Monoclonal Gammopathy in Renal Pathology

APCN X TSN 2025

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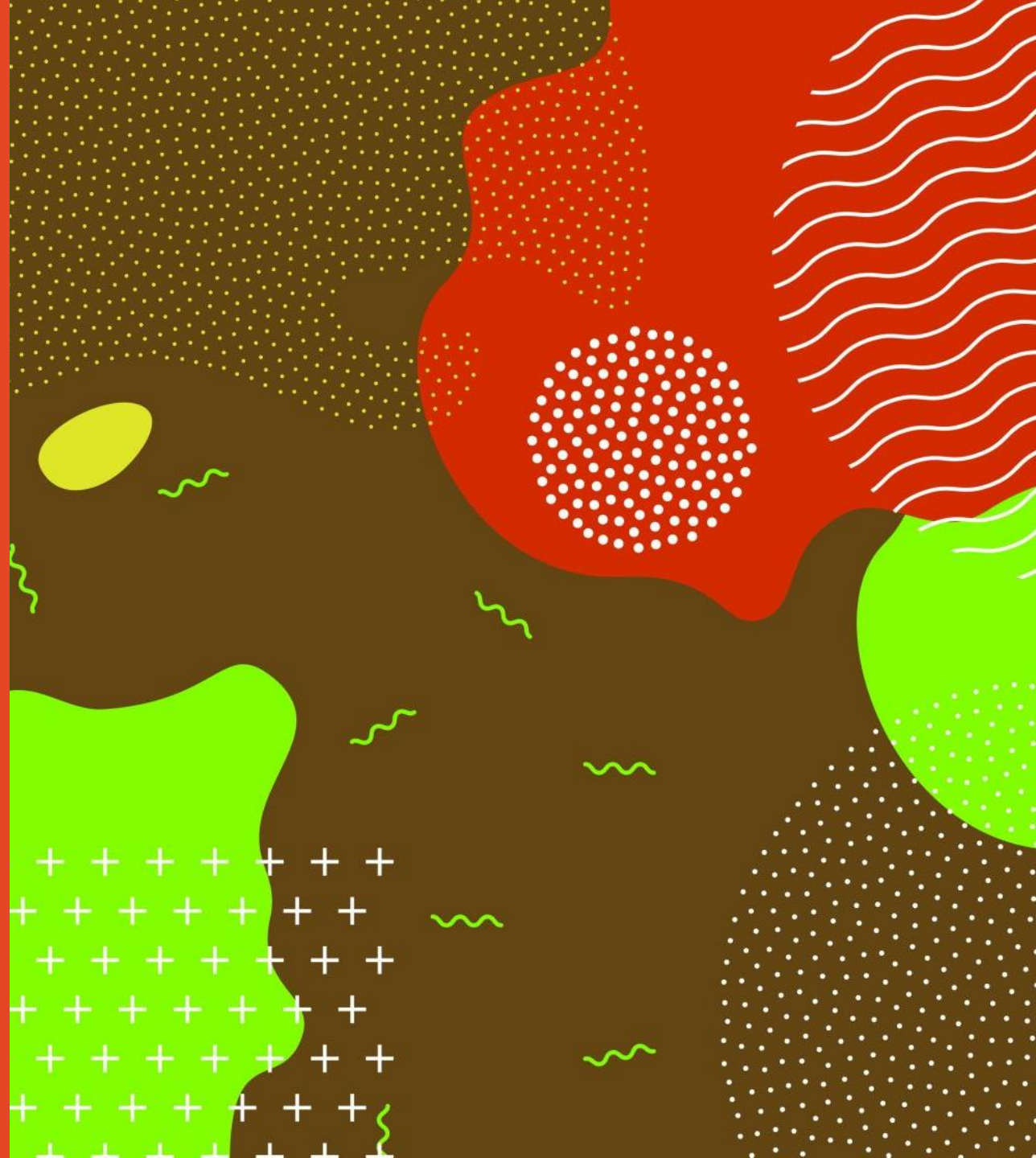


Disclosure

Served as medical advisor for Travere, Otsuka, Kira Pharma, Eledon, CSL-Behring, Dimerix, Alpine, Arrowhead, Novartis (Chinook)

Received honorarium from AstraZeneca, Amgen, Elli Lily and Baxter, Novartis.

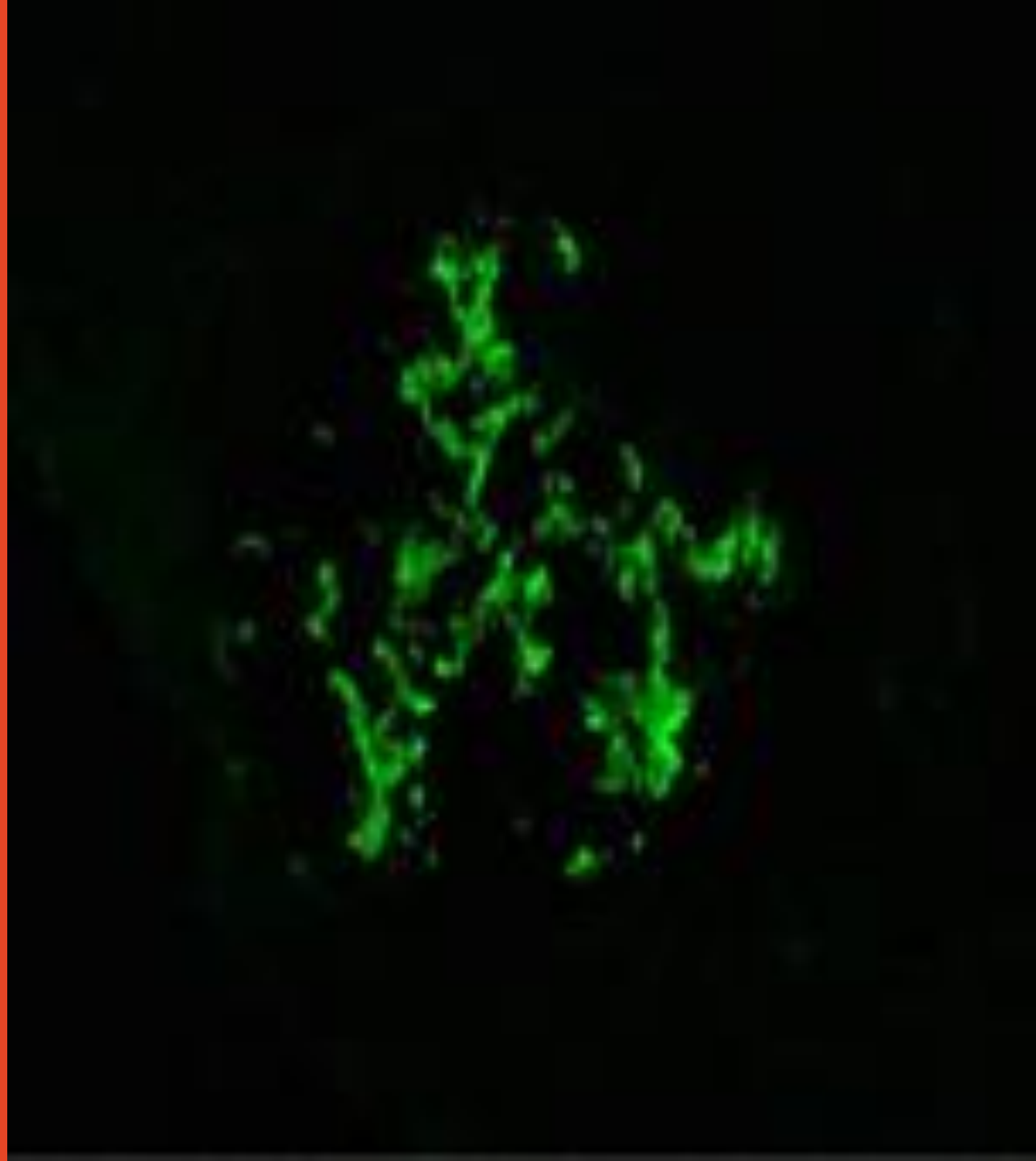
Served as a DMSC members in HEFEF trial (investigator initiated), ARGX-113-2203/AL-1103-014 Trial

Honorary Treasurer of Australia New Zealand Society of Nephrology (ANZSN) that received industry sponsorship for ANZSN activities

Outline

- Terminology
- Pathogenesis and histology
- Myth, controversy and progress

Monoclonality, light chains biology and terminology



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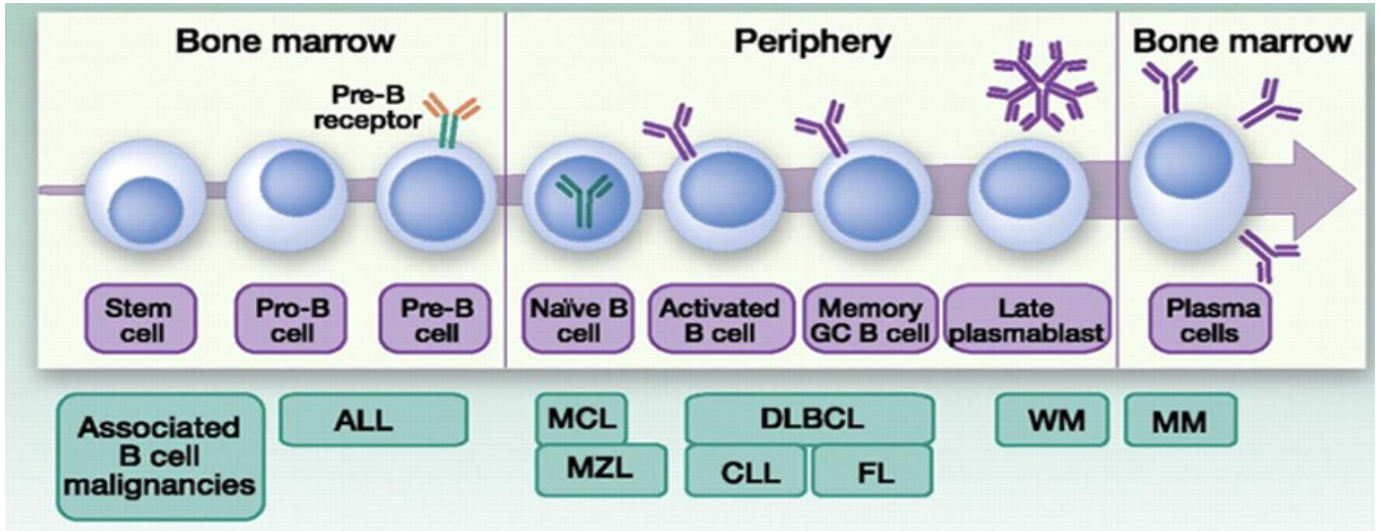
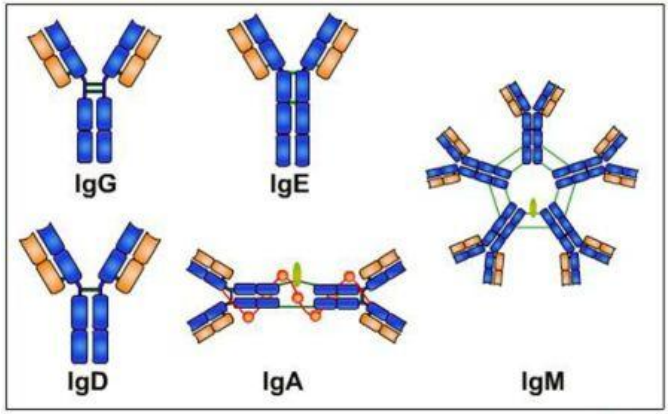
Clonal proliferation of Immunoglobulin producing B cells or plasma clone



In most cases the proliferating cells secrete immunoglobulin

- **IgG > IgM > IgA, IgE, IgD**
- **Light chain only**
- **Heavy chain only**
- **Non-secretory**



Polyclonal vs monoclonal gammopathy

- Polyclonal proliferation of B cells will secrete polyclonal immunoglobulins that is more likely associated with autoimmunity/infection
- In most cases of B cell malignancy there is monoclonal proliferation of cells that secrete monoclonal immunoglobulin

Secreted protein may have idiosyncratic properties:

Polyclonal

- Cryoglobulinaemia
- Cold-agglutinin disease
- IgA vasculitis/IgA nephropathy
- MPGN
- Immunothrombocytopaenic purpura

Monoclonal

- Systemic AL (light chain) amyloidosis
- Monoclonal immunoglobulin deposition diseases
  - Light chain deposition disease
  - Heavy chain deposition disease
  - Light- and Heavy-chain deposition disease
- Fibrillary glomerulonephritis
- Immunotactoid glomerulonephritis

Terminology

MGRS

nal disorder producing a
noclonal Ig that causes one or
more kidney lesions

Underlying haematologic disorder does not cause tumuor complications

or meet any specific criteria for any immediate specific therapy

Not a benign kidney condition!
ESKD (22%), CKD(38%)

MGUS

-Ig <30g/L (3g/dL) and <10% clonal plasma cells

Absence of organ damage

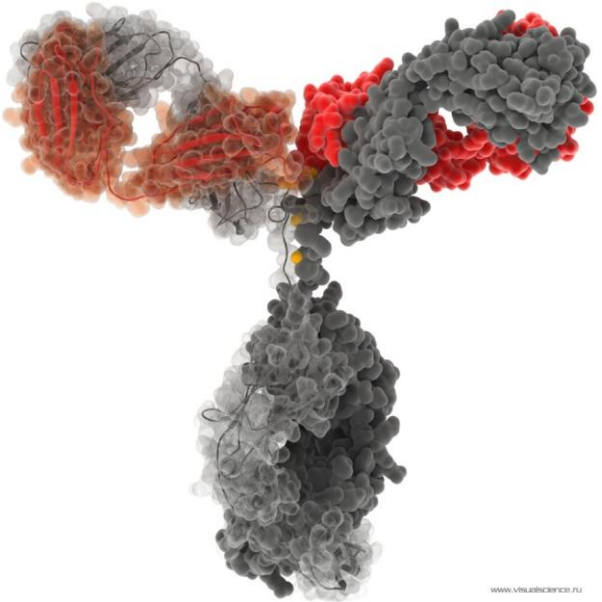
Premalignant condition

Aged-dependent
Frequency of MGUS 3% (Aged >50y), 5%(aged >70 y), and ~ 8% (aged >80 y)

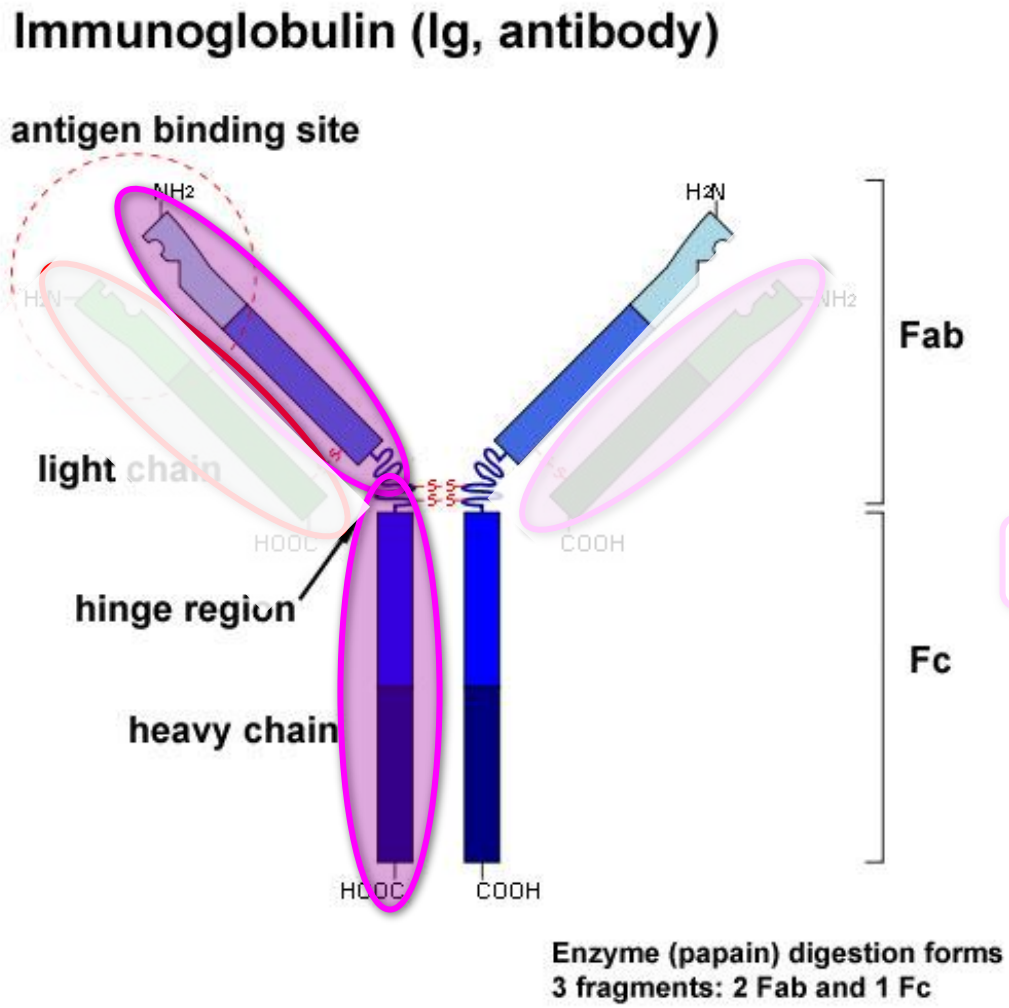
Nasr et al J Am Soc Nephrol. 2009 Sep;20(9):2055–2064

Chen at al. Haematologica. 108 June 2023

Immunoglobulin: HC and LC



HCDD



AL Amyloid

λ:κ 4:1

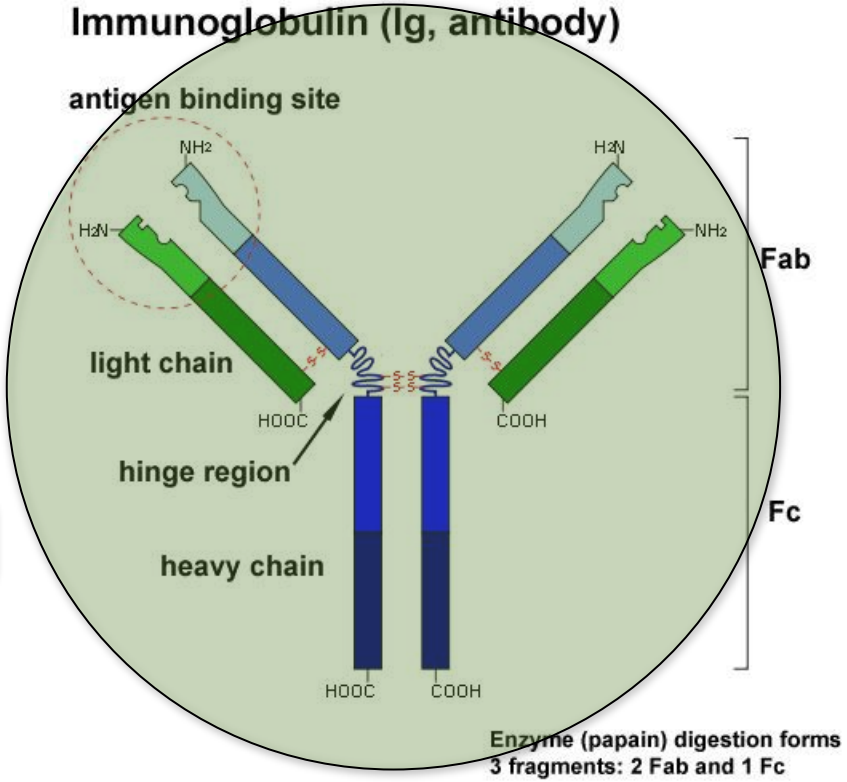
LCDD

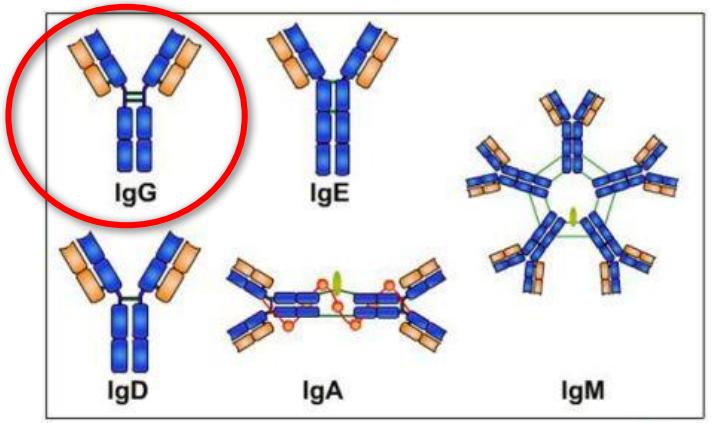
Enzyme (papain) digestion forms
3 fragments: 2 Fab and 1 Fc

Immunoglobulin

Fibrillary GN

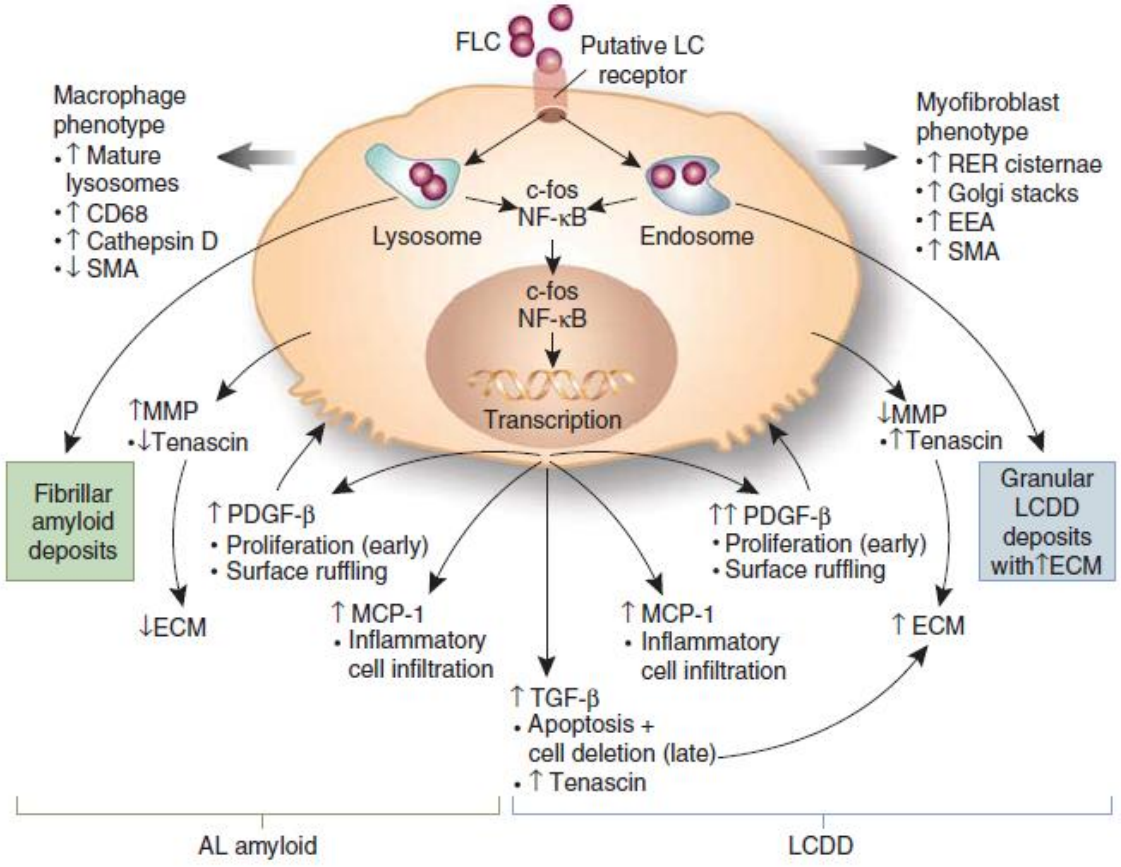
Immunotactoid GN



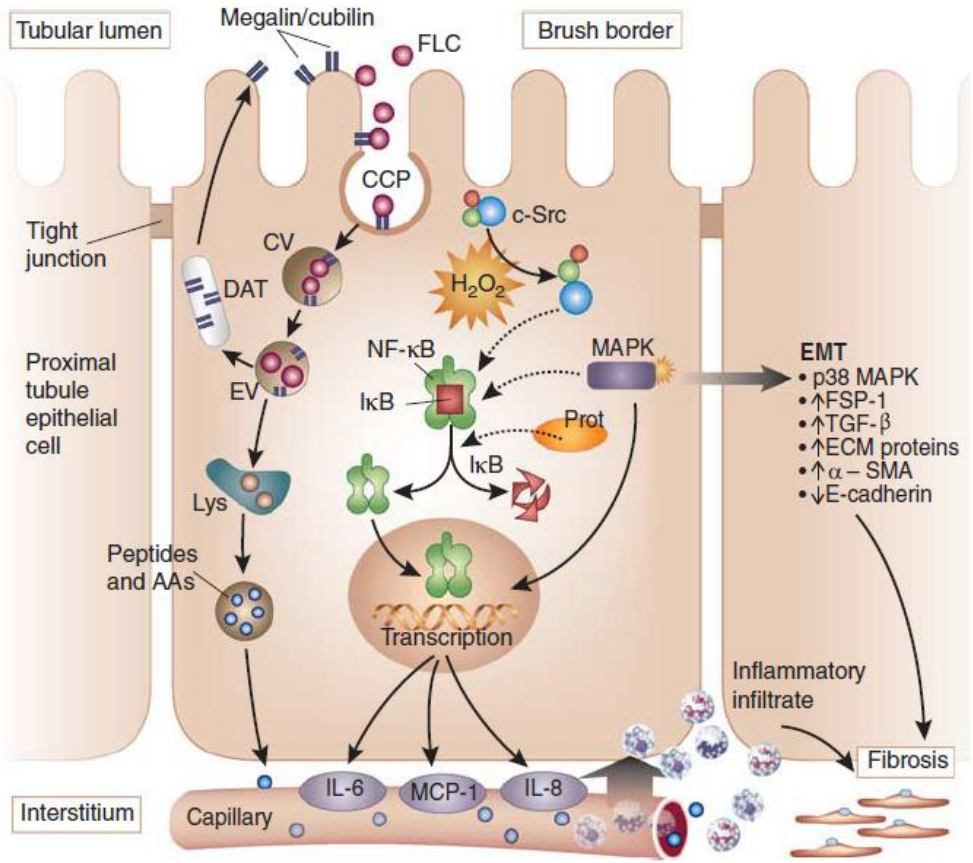


Mechanism of kidney injury by monoclonal gammopathy

Mesangial cells

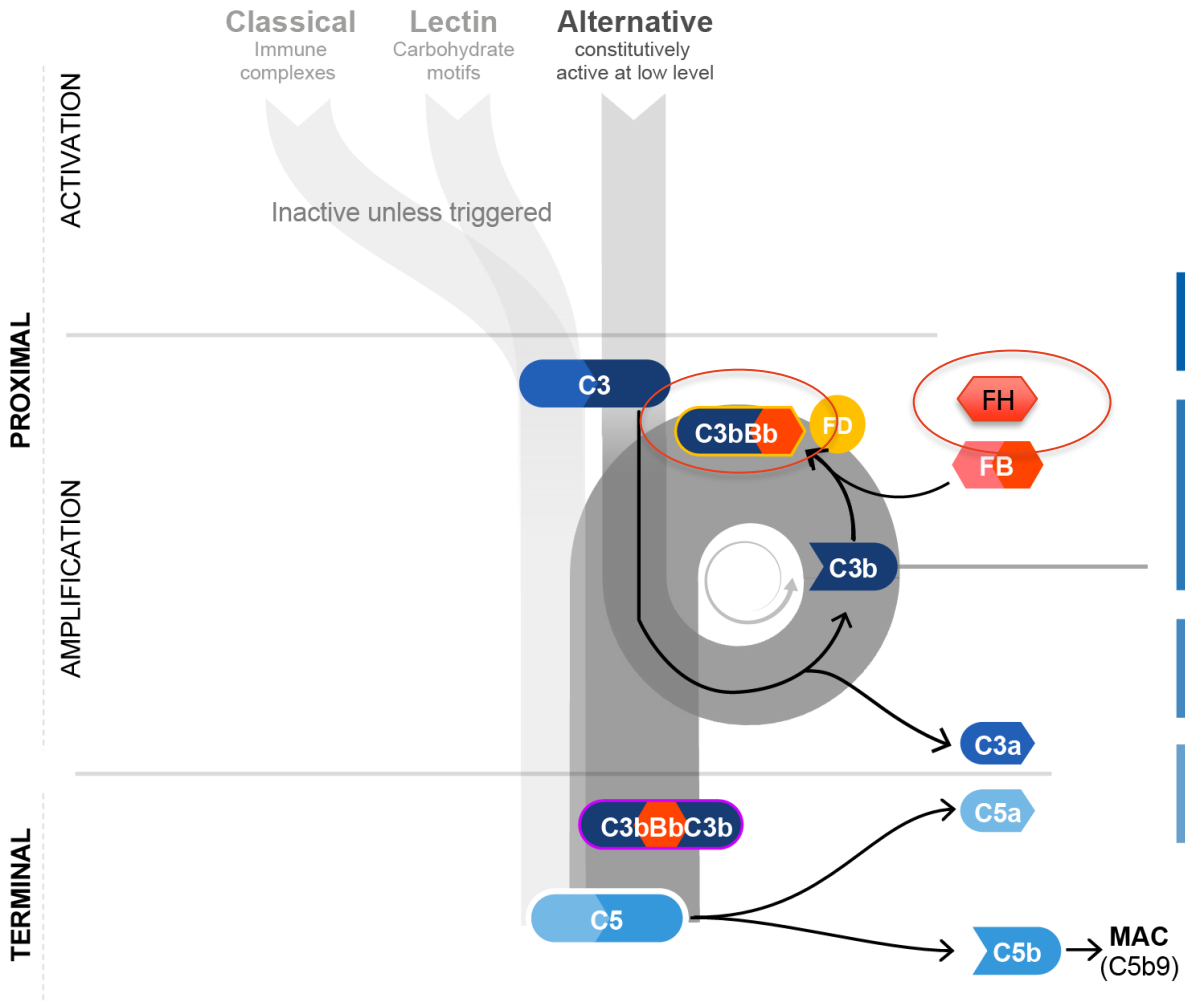


Tubular epithelial cells



K Basnayake et al. Kidney International (2011) 79, 1289–1301

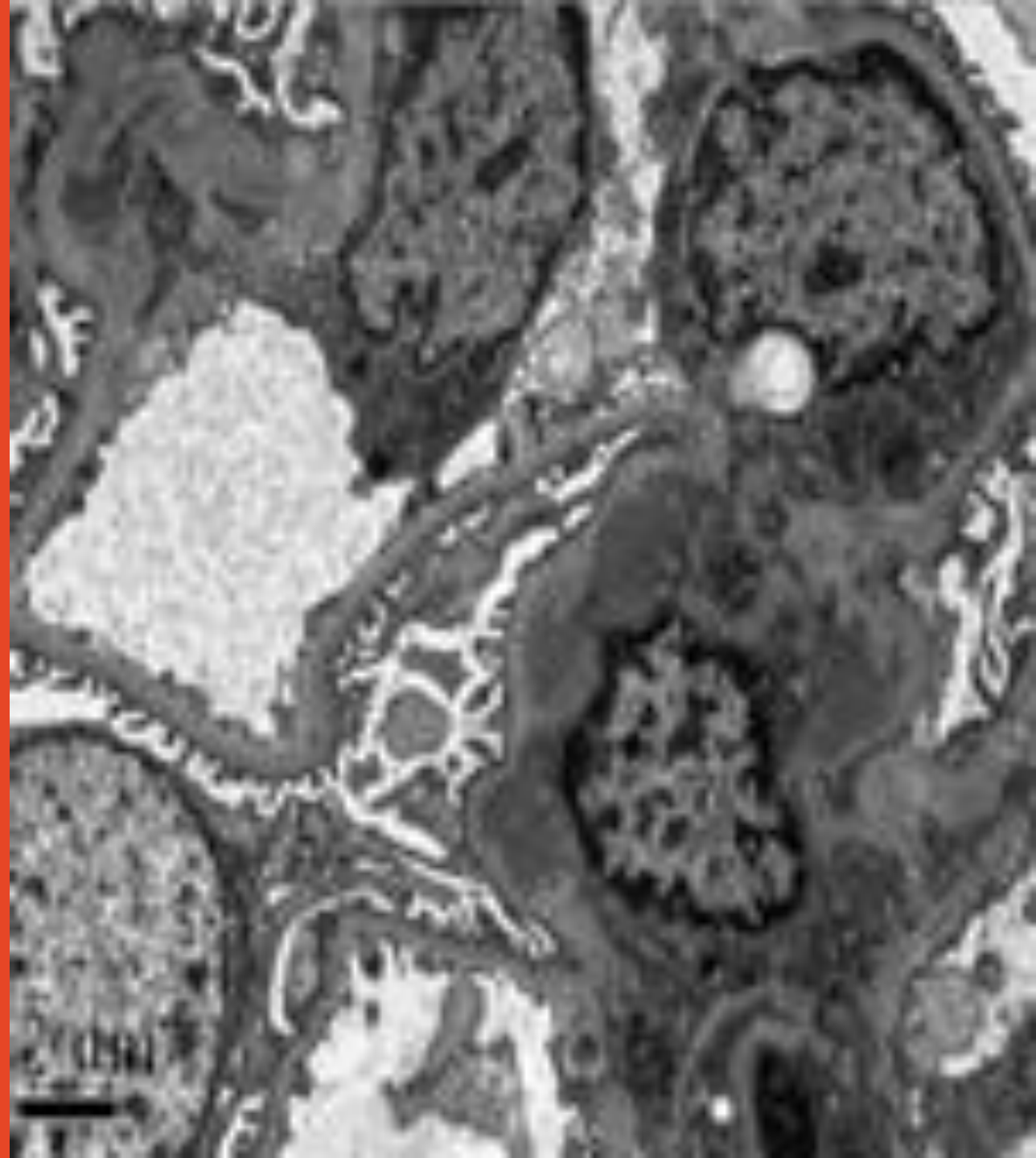
AP overactivation in MG-C3G

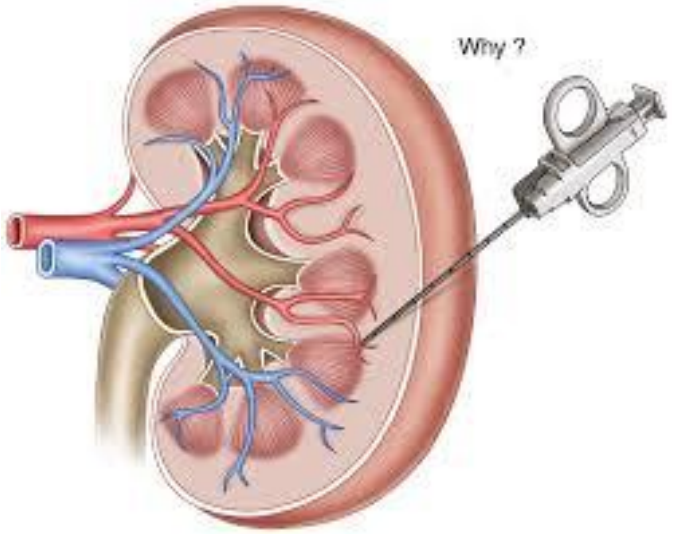


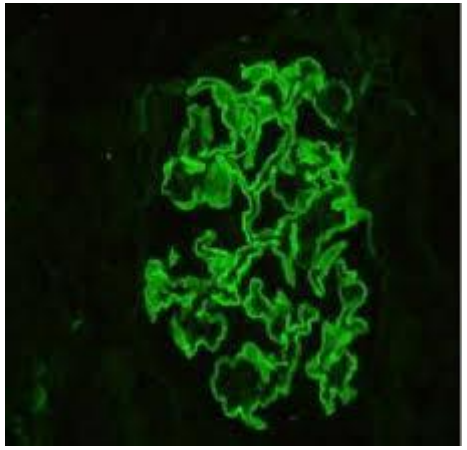
Secondary IC-MPGN	C3G and primary IC-MPGN
• Paraprotein • Infection • Autoimmunity	• Complement gene variants (factors and regulatory proteins) • Autoantibodies
Immune complexes	Dysregulated complement activation
Classical pathway	Alternative pathway

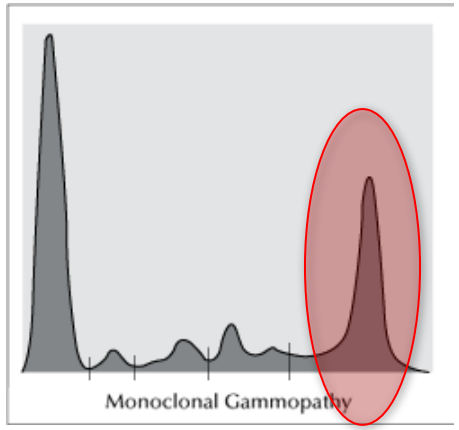
Smith RJH, et al. *Nat Rev Nephrol*. 2019;15(3):129–43 **3.**

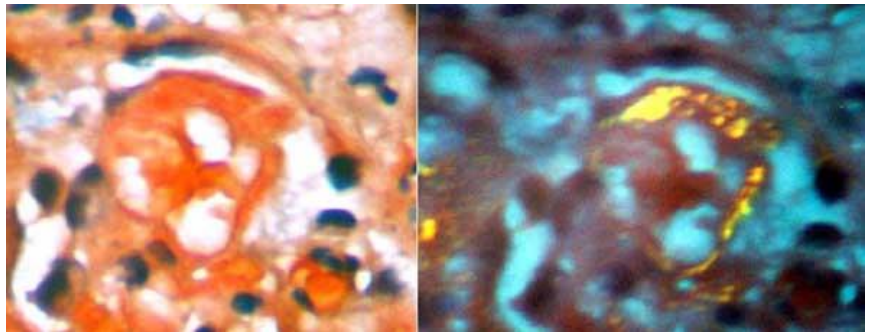
Histological classification of MGRS









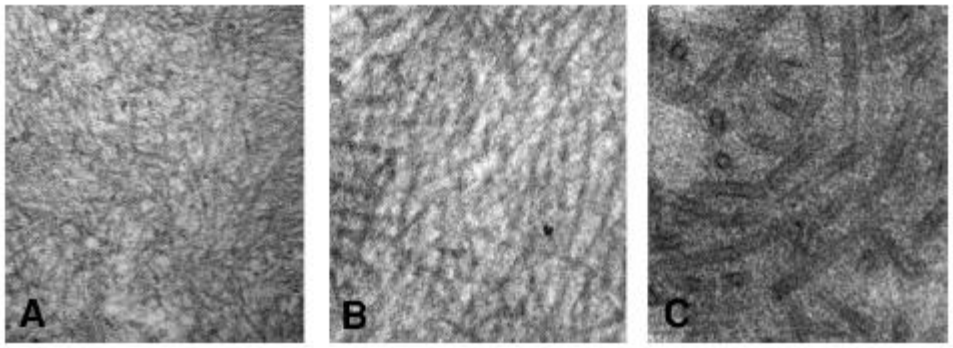


Detection of a circulating monoclonal immunoglobulin

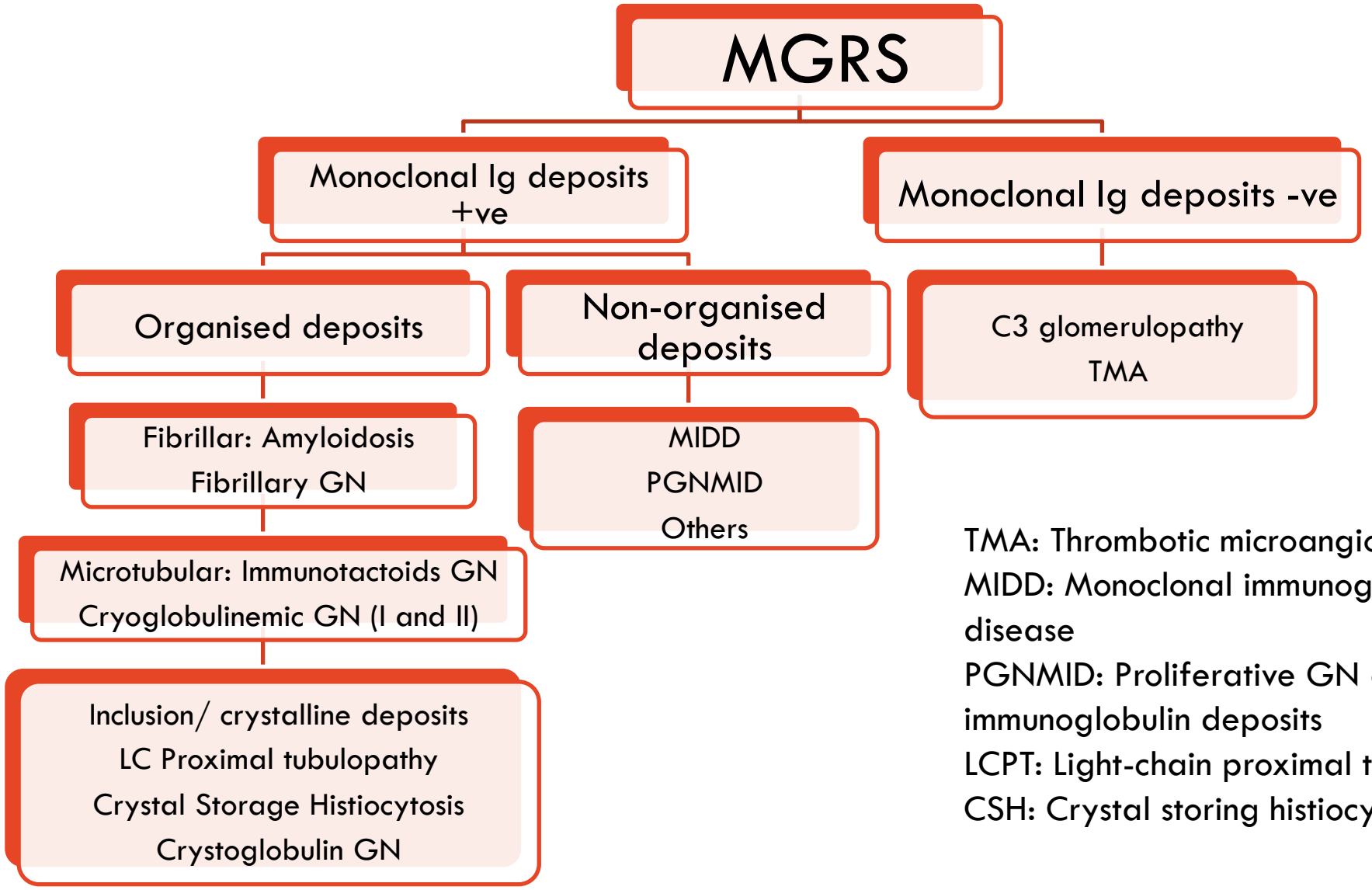
- Serum protein electrophoresis/immunofixation
- Urine protein electrophoresis/immunofixation
- Serum free light chain ratio

Kidney biopsy

- Light microscopy
- IF- Light-chains, heavy chains, Ig
- IgG subclasses
- C1q and C3
- EM



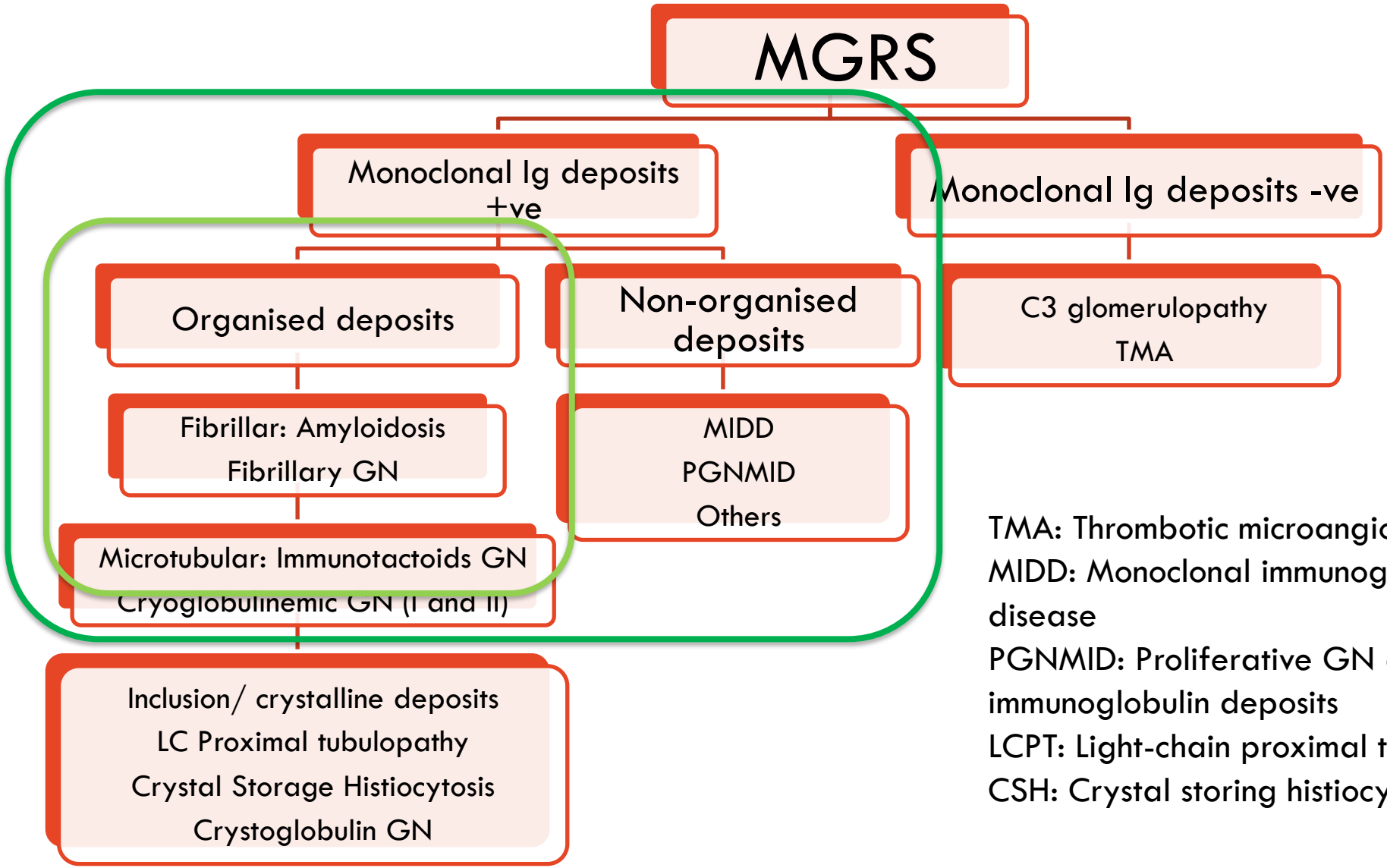
Histopathological Classification



TMA: Thrombotic microangiopathic
MIDD: Monoclonal immunoglobulin deposition disease
PGNMID: Proliferative GN and monoclonal immunoglobulin deposits
LCPT: Light-chain proximal tubulopathy
CSH: Crystal storing histiocytosis

Adapted Mancuso et al. Cancer medicine 2024

Histopathological Classification



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Monoclonal Immunoglobulin Deposits- MGRS congo red +ve

AL Amyloid

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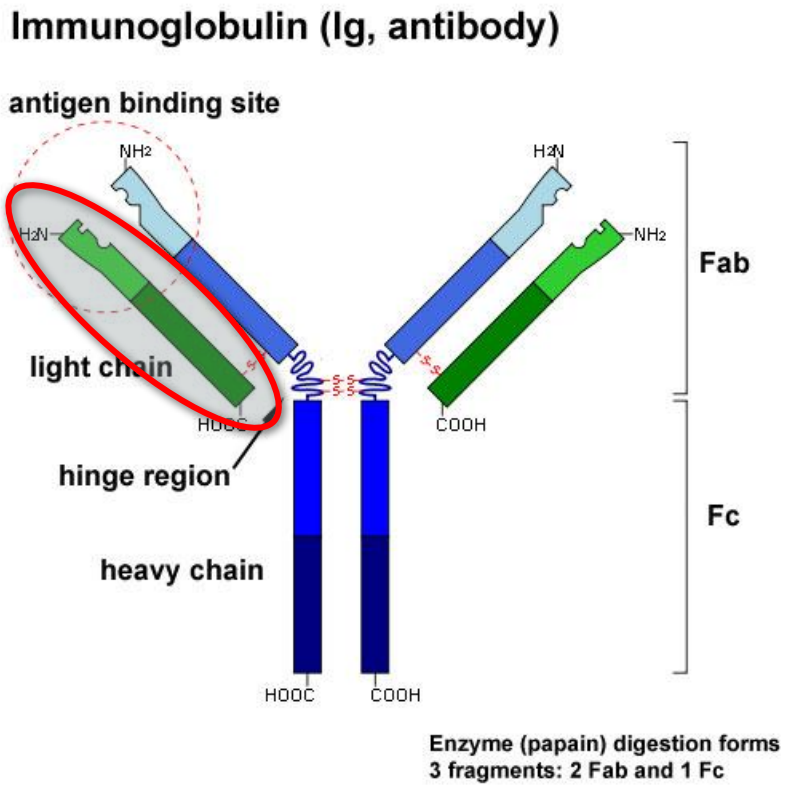
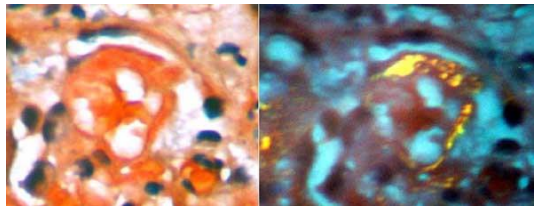
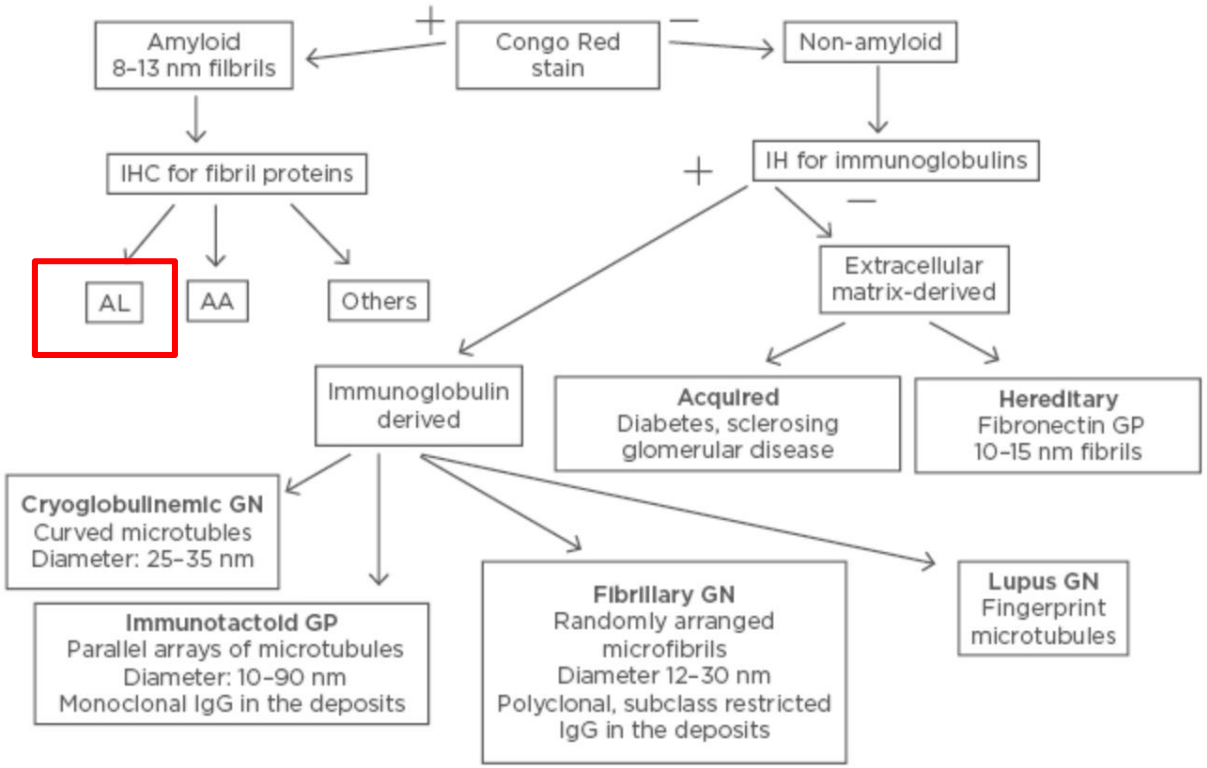






Wechalekar et al. Lancet 2016; 387: 2641–54

AL Amyloidosis

Most frequent form of acquired amyloidosis (in high income countries)

- Incidence 3-12 cases per million population

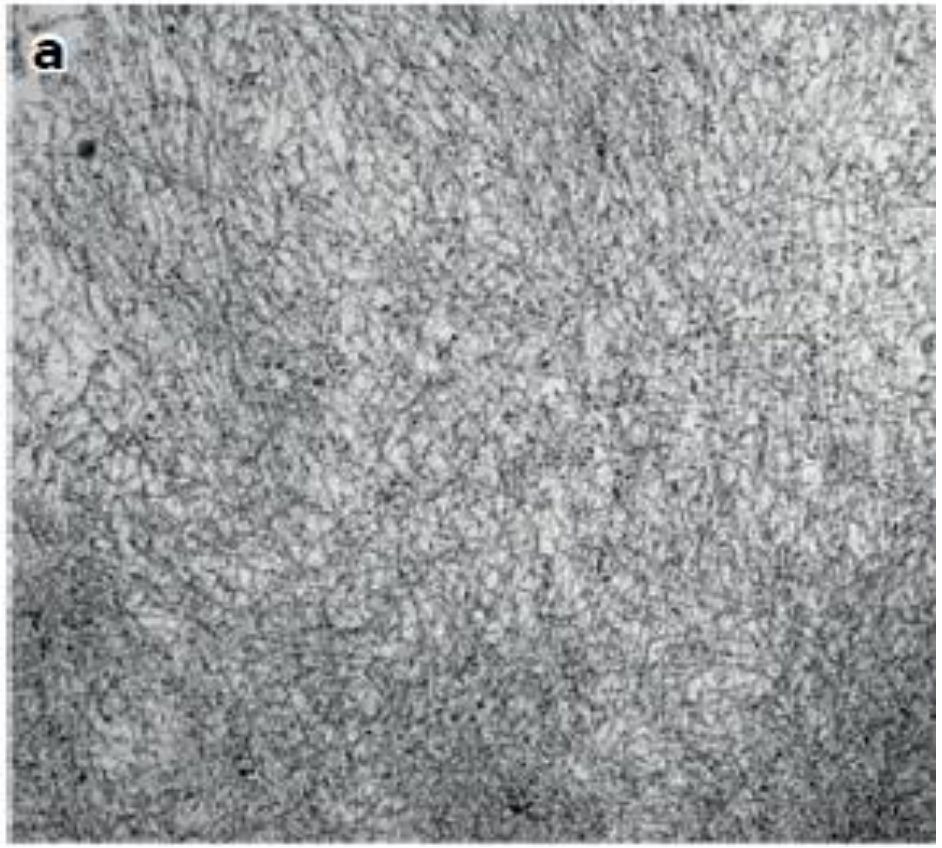
Composed of protein fibrils

- Fibrils have a diameter of 8-13nm
- Highly ordered abnormal cross b-sheet conformation

Amyloid deposits also contain minor non-fibrillary constituents

- glycosaminoglycans
- serum amyloid P component

Amyloid deposits can affect almost any organ system with diverse and non-specific C/F often delays in diagnosis



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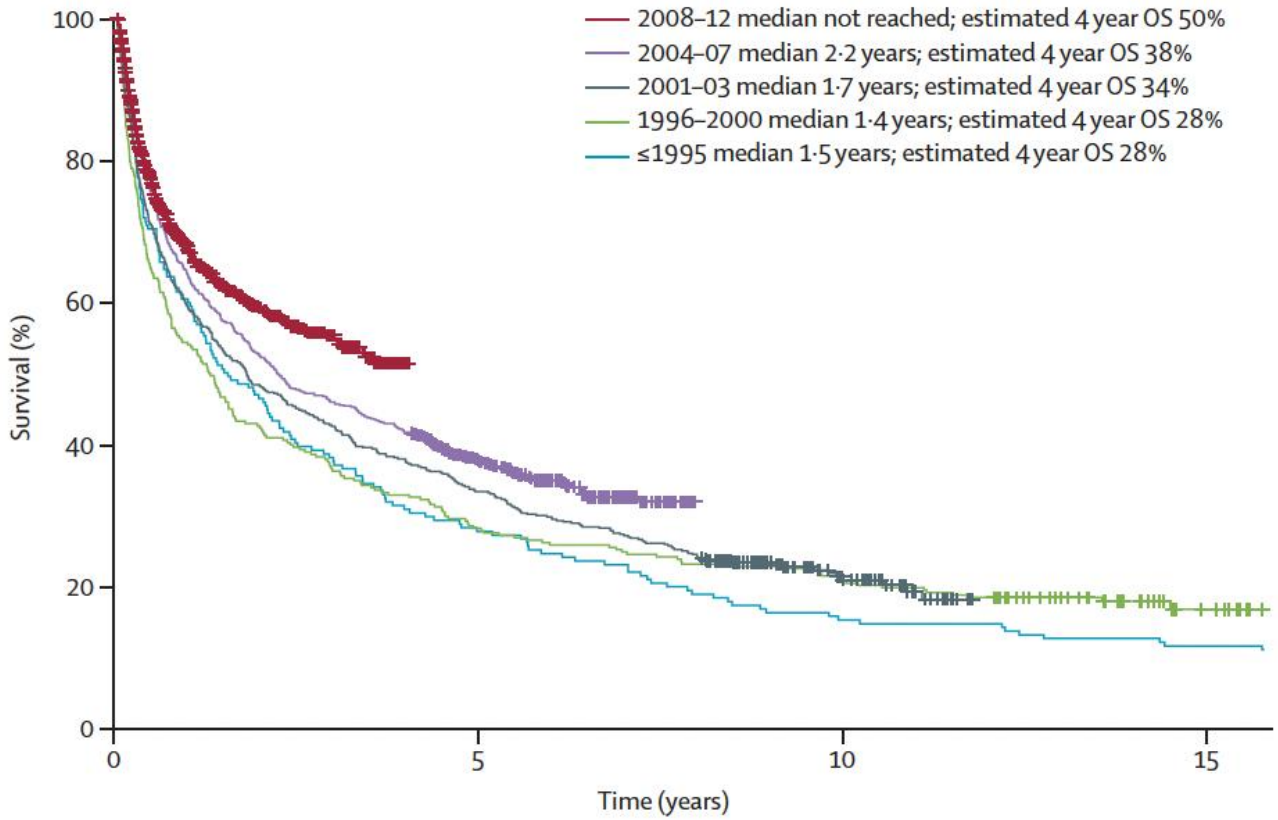
Prognosis AL amyloidosis

- Prognosis largely determined by the extent of organ damage
- Despite advances in treatment, mortality rate is 25% within 6 months
- Cardiac involvement most significant prognostic risk factor

- AL amyloid higher FLC, >10% plasma cells on BM worse prognosis.



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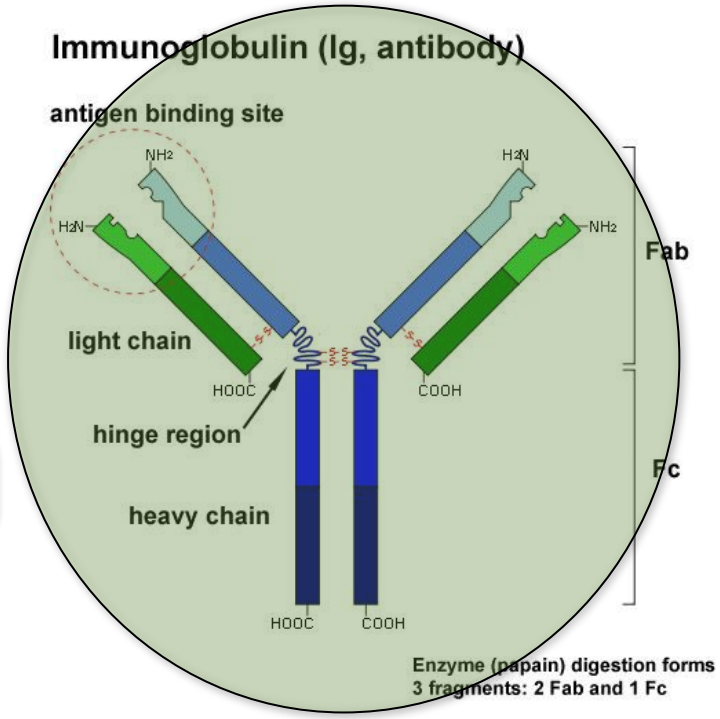
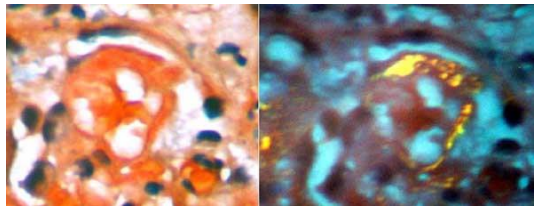
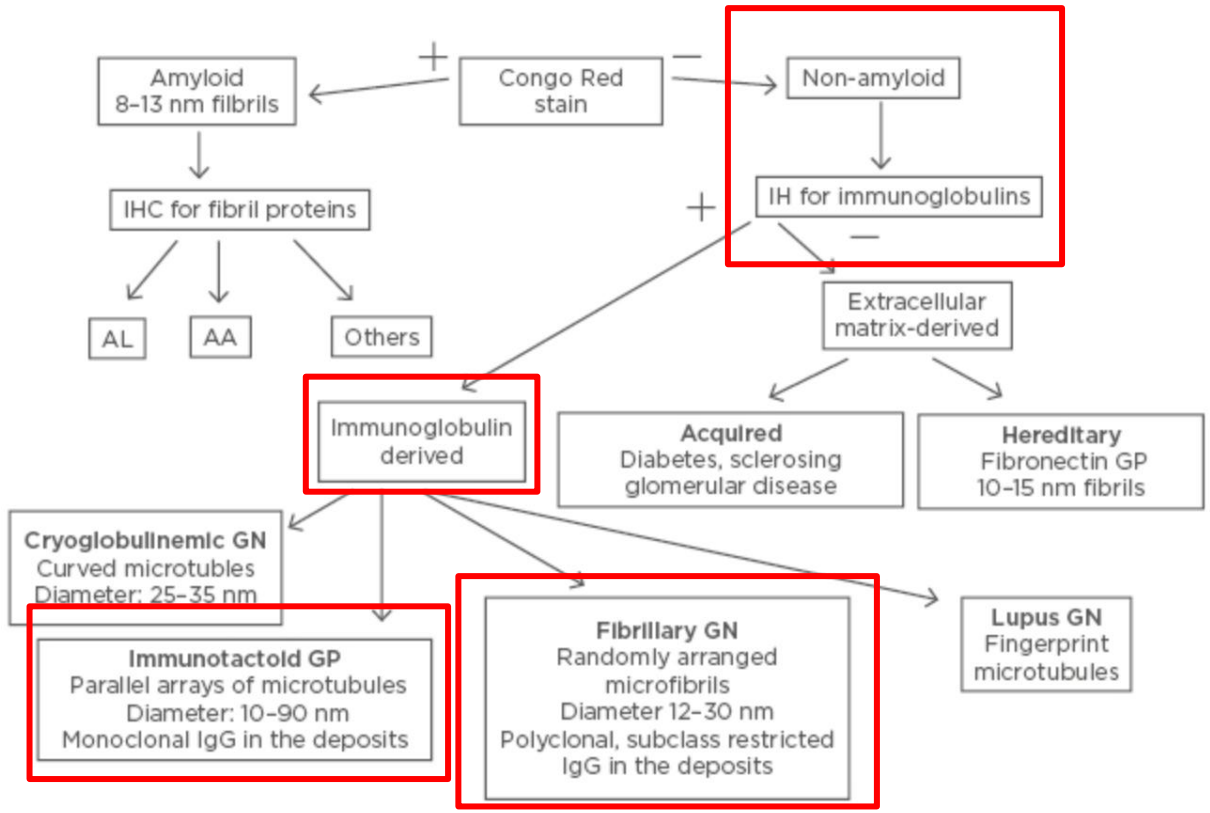
Monoclonal Immunoglobulin Deposits- Congo red -ve

Fibrillary GN

Immunotactoid GN







Epidemiology: Immunotactoid and fibrillary GN

Immunotactoid glomerulopathy

- Rare ~200 cases reported in last 35 years
- 1 in 2500 (0.04%) of native kidney biopsy specimens
- Median age of diagnosis ~60 years (10-86 years)
- Predominance in Caucasians (>90% white)
- Men 47-61% cases
- C/F:
  - proteinuria in all patients
  - Nephrotic syndrome in 60-70% cases
  - Haematuria in >70%
  - HTN in >65%
  - Renal impairment in >45% patients
  - Monoclonal (67%) vs polyclonal (33%)
  - MGRS 19-22%
  - 50% has underlying haematologic disease

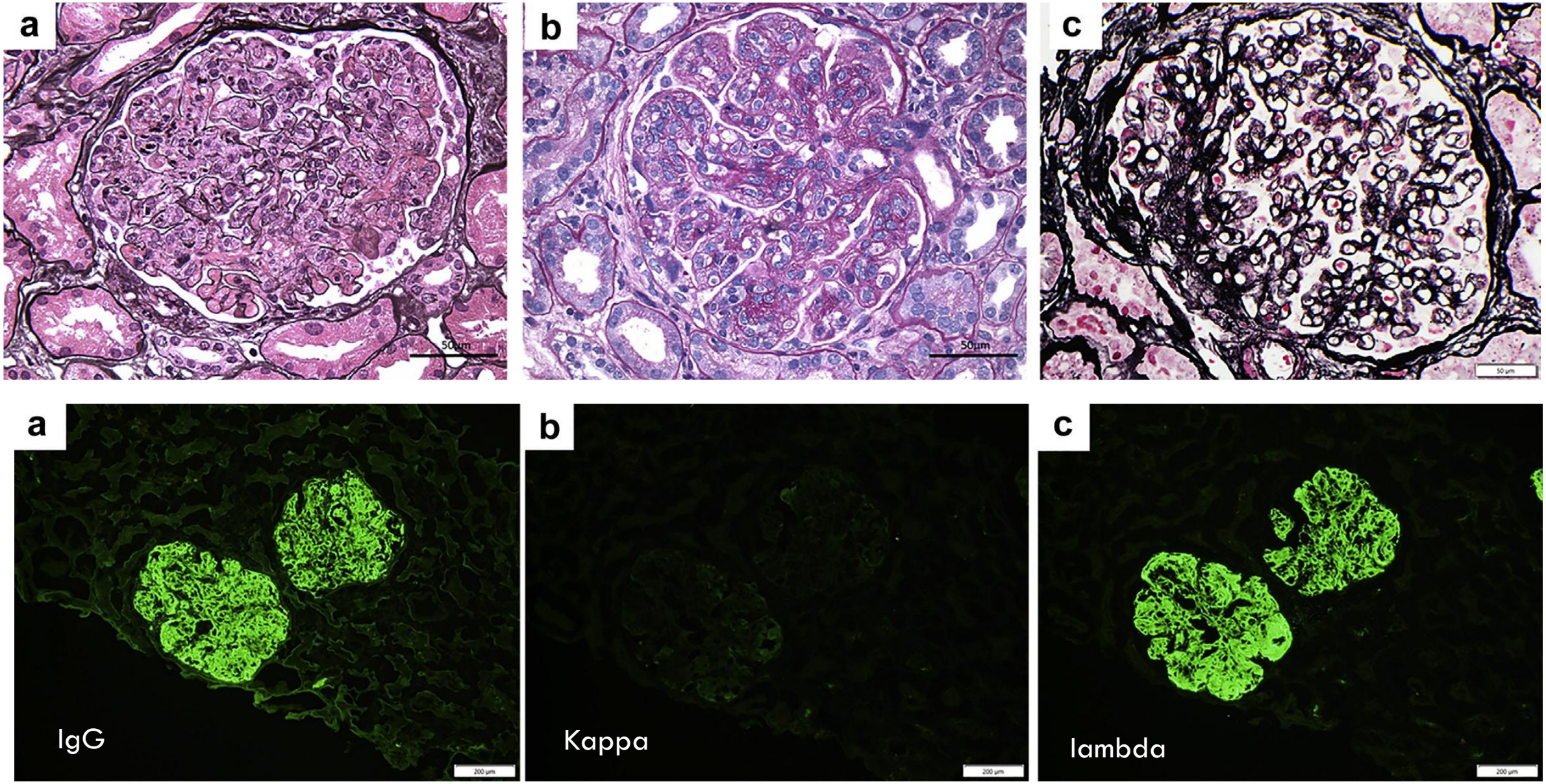
Fibrillary glomerulonephritis

- Rare ~200 cases reported in last 35 years
- incidence in native renal biopsies <1%
- Median age of diagnosis ~50-60 years
- Predominance in Caucasians (>90% white)
- Female 66% cases
- C/F:
  - Proteinuria in all patients
  - Nephrotic syndrome in 25-50% cases
  - Haematuria in >60-97%
  - HTN in >65%
  - Renal impairment in >70% patients
  - Haematologic malignancy uncommon
  - MGRS 10%
  - 1 in 4 have autoimmune disease or chronic infection

Nasr et al. Kidney International (2021)

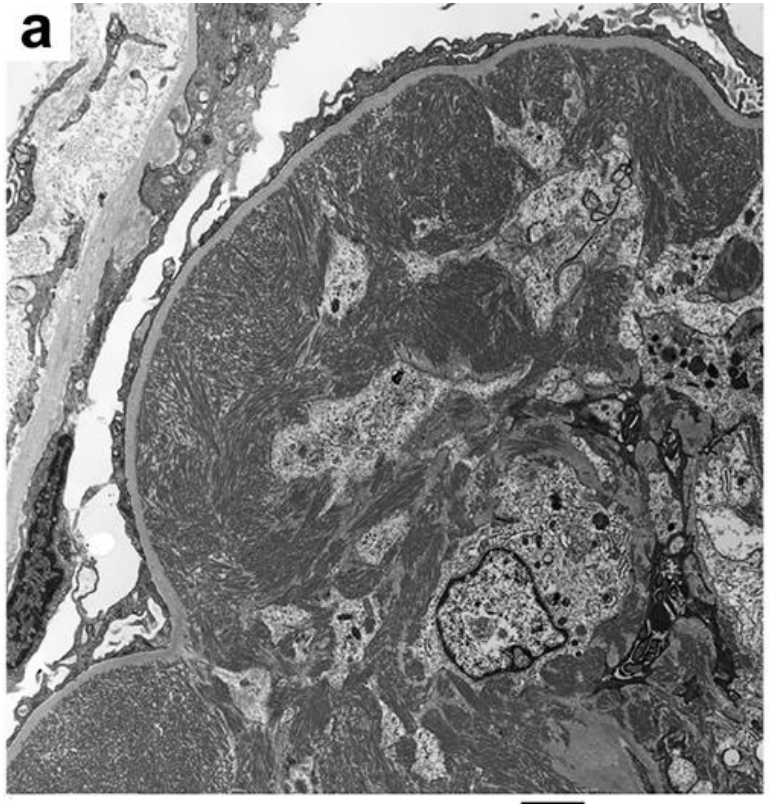
Rosenstock et al Kidney International Reports (2019) 4, 917–922

H&E and IF (Immunotactoid GN)

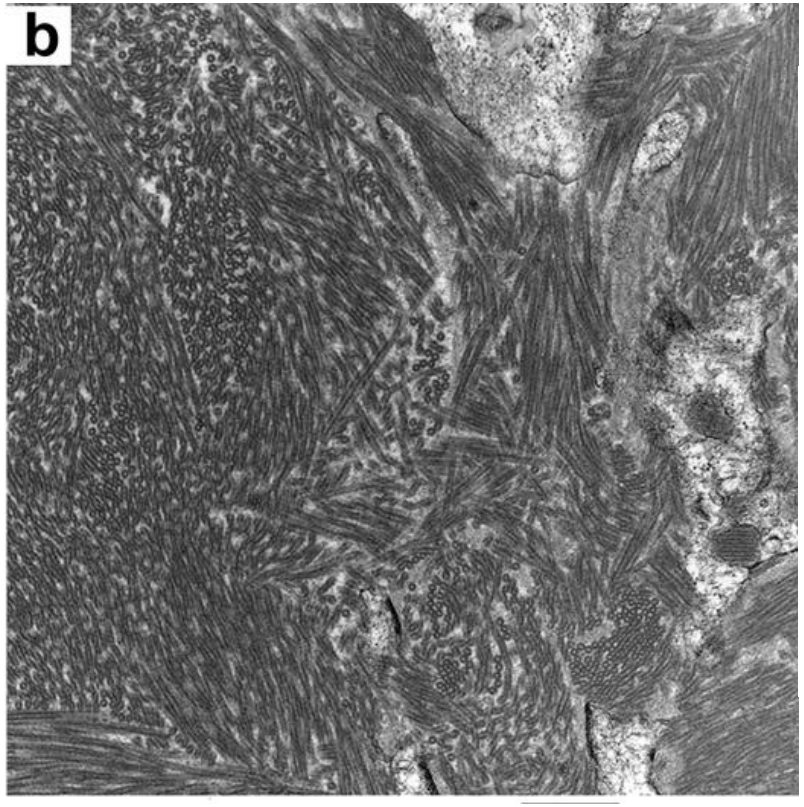


Nasr et al. Kidney International (2021)

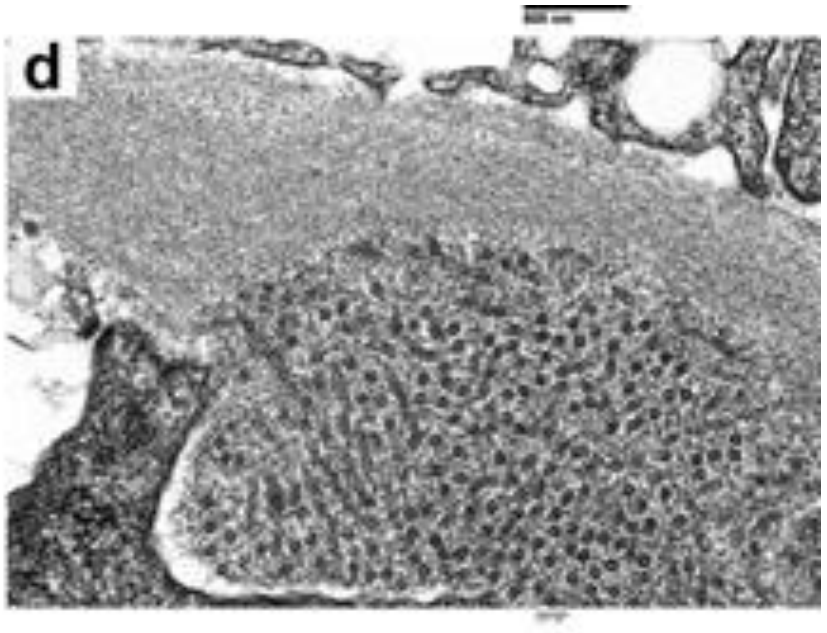
Electron microscopy: Immunotactoid GN



Subendothelial electron-dense deposits

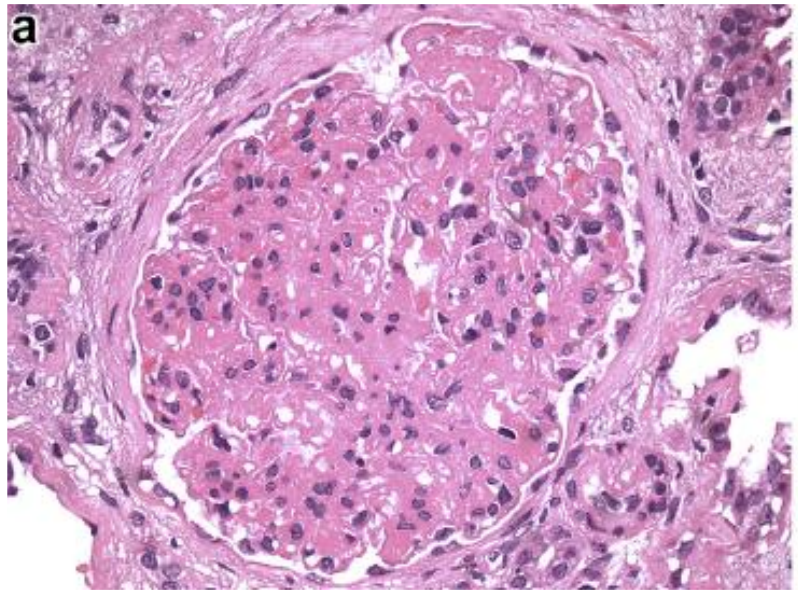


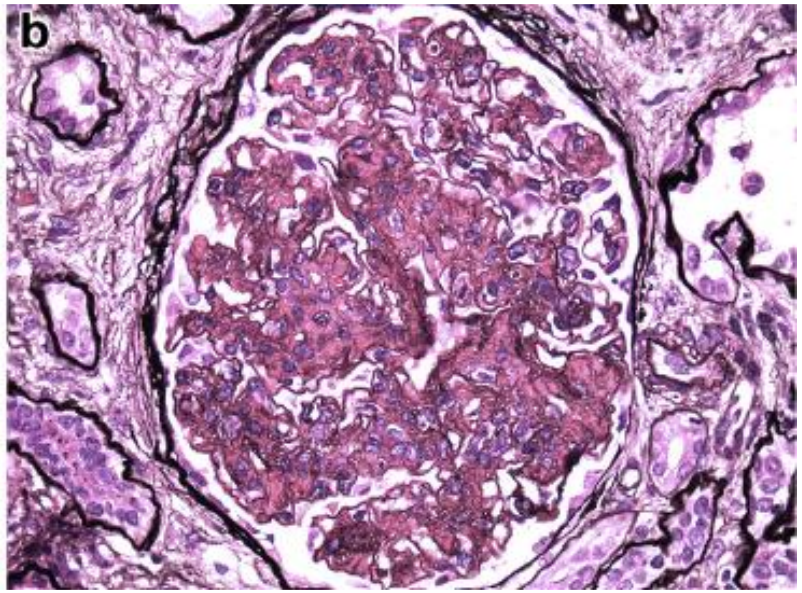
Parallel arranged microtubules
Diameter 10-60nm

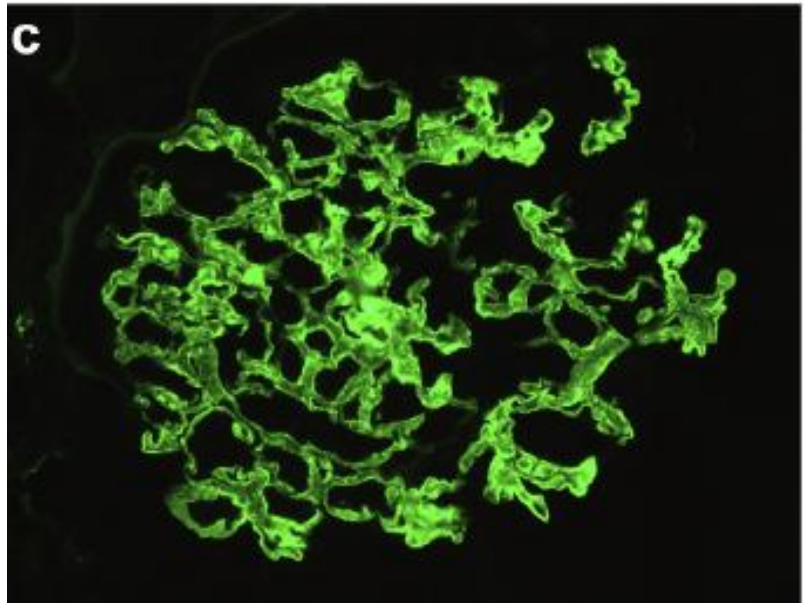


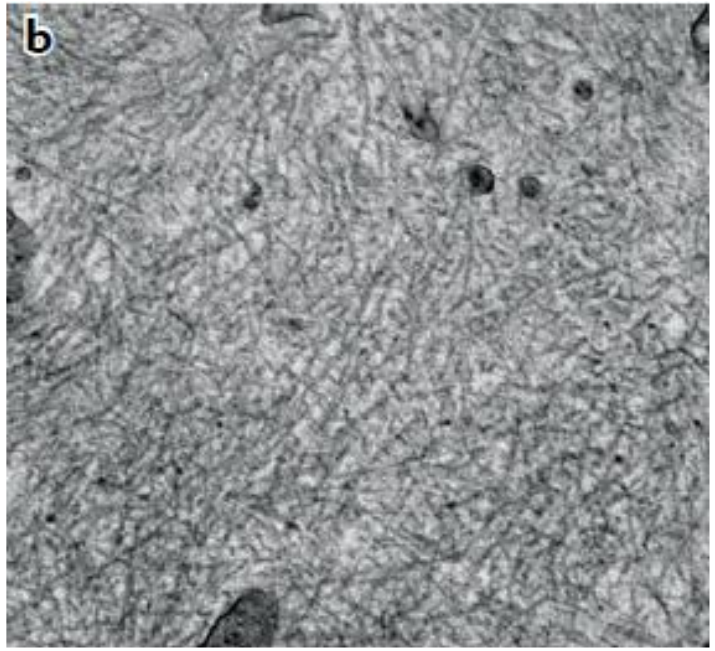
Hollow, lucent centres (organized deposit)

H&E and IF: Fibrillary GN





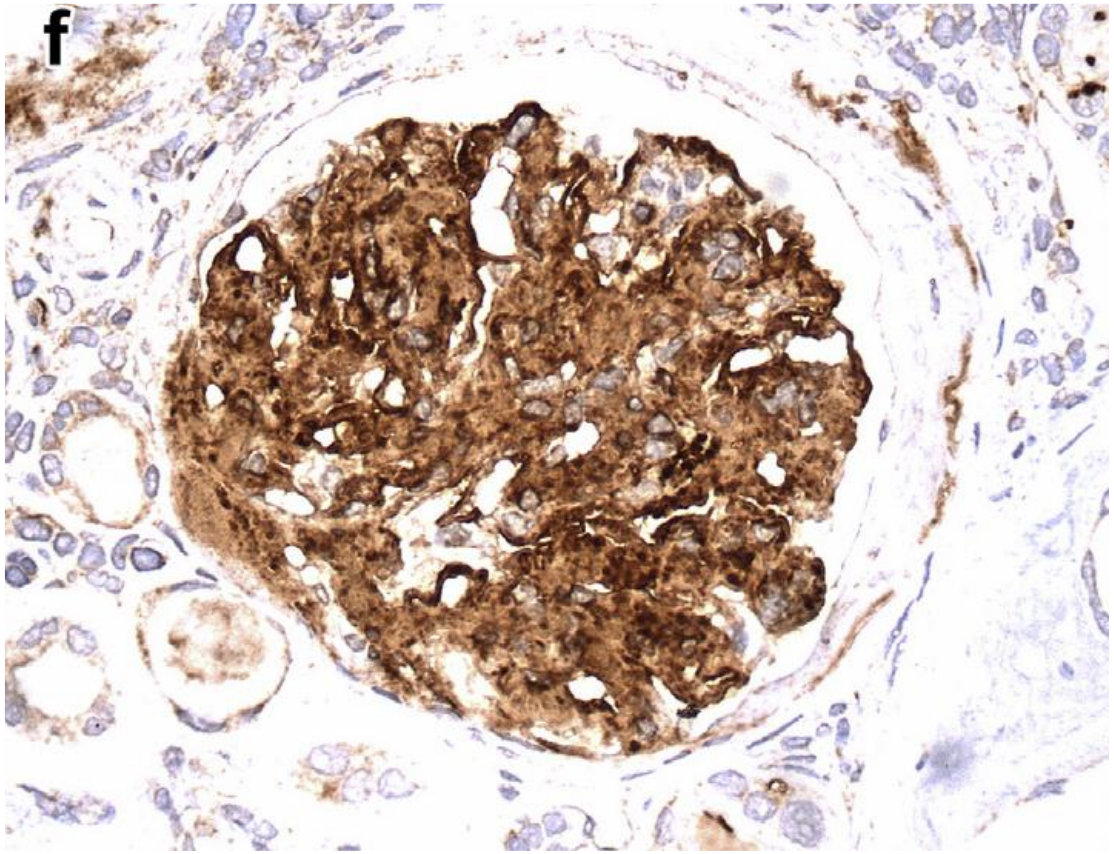




Mesangial & capillary wall/GBM deposition of microfibrils

- randomly arranged
- elongated
- non-branching
- ~twice diameter of amyloid fibrils
  - ❖ 20 nm (range, 12-24 nm)
- no apparent lumen

DNAJB9 in Fibrillary GN



- One of the most abundant proteins in the glomerular proteome
- Thought to play a role in Ig folding, unfolding, and degradation
- Co-localises with IgG and classic complement pathway proteins
- May act as an autoantigen
- Staining reported to have a sensitivity of 98% and specificity of 99% for the diagnosis of Fibrillary Glomerulonephritis

Differences and similarities

Immunotactoid glomerulopathy

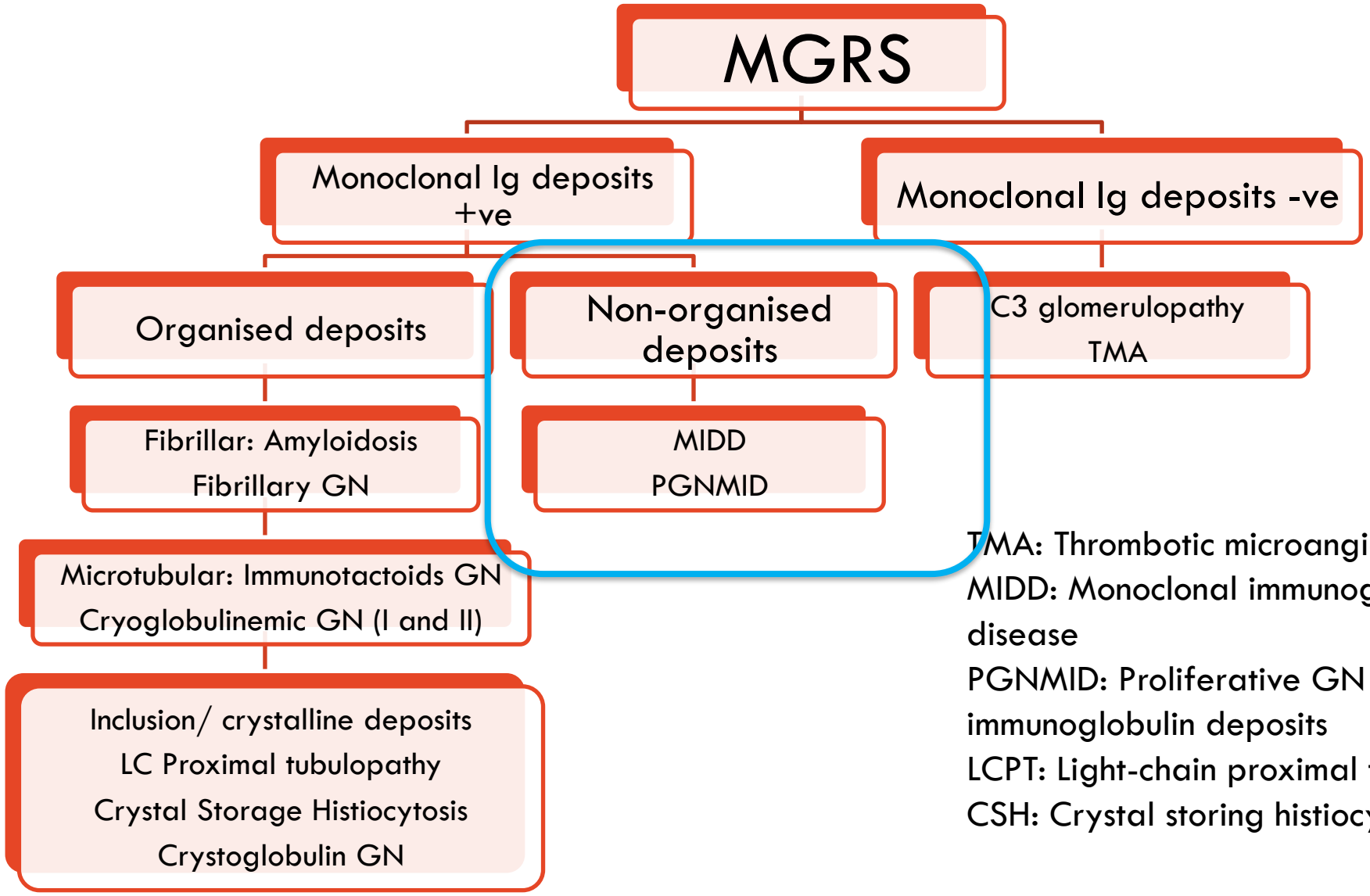
- Generally NOT a systemic disease
- Excellent kidney survival
- Extra renal involvement very rare
- Histo:
  - IF: Light chains restriction
  - Parallel-arranged microtubules (10–60 nm)
- Microtubular deposits have been reported in skin, nerve, lung and liver
- May be a/w haematological disorder

Fibrillary glomerulonephritis

- Patient survival good
- Kidney survival poor
  - ❖ Median time to kidney failure 24.4 $\pm$ 15.2 months
- Histology:
  - IF: IgG
  - DNAJB9 +ve
  - ❖ ANZDATA registry data:
    - ❖ 1/13 patients had recurrence with allograft failure 4.6 years later
    - ❖ 10-year patient and renal allograft survival similar to overall transplant population

- Renal transplantation is a viable option but risk of recurrence not negligible

Histopathological Classification



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Adapted Mancuso et al. Cancer medicine 2024

Monoclonal Immunoglobulin Deposition Disease (Randall Disease)

Characterized by the accumulation of non-organized (granular) deposits of intact or fragmented immunoglobulins that do not bind Congo red in visceral and soft tissues resulting in tissue damage

Most patients are in 5th to 6th decade of life
60% to 65% male predominance

Plasma Cells Dyscrasia (MM, WM)

B-Cell Neoplasm (CLL)

Light Chain Deposition Disease (LCDD)
- 80% of cases
- 80-90% are kappa light chains

Heavy Chain Deposition Disease (HCDD)
- 10% of cases
- Typically truncated gamma chains

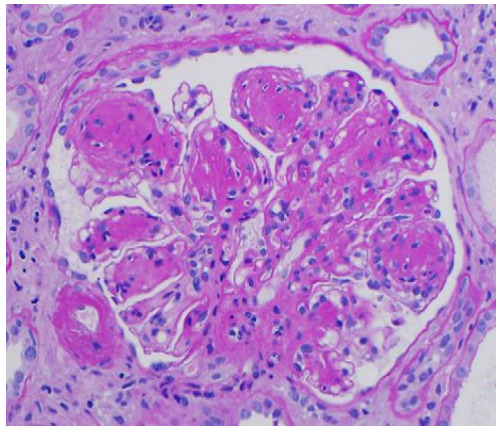
Light and Heavy Chain Deposition Disease (LHCDD)

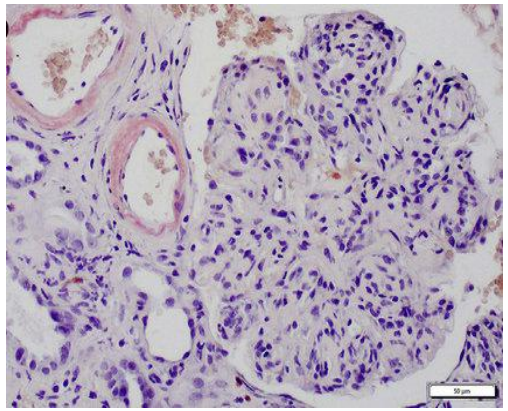
Demonstration of aberrant immunoglobulin deposits in affected organ

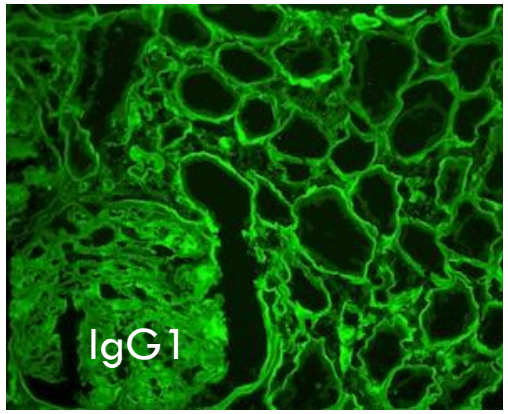
Kidneys (96%)	**Glomerular Deposits (Nephrotic Syndrome)**
	Tubular Deposits (Renal Impairment, Mild Proteinuria)
Heart (21%)	**Cardiomyopathy, Heart Failure**
Liver (19%)	**Hepatomegaly**
Peripheral Nerves (8%)	**Peripheral Neuropathy**

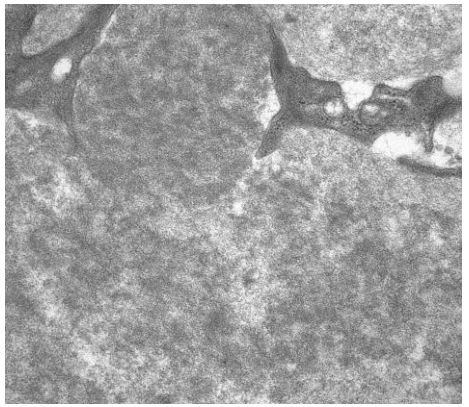
Histopathology:

MIDD







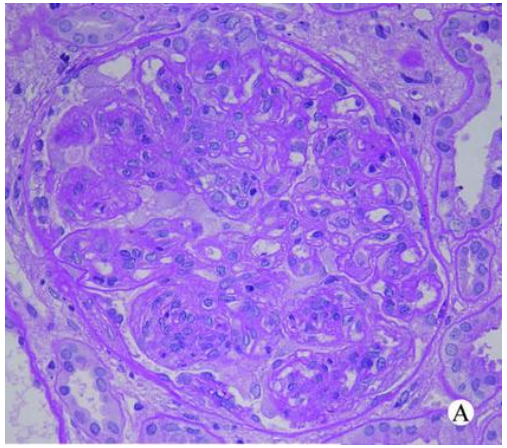


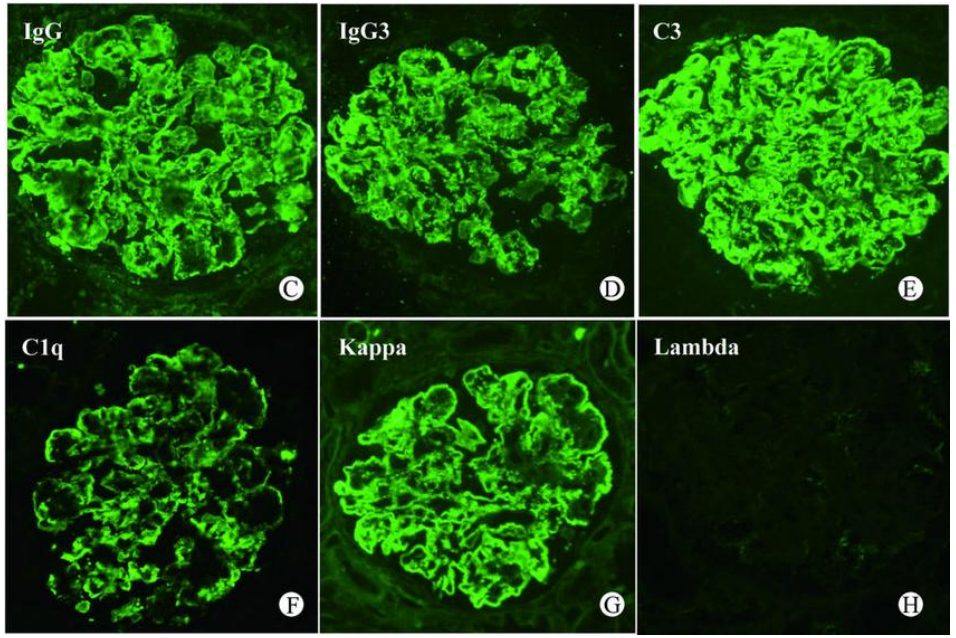
PGNMID

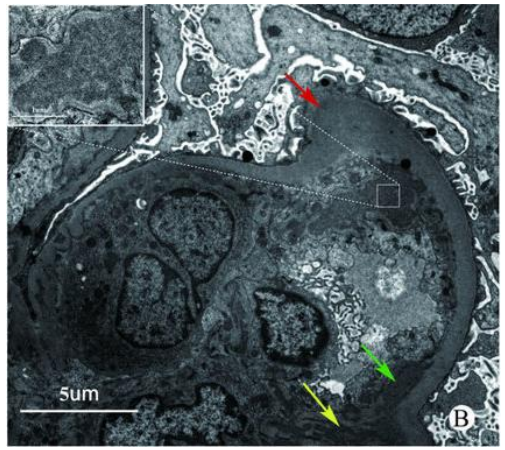
Histopathology:

MIDD

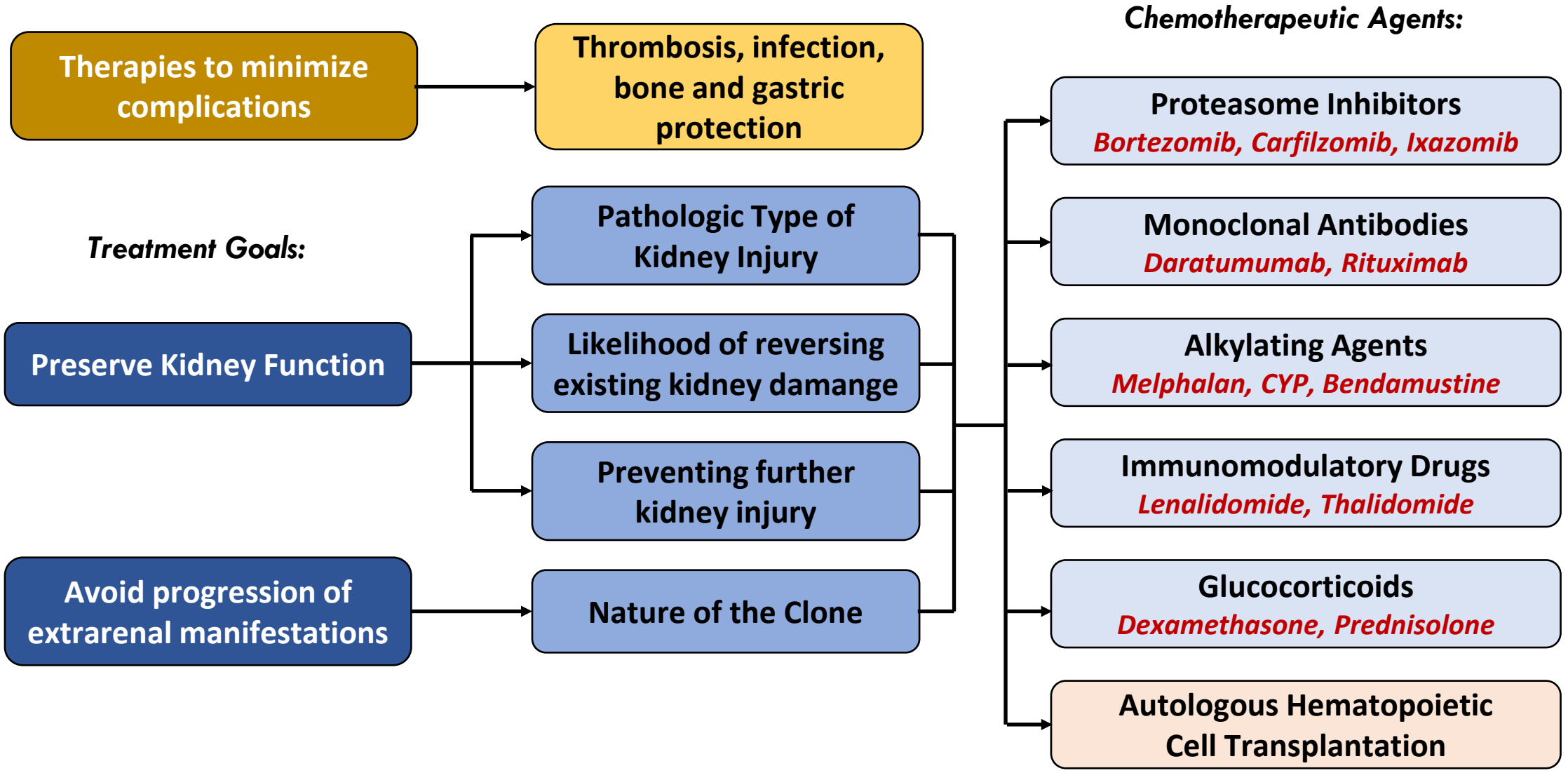
PGNMID



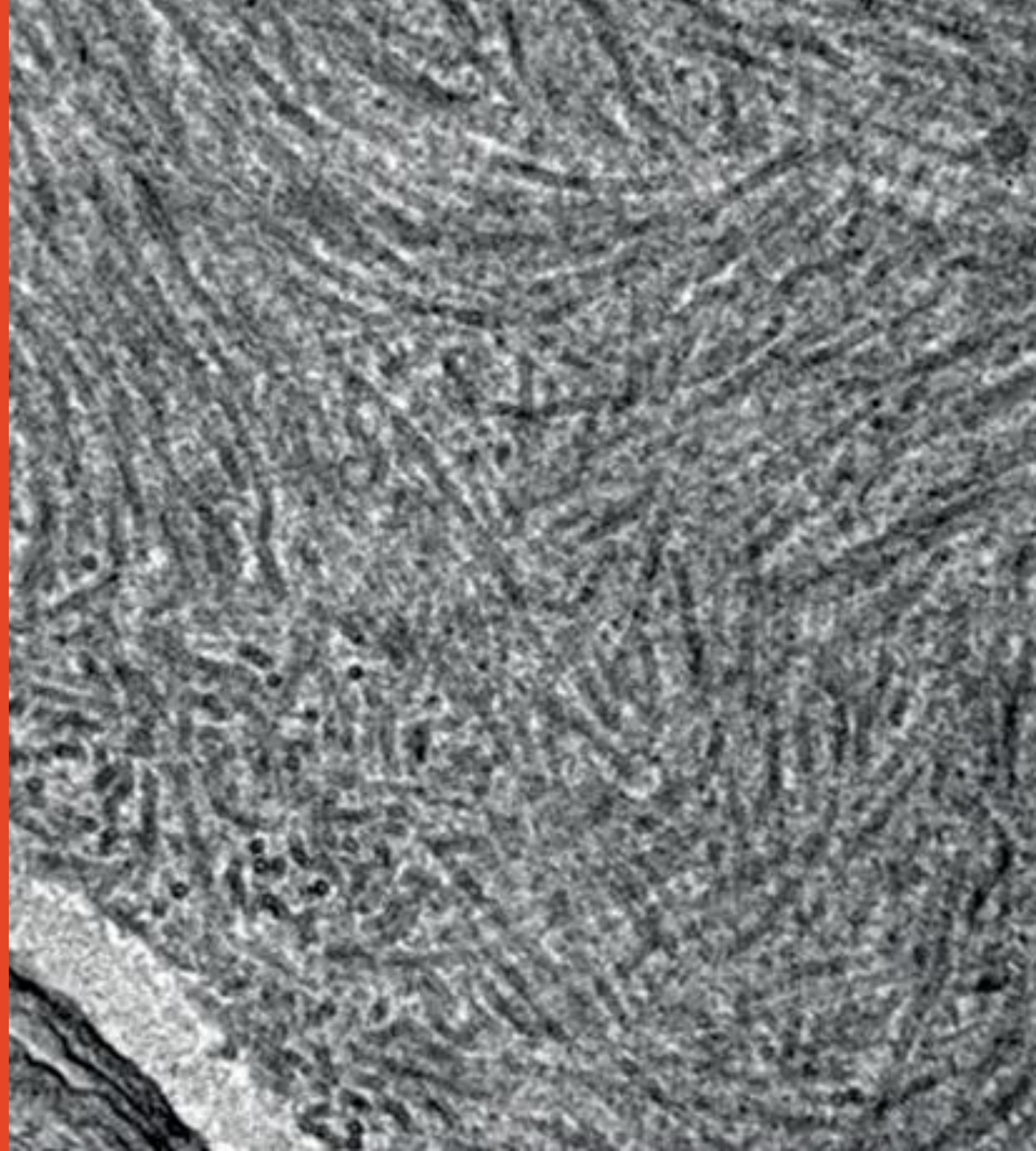




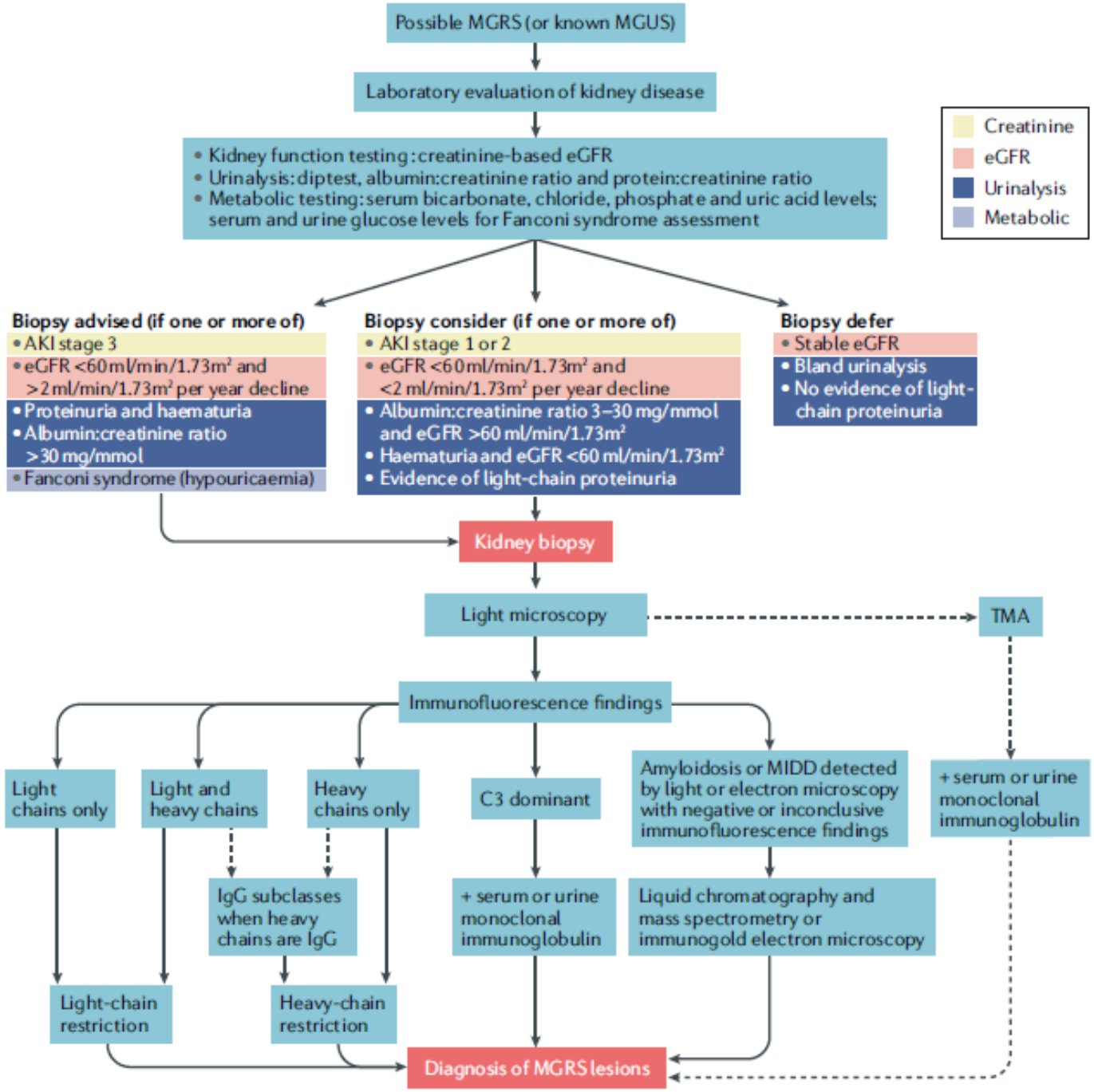
Treatment of MGRS



Myths, controversies and progress made



Diagnosis needs high end tools?



Leung et al. Nature Reviews | Nephrology Vol 15, (2019)

Risk of bleeding following kidney biopsy in MG

- 3.7% of kidney biopsy had major bleeding complications after kidney biopsy. (Similar to disease control)

4.1% vs 3.9%

	Percentage (*n*)	Bleeding Complications (*n*)
Amyloid	23.7 (35)	0
Cast nephropathy	62.2 (92)	6[a]
Mixed amyloid and cast	3.4 (5)	0
LCDD	0.7 (1)	0
Intraglomerular crystal deposition	0.7 (1)	0
ATN	2.7 (4)	0
Other renal findings[b]	6.8 (10)	0

ATN, acute tubular necrosis; LCDD, light chain deposition disease.

[a]Two of the six bleeding complications in patients with cast nephropathy were hematomas. One of these required radiologic intervention. The remaining four complications were significant hematuria and did not require radiologic intervention.

Fish et al Clin J Am Soc Nephrol. 2010 Nov;5(11):1977–1980.

4.0% vs 2.1%

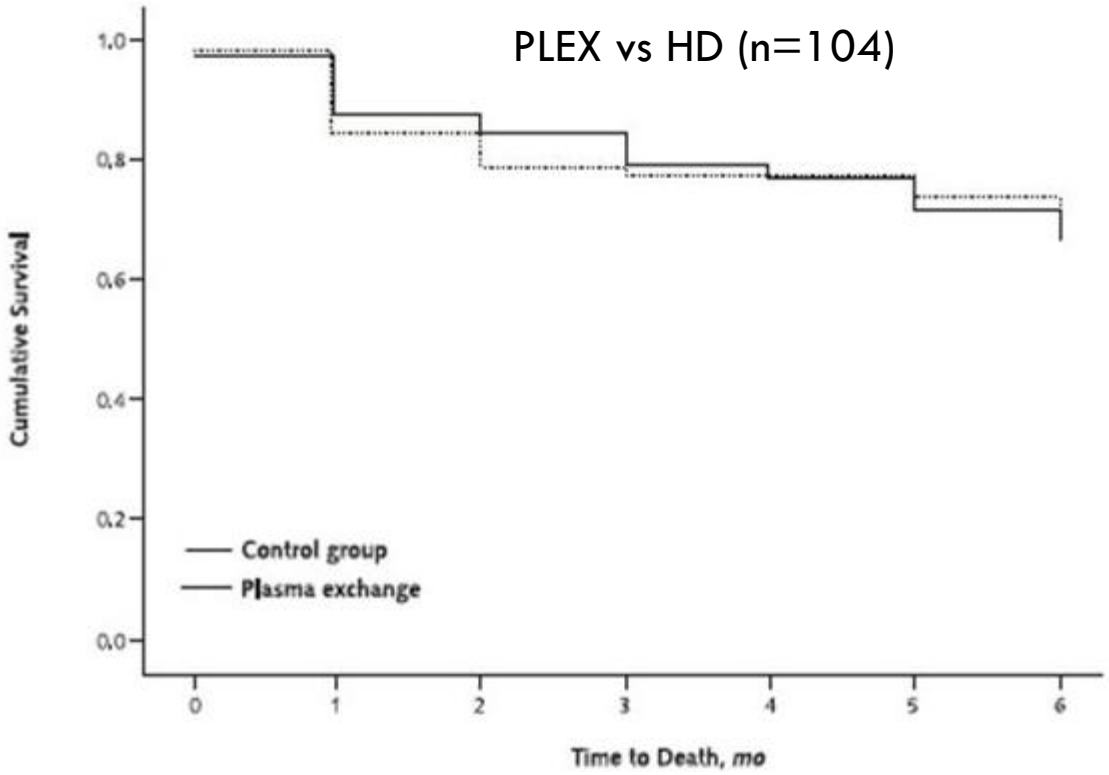
	Amyloidosis Group (n = 101)	Control Group (n = 188)	*P*
Biopsy variables			
Needle size (G)			0.04
15	1 (1.0)	0 (0.0)	
16	2 (2.0)	0 (0.0)	
18	97 (96.0)	187 (99.5)	
19	1 (1.0)	1 (0.5)	
Core number	2 (1-4)	2 (2-4)	0.3
Bleeding complications			
Any type of bleeding	10 (9.9)	20 (10.6)	0.8
Minor bleeding	6 (5.9)	16 (8.5)	0.4
Major bleeding	4 (4.0)	4 (2.1)	0.4

Soares et al AJKD Vol 52, (6p)1079-1083 (2008)

Pauekesakon et al Am J Kidney Dis . 2003 Jul;42(1):87-95

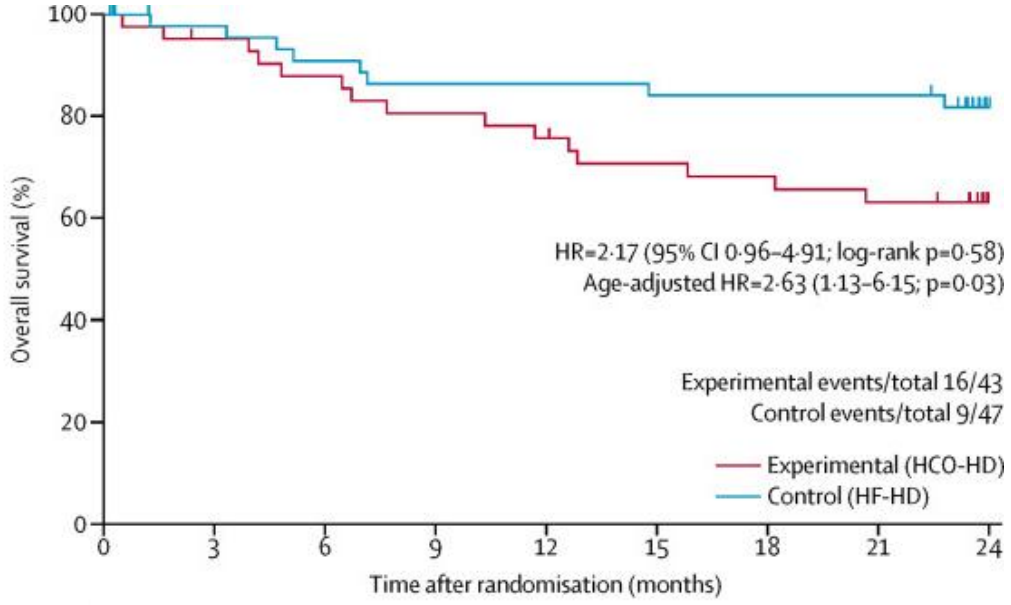
No role for PLEX or High cut-off dialysis

Plasma exchange in cast nephropathy



Clark WF et al. Ann Intern Med 2005; 143:777-784.

Removal of Monoclonal Gammopathy (High Cut-Off Hemodialysis)



Hutchison CA et al. Lancet Haematol 2019; 6:e217-e228.

Summary

Monoclonal gammopathy can lead of MGRS which is new classification of pathogenic clonal proliferative disorders that produce a nephrotoxic protein.

MGRS is not a benign kidney condition and now a recognized indication for initiating treatment target clonal proliferation.

Diagnosis often requires high level of clinical suspicious, kidney biopsy for H&E, IF and often specialized stains and EM, to demonstrate the presence of monotypic immunoglobulin deposits

Treatment requires personalization and joint care with a hematologist, balancing efficacy and safety against the patient's goals of care.

Thank you for your attention!

THE UNIVERSITY OF SYDNEY

CONCORD REPATRIATION GENERAL HOSPITAL

Kidney transplantation for MGRS with ESKD

- **High recurrence rate**
- **Kidney transplantation is recommended for patients who have experienced good outcomes with effective therapy**
- **Predictors:**
  - Heamatological remission
  - Type of MGRS
  - Other organs involvement e.g. heart, brains

AL amyloidosis

- macroglossia
- periorbital purpura

Restrictive cardiomyopathy with dominant RVF

- oedema
- raised JVP
- congestive hepatomegaly

Carpal tunnel syndrome

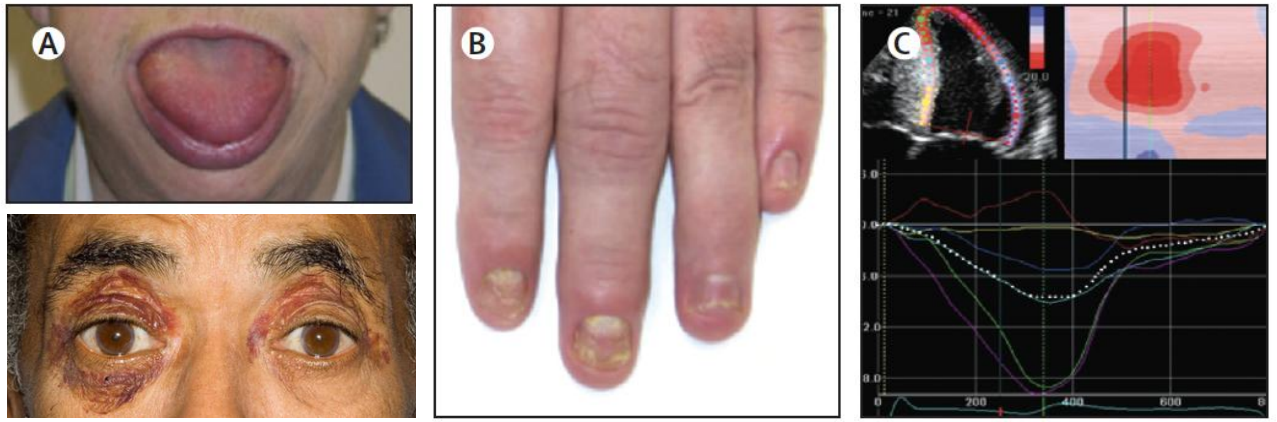
- common early sign of ATTR

Kidney involvement

- proteinuria
- nephrotic syndrome

Clinical features raising suspicion of amyloidosis

- Peri-orbital purpura
- Macroglossia (A)
- Nail dystrophy (B)
- Monoclonal protein and diastolic heart failure with preserved apical systolic function and "bulls-eye" on 2D strain imaging (C), thick-walled heart with low-voltage ECG, monoclonal protein and albuminuria, peripheral and autonomic neuropathy, and family history



Wechalekar et al. Lancet 2016; 387: 2641–54