HM/CH-1/L-12

AMYLOIDOSIS

CLASSIFICATION

- Primary and secondary
- Mesenchymal and parenchymal
- Pericollagenous and perireticulin
- Pattern I (tongue, heart, bowel, skeletal smooth muscle, skin, nerves), II (liver, spleen, kidneys, adrenals) and mixed

Web Table 4.10: Classification of Amyloidosis.

Category	Associated Disease	Biochemical Type	Organs Commonly Involved
A. SYSTEMIC (GENERALISED) AMYLOIDOSIS			
1. *Primary*	Plasma cell dyscrasias	AL type	Heart, bowel, skin, nerves, kidney
2. *Secondary (Reactive)*	Chronic inflammation, cancers	AA type	Liver, spleen, kidneys, adrenals
3. *Haemodialysis-associated*	Chronic renal failure	$A\beta_2M$	Synovium, joints, tendon sheaths
4. *Heredofamilial*			
i. *Hereditary polyneuropathies*	—	ATTR	Peripheral and autonomic nerves, heart
ii. *Familial Mediterranean fever*	—	AA type	Liver, spleen, kidneys, adrenals
iii. *Rare hereditary forms*	—	AApoAI, AGel ALys, AFib, ACys	Systemic amyloidosis
B. LOCALISED AMYLOIDOSIS			
1. *Senile cardiac*	Senility	ATTR	Heart
2. *Senile cerebral*	Alzheimer's, transmissible encephalopathy	Aβ, APrP	Cerebral vessels, plaques, neurofibrillary tangles
3. *Endocrine*	Medullary carcinoma type 2 diabetes mellitus	Procalcitonin Proinsulin	Thyroid Islets of Langerhans
4. *Tumour-forming*	Lungs, larynx, skin, urinary bladder, tongue, eye	AL	Respective anatomic location

(AL= Amyloid light chain; AA= Amyloid-associated protein; $A\beta_2M$= Amyloid β_2-microglobulin; ATTR= Amyloid transthyretin; APrP=Amyloid of prion proteins, Aβ= β-amyloid protein).

Web Table 4.11: Contrasting Features of Primary and Secondary Amyloidosis.

Feature	Primary Amyloid	Secondary Amyloid
1. *Biochemical composition*	AL (Light chain proteins); lambda chains more common than kappa; sequence homology of chains	AA (Amyloid associated proteins); derived from larger precursor protein SAA; No sequence homology of polypeptide chain
2. *Associated diseases*	Plasma cell dyscrasias e.g. multiple myeloma, B cell lymphomas, others	Chronic inflammation e.g. infections (TB, leprosy, osteomyelitis, bronchiectasis), autoimmune diseases (rheumatoid arthritis, IBD), cancers (RCC, Hodgkin's disease), FMF
3. *Pathogenesis*	Stimulus → Monoclonal B cell proliferation → Excess of Igs and light chains → Partial degradation → Insoluble AL fibril	Stimulus → Chronic inflammation → Activation of macrophages → Cytokines (IL1,6) → Partial degradation → AEF → Insoluble AA fibril
4. *Incidence*	Most common in US and other developed countries	Most common worldwide, particularly in developing countries
5. *Organ distribution*	Kidney, heart, bowel, nerves	Kidney, liver, spleen, adrenals
6. *Stains to distinguish*	Congophilia persists after permanganate treatment of section; specific immunostains anti-λ, anti-κ	Congophilia disappears after permanganate treatment of section; specific immunostain anti-AA

Web Table 4.12: Staining Characteristics of Amyloid. HM

Stain	Appearance
1. *H & E*	Pink, hyaline, homogeneous
2. *Methyl violet/Crystal violet*	Metachromasia: rose-pink
3. *Congo red*	Light microscopy: pink-red Polarising light: red-green birefringence
4. *Thioflavin-T/Thioflavin-S*	Ultraviolet light: fluorescence
5. *Immunohistochemistry (antibody against fibril protein)*	Immunoreactivity: Positive
6. *Non-specific stains:*	
i) Standard toluidine blue	Orthochromatic blue, polarising ME dark red
ii) Alcian blue	Blue-green
iii) PAS	Pink

SYSTEMIC AMYLOIDOSIS

- Primary systemic (AL) amyloidosis
  - 30% cases of AL amyloid: plasma cell dyscrasias (MM, Waldenstrom's, HCD, plasmacytoma, nodular lymphomas
  - Single clone of plasma cells: λ or κ light chains (Bence-Jones proteins); λ >>than κ
  - 70% idiopathic
  - More common form in developed countries
  - Location: heart, kidneys, bowel, skin, peripheral nerves, respiratory tract, skeletal muscle

SYSTEMIC AMYLOIDOSIS

- Secondary/ reactive (AA) systemic amyloidosis
  - Reactive or inflammatory
  - Ch. Infections (tuberculosis, bronchiectasis, leprosy, ch. OM, ch. PN, Ch. skin infections), non-infectious (autoimmune e.g. RA, IBD), tumours (RCC, HL), FMF
  - More common form in developing countries
  - Locations: kidneys, liver, spleen, adrenals

SYSTEMIC AMYLOIDOSIS

- Haemodialysis-associated ($A\beta_2M$) amyloidosis
  - Pts on long-term dialysis (>10 yrs)
  - Derived from β_2 microglobulin, a normal component of MHC
  - Location: BVs in synovium, tendon sheaths, subchondral bones
- Heredofamilial amyloidosis
  - Hereditary polyneuropathic (ATTR) amyloidosis
  - Familial Mediterranean fever (FMF) (AA)
  - Rare hereditary forms: AApoAI, AGel, ALys, AFib, ACys

LOCALISED AMYLOIDOSIS

- Senile cardiac amyloidosis (ATTR)
- Senile cerebral amyloidosis (Aβ, APrP)
- Endocrine amyloidosis (hormone precursors)
- Localised tumour-forming amyloid (AL)

DIAGNOSIS OF AMYLOID

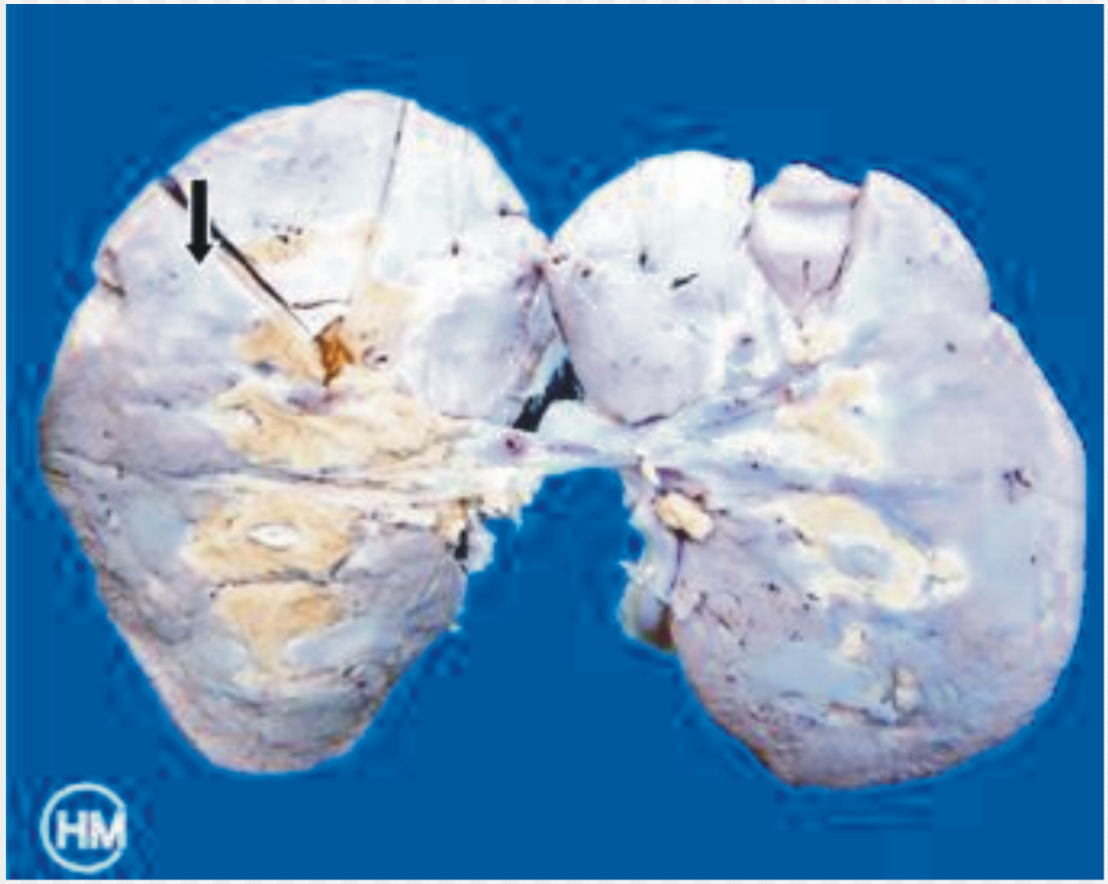
- Biopsy examination
- In vivo Congo red test
- Other tests (electrophoresis, immunoelectrophoresis)

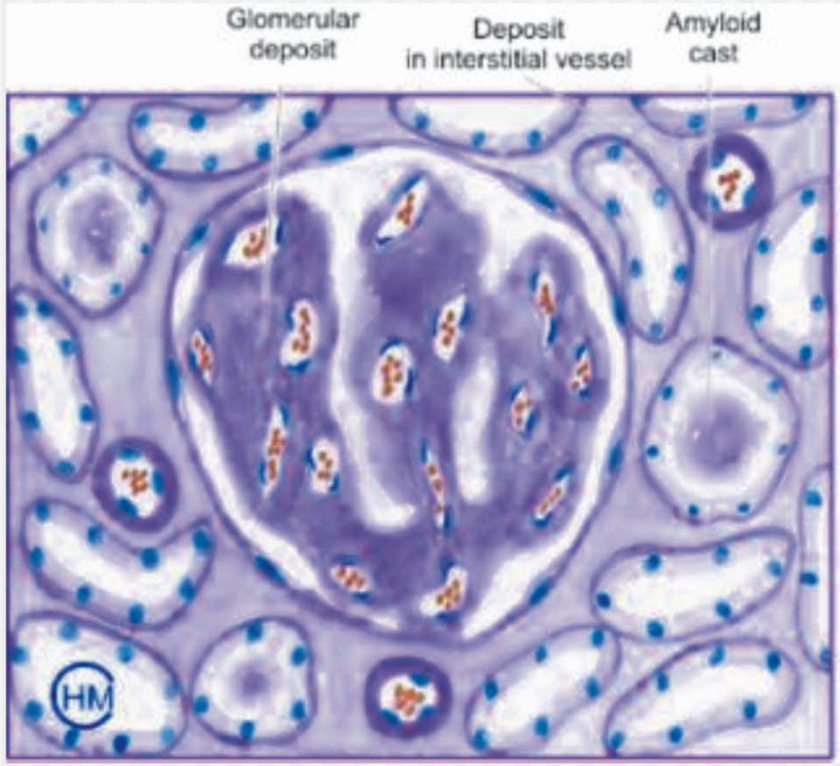
PATHOGIC CHANGES

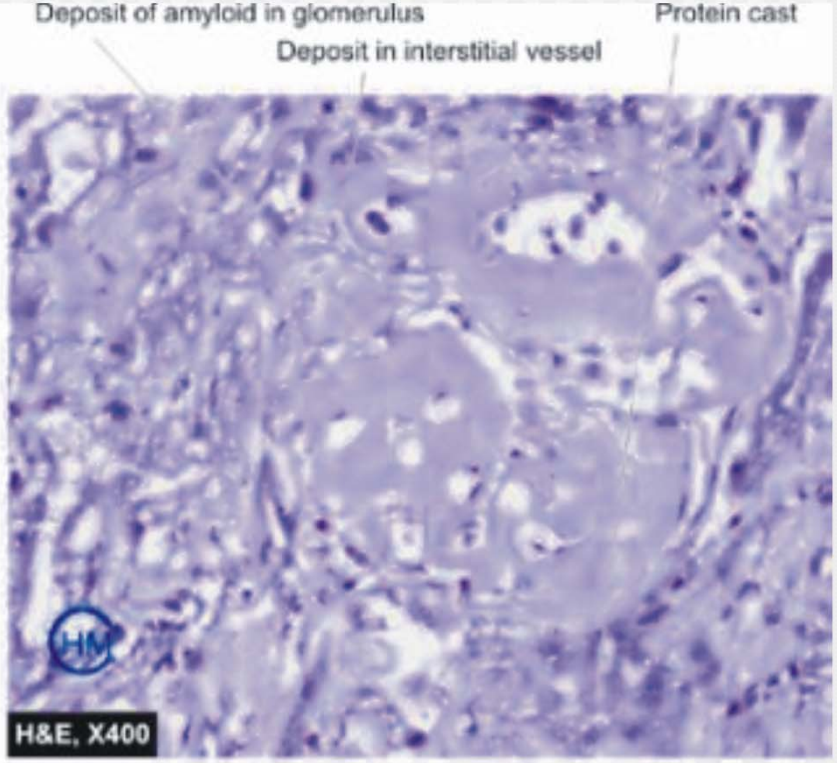
GENERAL FEATURES

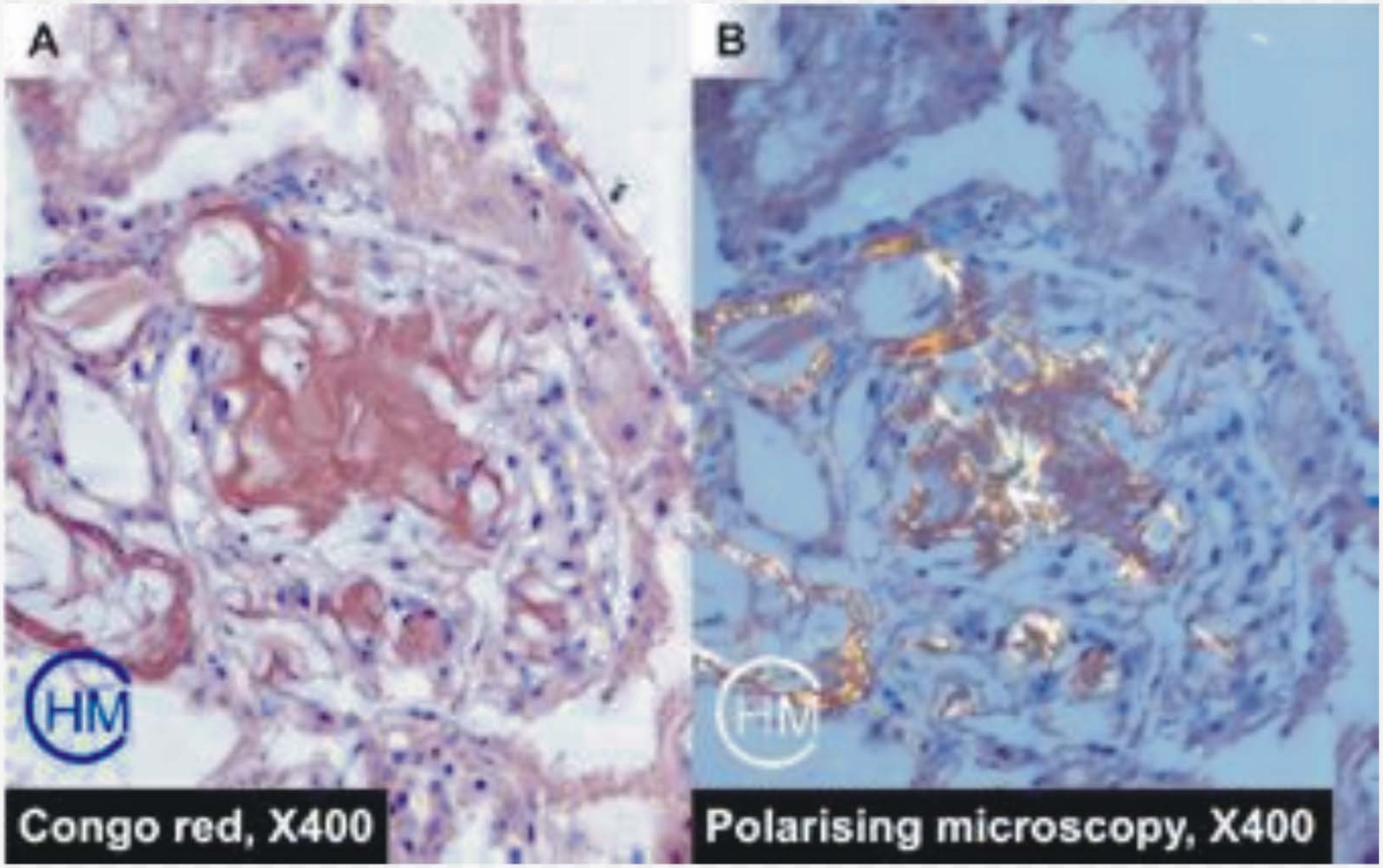
- GA
- ME

Amyloidosis kidneys

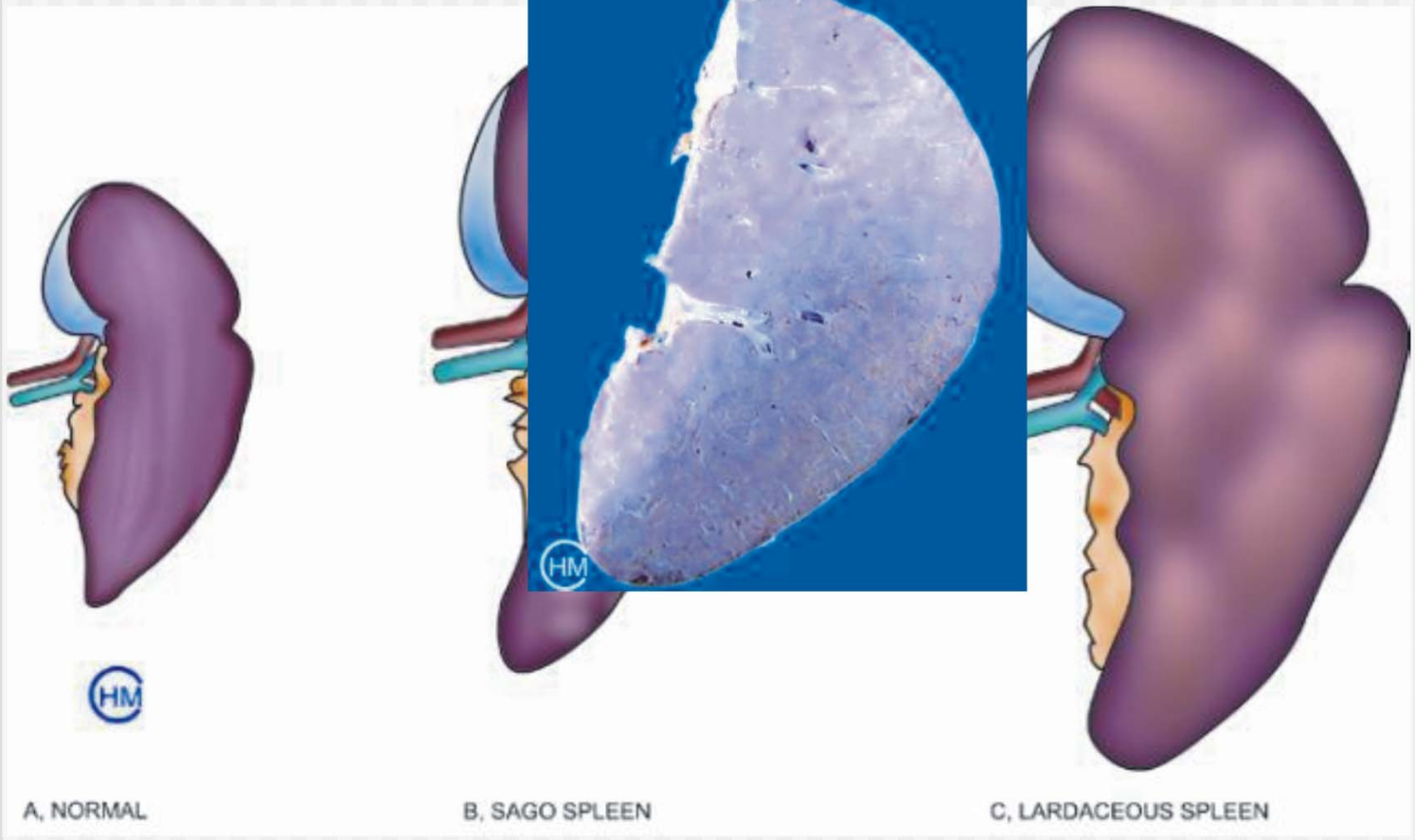


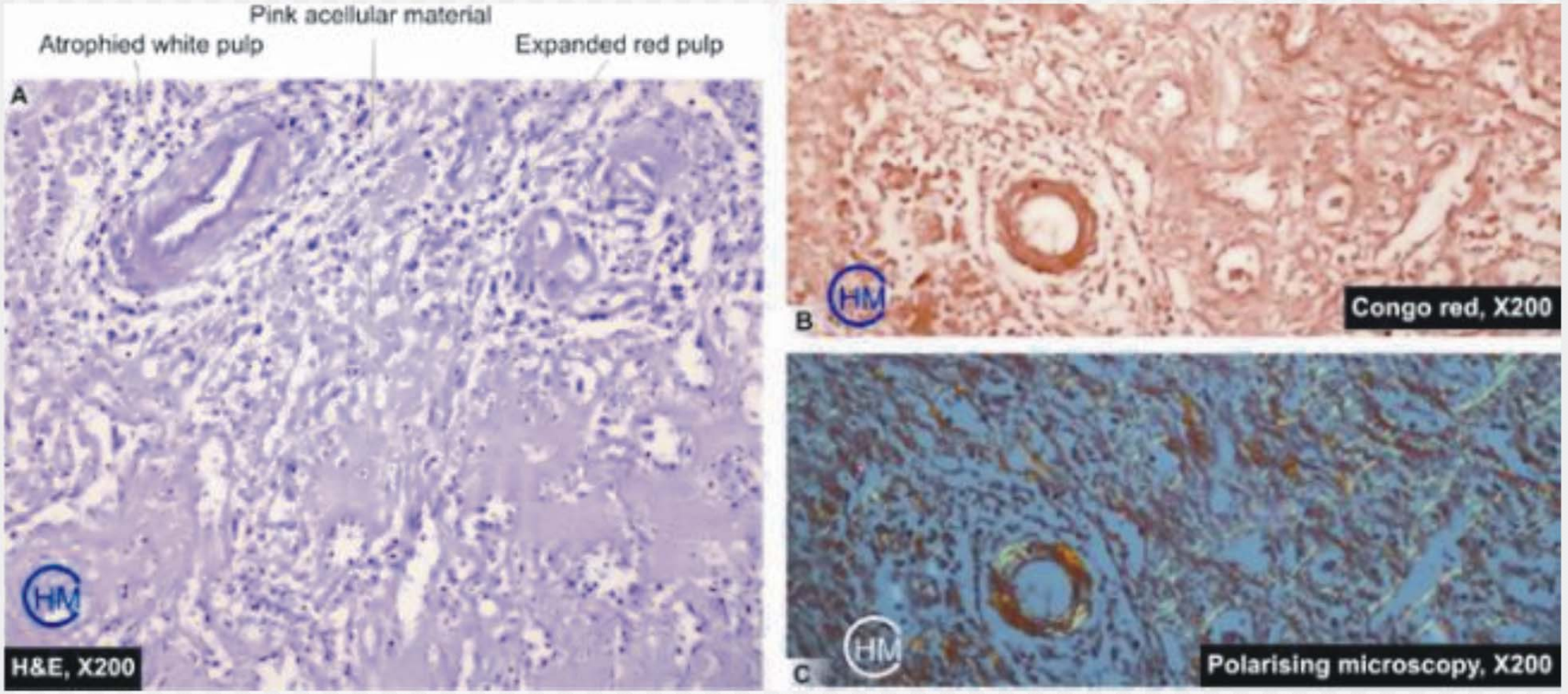

Glomerular deposit
Deposit in interstitial vessel
Amyloid cast
HM


Deposit of amyloid in glomerulus
Deposit in interstitial vessel
Protein cast
HM
H&E, X400

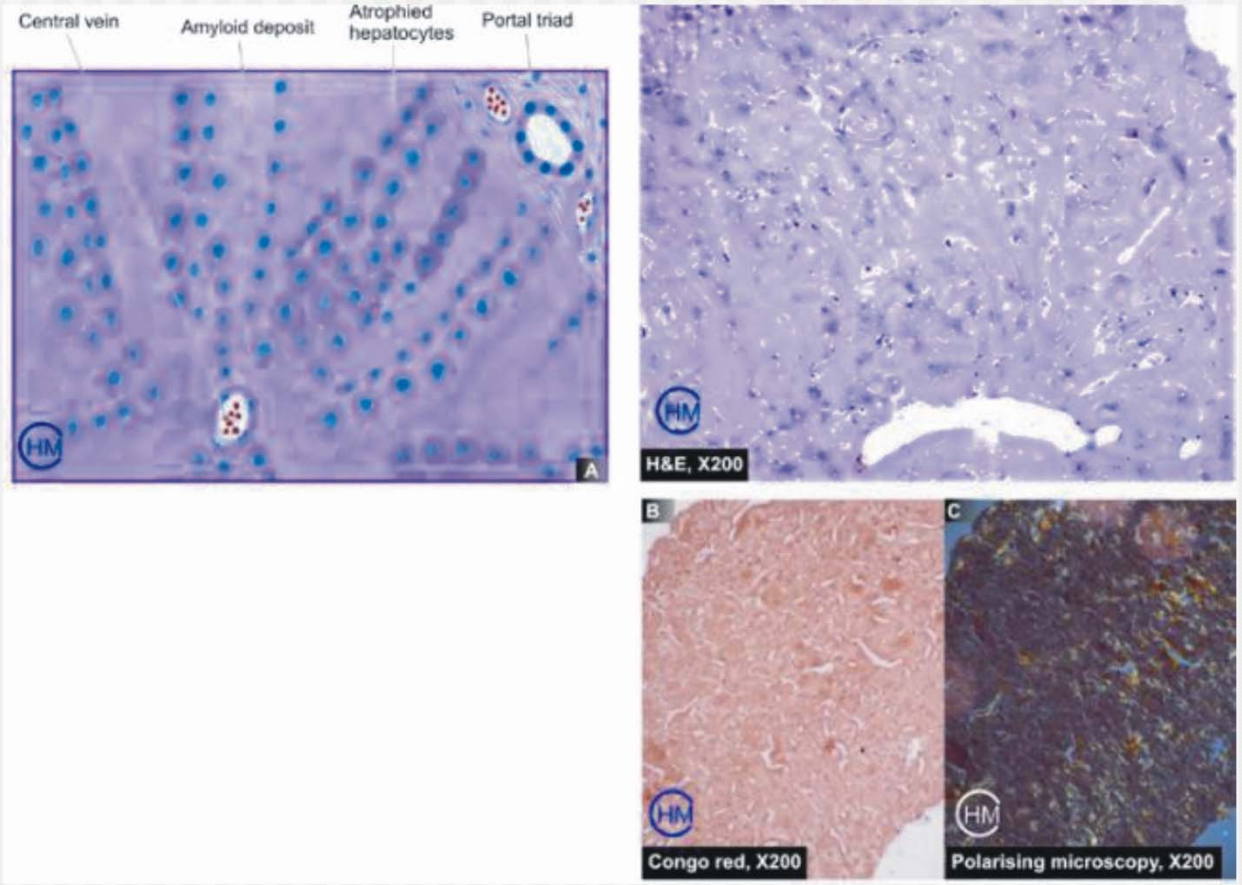

A
B
HM
HM
Congo red, X400
Polarising microscopy, X400

Amyloidosis spleen




Pink acellular material
Atrophied white pulp
Expanded red pulp
A
HM
H&E, X200
B
HM
Congo red, X200
C
HM
Polarising microscopy, X200

Amyloidosis liver



Amyloidosis heart

Amyloidosis alimentary tract

Amyloidosis of other organs