

Monoclonal Immunoglobulin Deposition Diseases

MIDD: Introduction

- Closely related disorders
- Visceral and soft tissue Ig deposition, resulting in compromised organ function
- Plasma cell neoplasms, part of spectrum of plasma cell myeloma; produce an immunoglobulin molecule that accumulates in tissue prior to the development of a large tumor burden; typically do not have overt myeloma at the time of the diagnosis.
- Chemically different manifestations of similar pathological processes, resulting in clinically similar but not identical conditions.

MIDD: Introduction

Two major categories

- **Primary amyloidosis:**
Fibrillary protein with a beta-pleated sheet structure, which binds Congo red with apple-green birefringence, and contains amyloid P component.
- **Light chain deposition disease and its variants (LCDD):**
Nonfibrillary, amorphous material that does not have a beta-pleated sheet configuration and does not bind to Congo red nor contain amyloid P component.

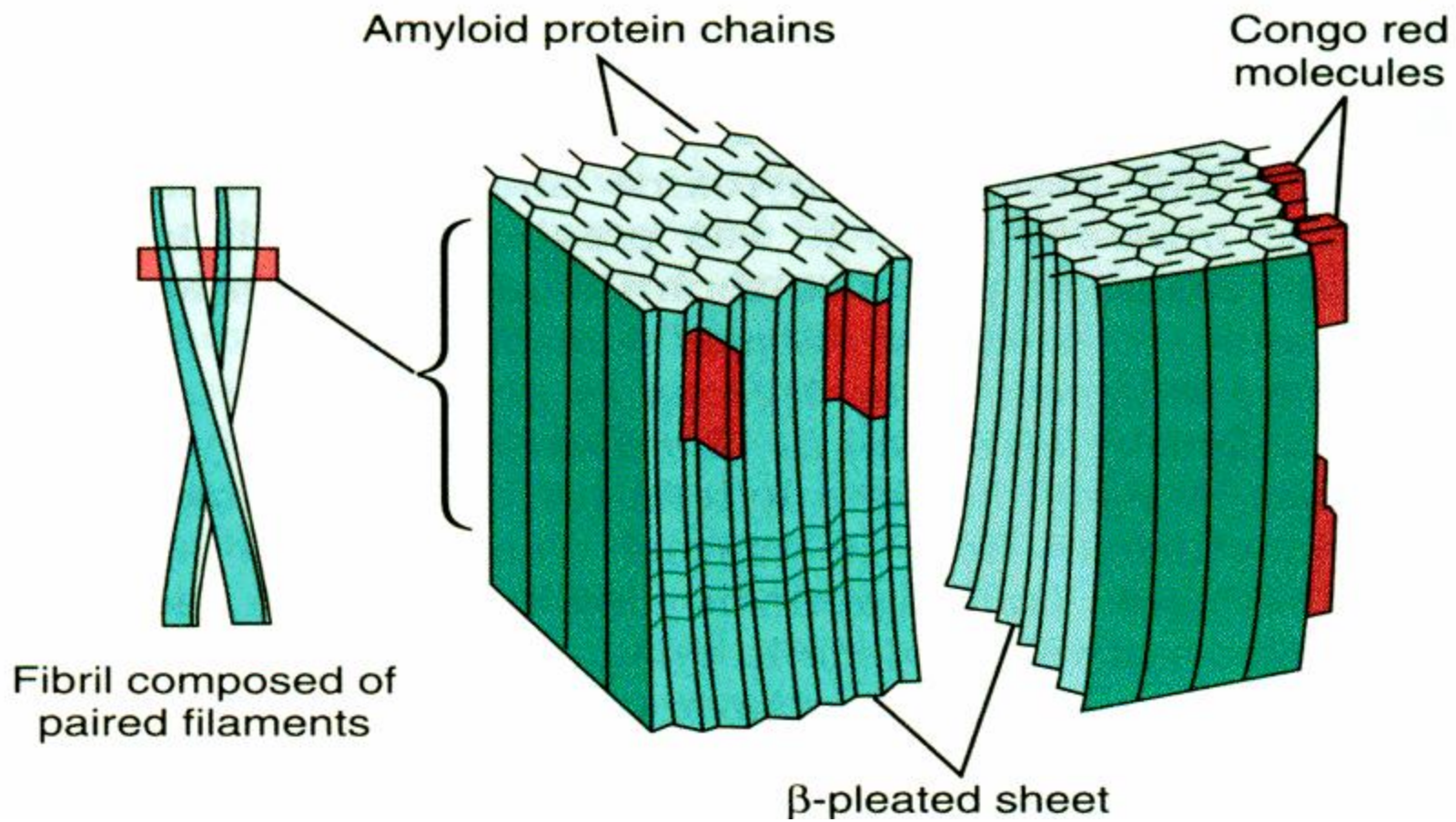
Variants: (1) Light and heavy chain deposition diseases (LHCDD); (2) Heavy chain deposition disease (HCDD)

MIDD: Introduction

Different Ig isotypes in MIDD variants

- Primary amyloidosis:
Most frequently lambda light chain with over-representation of the $V_{\lambda VI}$ variable region.
- Light chain deposition disease:
Most frequently kappa light chains (80%) with over-representation of the $V_{\kappa IV}$ variable region.

Primary amyloidosis



Primary amyloidosis: Epidemiology

- Rare disease in adults
- 80% with monoclonal immunoglobulin
- 20% having overt plasma cell myeloma
- 15% myeloma patients have or will develop primary amyloidosis

Primary amyloidosis: Sites of involvement

Plasma cell-related amyloid (AL) accumulates in

- Heart: congestive heart failure
- Liver: hepatomegaly
- Kidneys: nephrotic syndrome and/or renal failure
- Gut: malabsorption
- Tongue: macroglossia
- Nerves: sensorimotor peripheral neuropathy and loss of sphincter control
- Bone
- Diagnostic sites: abdominal subcutaneous fat pad, BM, or rectum

Primary amyloidosis: Clinical features

- Organomegaly:

Deposition of amyloid

- Bleeding:

Increased fragility of blood vessels from amyloid deposits

Binding of coagulation factor X and/or vascular structures to amyloid proteins

Primary amyloidosis: Pathophysiology

➤ Amyloidosis:

AL: primary or immunoglobulin-light chain (myeloma-associated) amyloidosis

AA: secondary amyloidosis (inflammation associated)

AF: familial amyloidosis

b2M: beta-2 microglobulin amyloidosis (hemodialysis-associated)

Primary amyloidosis: Pathophysiology

- **AL:** intact immunoglobulin light chains secreted by monoclonal plasma cells, ingested, processed and discharged by macrophages into the extracellular matrix. The accumulated AL amyloid includes both intact light chain and fragments of the variable NH₂-terminus region. All light chain V region fragments are amyloidogenic, with V_{λV1} fragments most frequently found.

Primary amyloidosis: Morphology

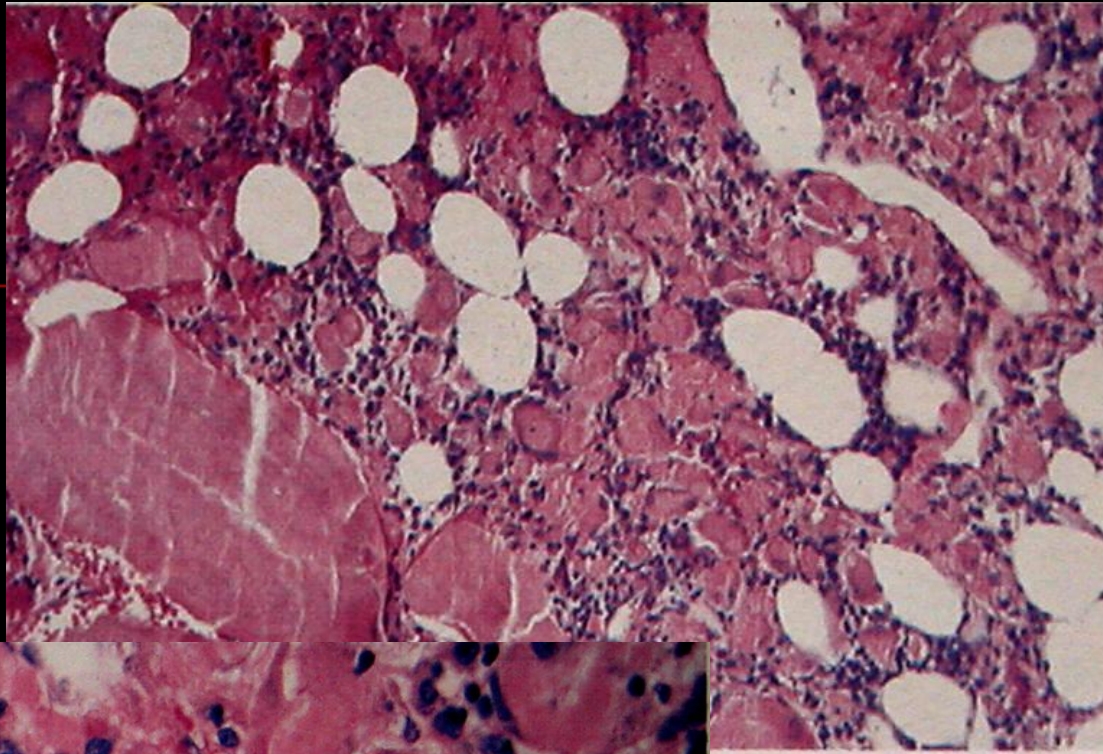
- **Macroscopy:**
Dense “porcelain-like” or waxy appearance.
- **Microscopy:**
H&E: amorphous, eosinophilic, waxy-appearing substance, with a characteristic cracking artifact, focally in thickened blood vessel walls, on basement membranes, and in the interstitium of tissues such as adipose tissue or bone marrow.
Macrophages and foreign-body type giant cells.
Increased plasma cells.



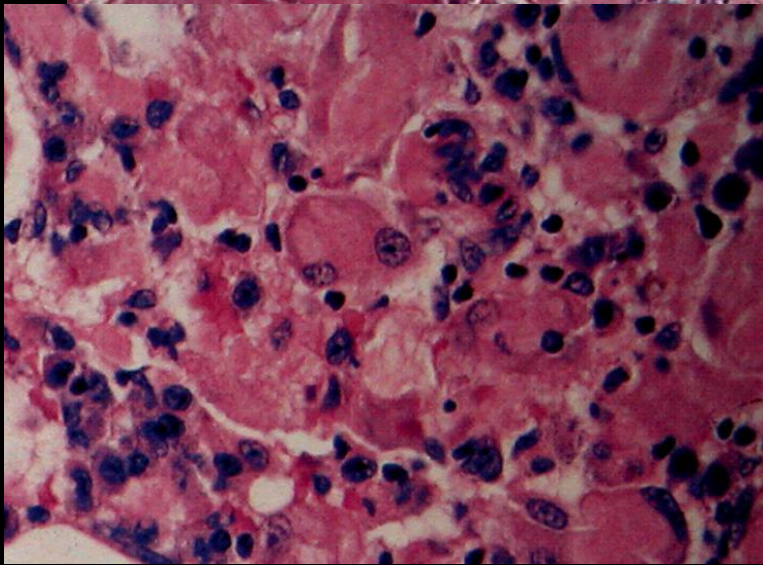
Amyloid in heart

Primary amyloidosis: Morphology

- **Microscopy:**
Congo red: pink-red by standard light microscopy and “apple-green” birefringence by polarization microscopy. The birefringence results from the stacked beta-pleated sheets caused by juxtaposed immunoglobulin molecules.

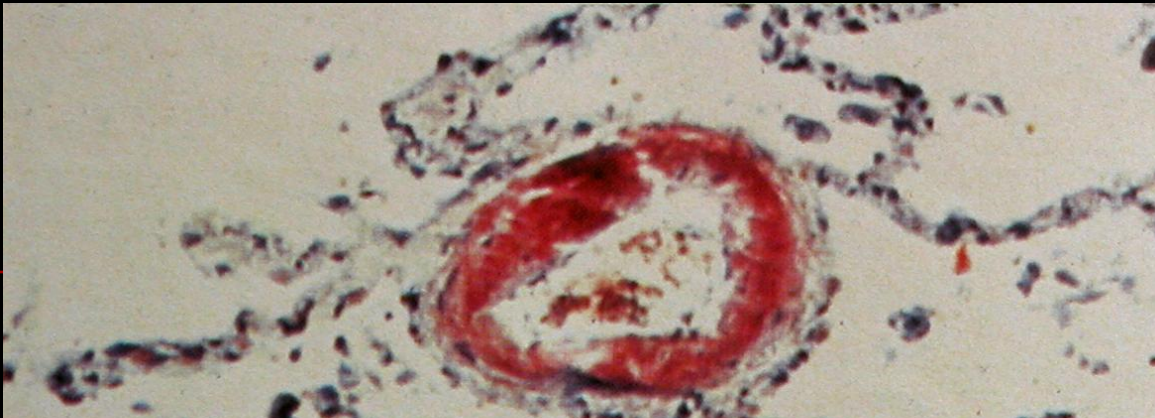


BM: pale, waxy
amorphous
deposits

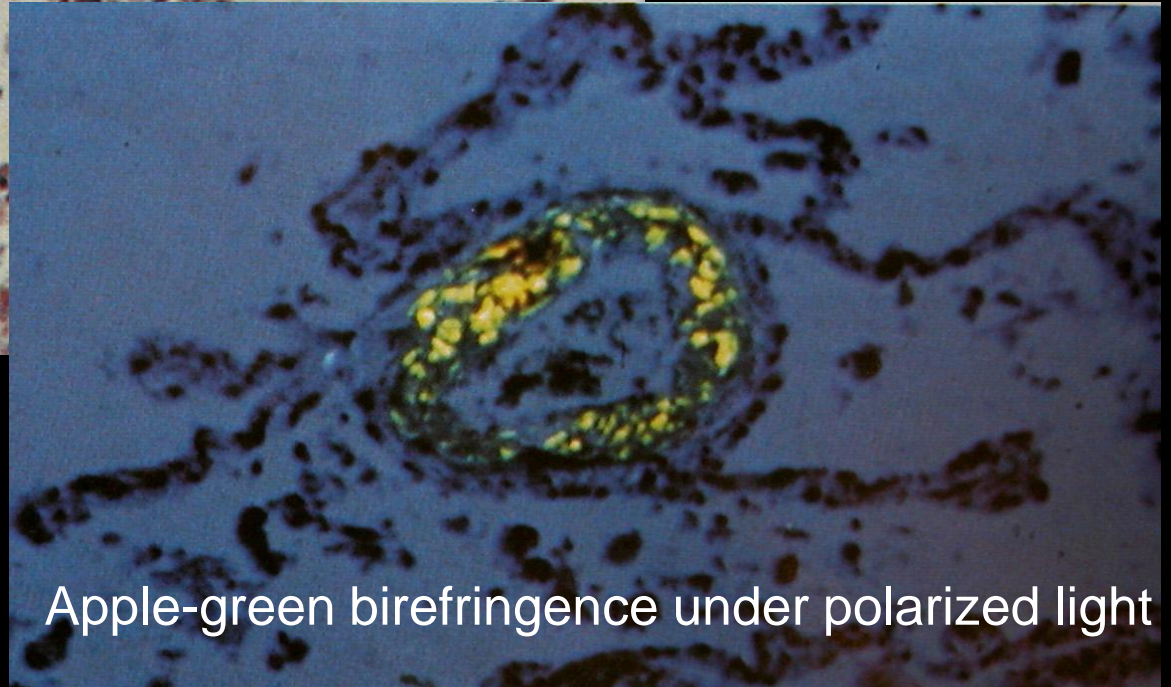


Associated histiocytes,
often multinucleated,
and neoplastic plasma
cells

Congo Red



Apple-green birefringence under polarized light



Primary amyloidosis: Immunophenotype

- Light chains: useful in distinguishing primary from secondary amyloidosis but background may be high in paraffin-embedded sections.
- Amyloid P-component: positive

Primary amyloidosis: Prognosis

Patients with plasma cell myeloma and amyloidosis have a shorter survival period than those with myeloma alone.

Monoclonal Light and Heavy Chain Deposition Disease

MLHCDD: Definition

- Plasma cell neoplasms that secrete an abnormal light or less often heavy chain or both.
- Do not form amyloid β -pleated sheets, do not bind Congo red or contain amyloid P-component
- Deposit in tissues causing organ dysfunction
- Include LCDD, HCDD, and LHCDD

MLHCDD: Epidemiology

- Rare (<70 cases described)
- Age range: 33-79 years (56 year median)
- Usually associated with MGUS or myeloma
- No selective ethnicity; equal incidence in male and female

MLHCDD: Site of Involvement

- Many organs, most commonly kidneys, liver, heart, nerves, blood vessels and occasionally joints
- Prominent deposition of aberrant Ig on basement membranes, elastic and collagen fibers
- Vascular occlusion and microaneurysm formation may occur

MLHCDD: Clinical Features

- Organ dysfunction: nephrotic syndrome, renal failure, arthritis, congestive heart failure, and coagulopathy (FX deficiency) due to liver involvement.
- IgG3 or IgG1: hypocomplementemia.
- Monoclonal gammopathy: 85% of cases.
- No M-component: in 15%; representing strong tissue binding of the aberrant Ig

MLHCDD: Pathophysiology

- Monoclonal Ig in non amyloid MIDD: structural changes due to deletion and mutation. Alteration in physiochemical properties (more cationic with altered hydro-phobia) or aberrant glycosylation, which favor tissue binding and deposition.

MLHCDD: Pathophysiology

HCDD

-CH1 deletion->fail to bind to Heavy Chain Binding Protein and secreted prematurely

-Substitutions in variable (V) regions: tissue deposition and binding blood elements

LCDD

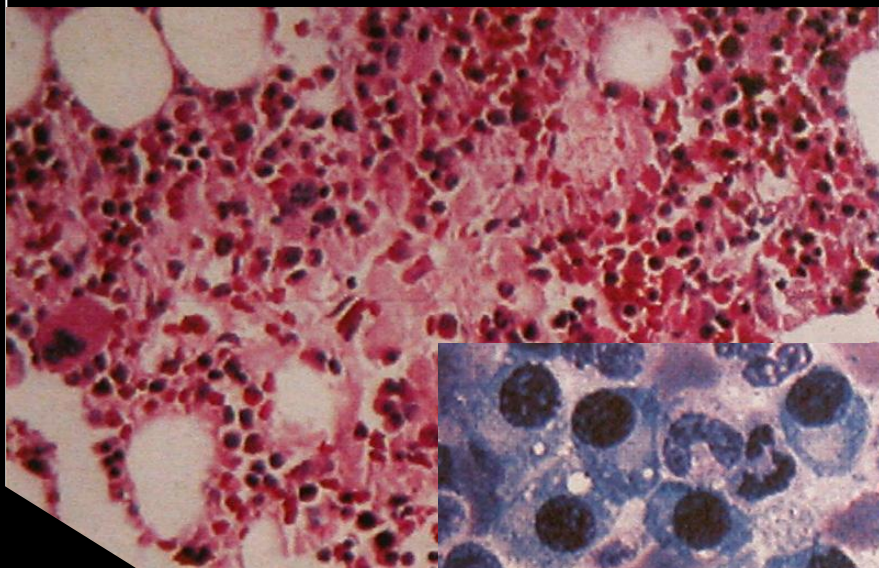
Multiple mutations in light chain variable (V) regions, with kappa light-chain of type $V_{\kappa IV}$ over expressed.

MLHCDD: Morphology

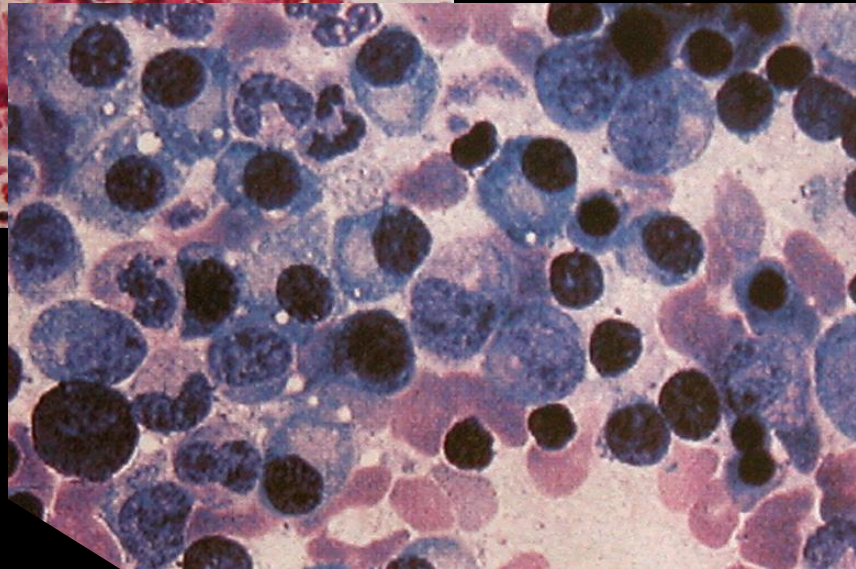
- Monoclonal Ig deposit: non-amyloid, nonfibrillary, amorphous eosinophilic material, negative for Congo Red.
- Refractile eosinophilic material in glomerular and tubular basement membranes, but may also be seen in bone marrow and other tissues.
- EM: discrete, dense punctate granular, nonfibrillary deposits

MLHCDD: Morphology

- X-ray diffraction: absence of the beta-pleated sheet structure
- Commonly few plasma cells in the organs with Ig deposition; Ig produced in the BM and reach the site via circulation.
- BM plasmacytosis: 50-60% cases

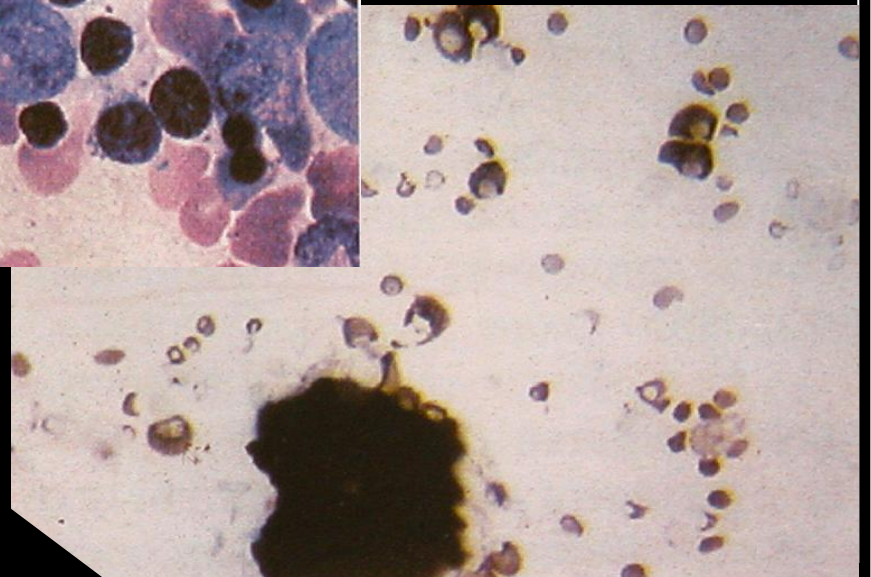


BM: patches of pale amorphous material



BM: numerous plasma cells

Joint fluid: clumps of amorphous material and plasma cells, both staining for kappa light chain

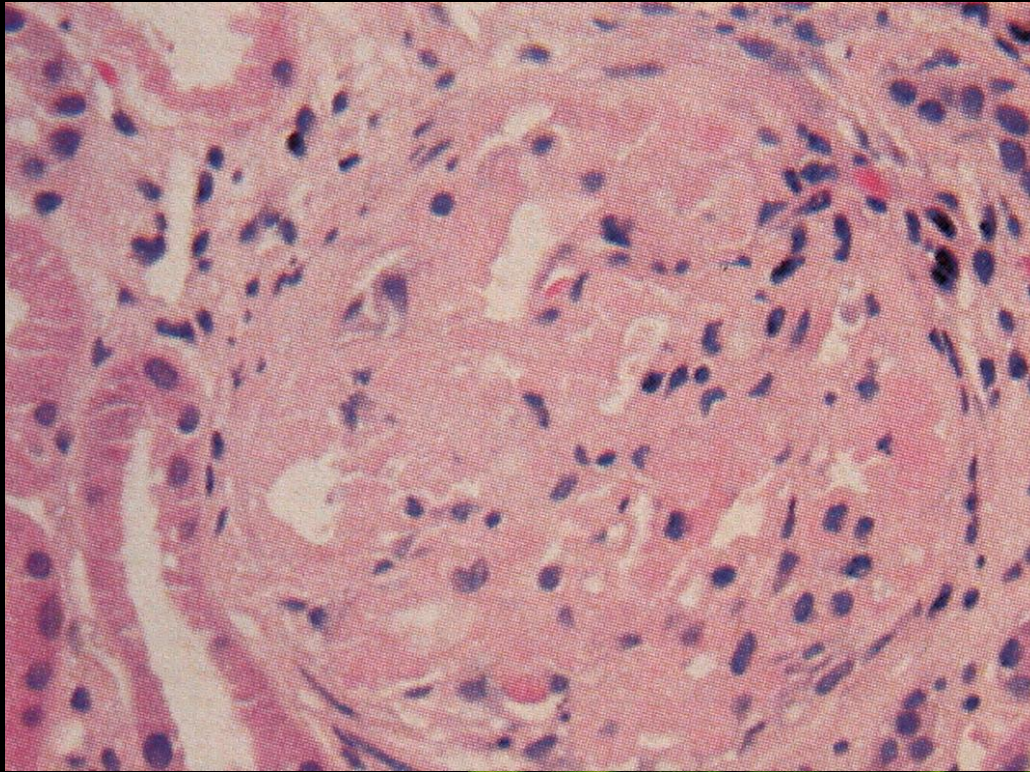


MLHCDD: Immunophenotype

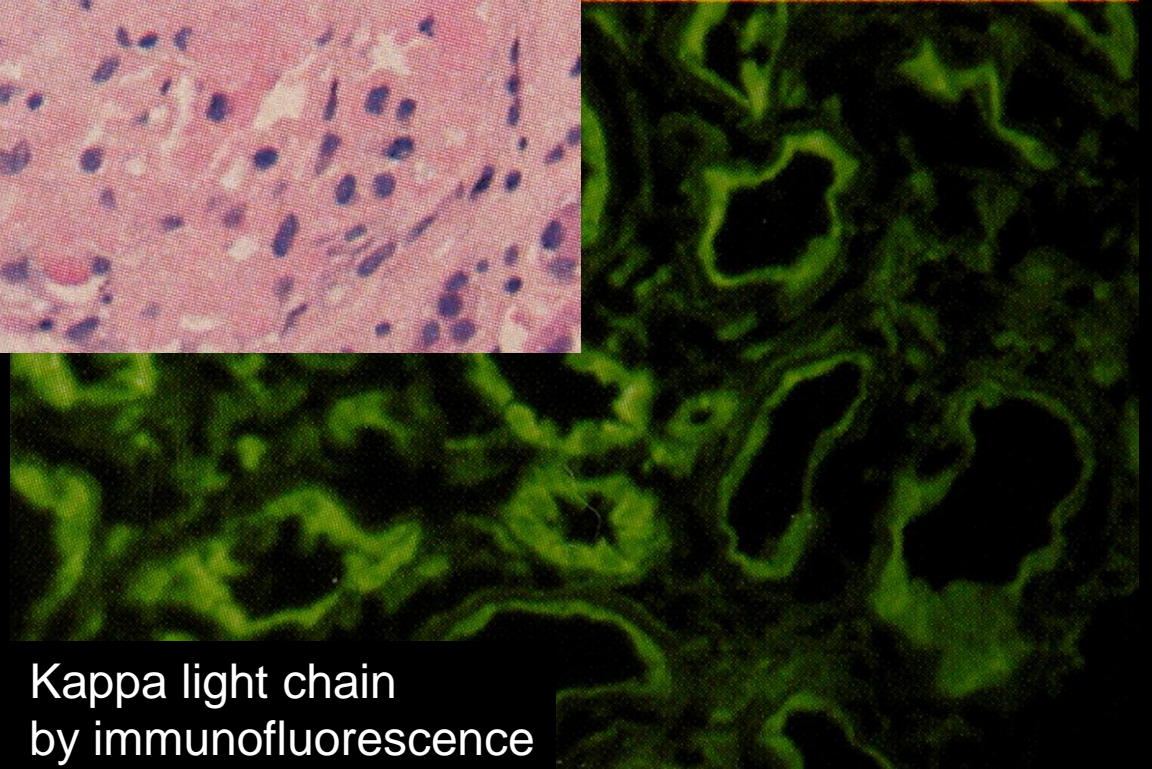
- LCDD: prevalence of kappa light-chain (80%) with over representation of $V_{\text{kappa IV}}$ variable region

In contrast with primary amyloidosis which has a predominance of lambda light-chain with over representation of the $V_{\text{lambda VI}}$ variable region.

- Immunofluorescence: prominent, smooth, ribbon-like linear peritubular deposits of monotypic Ig along the outer edge of the tubular basement membrane.
- BM: aberrant k/l ratio, even without overt plasmacytosis



LCDD in kidney



Kappa light chain
by immunofluorescence

MLHCDD: Prognosis

- Very poor
- Fatal within 1-2 years even in the absence of aggressive plasma cell proliferation