Overview on amylodosis (part 2)

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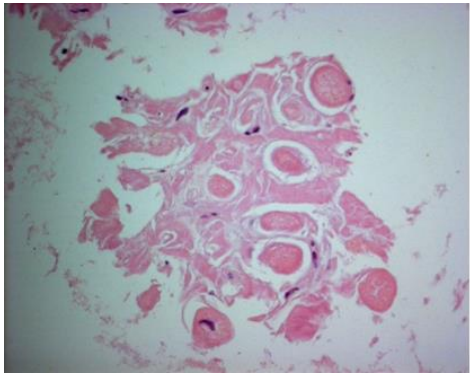
The amyloidoses

- All amyloidoses possess same staining and ultrastructural properties:
  - In HE staining: homogenous eosinophilic appearance
  - electron microscope: fibrillar structure with extensive beta sheet secondary structure
- distinguishing AL from other forms of systemic amyloidosis is critical
  - AL treatment is ineffective and harmful in these entities



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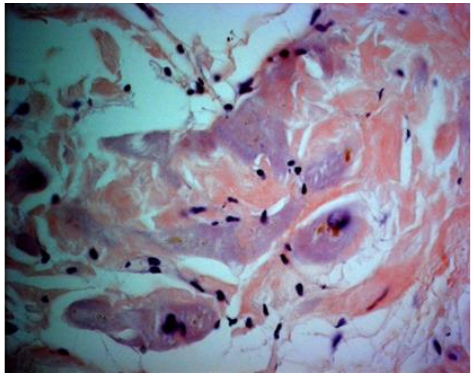

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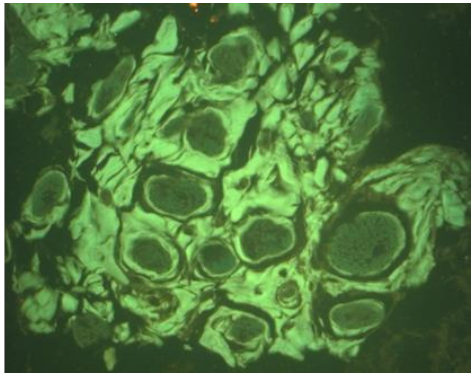


thioflavine

Classification

- historical classification according to clinical or pathological features:
  - primary idiopathic amyloidosis
  - secondary amyloidosis
  - familial/hereditary amyloidosis
  - senile
  - dialysis associated
  - myeloma associated
- new classification is etiologically based on chemical nature of the fibrillar component

Protein precursor of amyloid deposits

Protein class	Precursor protein (abbreviation)	Amyloid type	Clinical type
High-density apolipoproteins	(Apo) serum AA	AA	Associated with amyloid complicating chronic infections or inflammatory diseases, and some heredofamilial periodic fever syndromes, such as familial Mediterranean fever
	Apolipoprotein A-I (ApoAI)	AApoAI	Age-related amyloid occurring in the aortic intima, and some hereditary neuropathic or cardiopathic amyloidoses[1,2]
	Apolipoprotein A-II (ApoAII)	AApoAII	Some hereditary nephropathic amyloidoses[3]
Immunoglobulin (Ig) gene superfamily	Ig L chain/Ig H chains (IgL/IgH)	AL/AH	Primary and myeloma-associated amyloidosis
	Beta-2 microglobulin	Aβ2m	Dialysis amyloidosis
Neuroendocrine	(Pro)Calcitonin	ACal	Amyloid complicating C-cell thyroid tumors
	Islet amyloid	AIAPP	Islet cell amyloid in insulinomas, type II diabetes mellitus, and aging[4]
	Atrial natriuretic peptide	AANF	Isolated atrial amyloidosis of aging
	Prolactin/Apro	APro	Prolactinomas/aging
	Insulin	AIns	Local amyloid complicating use of the insulin pump
Cytoskeleton-related	Gelsolin	AGel	Hereditary neuropathic amyloid associated with corneal lattice dystrophy and cutis laxa (Meretoja syndrome)[5]
	Keratin	Does not yet have nomenclature designated	Cutaneous amyloid
	Keratoepithelin	AKer	Hereditary granular, lattice, and avellino corneal dystrophies[6]
Transport protein	Transthyretin (TTR; prealbumin)	ATTR	Hereditary neuropathic and/or cardiopathic amyloids; vitreous amyloidosis; leptomeningeal or renal amyloid in some kindreds; senile systemic amyloidosis[7]
Cerebrovascular/neurodegeneration	Amyloid precursor protein (APP)	ABeta	Hereditary and sporadic Alzheimer disease; congophilic cerebral angiopathy[8,9]
	Prion protein (PRP)	APrPsc	Hereditary and sporadic spongiform encephalopathies[10]
	BRI gene product	ABri/ADan	Hereditary dementias (British and Danish types)[11]
	Cystatin C (Cys - C)	ACys	Hereditary cerebrovascular hemorrhage with amyloidosis (Icelandic type)[12]
Coagulation protein	Fibrinogen alpha chain	AFib	Hereditary nephropathic amyloidosis[13]
Enzyme	Lysozome	ALys	Hereditary nephropathic amyloidosis; may have marked hepatic, splenic and gastrointestinal amyloid deposits[13]
VLDL/Chylomicron-associated apolipoprotein	Apolipoprotein IV (Apo AIV)	AApoAIV	Renal medulla and systemic disease[14,15]
Lung surfactant protein	Lung surfactant protein	ASPC	Interstitial lung disease[15,16]
Gallectin	Gallectin 7	AGAI7	Localized skin[15,17]
Other	Keratoepithelin	AKer	Various familial corneal dystrophies[6]
	Lactoferrin	ALac	Corneal amyloidosis associated with trichiasis
	Odontogenic ameloblast-associated protein	AOaap	Calcifying epithelial odontogenic tumors (CEOTs)
	Semenogelin 1	ASem1	Senile seminal vesicle amyloid
	Lactadherin	AMed	Senile aortic amyloid; media deposition
	Leukocyte chemotactic factor 2	ALect2	Amyloid nephropathy

Systemic Amyloid A (SAA)

- worldwide most common systemic amyloidosis
- amyloid deposition accompanying chronic/recurring inflammatory disease
- ethnic variation in prevalence of AA: nature vs nurture
- Undertreated or longstanding infections or inflammation in persons in 'emerging countries' with lower degree of industrialization
- renal disease is most common : 80% -> nephrotic syndrome, tubular disorders, renal insufficiency
- cardiac involvement, hepatosplenomegaly, neuropathy: rare
- Causes:
  - infections: TBC, leprosy, osteomyelitis
  - inflammation: RA, Crohn
  - neoplastic: RCC, atrial myxoma, Hodgkin -> inflammation/cytokine production
  - inherited: familial Mediterranean fever -> SC fat aspiration generally not useful
    - autosomal recessive disease, fever, arthritis, serositis, rash, high SAA production
    - mutations in granulocyte genes
    - colchicine 3x/d reduces inflammation, inhibits AA formation in mice experiments, use of colchicine outside FMF is anecdotal

SAA: pathogenesis

- fragments of acute phase reactant serum amyloid A
- precursor apoprotein of serum amyloid A (Apo SAA), produced as part of a normal inflammatory response
  - increases the affinity of high-density lipoproteins (HDL) for macrophages during acute phase : 'reverse cholesterol metabolism' ->binds to HDL in serum -> acute phase reactant is formed
  - chemoattractant activity for monocytes and lymphocytes
  - release of proinflammatory cytokines and G-GSF
- 3 isoforms > different genes
- immunohistology can be used to identify AA: anti-AA antiserum
- treatment: reducing inflammation e.g. TNF inhibitors, IL6-inhibitor, diflunisal (NSAI)

β_2-microglobulin amyloid (dialysis related)

- β_2M is the light chain component of the HLA complex
- renal excretion and catabolization-serum accumulation in case of renal failure
- formerly: pore size of conventional dialysis membranes did not allow filtration of β_2M -> levels x30-60
  - after minimum 5y of hemodialysis, 20% ay 10y, 40% at 15y, >80% at 20y
  - reduction by improved dialysis techniques
- also reported in peritoneal dialysis and in renal failure without dialysis
- deposition in synovial membranes
- symptoms:
  - osteoarticular deposition: carpal tunnel, trigger finger, bone cysts, rotator cuff
  - X-ray lesions resembling myeloma!
  - heart, GI, liver, lung, prostate, adrenals, tongue
- renal biopsy: amyloid staining with anti-β_2M antiserum, SC fat not helpful
- DD hereditary renal amyloidosis: Apo AI, Apo AII Afib, ALys
- treatment: renal transplantation can arrest amyloid progression

Senile Systemic Amyloidosis (SSA)

- SSA is caused by deposition of wild type transthyretin (TTR)
- male predominance, most commonly >70 years
- massive ventricular deposition: infiltrative cardiomyopathy
  - cardiomegaly
  - heart failure
- Wild-type TTR may also be deposited in the lungs, hence 'systemic' however, lung deposition is usually clinically insignificant
- slower disease progression and longer survival than AL
- anti-TTR ab for immunohistochemical staining
- Treatment: symptomatic, anectotal use of colchicine

- asymptomatic amyloid deposition is a common finding on autopsy
- in the majority of cases, these deposits are of no clinical significance, but there is an association between atrial amyloidosis and atrial fibrillation

organ-specific amyloidosis

- localized amyloidosis
  - local collection of plasma cells producting AL precursor
  - skin, larynx, brain, isolated bladder amyloidosis, tracheobronchial tree, pulmonary nodules
  - treated by laser techniques to destroy local plasma cell collecton (no randomized trials)

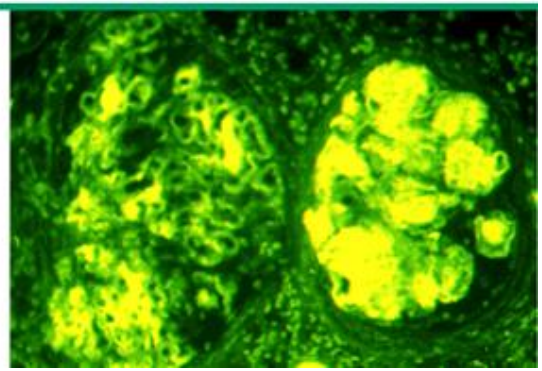
- locally produced proteins
  - Atrial amyloid: AANF
  - pancreatic isles, diabetes II: AIAPP
  - pituitary adenoma: aPro
  - corneal amyloidosis
  - aorta: in all elderly deposition of medin, a fragment of lactadherin, produced in aortic smooth muscle cell

- Primary CNS amylodosis
  - Alzheimer disease
  - amyloidosis cystatin C (Acys)
  - prion disease: oa Creutzfeldt-Jakob, BSE, kuru

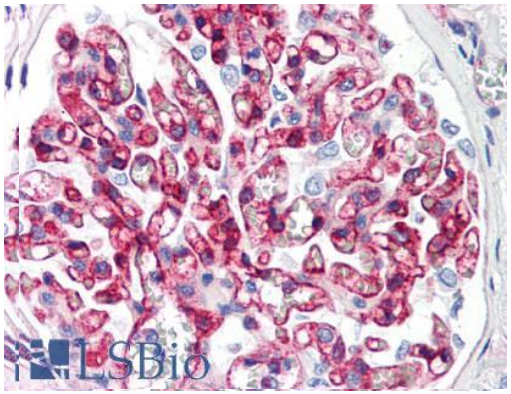
Immunohistochemistry: for some types

anti-AA

Immunofluorescence microscopy revealing secondary amyloidosis



anti-β_2M



anti-TTR