Szervusz [hi] everybody!

LOYOLA UNIVERSITY CHICAGO

Preparing people to lead extraordinary lives

Renal Injury due to Monoclonal Gammopathy

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International Kidney Monoclonal Gammopathy

Renal Pathology Society

International Society of Amyloidosis

ASN 2016

Chicago

Objectives

On completion of this activity, the participant should be able to:

1. contrast and compare the clinical features & kidney biopsy findings of amyloidosis and light chain deposition disease
2. contrast and compare the clinical features & kidney biopsy findings with different fibrillary deposits
3. contrast and compare the clinical features & kidney biopsy findings with monoclonal versus polyclonal non-organized deposits
4. contrast and compare the clinical features and kidney biopsy findings direct versus indirect injury by monoclonal proteins
5. contrast and compare the clinical features and kidney biopsy findings in distal versus proximal nephron injury
6. explain the rationale for pathogenetic classification of kidney diseases

Disclosure:

- nothing to disclose

Outline:

1. Definitions, laboratory tests
2. Glomerular/vascular injury
3. Direct versus indirect injury
4. Tubulo-interstitial injury
5. Summary

Monoclonal gammopathies:

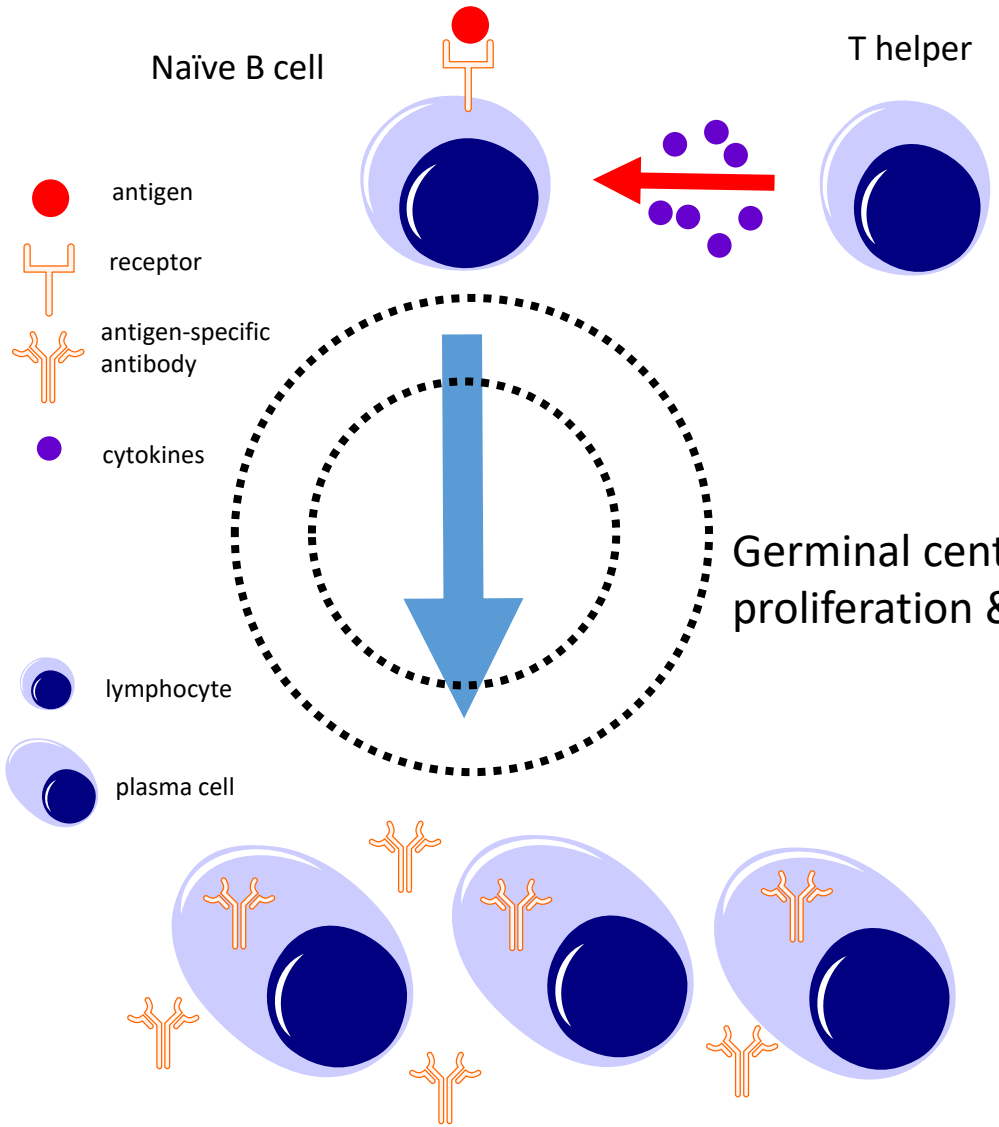
- wide spectrum of related diseases
- immunoglobulins aka paraproteins, aka “M-component”
- clonal plasma cells or B lymphocytes

1. Picken MM. Monoclonal Gammopathies: Glomerular and Tubular Injuries. In: Pathobiology of Human Disease. A dynamic encyclopedia of disease mechanisms. Ed: LM McManus, RN Mitchell, Elsevier 2014, pages 2831-2852 http://dx.doi.org/10.1016/B978-0-12-386456-7.05411-3

2. Picken, M.M., Herrera, G.A., Dogan A. (Eds.), Amyloid and Related Disorders in Surgical Pathology and Clinical Correlations. 2nd ed. 2015. Springer, New York

3. Herrera, G. A. and M. M. Picken. Renal diseases associated with plasma cell dyscrasias, Waldenstrom macroglobulinemia and cryoglobulinemic nephropathies. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Heptinstall's Pathology of the Kidney. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2014; pp 951-1014.

4. Bridoux F, Leung N, Hutchison CA, Touchard G, Sethi S, Fermand JP, Picken M, Herrera G, Kastritis E, Merlini G, Roussel M, Kyle RA, Nasr SH, on behalf of the International Kidney and Monoclonal Gammopathy Research Group. Diagnosis of monoclonal gammopathy of renal significance. Kid Int, 2015 Apr;87(4):698-711



Immunoglobulins:
- produced in response to antigens
- each B cell produces a single species of antibody with unique antigen binding site

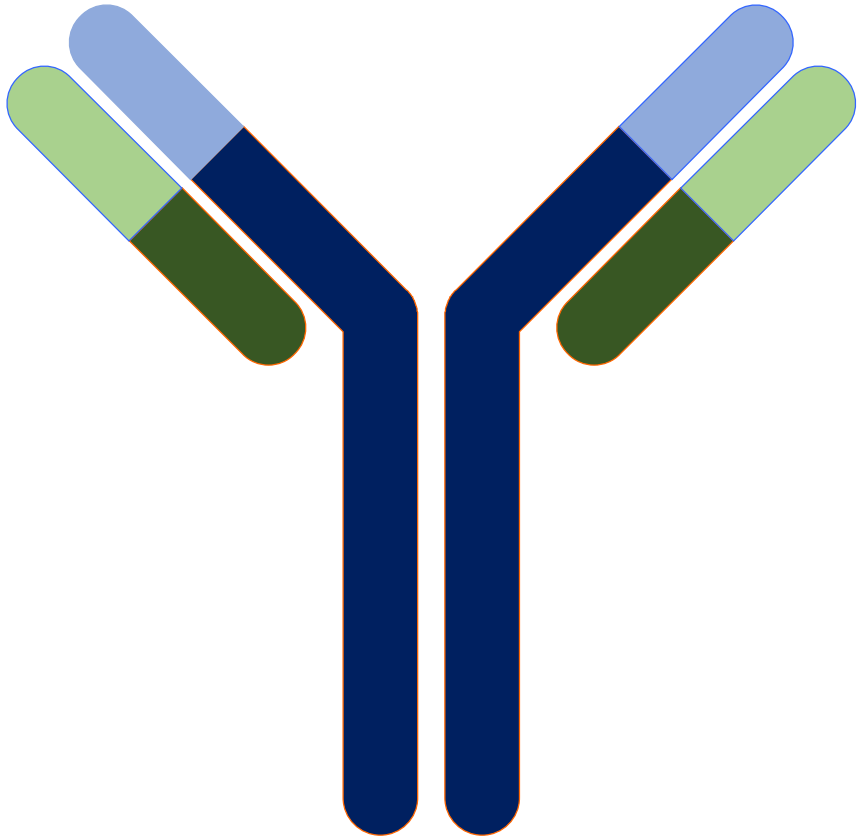
Naïve or memory cell:
- activation by exposure to antigen matching its surface receptor
- proliferation (T helper cell)
- differentiation into an antibody-secreting effector cell

Germinal center:
proliferation & differentiation

- effector B cells begins secreting antibodies
- differentiate into plasma cells

Paraprotein
aka monoclonal M-protein:

-intact immunoglobulin
-light chain only
-heavy chain only

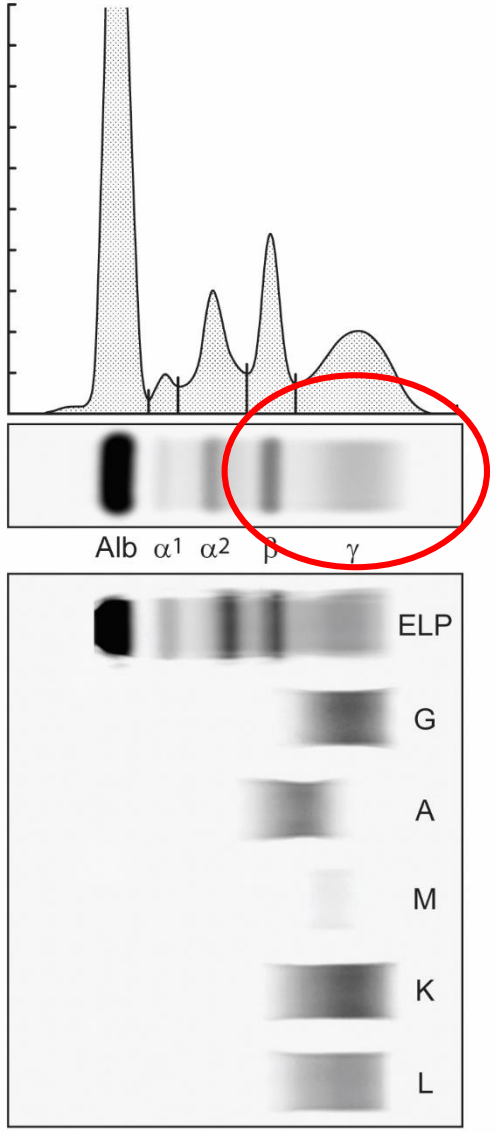


IgG γ, monomer
IgM μ, pentamer
IgA α, dimer(secretion), monomer (serum)
IgE ε
IgD δ
λ
K
κ/λ = 2:1

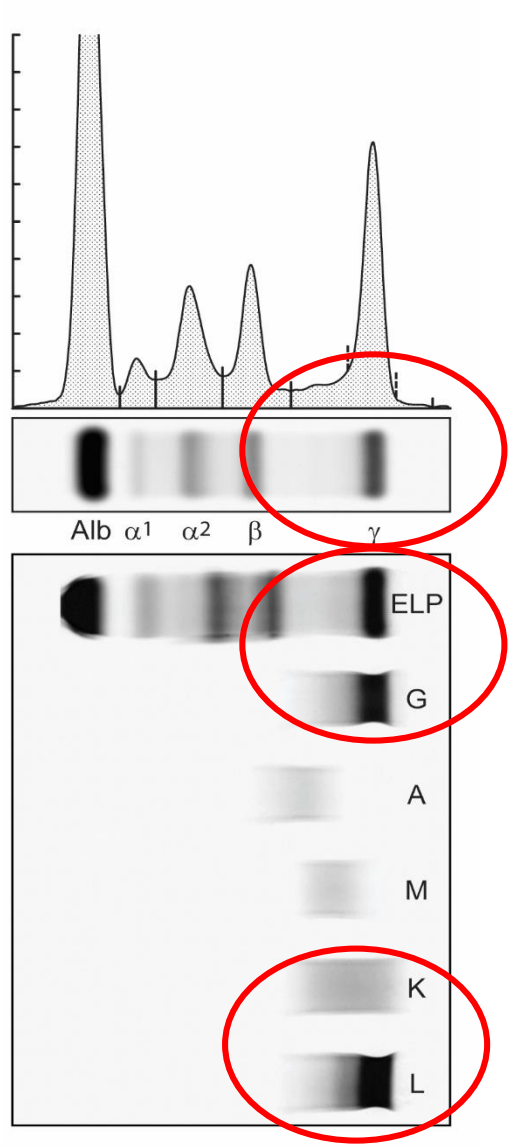
Diagrammatic representation of the IgG molecule. Dark blue = heavy chain constant region (CH1, CH2, CH3); dark green = light chain constant region; light blue = heavy chain variable region; light green = light chain variable region

Protein electrophoresis

Protein Immunofixation electrophoresis

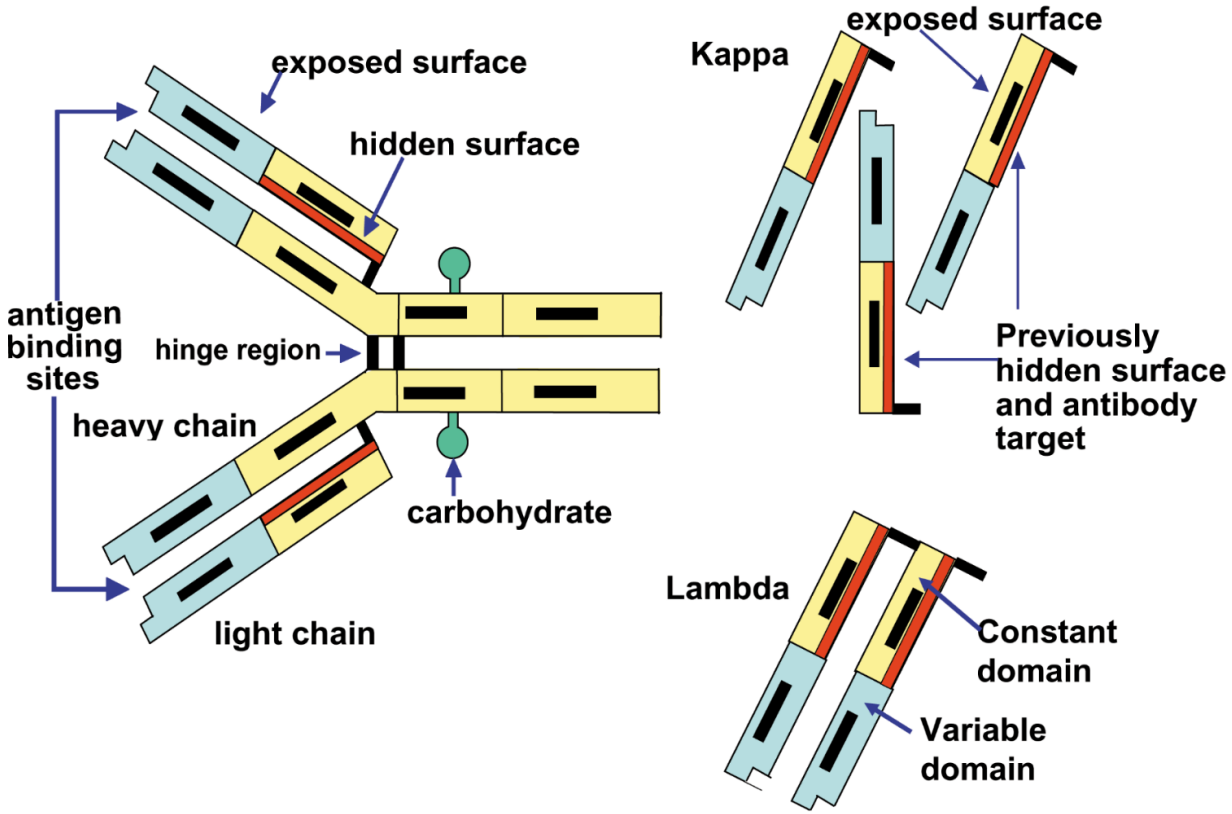


NORMAL SERUM: gamma fraction exhibit a smooth Gaussian distribution indicating a polyclonal distribution



MONOCLONAL IgGλ: gamma fraction exhibit a discrete band indicating a monoclonal protein

Serum free light chain assay (FLC)



IgG intact molecule (left) and free light chains (right). The hidden surfaces of the light chains (red) are tightly bound to the heavy chains by noncovalent interactions. In free light chain which are no longer bound to heavy chain, these surfaces provide the specific targets for the FLC antisera

Bradwell, A.R. Serum Free Light Chain Analysis, 5th ed. [7]

Hevylite® assay (HLC) targets junctional epitopes between the κ or λ LCs and heavy chains to provide quantification of intact HLC pairs. This test separately measures serum IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, and IgMλ concentrations. Calculation of the ratio between individual HLC isotype pairs, e.g. IgGκ/IgGλ (HLCr), allows identification of clonal disease in the same manner as FLCr

Sensitivity of the current diagnostic tests

improved but NOT 100%!!!

Test	Sensitivity
FLC κ/λ ratio	91%
Serum IFE	69%
Urine IFE	83%
FLC κ/λ ratio and urine IFE	91%
FLC κ/λ ratio and serum IFE	**99%**
Serum IFE and Urine IFE	95%
All 3 tests	99%

SFLchains:
- much shorter half-life in the circulation than intact immunoglobulins
- monitoring of responses to chemotherapy
- in renal insufficiency ratio of κ/λ useful

Sensitivity of different diagnostic tests and their combinations in 110 patients with AL amyloidosis at the time of disease diagnosis. *Bradwell, A.R. Serum Free Light Chain Analysis, fifth ed. [7].*

Simplified classification of the Plasma Cell Dyscrasias

	Multiple Myeloma	Smoldering Myeloma	MGUS
Bone marrow monoclonal plasma cells	≥10%	≥10%	<10%
Monoclonal protein serum and/or urine	≥30g/L	≥30g/L	<3.0g/L
hypercalcemia	+	-	-
renal insufficiency	+	-	-
anemia	+	-	-
bone lesions	+	-	-

Simplified classification of the Plasma Cell Dyscrasias

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hypercalcemia	+	-	-	-
renal insufficiency	+	-	-	+
anemia	+	-	-	-
bone lesions	+	-	-	-

Distribution of plasma cell disorders in clinical practice

MGUS	**61%**
Multiple myeloma	**17%**
AL amyloidosis	**9%**
Smoldering myeloma	**4%**
Lymphoproliferative disease	3%
Solitary or extramedullary plasmacytoma	2%
Macroglobulinemia	2%
Other	2%

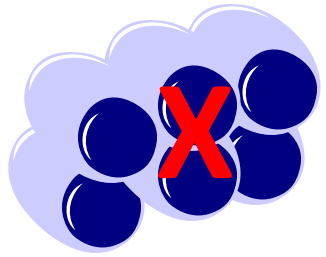
From the Mayo Clinic Dysproteinemia data base, 1960-2003; n=31,479 [adapted from 6]

MGUS:
- progression to malignancy/overt lymphoproliferative disorder
- progression to MGRS
- no progression

MGUS: IgM versus non-IgM
- IgM → Waldenström macroglobulinemia
- non-IgM → multiple myeloma
- light chain → multiple myeloma

MGRS:
- renal insufficiency/proteinuria
- monoclonal deposits in the kidney or indirect kidney injury

B-cell neoplasia M-component related diseases



Progression - rare

Clone size

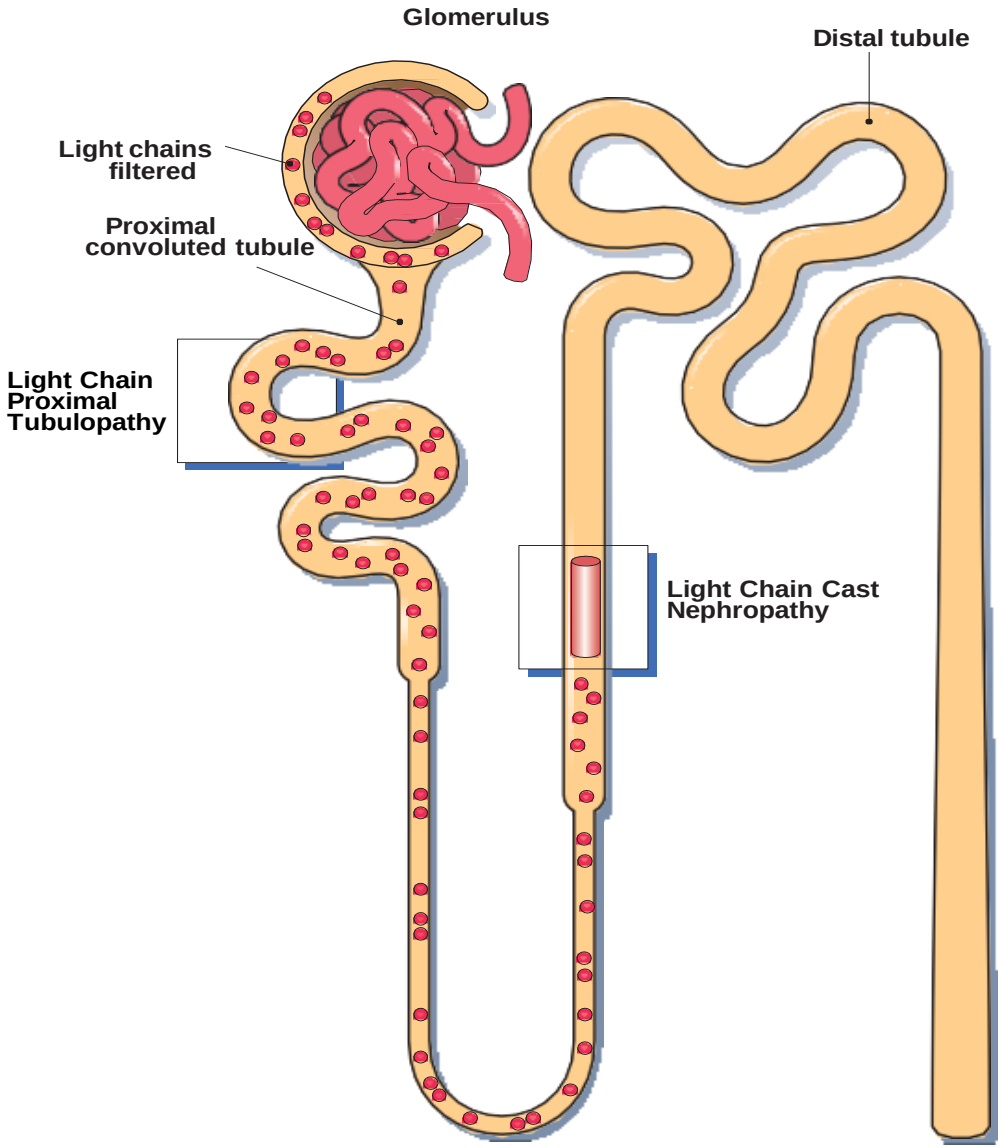
Advances in treatment:
- chemotherapy/stem cell transplantation
- immunomodulatory drugs
- antibodies…

Clinical manifestations due to clone:
- bone lesions
- hypercalcemia
- infections
- anemia
- systemic symptoms

none

Clinical manifestations due to M-protein:
light chain cast nephropathy
hyperviscosity

AL, LCDD, non-organized deposits with end-organ damage:
kidney, heart, liver failure, polyneuropathy, other


Glomerulus
Distal tubule
Light chains filtered
Proximal convoluted tubule
Light Chain Proximal Tubulopathy
Light Chain Cast Nephropathy

Systematic approach to kidney evaluation:

- location of paraproteins:
    1. glomerular/intravascular
    2. tubulo-interstitial
    3. other – indirect injury

- correlation with immunofluorescence[IF]/immunohistochemistry[IHC]: clonality
- correlation with electron microscopy [EM]: organized versus non-organized deposits
- defining features by IF, by EM or both
- clinical correlation

Pathomechanism: direct versus indirect paraprotein induced injury

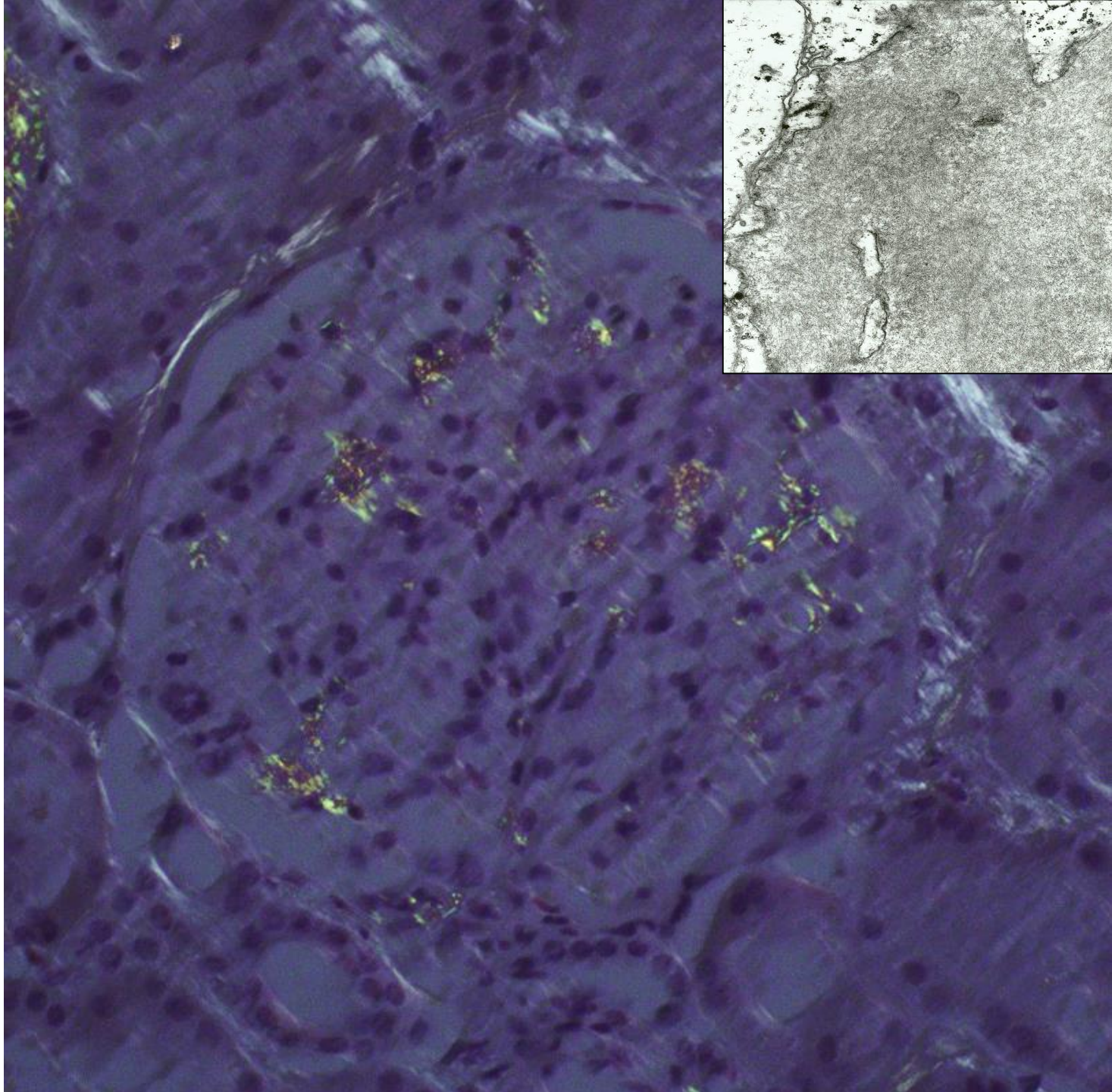
Amyloidosis defining feature =
Congo red stain birefringence under polarized light

Immuno (IF/IHC) stains are variable depending on amyloid type

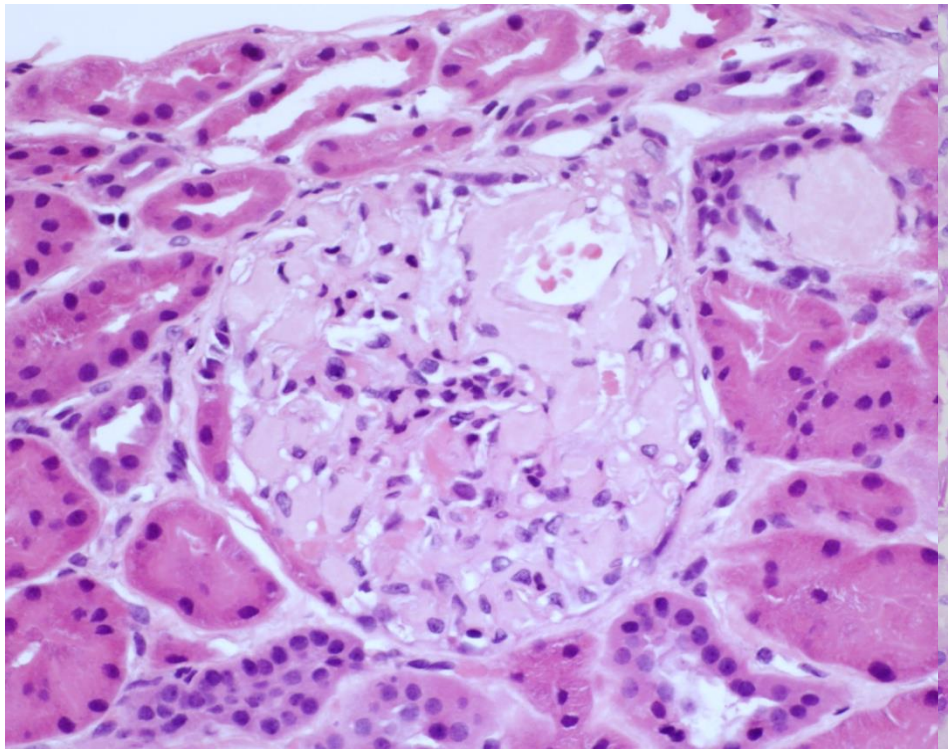
Light microscopy variable depending on disease stage

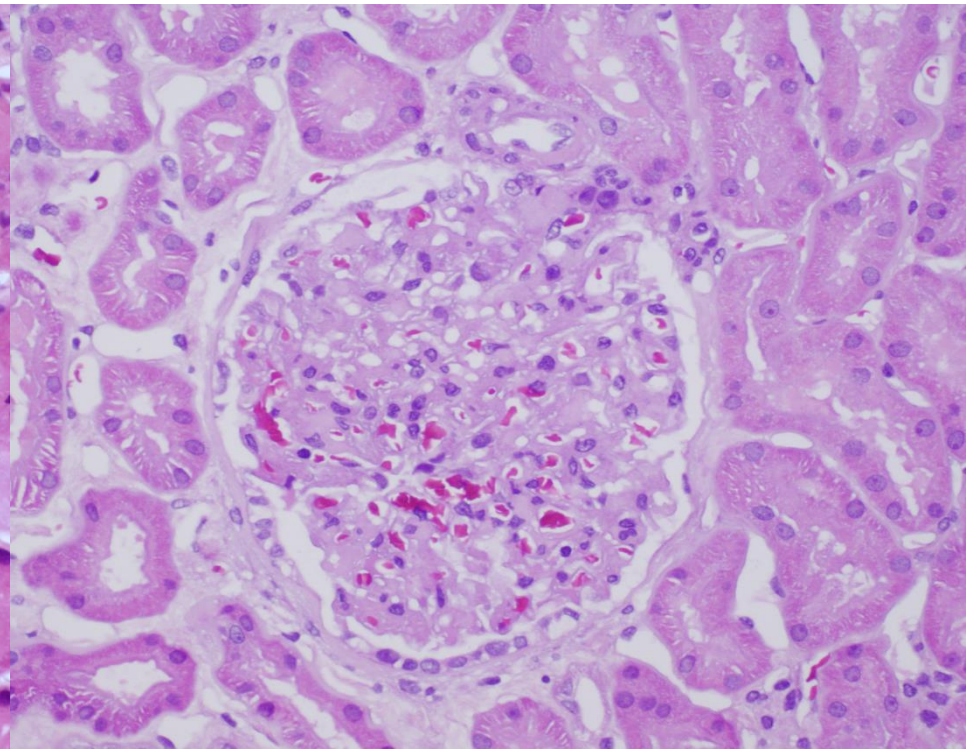
Electron microscopy [insert] = supportive by showing characteristic fibrils but not required if Congo red stain is diagnostic

Picken MM, 2015 [9]



Light microscopy [LM]= neither sensitive nor specific

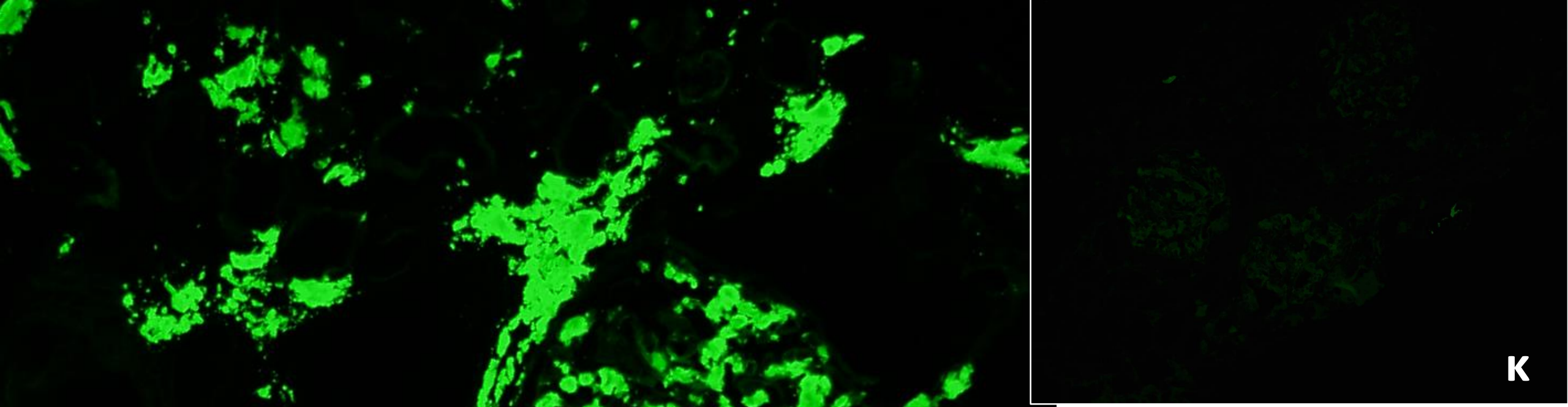




Clinical: proteinuria/nephrotic syndrome
LM - mesangial expansion:
- diabetes
- amyloidosis, LCDD

Picken MM 2014 [1]

Proteinuria/nephrotic syndrome
LM - normal/almost normal glomeruli: **THINK EARLY STAGE!!!**
- minimal change disease/Focal & segmental glomerular sclerosis
- membranous nephropathy
- diabetes
- early lupus
- amyloidosis, LCDD…



AL = amyloidosis derived from immunoglobulin light chain:

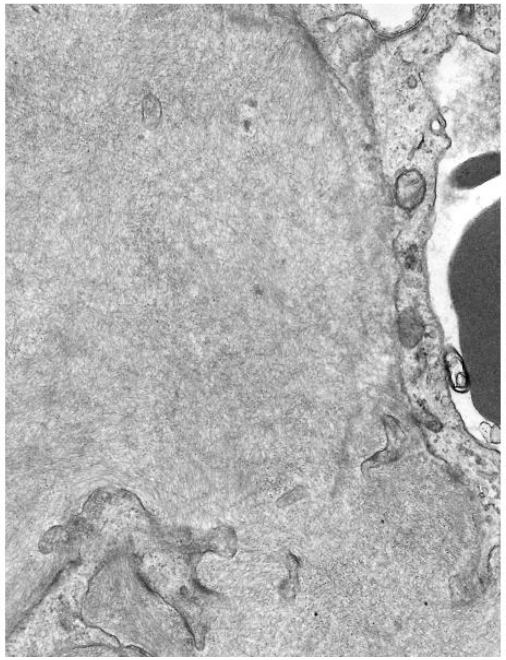
- the most common type of systemic amyloidosis
- amyloid type diagnosed by demonstration of light chain restriction by immune stains

AH = amyloidosis derived from Immunoglobulin heavy chain (rare)

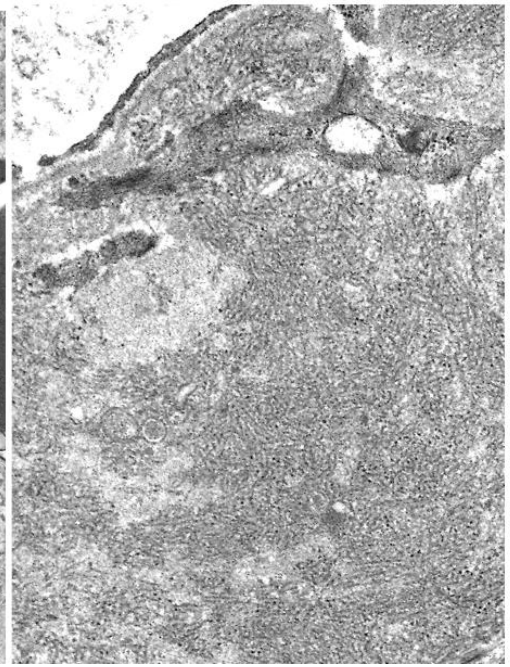
Kidney 70%: nephrotic syndrome, renal failure; heart 70%

Picken MM 2014 [1]

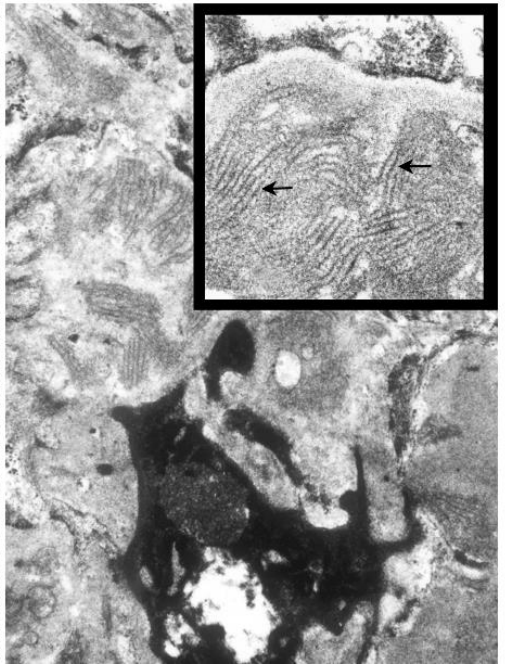
Electron microscopy – differential diagnosis of fibrillary deposits:



Amyloid:
fibrills ~ 8-10 nm
in thickness
haphazardly arranged,
straight fibrils,



Fibrillary GN:
fibrils ~ 20-30 nm
in thickness
haphazardly arranged,
straight fibrils,



Immunotactoid GN:
microtubules >30 nm
in diameter,
focal parallel alignment

Fibrillary GN: rare (0.5-1%)
Proteinuria, hematuria, renal insufficiency, HTN
mesangium, glomerular basement membranes, or both
IF: polyclonal IgG and complement
Common: underlying malignancy,
some - dysproteinemia, or
autoimmune diseases
Prognosis poor, rare remission without immunosuppressive therapy *Nasr et al [11]*

Immunotactoid GN:
10-fold rarer than fibrillary GN
deposits *usually* monoclonal
overlap with cryoglobulinemic GN?

IGN and cryoglobulinemic nephropathy
= part of the spectrum of renal manifestations in patients with circulating cryoglobulins?

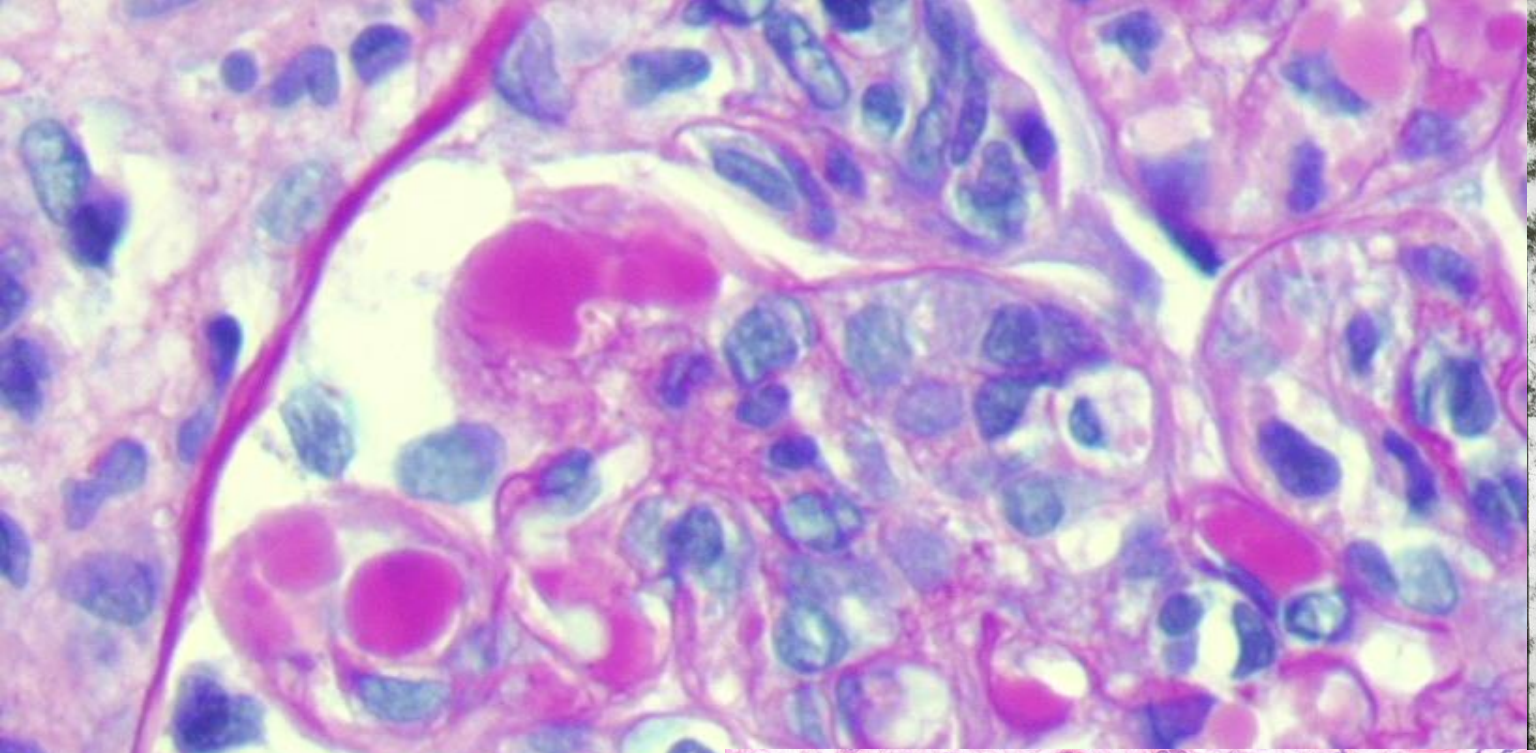
Cryoglobulins:

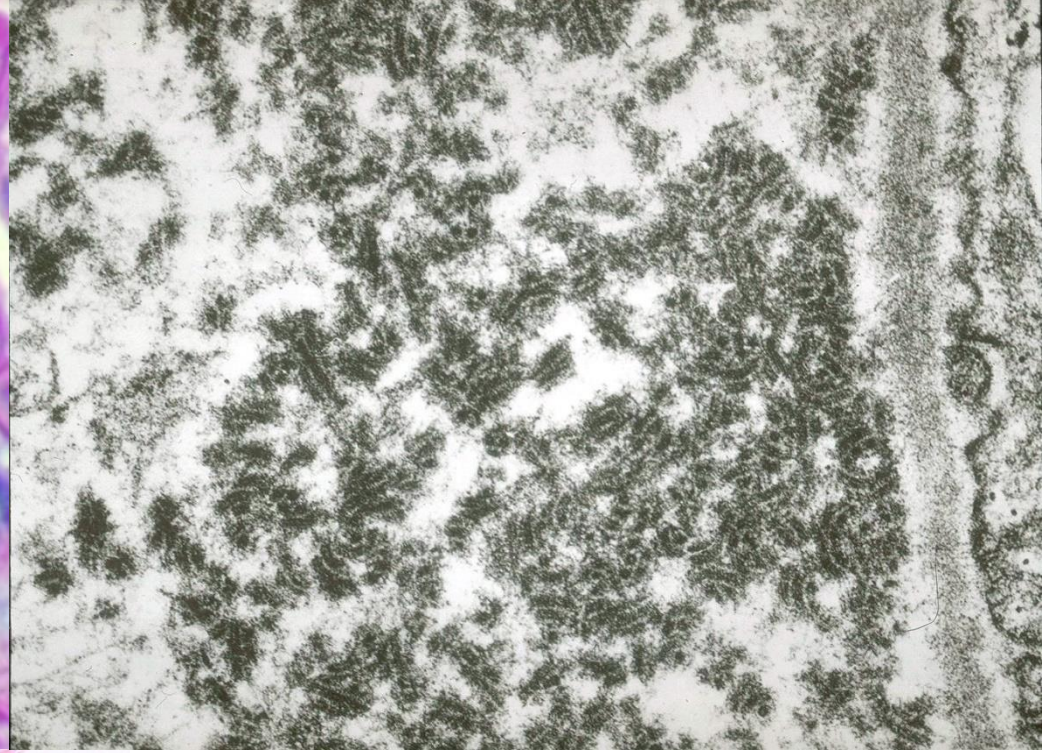
– proteins that become insoluble at reduced temperatures

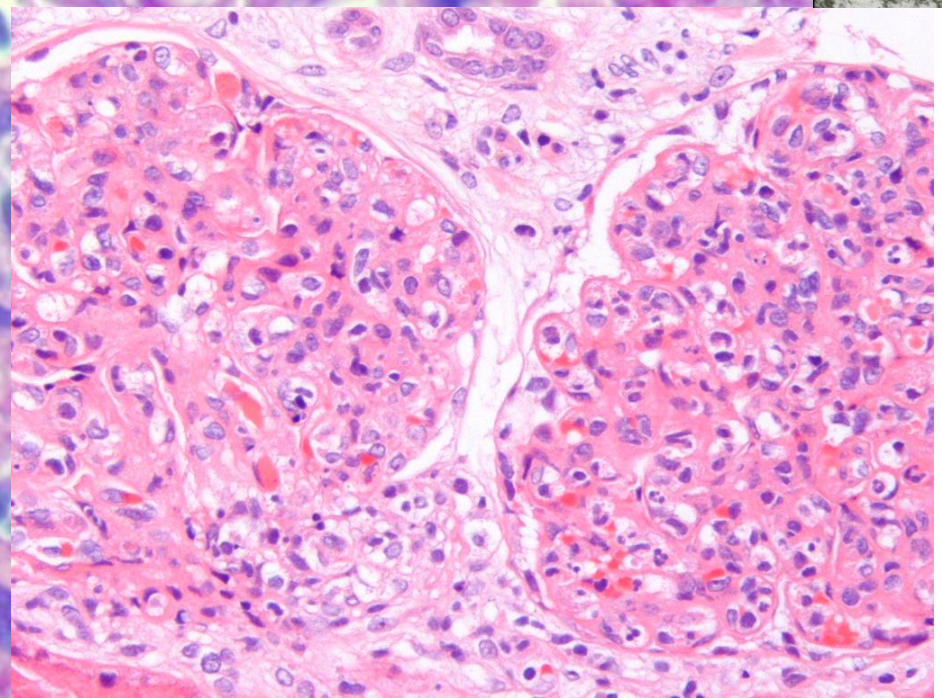
Type I = 10-15%, multiple myeloma, Waldenström macroglobulinemia
- monoclonal paraprotein

Types II = 50-60%
- immune complexes: monoclonal IgM-polyclonal IgG or IgA (RF function)

Type III = 25-30%, SLE, rheumatoid arthritis
- polyclonal IgM and IgG







IF: IgG-κ

EM: organized deposits
(may be focal)
courtesy of Michael Mihatsch

LM: membranoproliferative pattern of injury

Organized deposits:
amyloidosis, fibrillary, immunotactoid and cryoglobulinemic

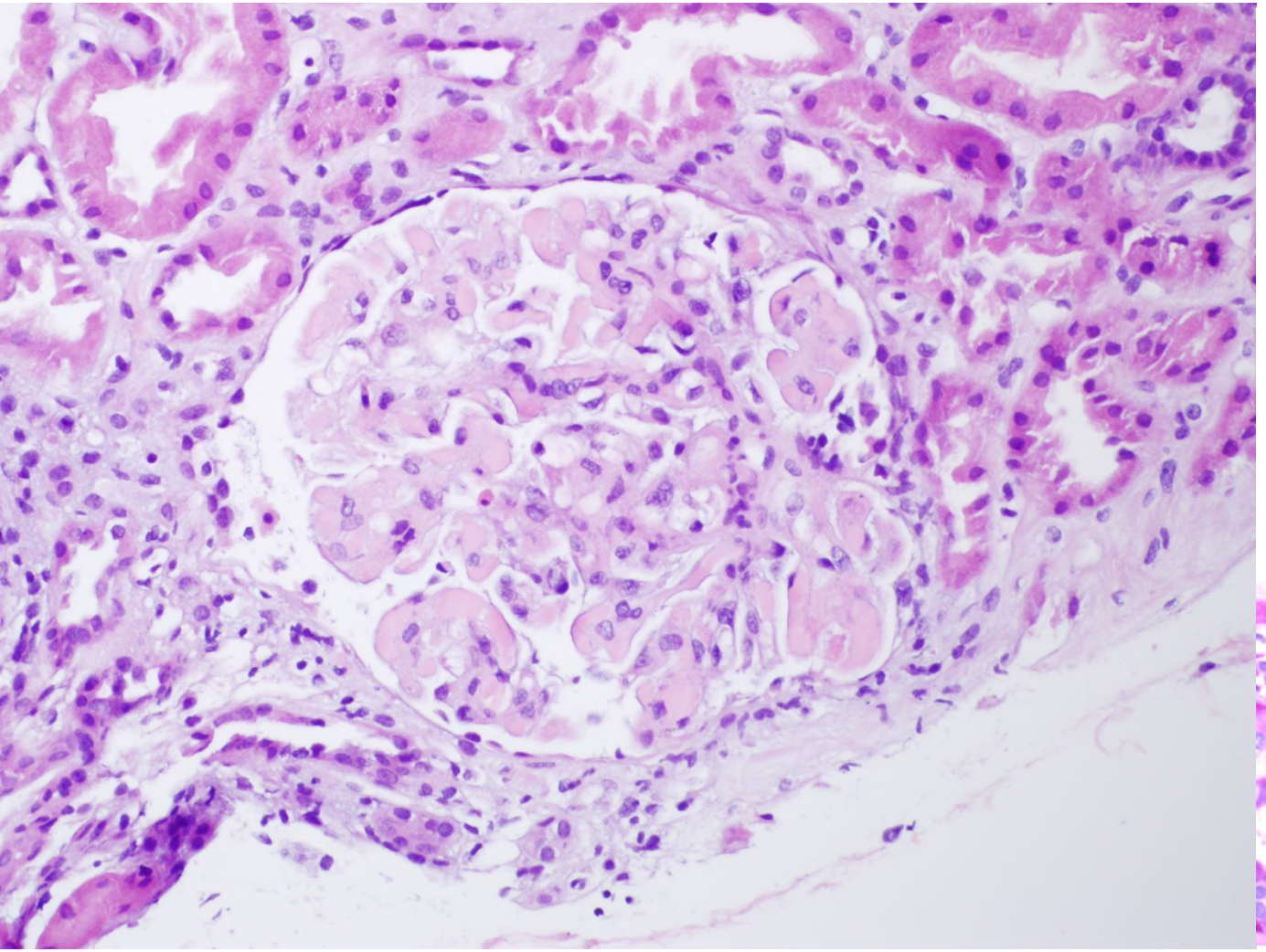
deposits	location	Congo red	paraprotein	diagnosis
fibrils 8-10 nm in thickness	extracellular	(+)	AL/AH-100% non-AL/AH: 0%	amyloidosis
fibrils 20-30 nm in thickness	extracellular	(-)	some	fibrillary glomerulonephritis
microtubules >30 nm in diameter	extracellular	(-)	usually	immunotactoid glomerulonephritis
microtubules, curvilinear, annular-tubular structures, and fingerprints, focal	Extracellular subendothelial & intraluminal	(-)	100% 0%	Cryoglobulin type I, II Type III

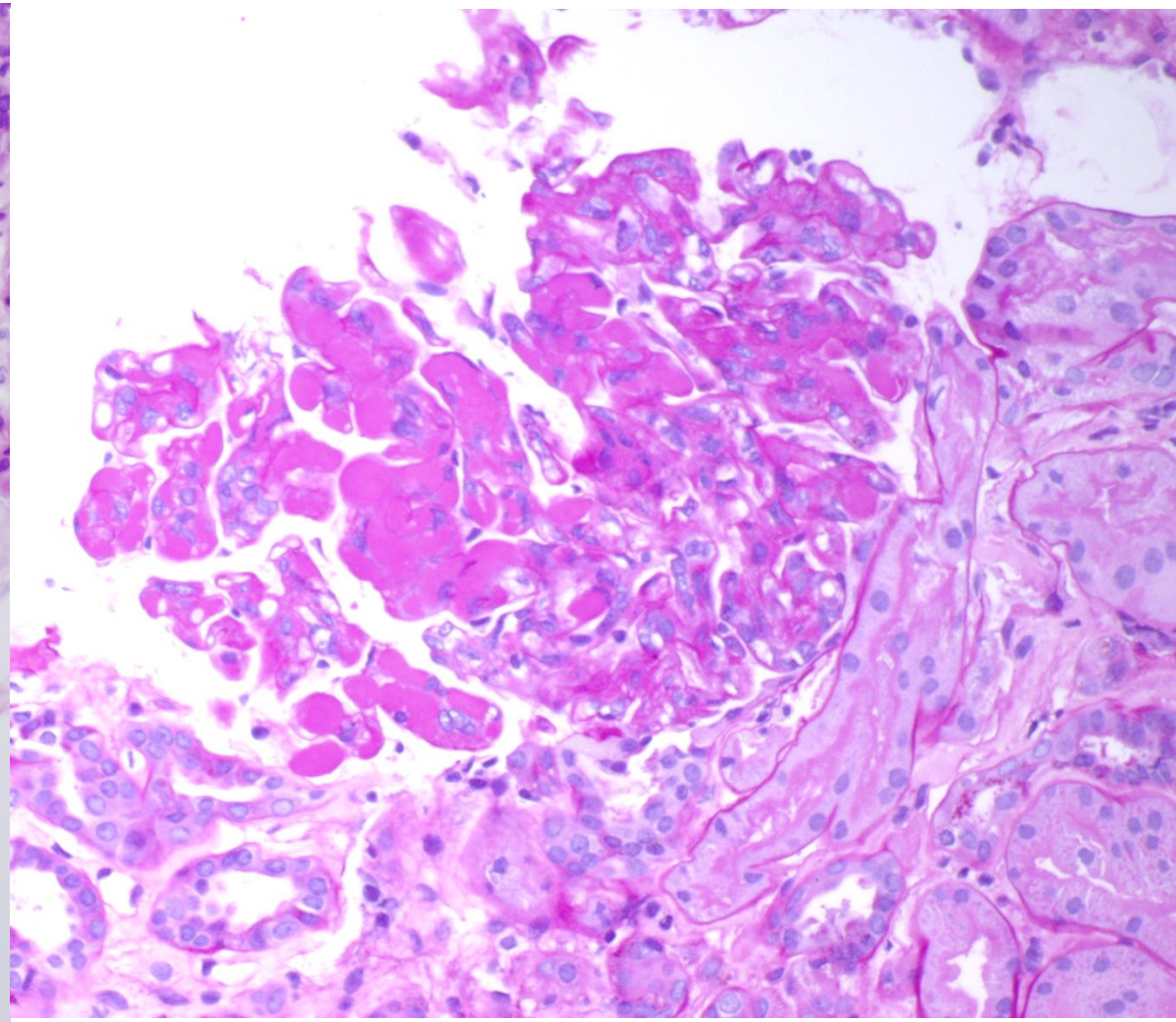
Waldenström's macroglobulinemia
aka **lymphoplasmacytic lymphoma**

clinicopathologic entity:
- bone marrow lymphoplasmacytic lymphoma + **IgM** monoclonal gammopathy
- anemia, hyperviscosity, lymphadenopathy, hepatomegaly or splenomegaly

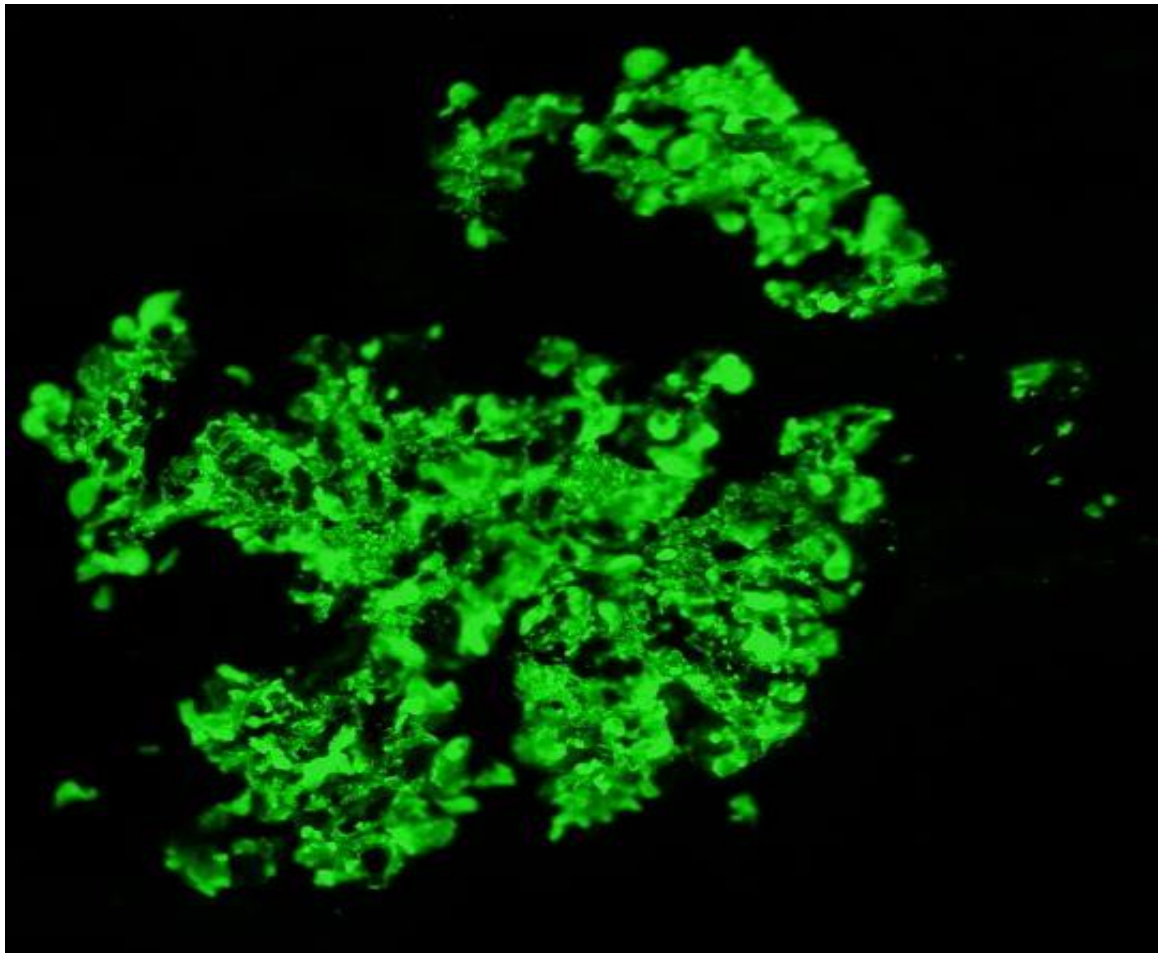
Other pathologies:
- Bence Jones proteinuria 40%, > 1 g/d 3%
- cryoglobulins 20%
- AL

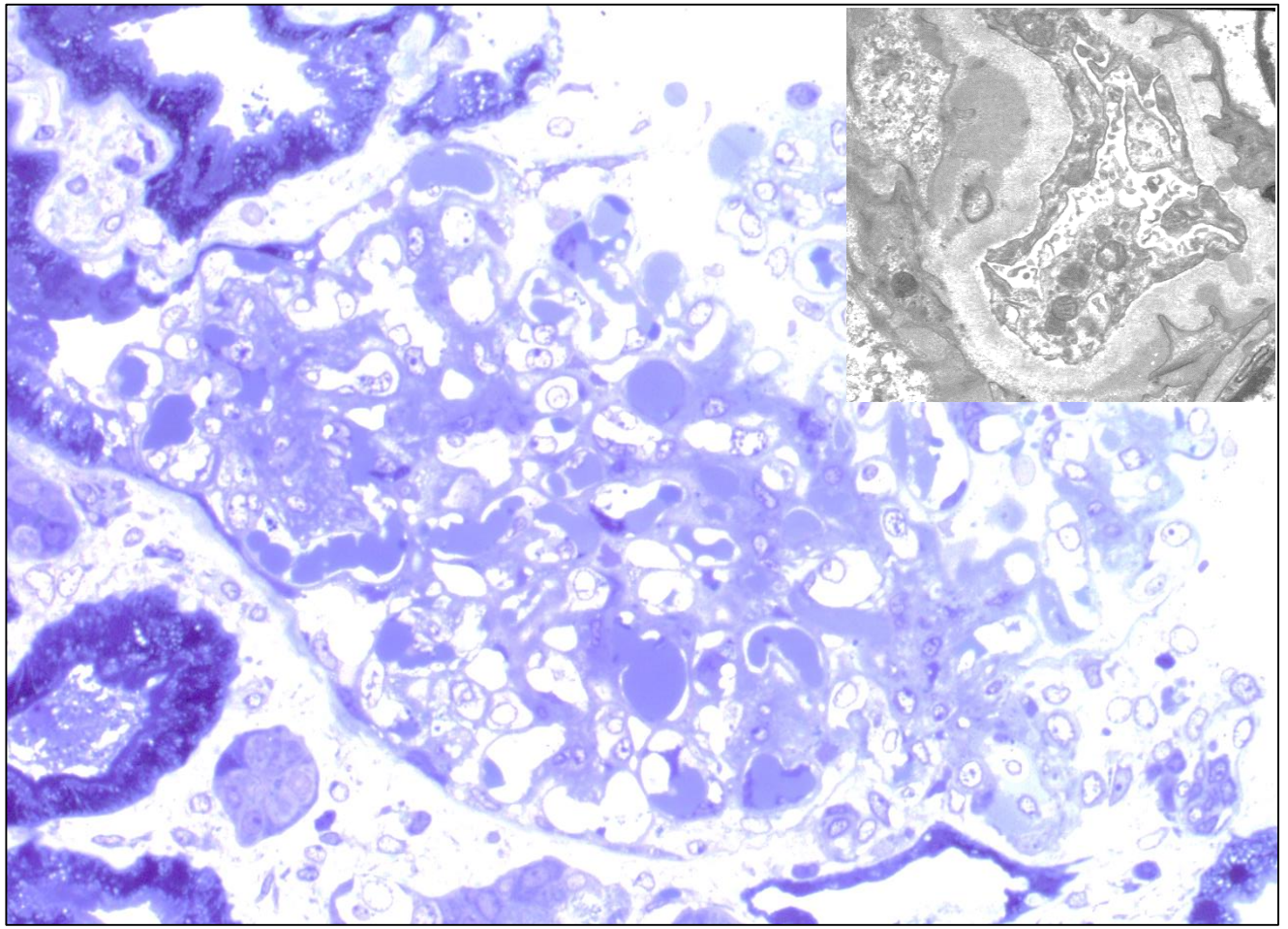
rare, 1-2% of hematologic cancers, US: ~ 1,500/year
"indolent lymphoma", incurable but treatable





Waldenström macroglobulinemia





IF: IgM-κ glomerular capillaries + intracapillary thrombi

Crystalglobulinemia: intravascular crystals

- very rare
- pathomechanism not clear: crystallization of monoclonal proteins in the systemic vasculature with vascular injury, thrombosis, and occlusion

Crystalline nephropathy – differential diagnosis:

(A) non-paraprotein crystals **- nephrocalcinosis and oxalate nephropathy, most common** **- urate nephropathy, cystinosis, dihydroxyadeninuria, less frequent** **- drug-induced crystalline nephropathy (indinavir, triamterene)**	**(B) paraprotein crystals:** **- intracellular crystals:** **light chain proximal tubulopathy/crystal-storing histiocytosis** - **intratubular crystals, rare [12]** - **Intravascular, very rare [12, 13]**

Differential diagnosis of intracapillary paraprotein:

- cryoglobulinemia,
- Waldenström macroglobulinemia,
- crystalglobulinemia

SKIN FREQUENTLY INVOLVED

Monoclonal gammopathy of cutaneous significance

D. Lipsker, 2016 [16]

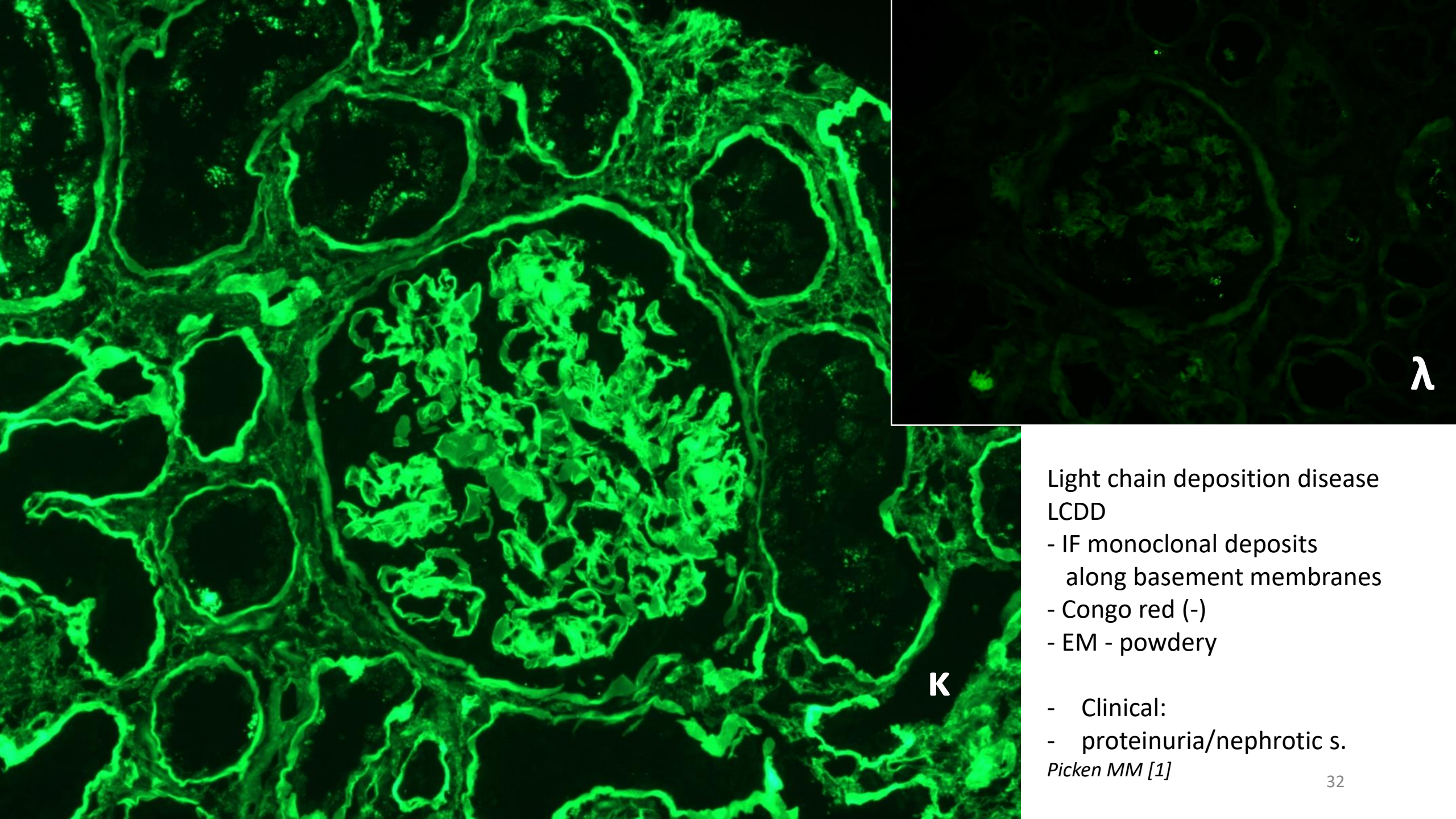
Journal of the European Academy of Dermatology and Venereology
8 AUG 2016 DOI: 10.1111/jdv.13847 [14]
http://onlinelibrary.wiley.com/doi/10.1111/jdv.13847/full#jdv13847

Monoclonal Immunoglobulin deposition Disease[MIDD]:

Light Chain Deposition Disease (LCDD), most common
Light/Heavy chain Deposition Disease, rare
Heavy Chain Deposition Disease, rare

Defining feature = immunostain with characteristic pattern of distribution

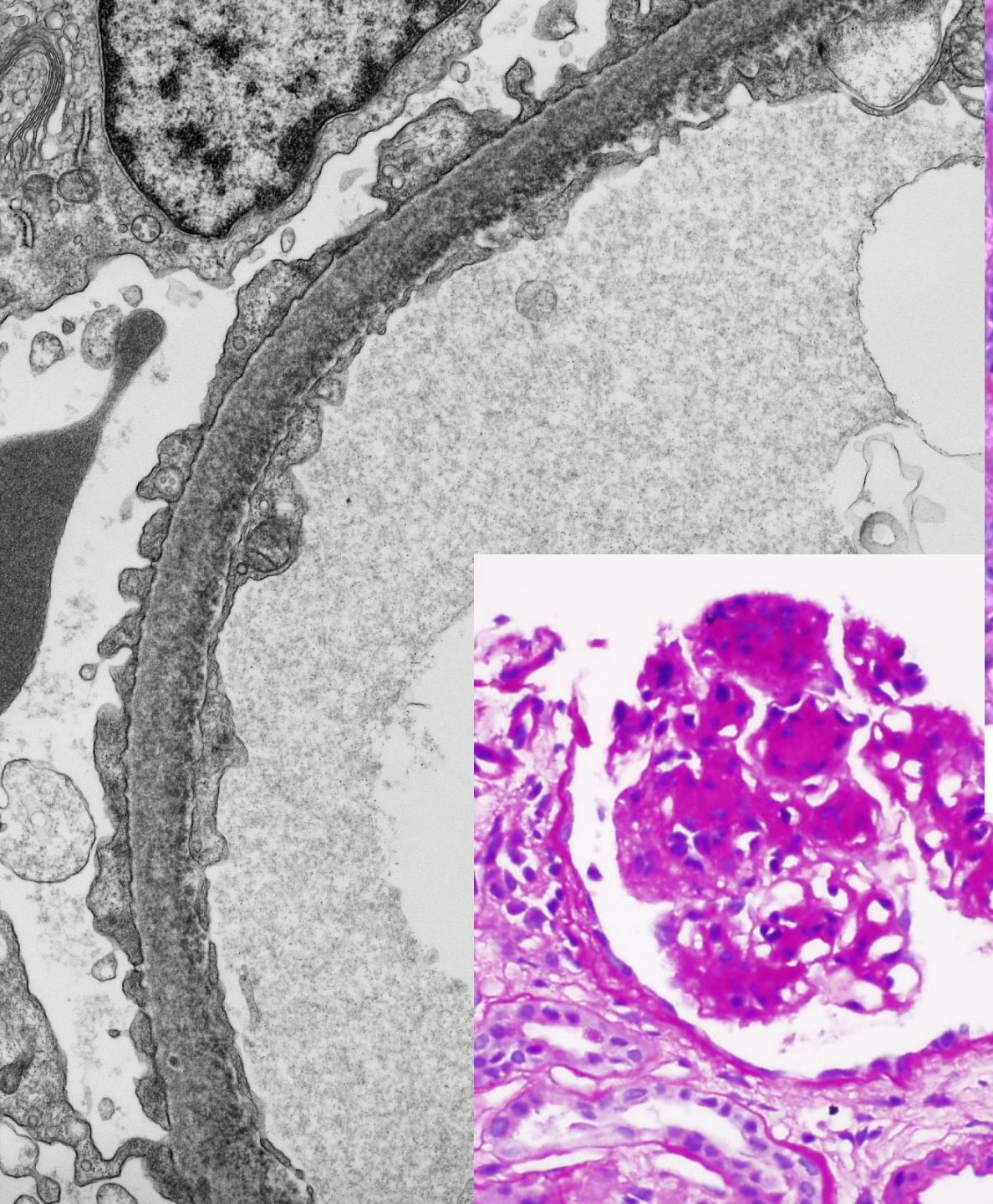
LCDD-κ>LCDD-λ

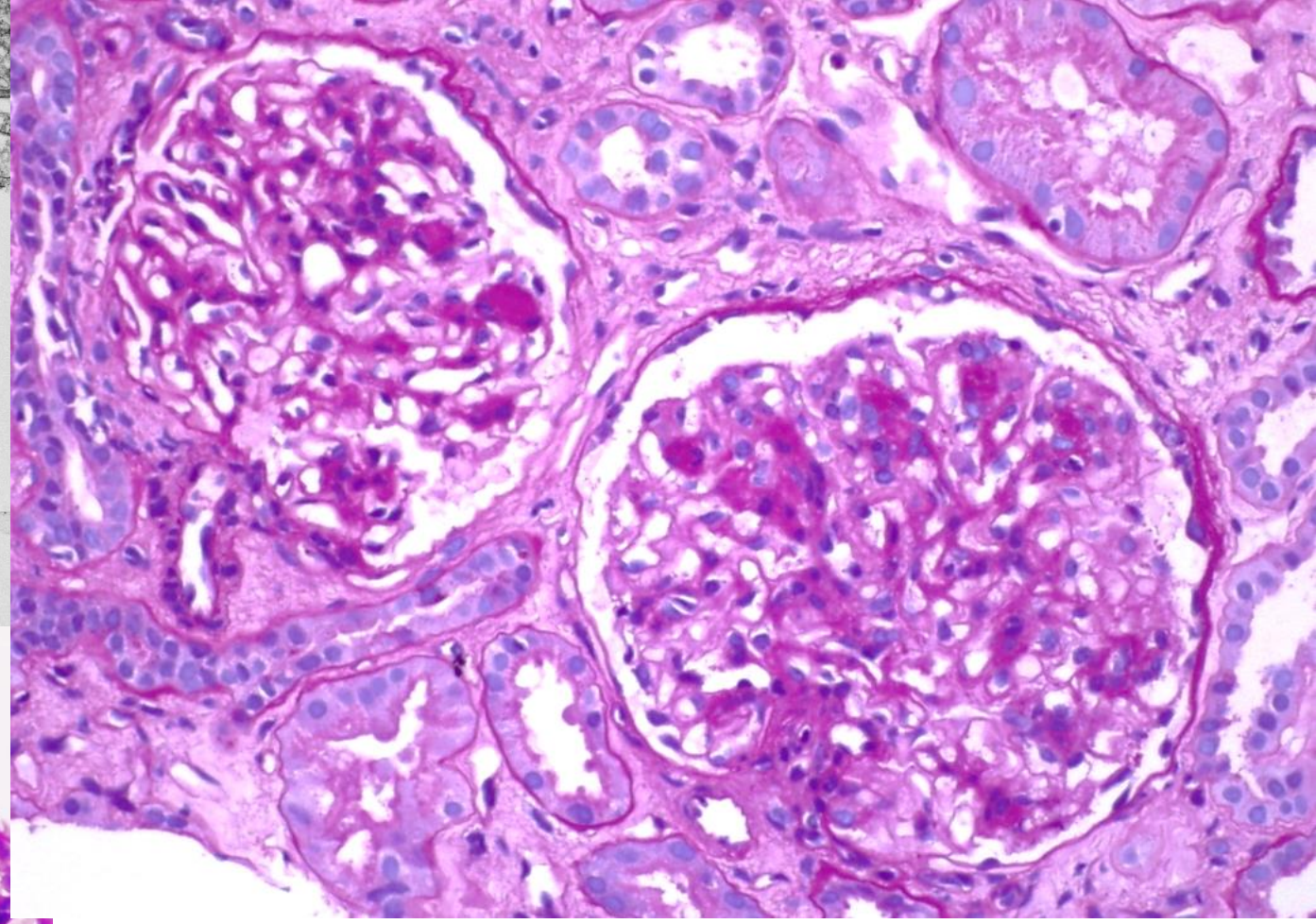


Light chain deposition disease
LCDD
- IF monoclonal deposits
  along basement membranes
- Congo red (-)
- EM - powdery

- Clinical:
- proteinuria/nephrotic s.

Picken MM [1]





MIDD: LCDD, HCDD, LHCDD

- monoclonal deposits along basement membranes
- Congo red (-)
- EM: non-fibrillary, powdery
- Light microscopy = variable!!!

May be associated with other paraprotein pathologies

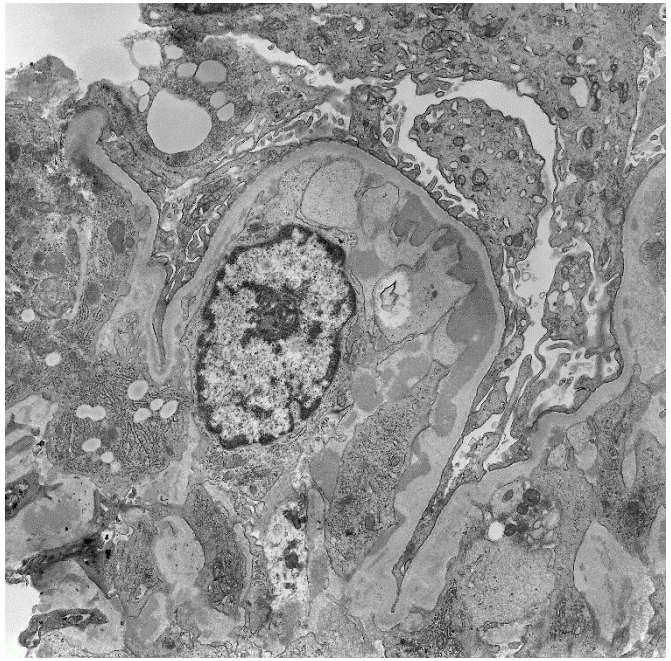
Picken MM 2014 [1]
Nasr et al 2009 [15]

Glomerulonephritis with non-organized deposits immune complex-like

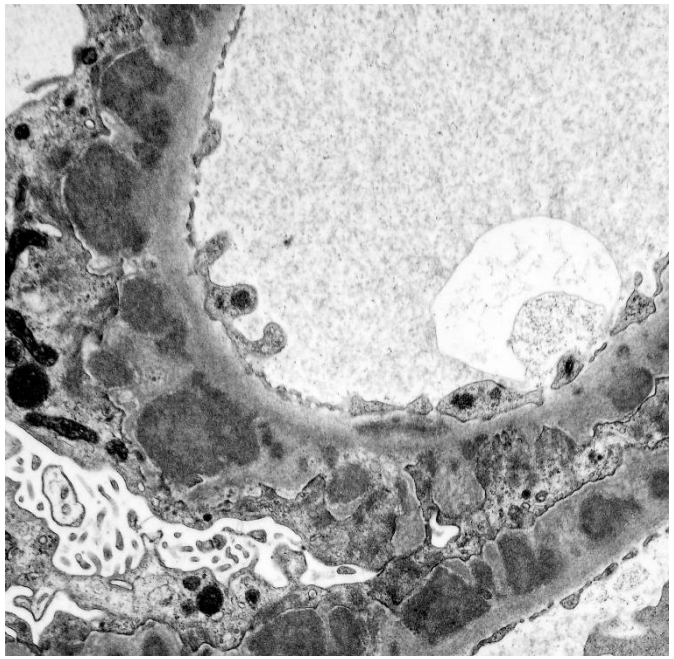
LM variable: proliferative(MPGN),membranous

IF: IgG3-kappa

EM: immune complex-like deposits



Abundant, large, granular electron-dense mesangial and subendothelial deposits.



Abundant, medium-sized, granular electron-dense subepithelial and intramembranous deposits

Samih H. Nasr et al. JASN 2009;20:2055-2064 [16]

C3 Glomerulonephritis

- proliferative glomerulonephritis
- IF: C3 and no immunoglobulins
- EM: electron dense deposits, non-organized, immune-complex-like

Pathomechanism: dysregulation of the alternative pathway of complement

Dysregulation of the alternative pathway of complement - C3 glomerulopathies:
C3 glomerulonephritis & Dense Deposit Disease

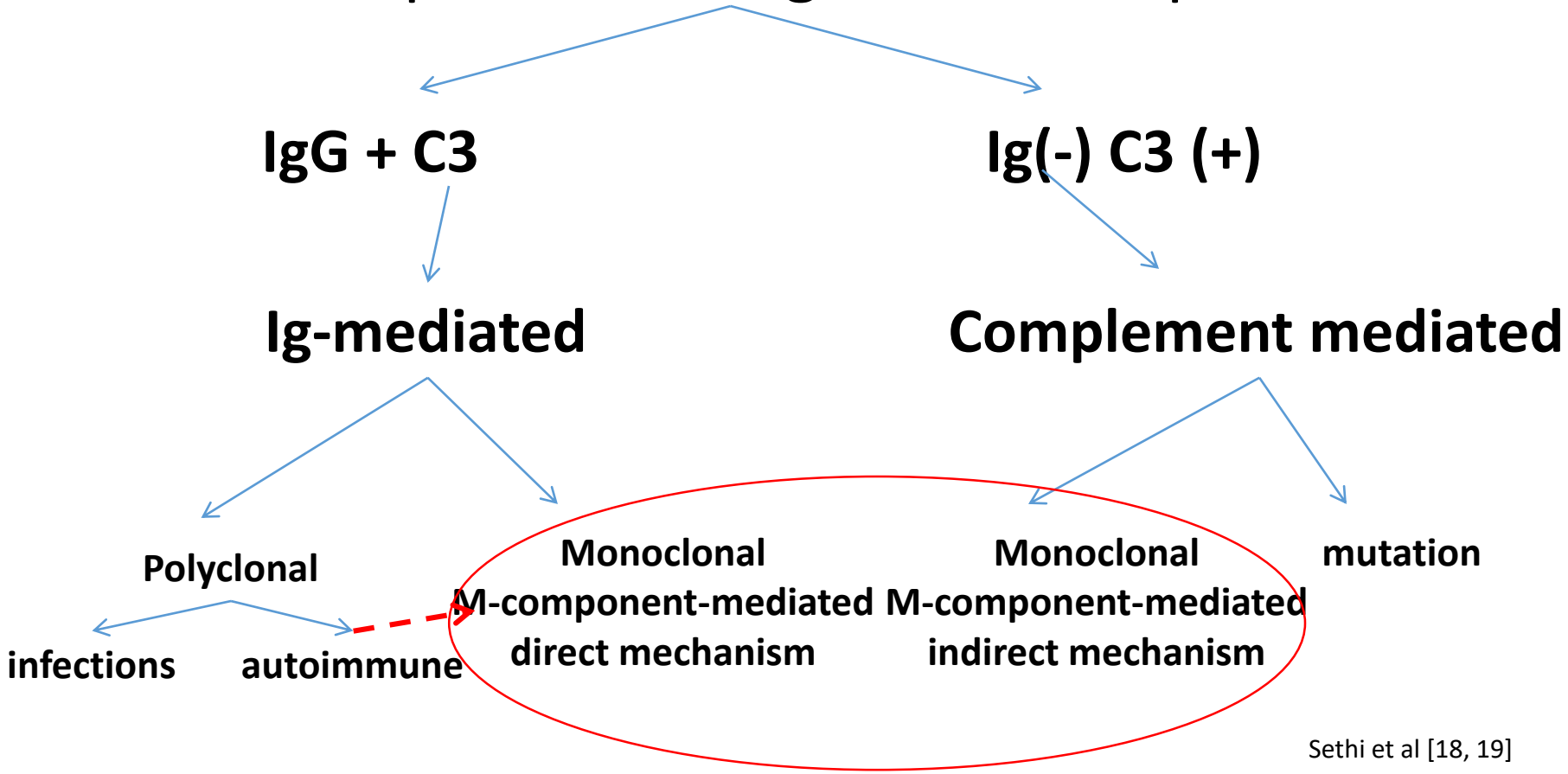
- mutations
- functional inhibition of regulating proteins
- functional inhibition of regulating proteins by a monoclonal gammopathy

= indirect paraprotein induced injury

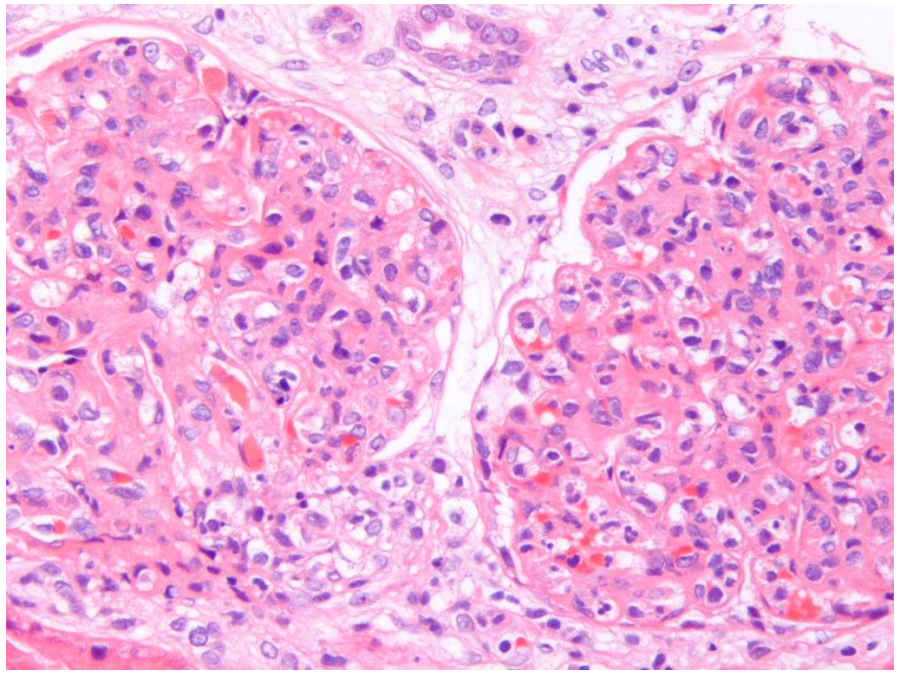
Bridoux et al, CJASN 2011 [17]

Evolution of classification of membranoproliferative pattern of glomerular injury towards pathogenetic classification

Membranoproliferative glomerulonephritis:



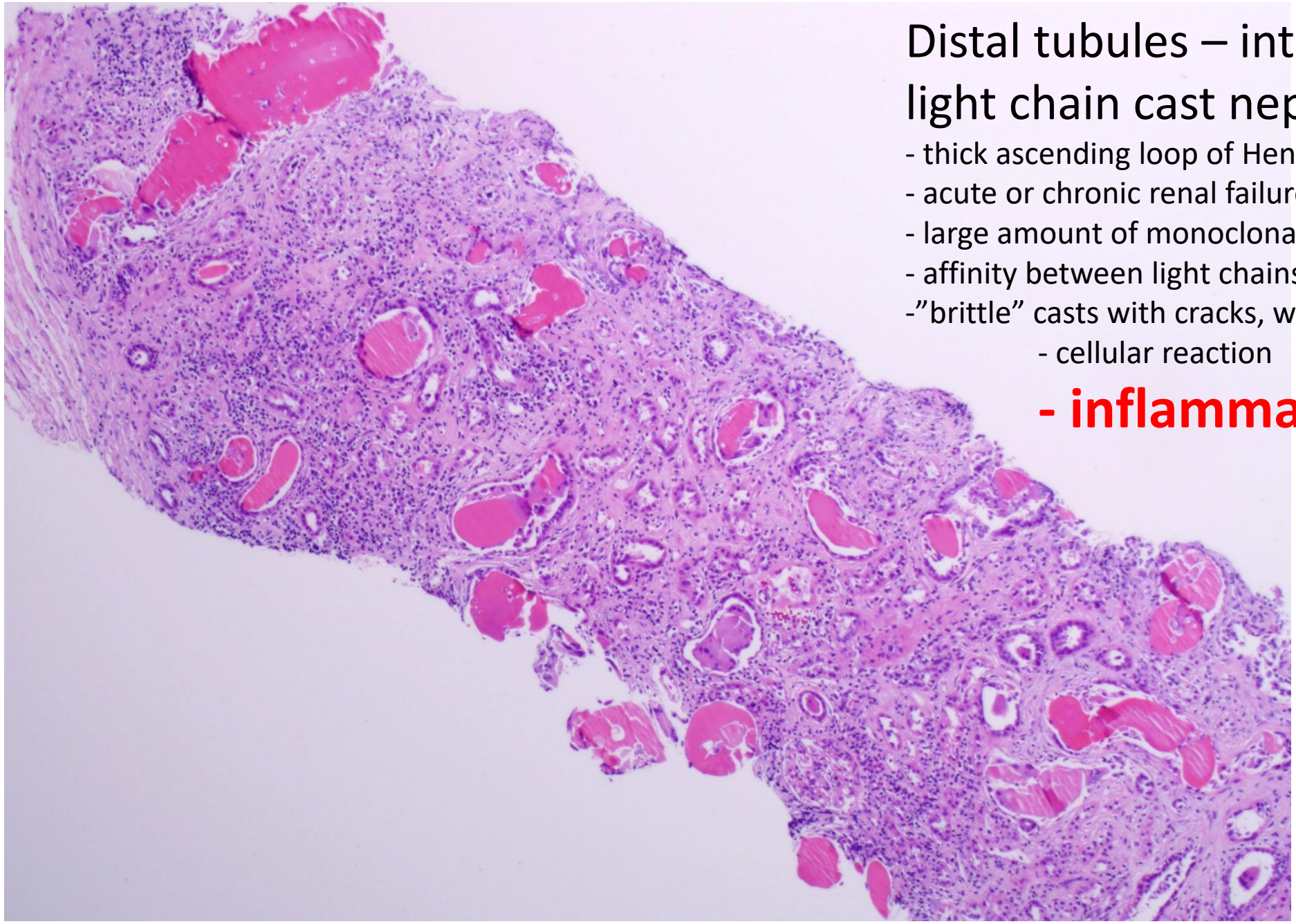
Sethi et al [18, 19]



Monoclonal gammopathy is an important cause of membranoproliferative glomerulonephritis (MPGN):

all (adult) patients with MPGN should be evaluated for an underlying monoclonal gammopathy

to examine the tubules and the interstitium!!!



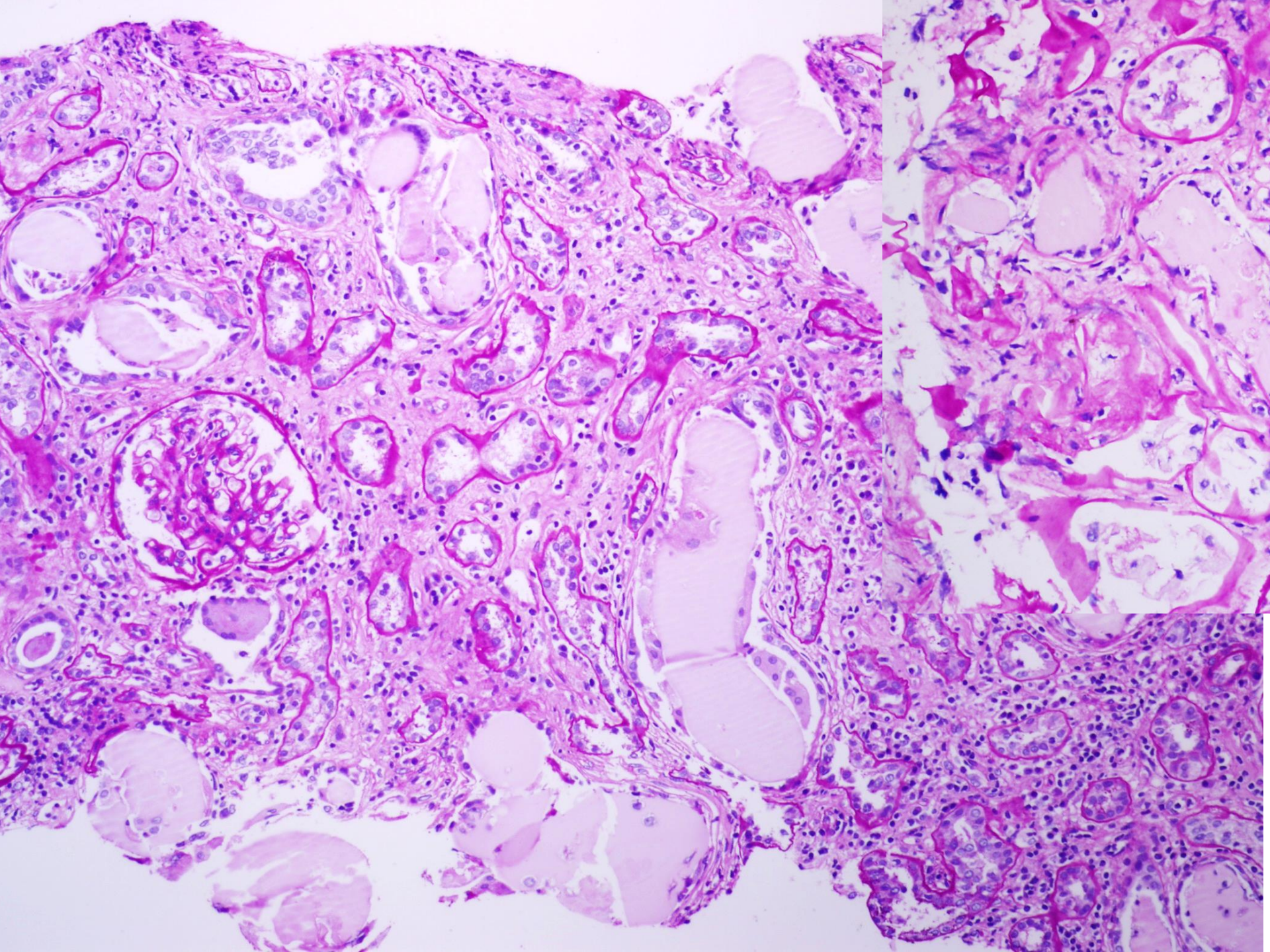
Distal tubules – intratubular light chain

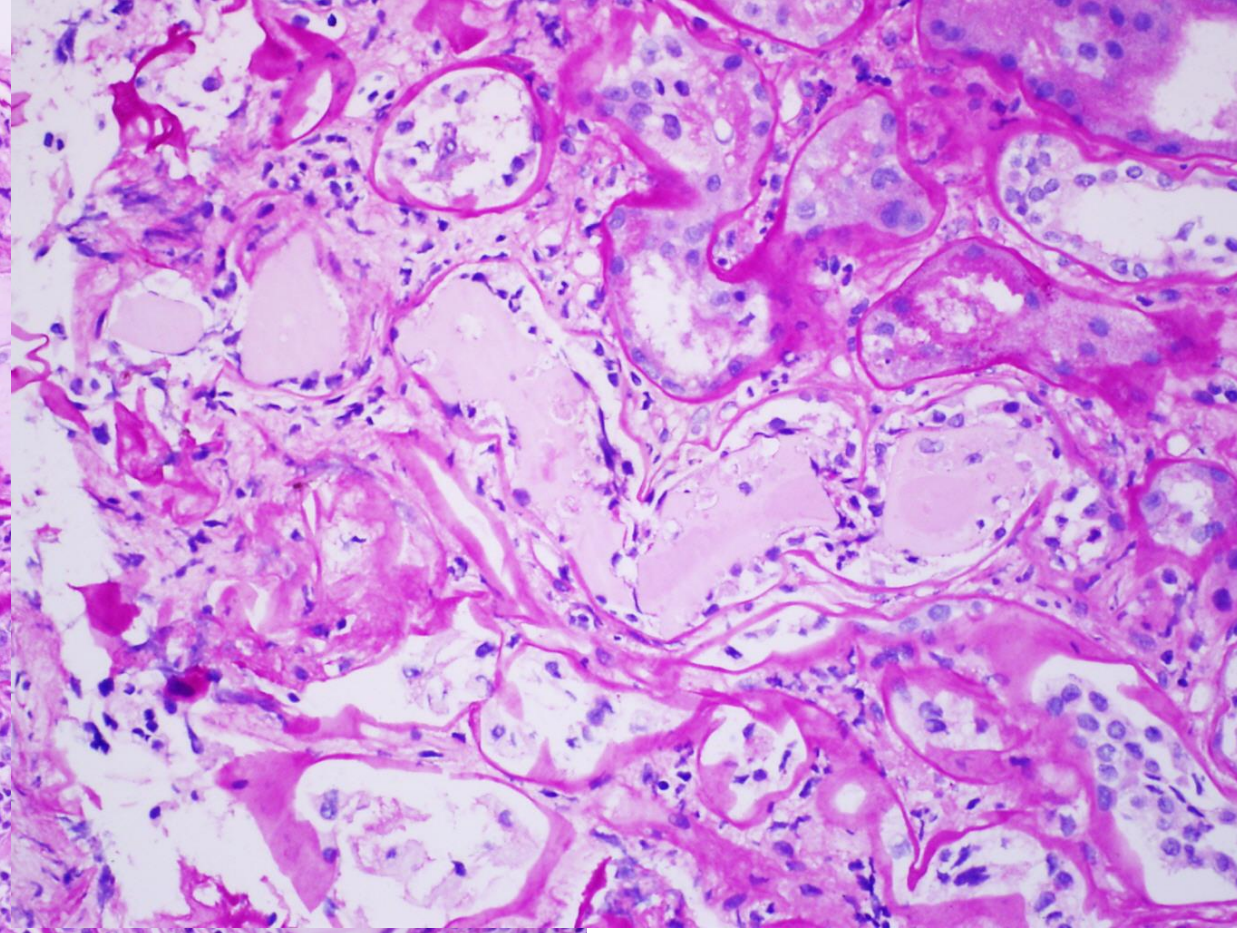
light chain cast nephropathy:

- thick ascending loop of Henle
- acute or chronic renal failure
- large amount of monoclonal free light chains
- affinity between light chains with uromodulin (Tam Horsfall protein)
-"brittle" casts with cracks, weakly PAS (+),
- cellular reaction

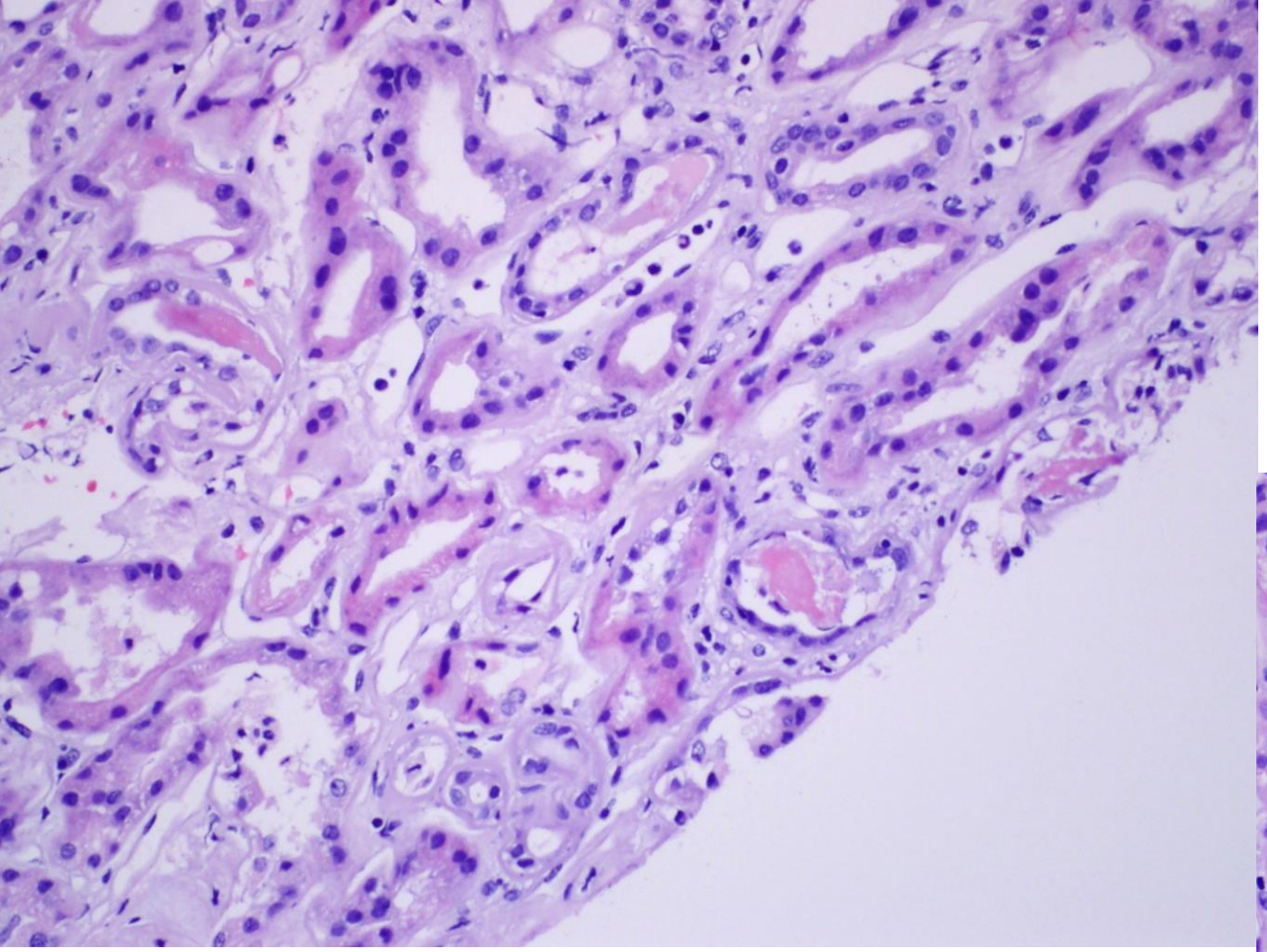
- inflammation, fibrosis

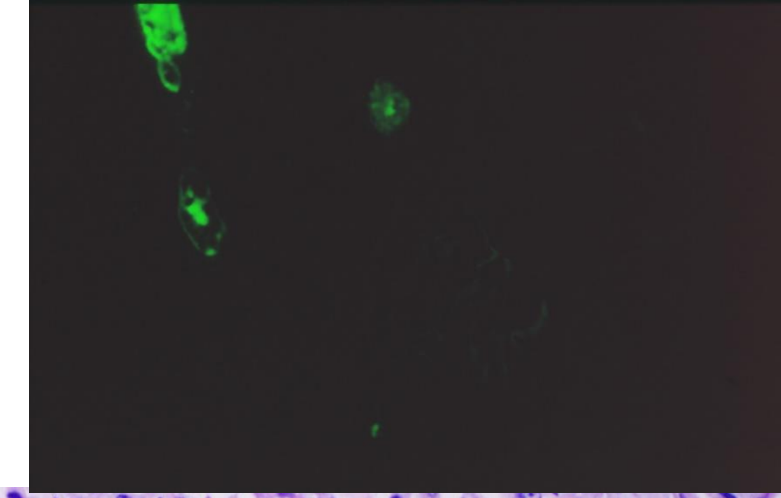
Picken MM 2014 [1]

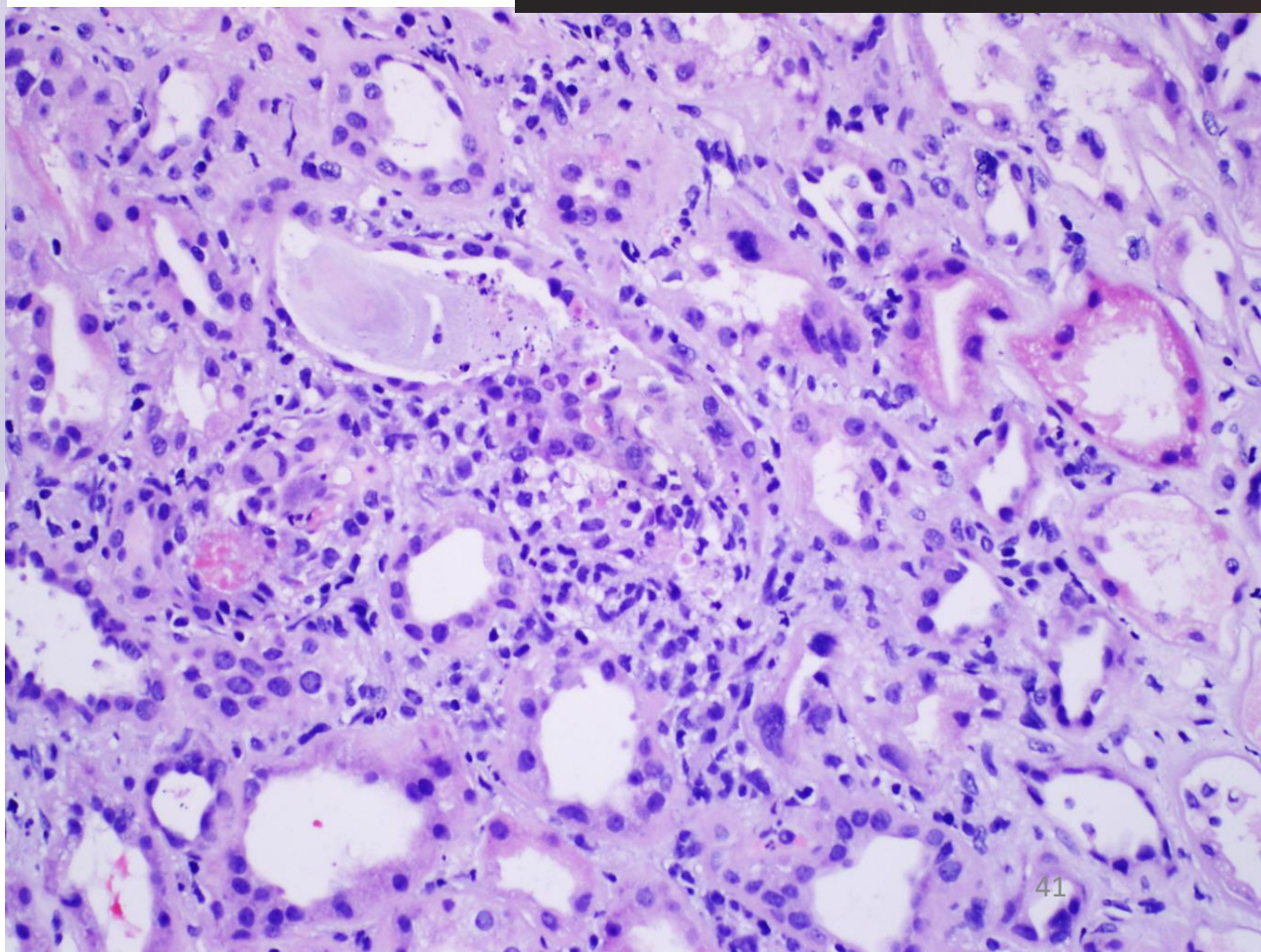




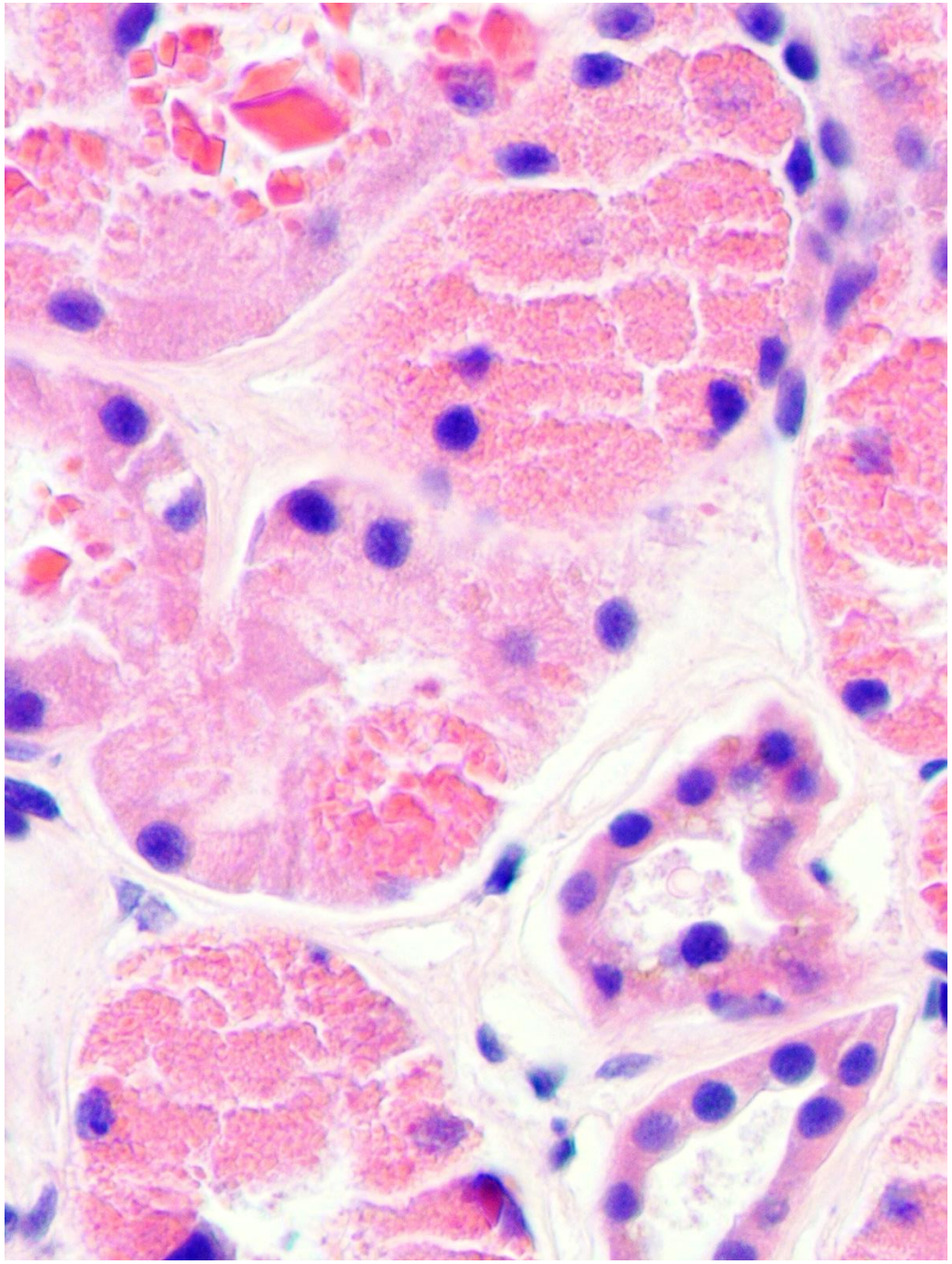
Picken MM 2014 [1]
- light chains casts = weakly PAS positive
- cellular reaction around casts

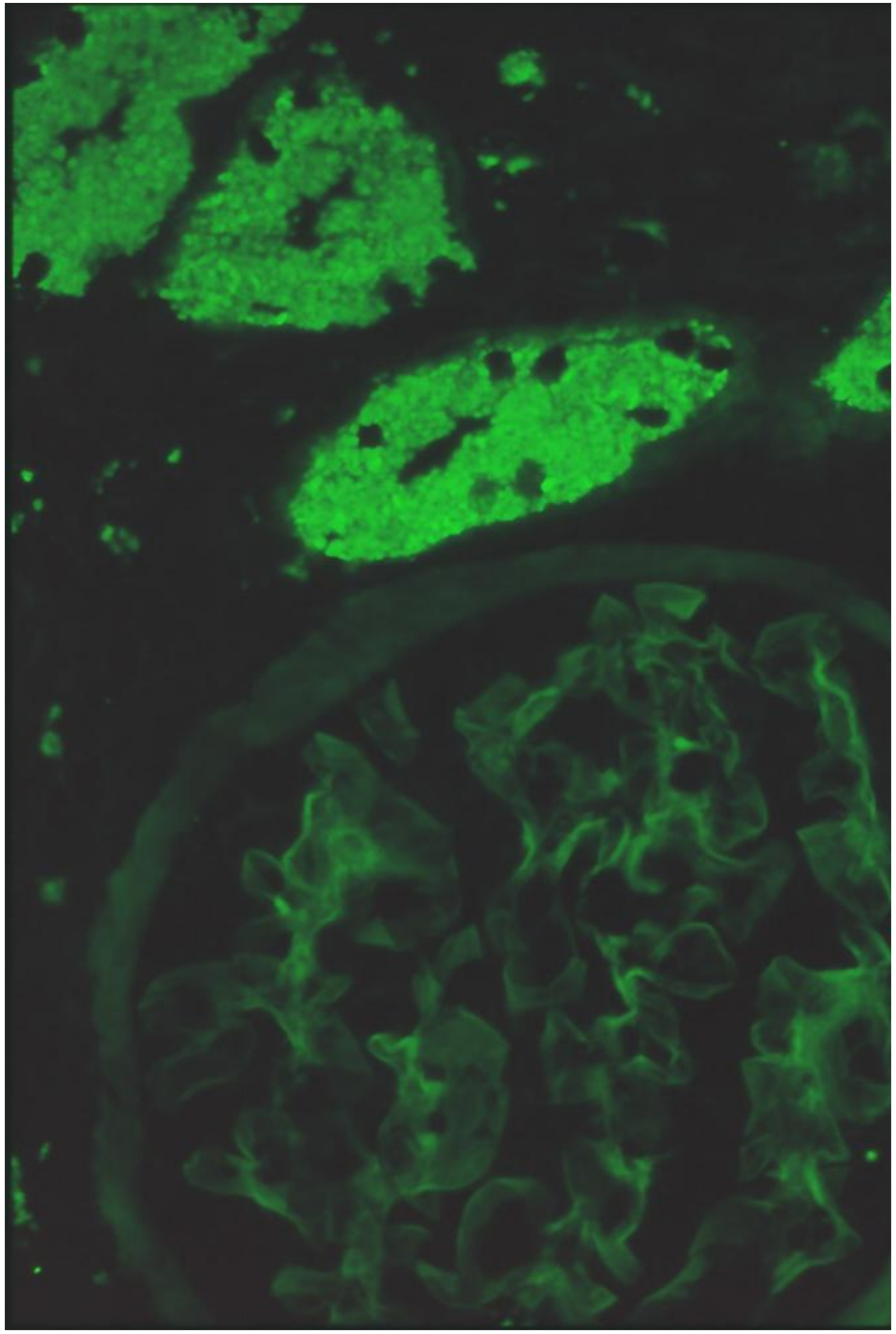






Differential Diagnosis:
early light chain cast nephropathy versus
Interstitial nephritis



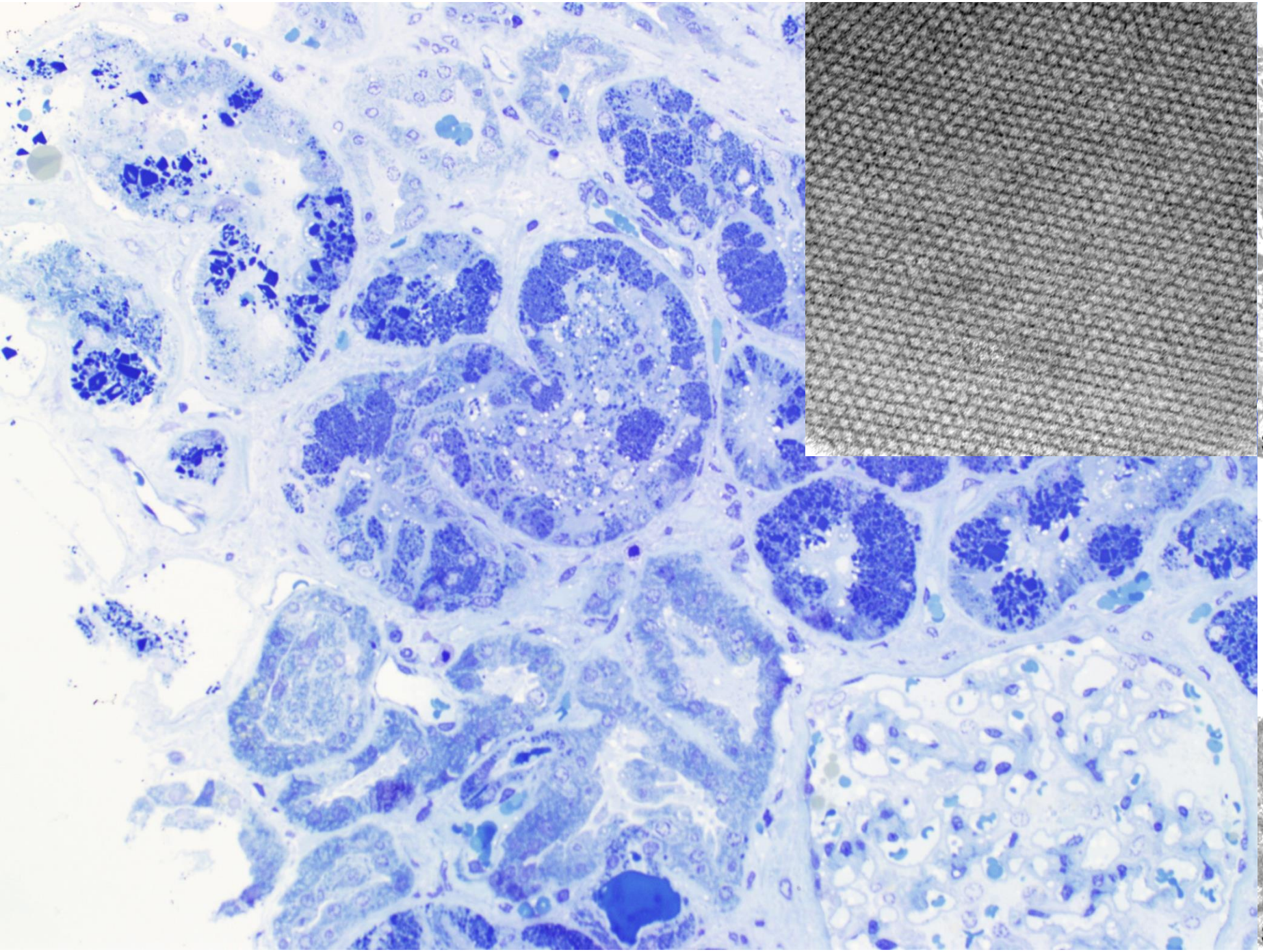


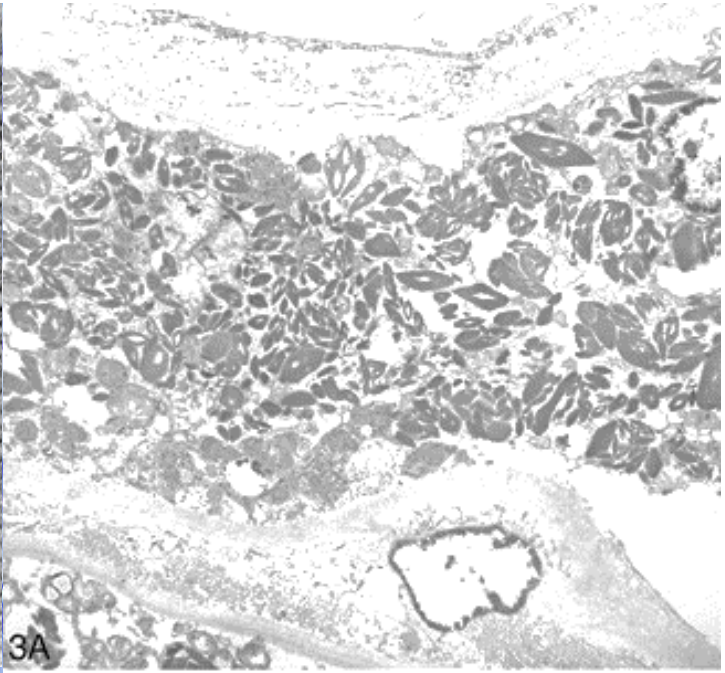
LCPT: **L**ight **C**hain **P**roximal **T**ubulopathy with crystals

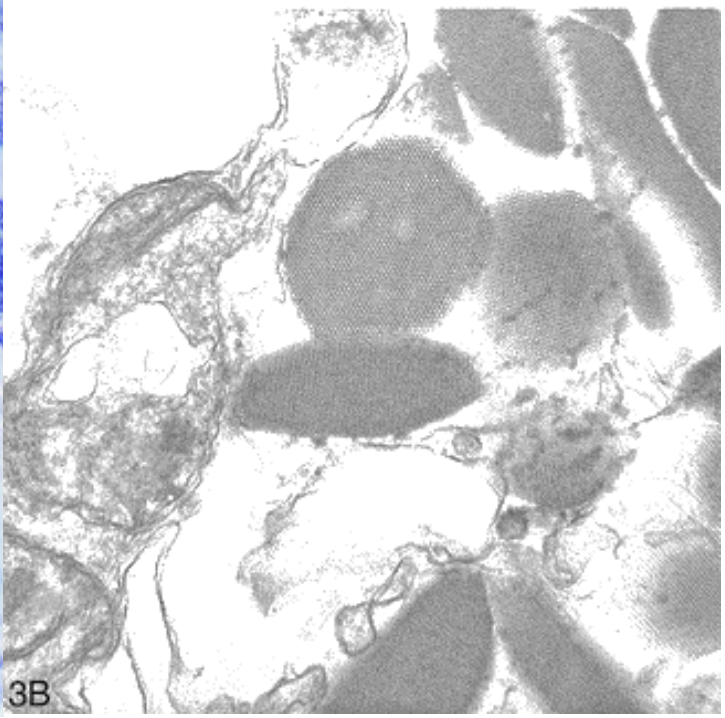
Intracellular organized

Clinical: slowly progressing renal failure with/without Fanconi syndrome, complete or partial
(glucose, amino acids, uric acid, phosphate, and bicarbonate)

Recurrence in kidney Transplant!!!
[20, 21]




3A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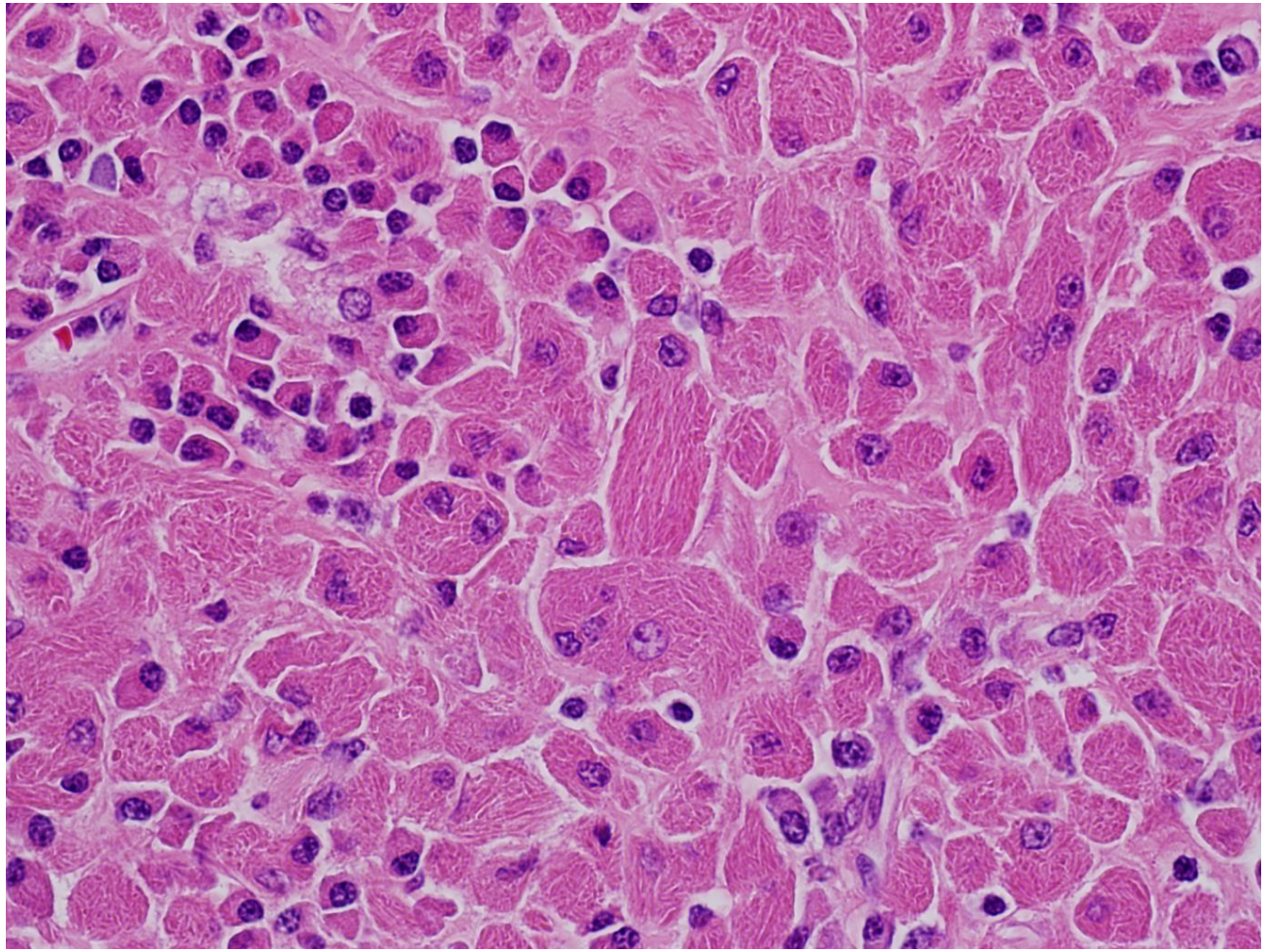
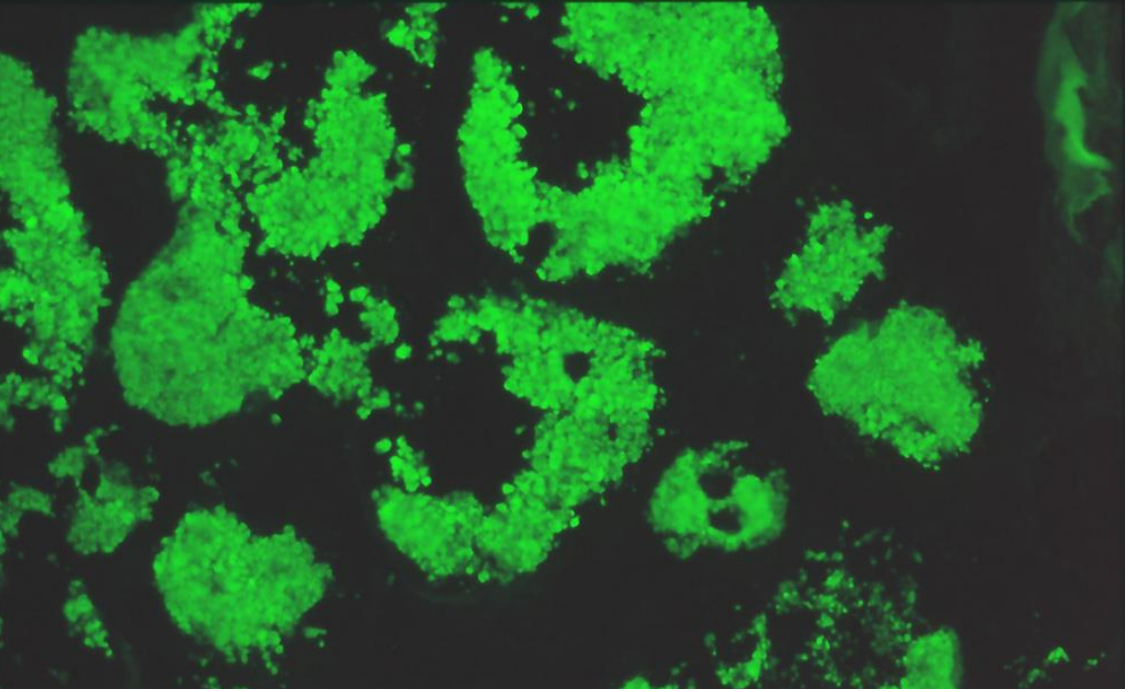
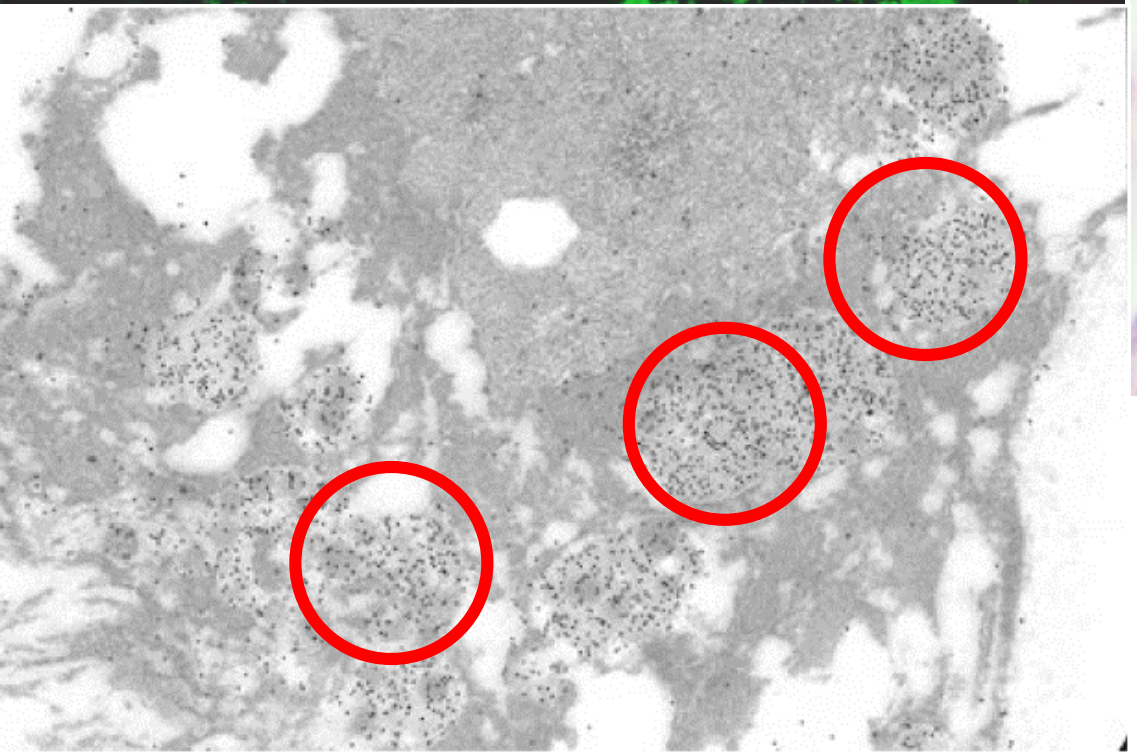
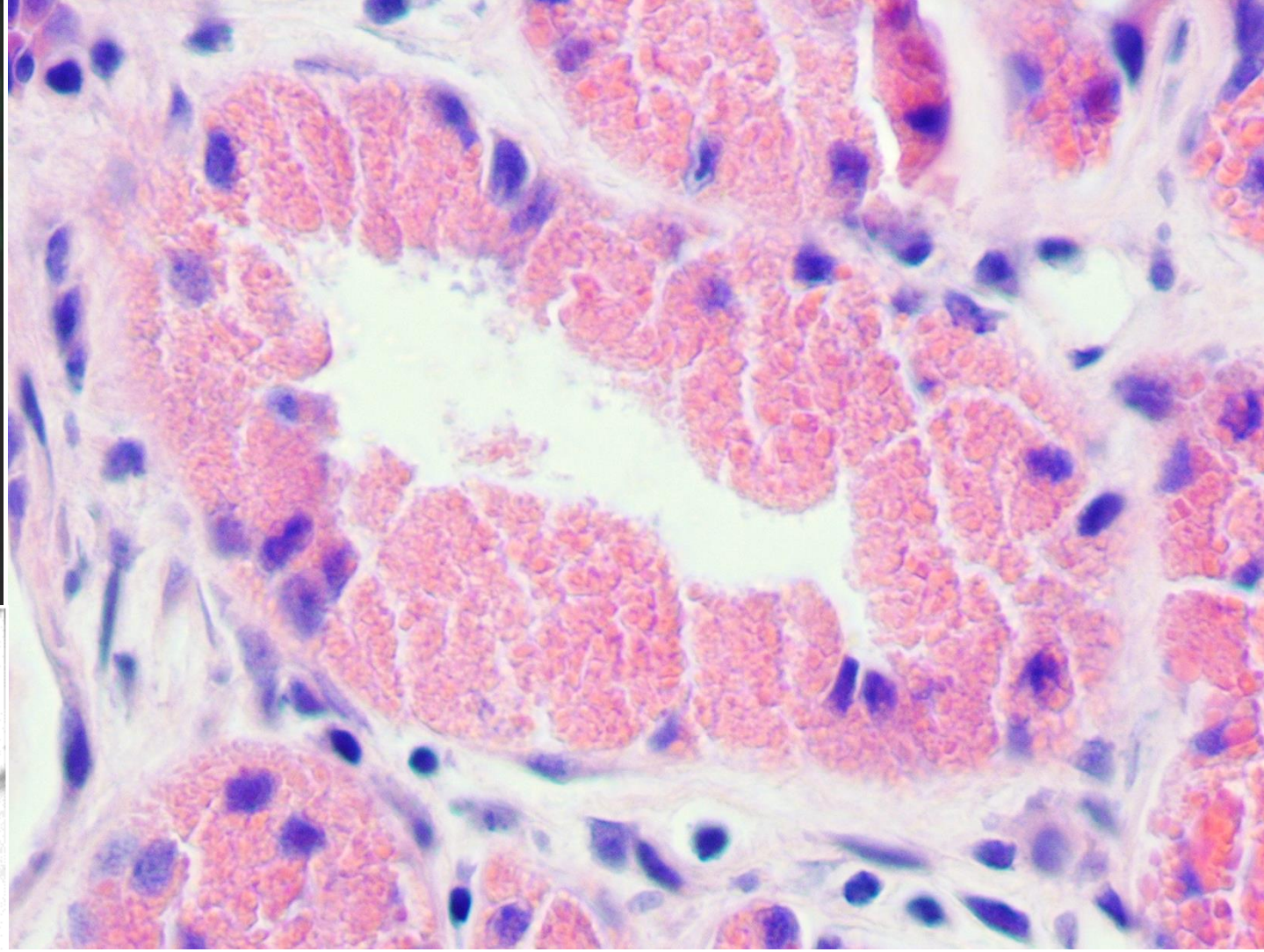


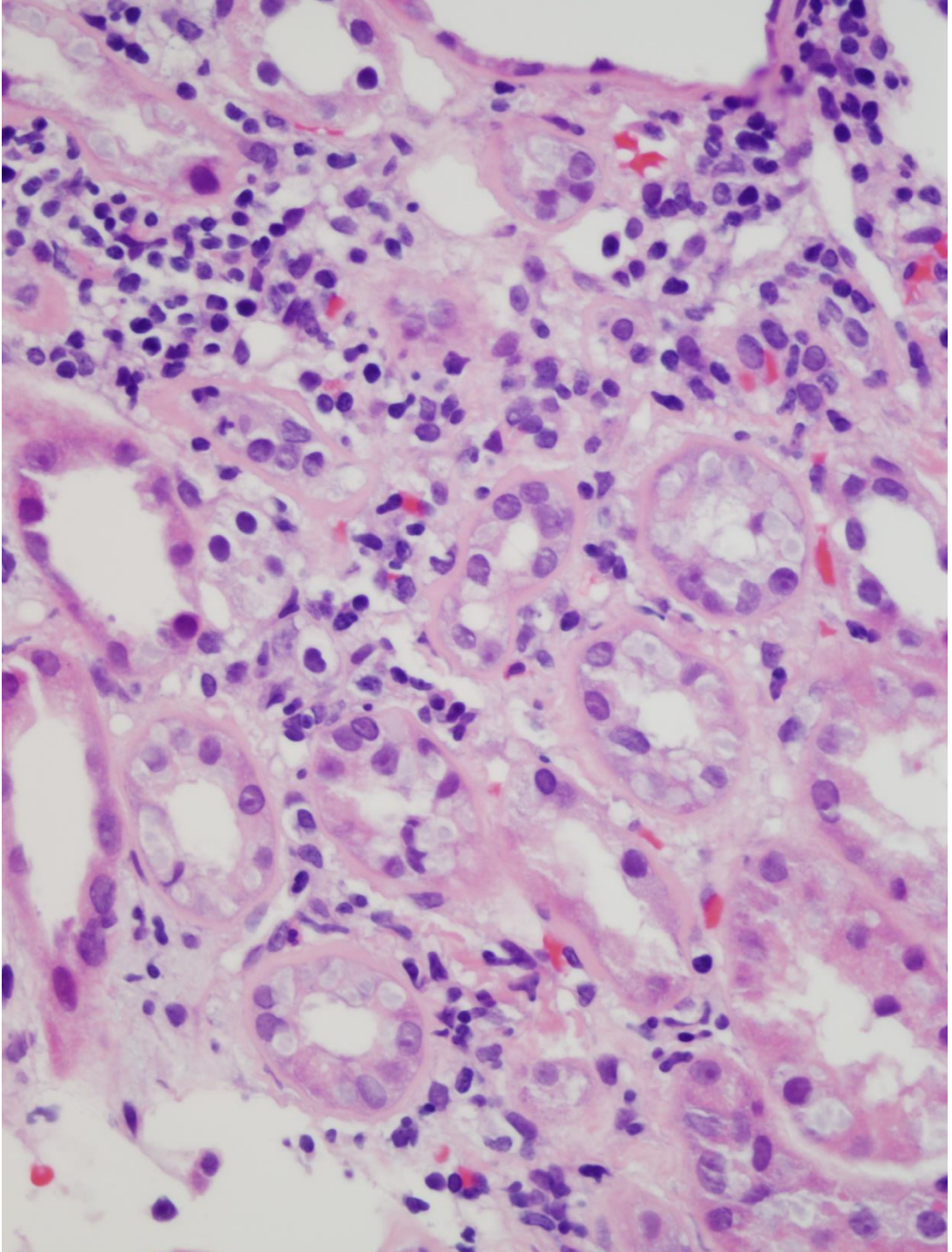
CSH: **C**rystal **S**toring **H**istiocytosis: kidney, systemic *[21], [22]*

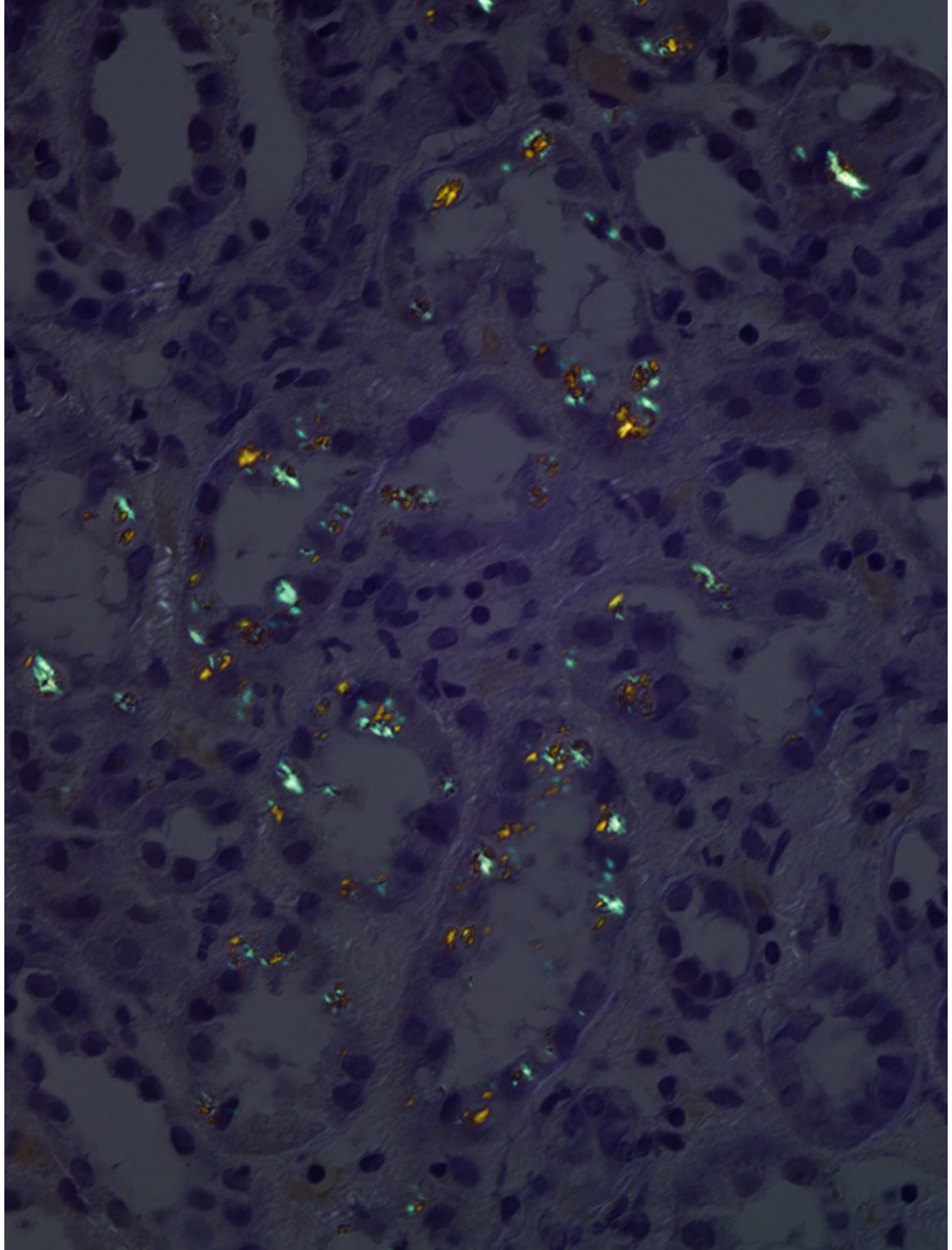






Light Chain Proximal Tubulopathy – non-crystalline
Intracellular non-organized
More common than crystalline!!! [20]





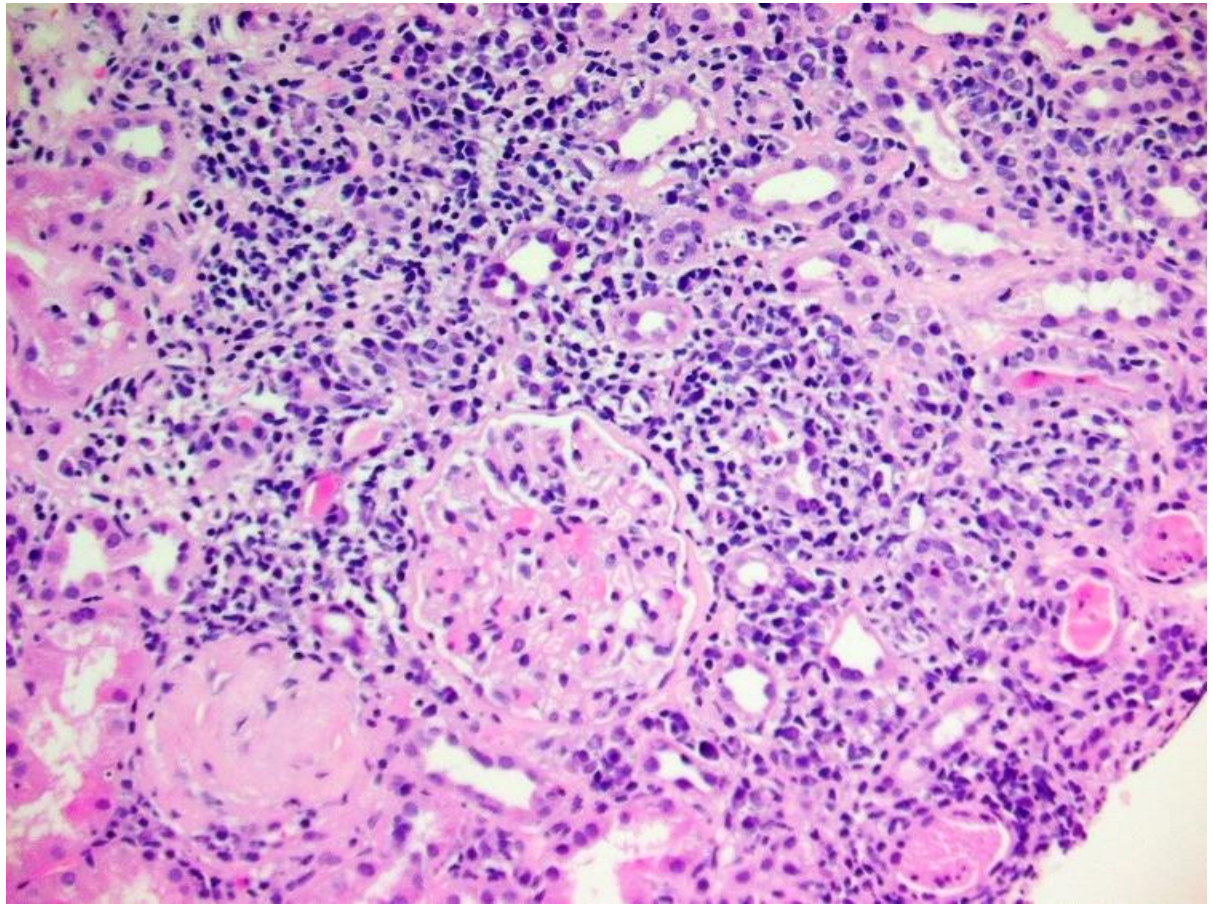
Amyloid Inclusions

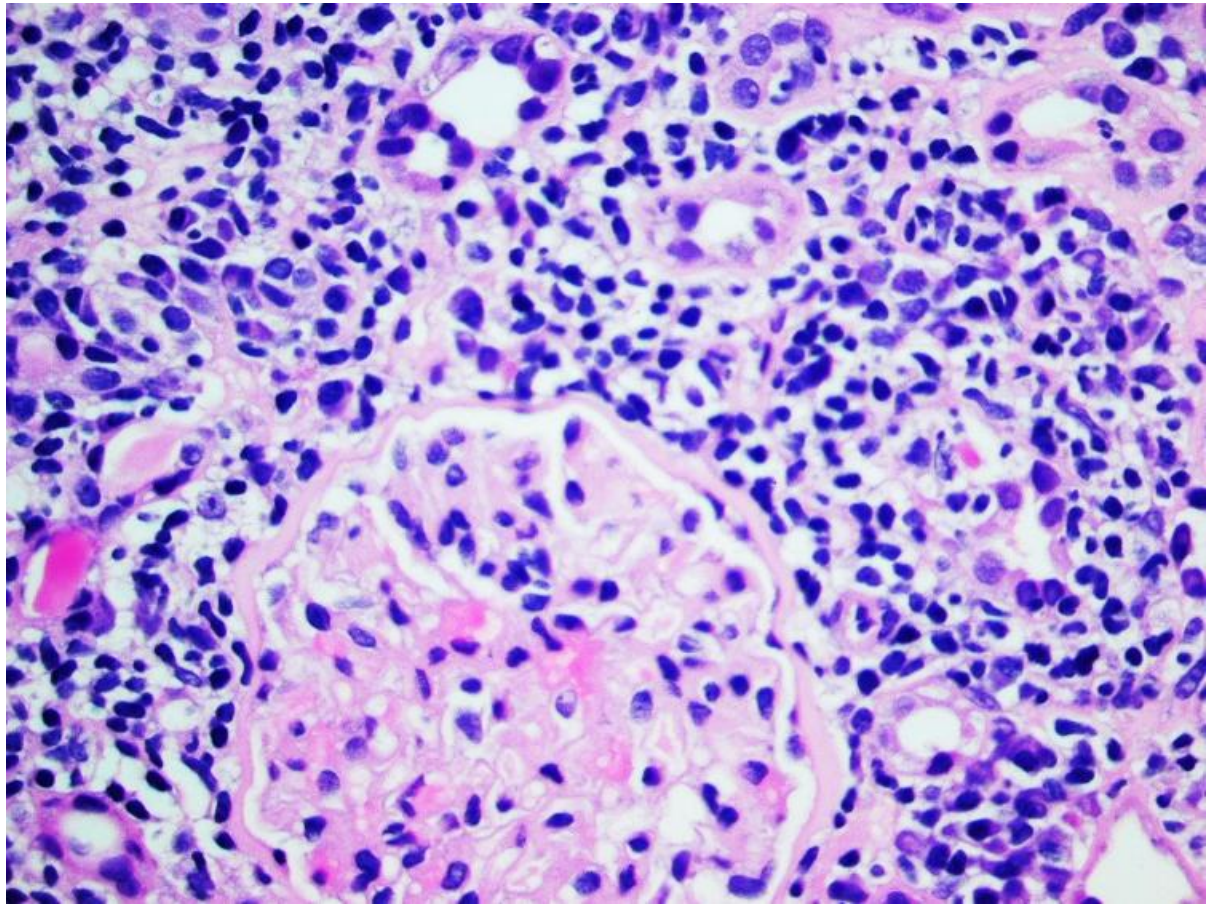
Interstitial Infiltrate

Slide courtesy of Chris Larsen

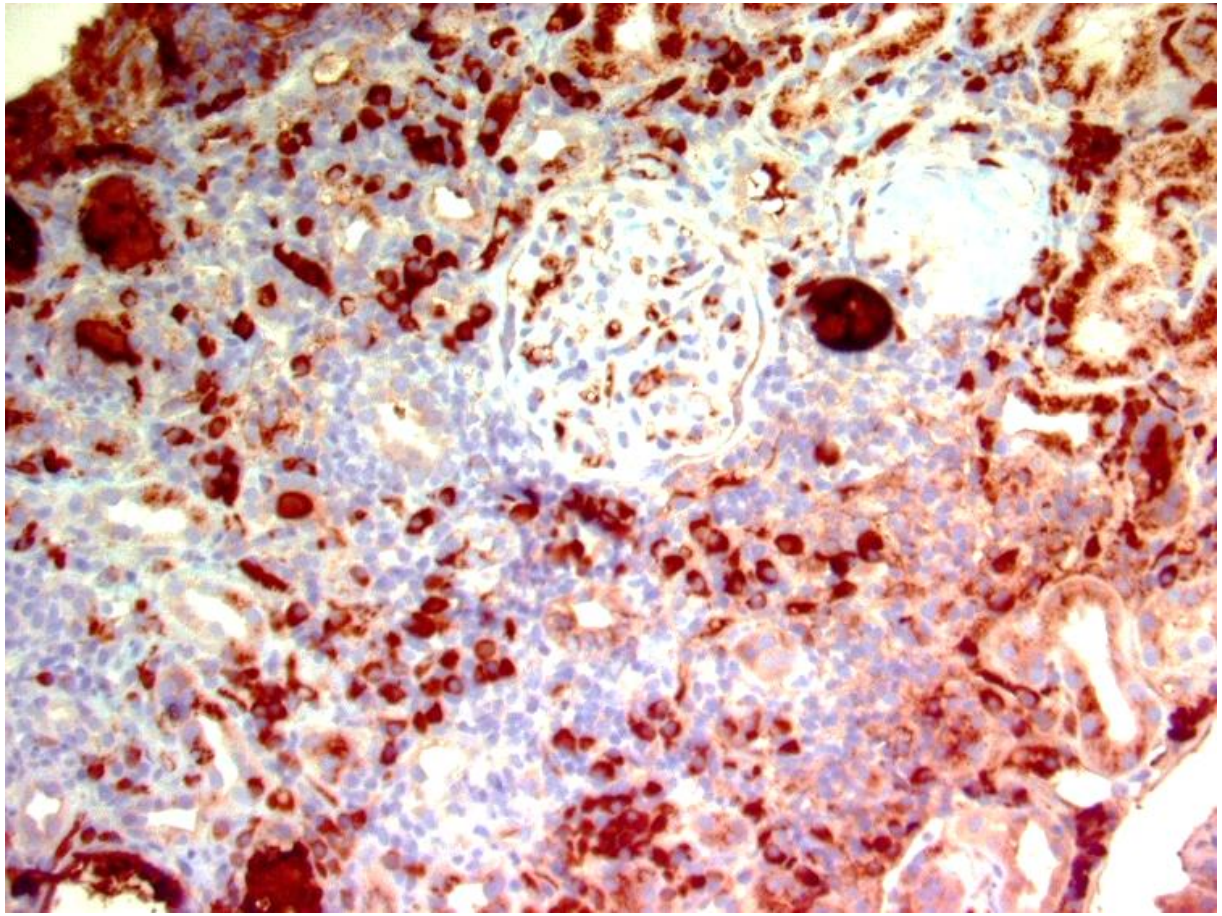
Intracellular monoclonal immunoglobulin:

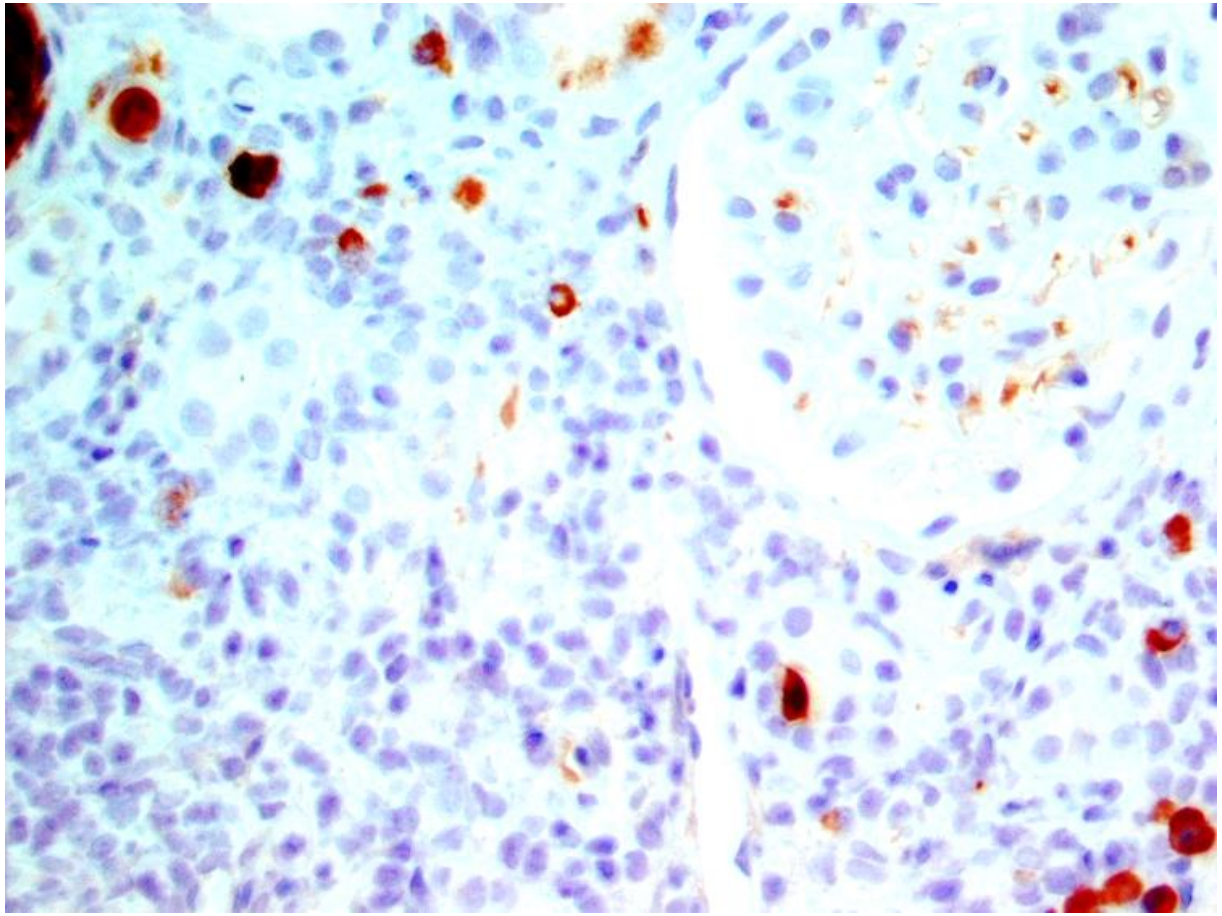
1. **Crystalline**
2. **Non-crystalline**
3. **Fibrillar**





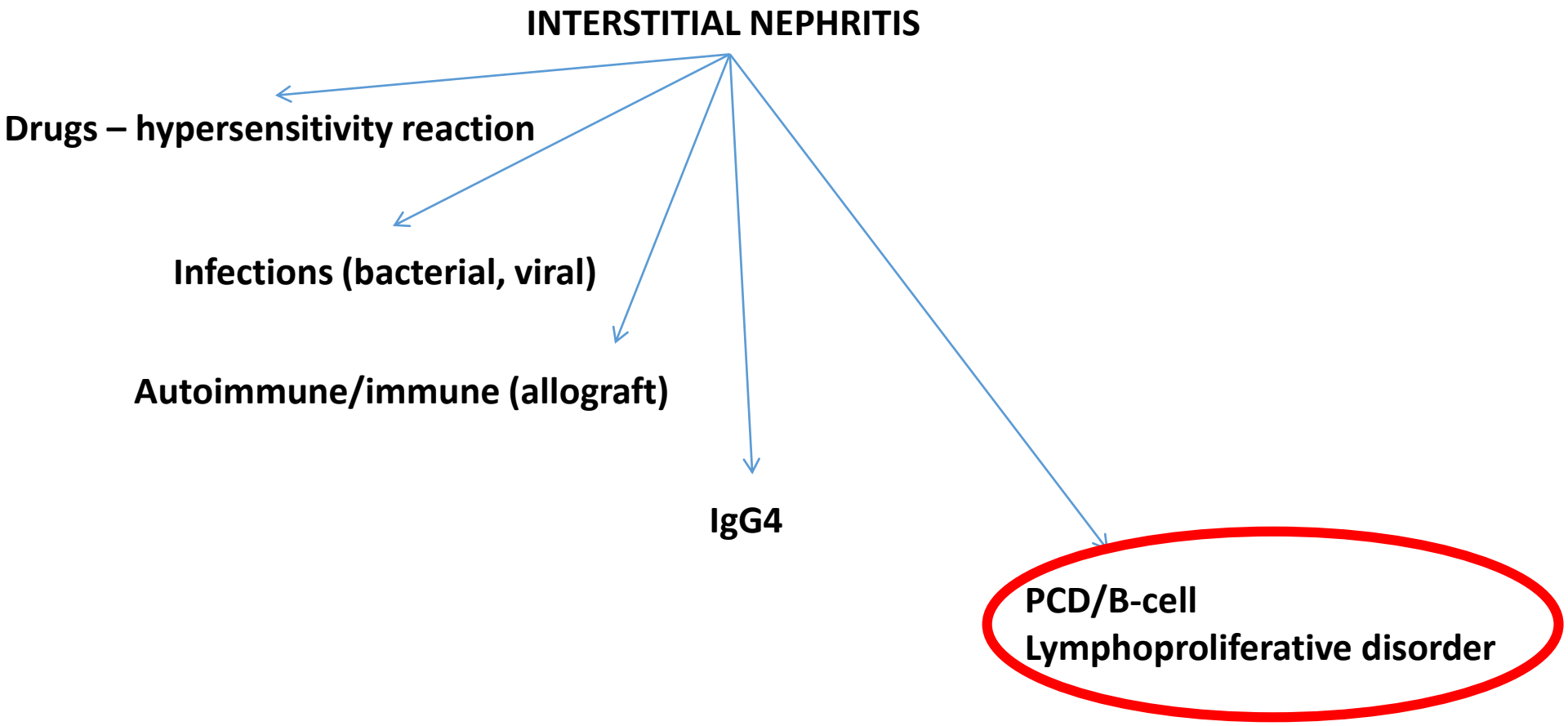
Interstitial infiltrate – differential diagnosis:
interstitial nephritis versus underlying plasma cell dysplasia versus monoclonal infiltrate
Beware of “interstitial nephritis” masking underlying PCD!





Monoclonal infiltrates – demonstration of light chain restriction by immunohistochemistry: left positivity for κ while stain for λ (right) shows rare positive cells

Interstitial nephritis – differential diagnosis pathogenetic classification



Conclusions:

Morphologic pattern of injury versus pathogenetic classification
Importance of immunofluorescence and electron microscopy
Light microscopy frequently shows overlapping morphologies and is not specific
Light microscopy - importance for prognosis
>1 pattern of injury
Clinical correlation, overlapping features clinically
Some MGRS entities may be rather indolent but ultimately lead to renal failure, recur in kidney transplants
Focus on early diagnosis
Comprehensive evaluation

Thank you

Questions?

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