binding…more so in spleen….therapeutic splenectomy

- Respiratory:

- Upper n Lower resp tract n pulm parenchyma

Clinical Manifestations

- AL:-

i. Unexplained nephrotic synd
ii. Malabs synd/ Chr diarrhoea
iii. Peripheral neuropathy
iv. Cardiomyopathy
v. Hepatomegaly
vi. Carpal tunnel synd

- ➢ Median survival (untreated) ≈ 1 yr

Clinical Manifestations

- AA:-

i. Proteinuria
ii. Hepatomegaly
iii. Unexplained GI disease

- In asso with Chr infections (TB/Leprosy/ Osteomyelitis) or Chr inflammation (RA/IBD)

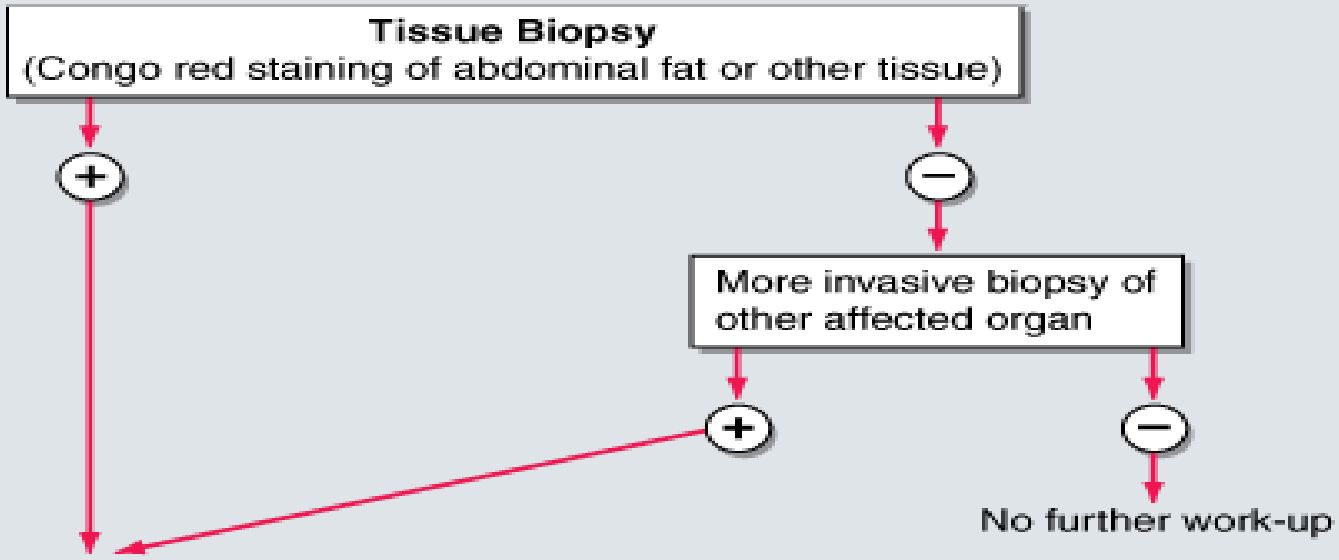
Clinical Manifestations

- Hereditary Amyloidosis:-
- Peripheral or autonomic neuropathy in asso with

i. Unexplained renal ds/nephrotic synd
ii. CMP

- Median survival (untreated) ≈ 7-15 yrs

Clinical Suspicion of Amyloidosis

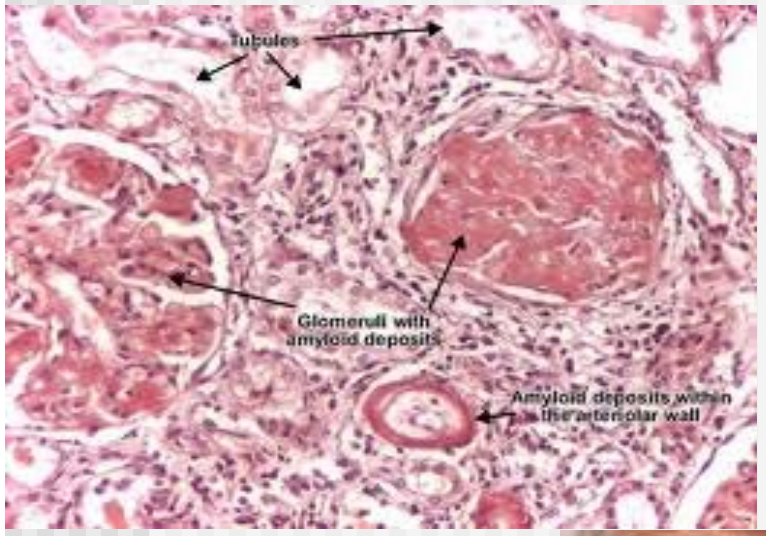


Immunohistochemical staining of biopsy	Identify	Diagnosis
→ Kappa or lambda light chain	Monoclonal protein in serum or urine Plasma cell dyscrasia in bone marrow	AL amyloidosis *(Screen for cardiac, renal, hepatic, autonomic involvement, and factor X deficiency)*
→ Amyloid A protein	Underlying chronic inflammatory disease	AA amyloidosis *(Screen for renal, hepatic involvement)*
→ Transthyretin	Mutant transthyretin +/- family history	Familial ATTR amyloidosis *(Screen for neuropathy, cardiomyopathy; screen relatives)*
	Wild-type transthyretin (usually males >65, cardiac)	Age-related or senile systemic amyloidosis
→ Negative	Mutant ApoAI, ApoAII, fibrinogen, lysozyme, gelsolin	Familial amyloidosis of rare type *(Screen for renal, hepatic, GI involvement)*

From Misfolded Proteins to Well-Designed Treatment

Treatment:

AL	AA	Familial Amyloidosis
Immunosupressive therapy Cyclic oral Melphalan & Prednisolone (CHR=5%) High dose IV Melphalan With Stem cell rescue (CHR=40%) Aggressive therapy often curtailed by low performance status, advanced cardiac disease Supportive therapy for nephrotic synd, CMP, OH (midodrine)	Aggressive treatment for underlying inflammatory condition Surgical excision for infection Colchicine 1.2-1.8mg/d for FMF Eprodisate for AA renal disease irrespective of underlying disorder--- prevents amyloid fibril formation	Organ transplant (Liver) Genetic counselling


Tubules
Glomeruli with amyloid deposits
Amyloid deposits within arteriolar wall