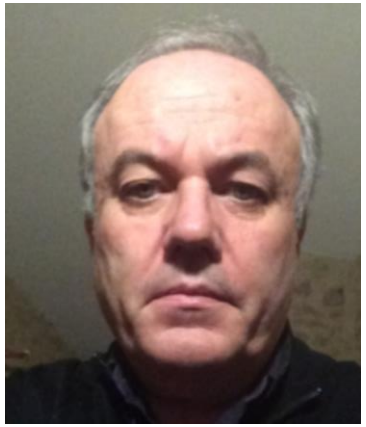

ERKNet
The European Rare Kidney Disease Reference Network

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WGIKD working group
Working Group on Inherited Kidney Disorders

WELCOME TO

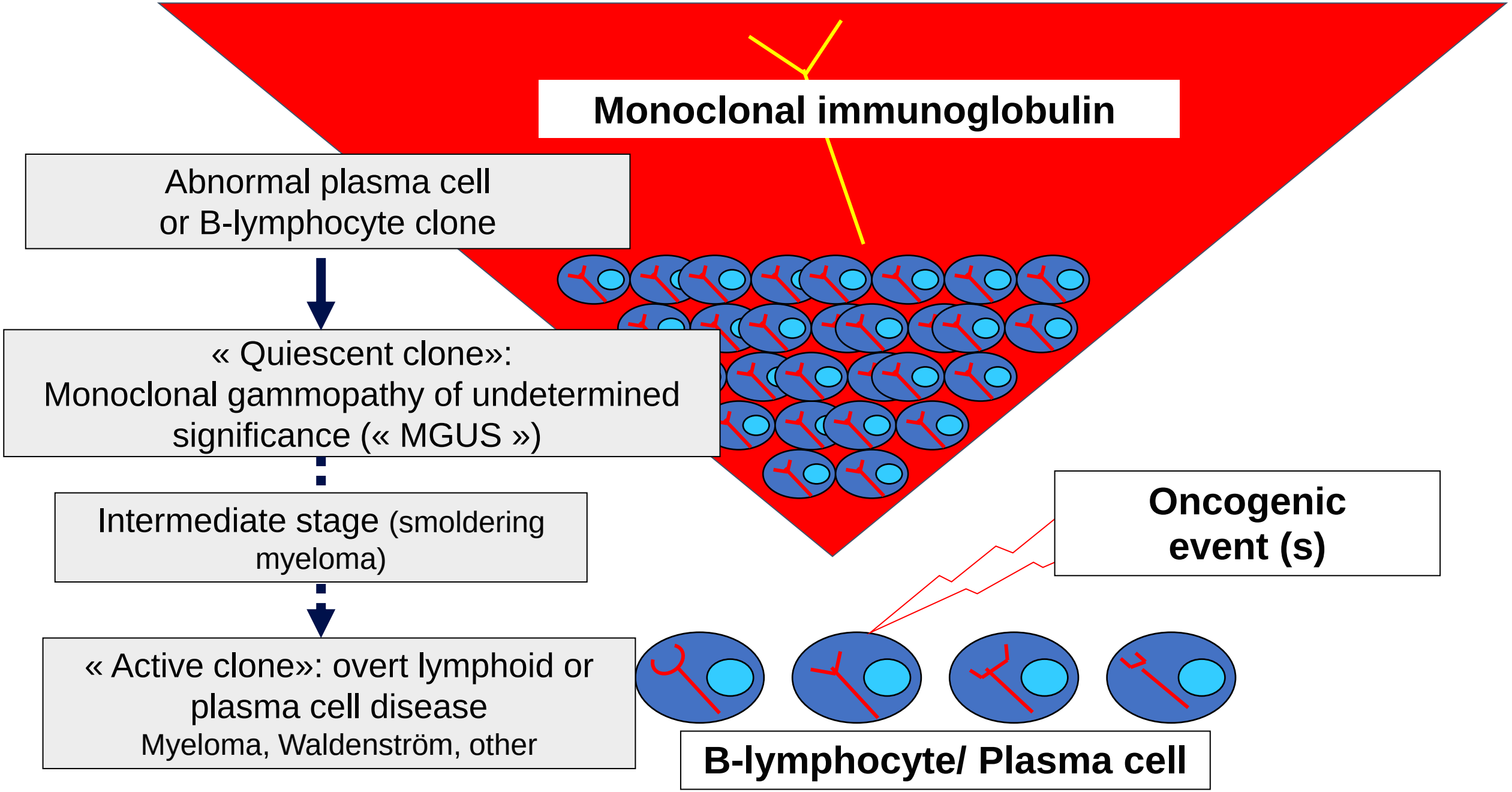
ERKNet
Advanced Webinars on Rare Kidney Disorders

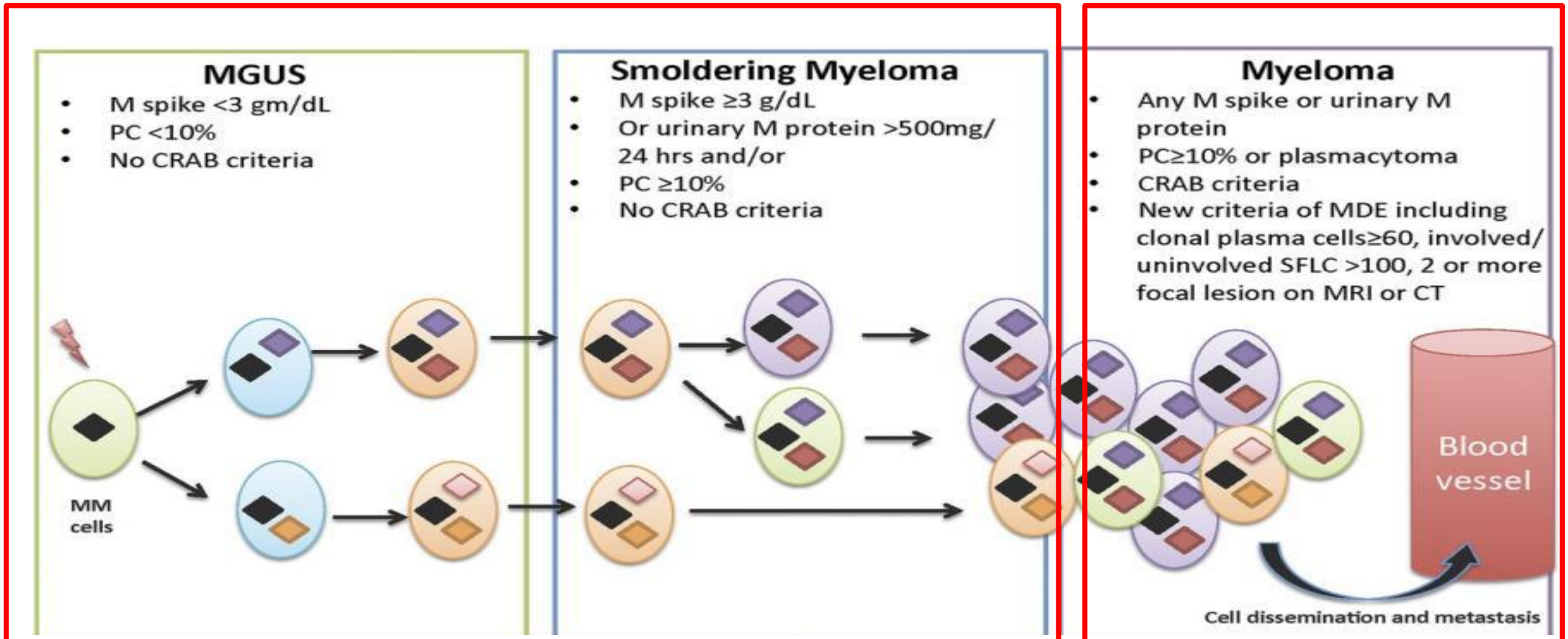
Date: 16 February 2021

Topic: Paraprotein associated disease

Speaker: Frank Bridoux

Moderator: Jack Wetzels


Monoclonal immunoglobulin
Abnormal plasma cell
or B-lymphocyte clone
« Quiescent clone»:
Monoclonal gammopathy of undetermined significance (« MGUS »)
Intermediate stage (smoldering myeloma)
« Active clone»: overt lymphoid or plasma cell disease
Myeloma, Waldenström, other
Oncogenic event (s)
B-lymphocyte/ Plasma cell



Surveillance

Surveillance / clinical trial

Treatment
Anti-plasma cell agents

Ghobrial IM, et al. Blood 2014;124:3380-3388

Concepts of MGRS and MGCS


blood

Monoclonal gam
undetermined o

Nelson Leung,[1,2] Frank Br
Angela Dispenzieri,[2] Kevi
Gammopathy Research G

[1]Division of Nephrology and Hype
Transplantation, University Hospi
Birmingham, United Kingdom; [5]D
France, France; and [7]Division of

MGR(C)S = small plasma cell or B-cell clone

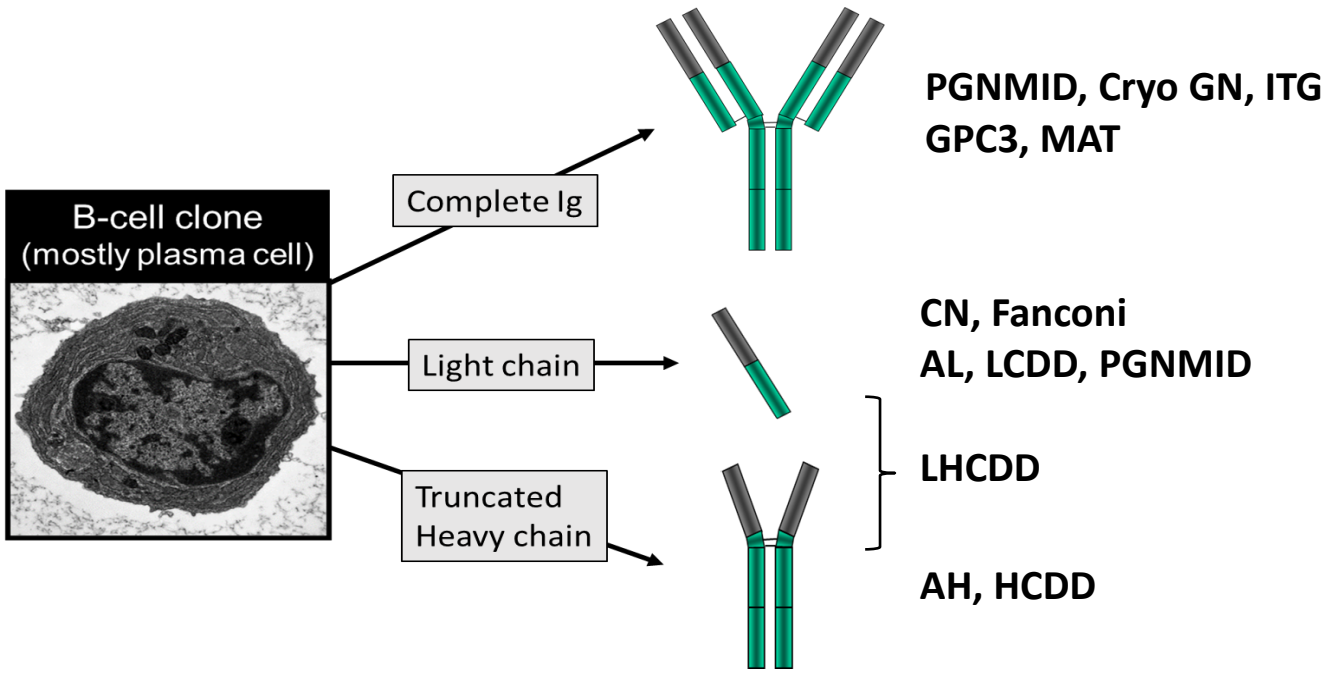
+

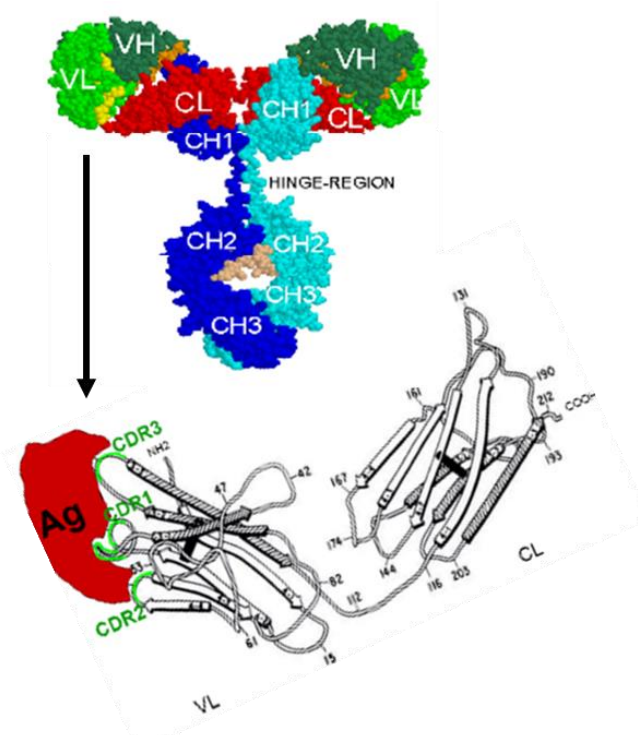
Renal disease (or other organ/tissue involvement)
directly (deposition) **or indirectly** (autoantibody activity, complement activation, production of cytokines)
induced by the secreted monoclonal Ig

Treatment = clone-targeted chemotherapy

Renal toxicity of monoclonal immunoglobulins

- Intrinsic property, not all monoclonal Igs are nephrotoxic !
- Nephrotoxity of monoclonal Igs determined by:
  - **molecular characteristics** (mutations in the variable domain++)
  - **functional properties of monoclonal Ig :** complement activation, autoantibody activity…)
- Independent of the tumor mass (exception: LC cast nephropathy)

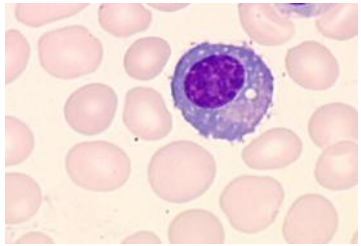


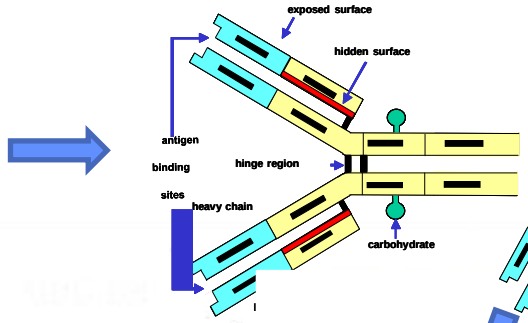


Variable domain mutations

Sirac C. Nat Rev Nephrol 2018; 14:246-64

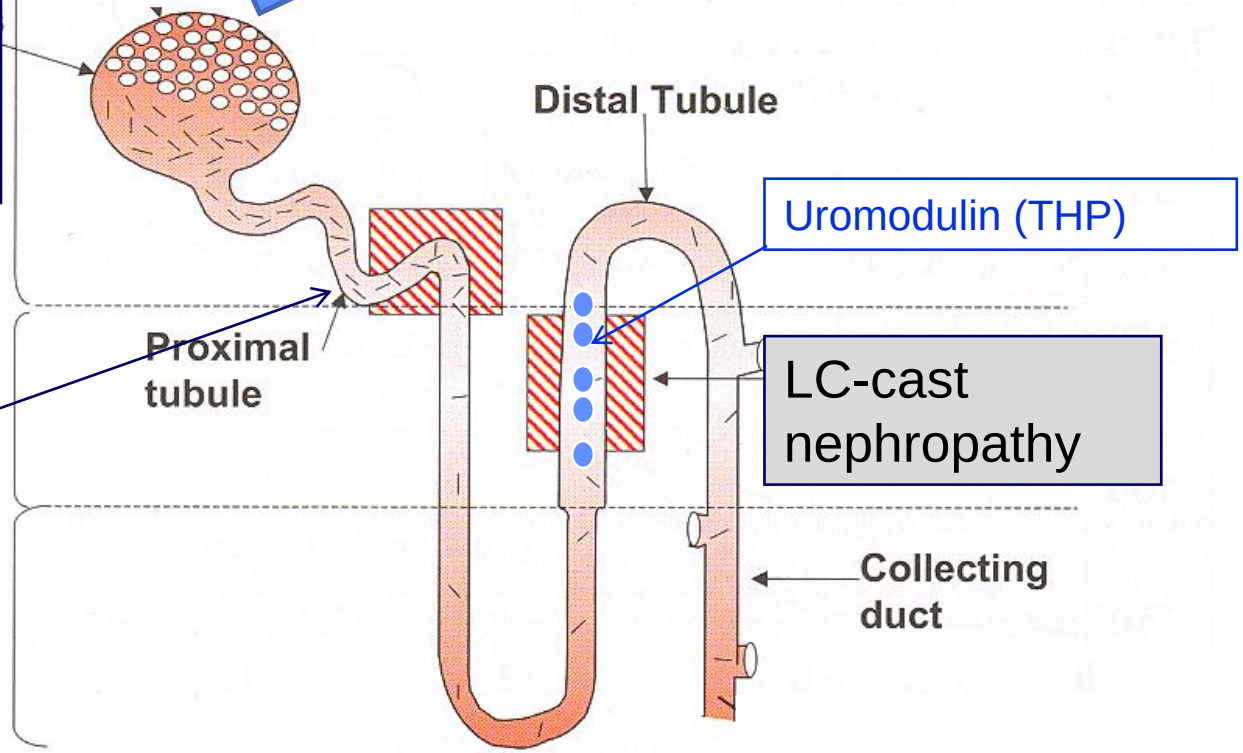
Renal toxicity of Ig light chains





AL amyloidosis
LCDD
LC-PGNMID

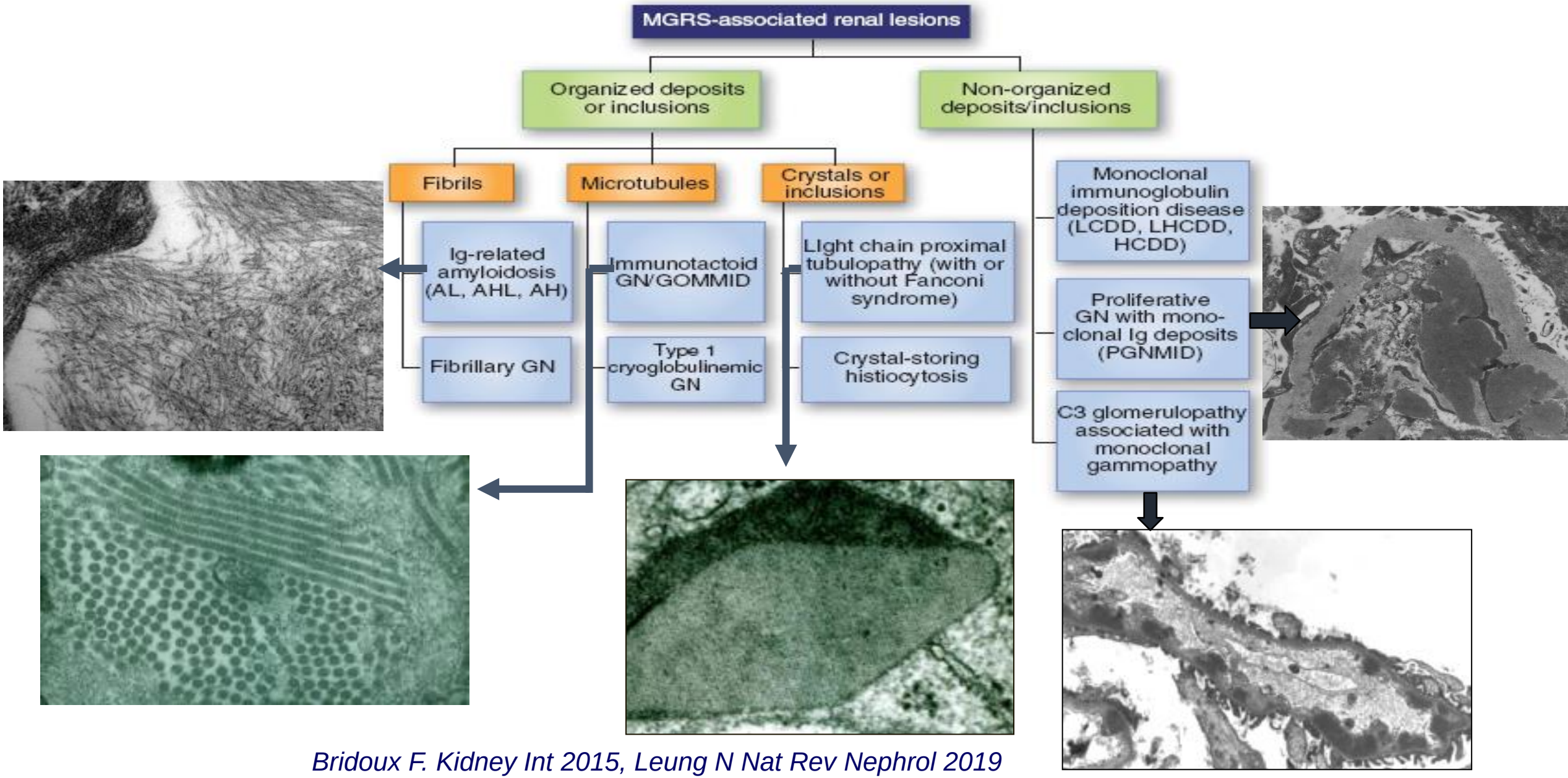
LC-Fanconi syndrome



Uromodulin (THP)

LC-cast nephropathy

Classification of MGRS-associated renal lesions



Bridoux F. Kidney Int 2015, Leung N Nat Rev Nephrol 2019

Renal disease and monoclonal gammopathy

Diagnostic approach

Analysis of proteinuria (UPEP)

Albuminuria < 30%

Tubular proteinuria

↓

LC Fanconi syndrome

- Monoclonal κ LC
- CKD + proximal tubulopathy
- Osteomalacia
- MGRS (MGUS or smoldering MM)

Overflow proteinuria (LC)

↓

LC cast nephropathy

- Monoclonal LC (κ or λ)
- AKI
- Bone lytic lesions
- Symptomatic MM

Renal disease and monoclonal gammopathy

Diagnostic approach

Analysis of proteinuria (UPEP)

Albuminuria > 30-40% → **Glomerular disease** → **type?**

Kidney biopsy:

- Light microscopy (Congo-red staining ++)
- Immunofluorescence (antibodies specific for Ig LC ± IgG sub-classes)
- Electron microscopy (EM)
- If required: LMD/LC-tandem MS (proteomics), immuno-EM

Monoclonal gammopathy and renal disease

When to perform a kidney biopsy?

- Prevalence of monoclonal gammopathy increases with age:
  - 3.2% after 50 yrs
  - 7.5% after 85 yrs
- Prevalence of MGRS among patients with MGUS and renal diseases: 40%
- Indications for a kidney biopsy in a patient with MGUS and renal disease:
  - No other cause
  - other cause but atypical presentation or disease course (unexplained increase in proteinuria or decrease in GFR)
  - Renal manifestations and monoclonal gammopathy in a young patient (aged <50 yrs)
- Incidence of post-biopsy hemorrhagic complications (~ 4%) similar in MGRS *vs* other nephropathies

Leung N, et al. Nat Rev Nephrol 2019; 15:45-59 *Klomjit N, et al. JASN 2020; 31: 2400-11*

Hematological workup in MGRS

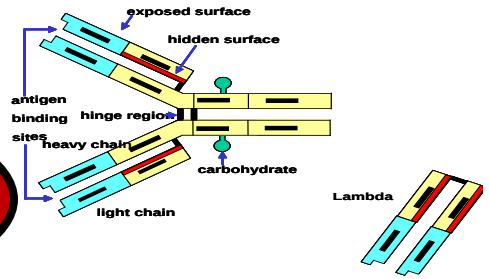
- **Characterization of the monoclonal gammopathy :**
  - Serum and urine protein **electrophoresis** (quantification of M-spike) and **immunofixation**
  - **Serum FLCs** :

    Kappa/lambda ratio (Binding Site): 0.26-1.65 if normal renal function
    0.34-3.10 if «renal insufficiency »
  - Immunoblot: sensitivity ++, identification of IgG sub-class, CH1 deletion….
  - Mass spectrometry (“Mass-fix”)
- **Identification of the pathogenic clone :**
  - **Bone marrow studies:**
    Flow cytometry (search for plasma cell AND B-cell clone) +/-molecular biology (NGS)
    Cytogenetics (FISH, NGS) : MYD88 L265P mutation (Waldenström), t(11;14) (AL amyloidosis)….
  - Immunophenotyping of circulating lymphocytes (CLL)
- **CT-scan of thorax-abdomen-pelvis (lymph node biopsy) +/- PET -scan (IgM)**

Fermand JP. Blood 2013; 122: 3583-90
Leung N. Nat Rev Nephrol 2019; 15:45-59

MGRS: principles of management

Type? plasmacytic? lymphocytic?



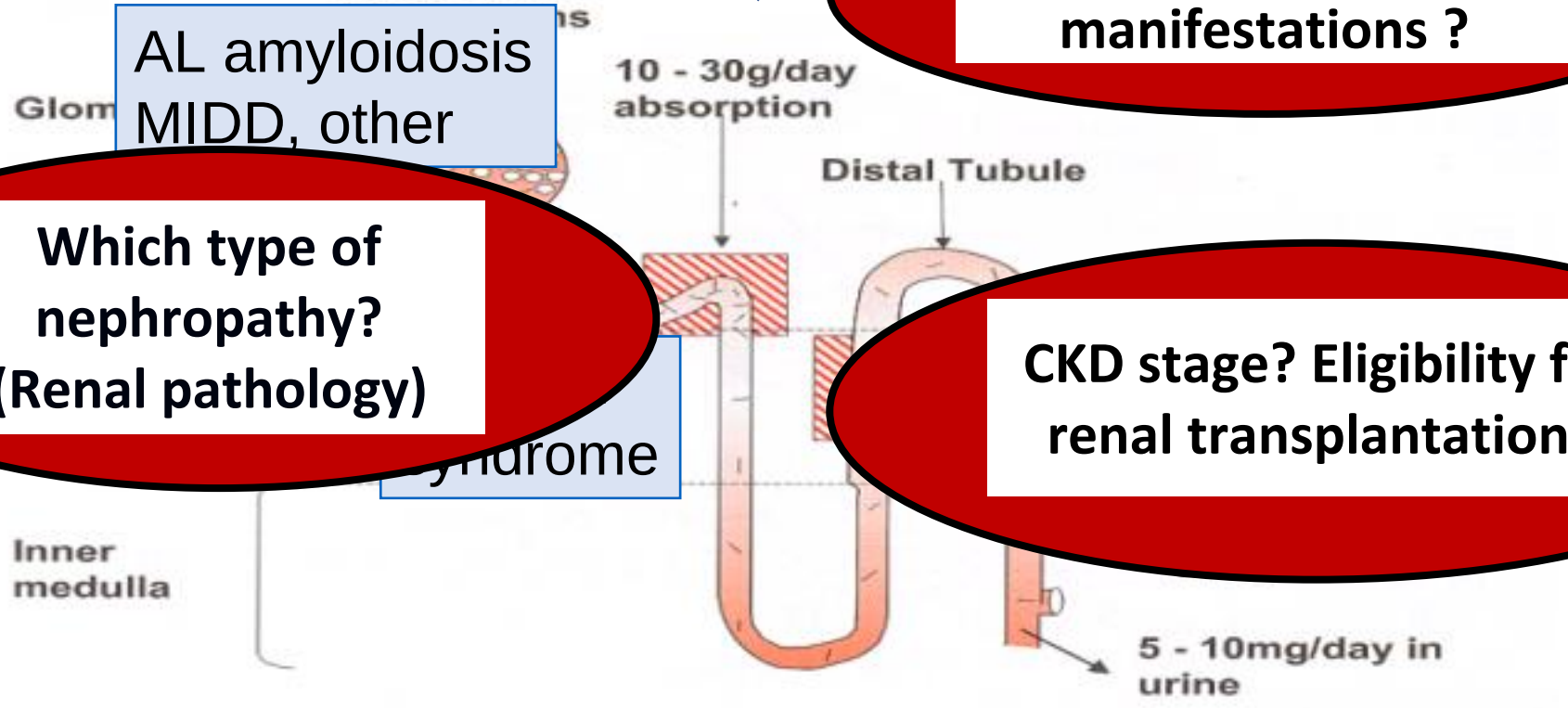
Extra-renal manifestations ?

AL amyloidosis
MIDD, other

Which type of nephropathy? (Renal pathology)

ynd rome

CKD stage? Eligibility for renal transplantation?



Fermand JP. Blood 2013; 122: 3583

MGRS : principles of chemotherapy

- **Adapted to the nature of the underlying clone**
  - **Plasmacytic**: anti-myeloma agents (bortezomib-based)
  - **Lymphocytic**: treatment as in WM or B-cell lymphoma (rituximab-based)
  - **When the clone is not identified** :
    - ✓ IgG, IgA or LC-only monoclonal gammopathy : anti-myeloma agents
    - ✓ IgM monoclonal gammopathy: rituximab-based

- **Adapted to pharmacokinetics (*renal elimination)***
  - **Alkylating agents** : cyclophosphamide, bendamustine, (melphalan : dose adaptation)
  - **Proteasome inhibitors** : bortezomib, carfilzomib, ixazomib
  - **Imids**: thalidomide, pomalidomide (lenalidomide : dose adaptation)
  - **Monoclonal antibodies:**
    - ✓ Anti-CD20: rituximab, ofatumumab,…
    - ✓ Anti-plasma cells: daratumumab (anti-CD38)

- **Taking into account potential nephrotoxicity (carfilzomib)**

Fermand JP, et al. Blood 2013; 122: 3583-90

MGRS : assessment of treatment efficacy

- **Organ response is delayed after hematological response**

- **Treatment efficacy = quality of hematological response**

✓**Measurable FLCs** (AL amyloidosis criteria)
PR: ≥ 50% reduction in dFLC (dFLC = pathogenic FLC – other LC isotype)
VGPR : dFLC < 40 mg/L (or dFLC reduction > 90%)
CR : negative serum and urine immunofixation with normal FLC ratio

✓**Normal FLCs**: response based on M-spike and immunofixation

Fermand JP, et al. Blood 2013; 122: 3583-90 *Cohen C, et al. Kidney Int 2015; 88:1135-43*

Question 1:

Among the following tests, which one should not be used in the diagnostic workup of MGRS :

1. Serum immunofixation
2. Urine immunofixation
3. Serum free light chains
4. Urine free light chains
5. Bone marrow smears or biopsy

Question 1:

Among the following tests, which one should not be used in diagnostic workup of MGRS :

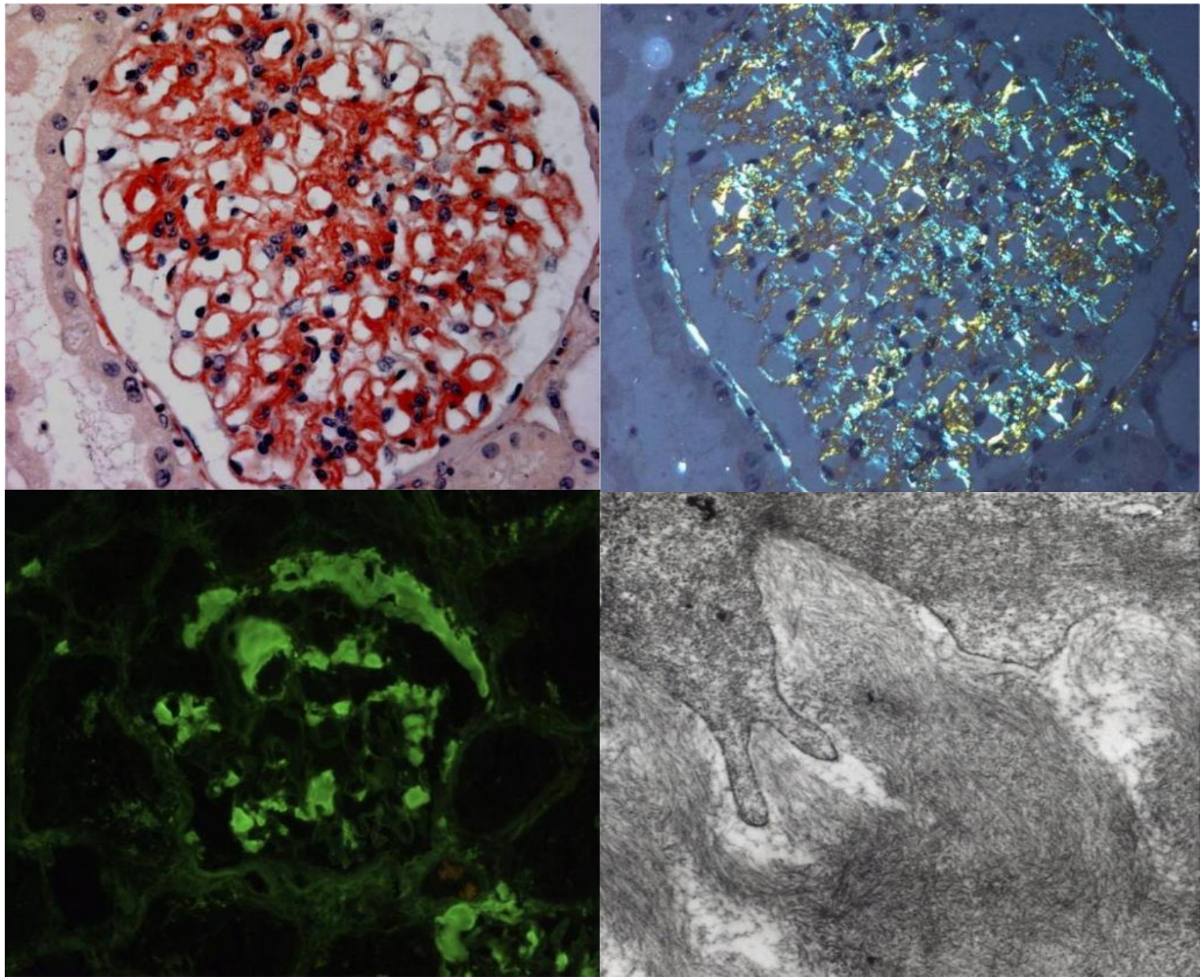
1. Serum immunofixation
2. Urine immunofixation
3. Serum free light chains
4. Urine free light chains
5. Bone marrow smears or biopsy

Systemic AL amyloidosis

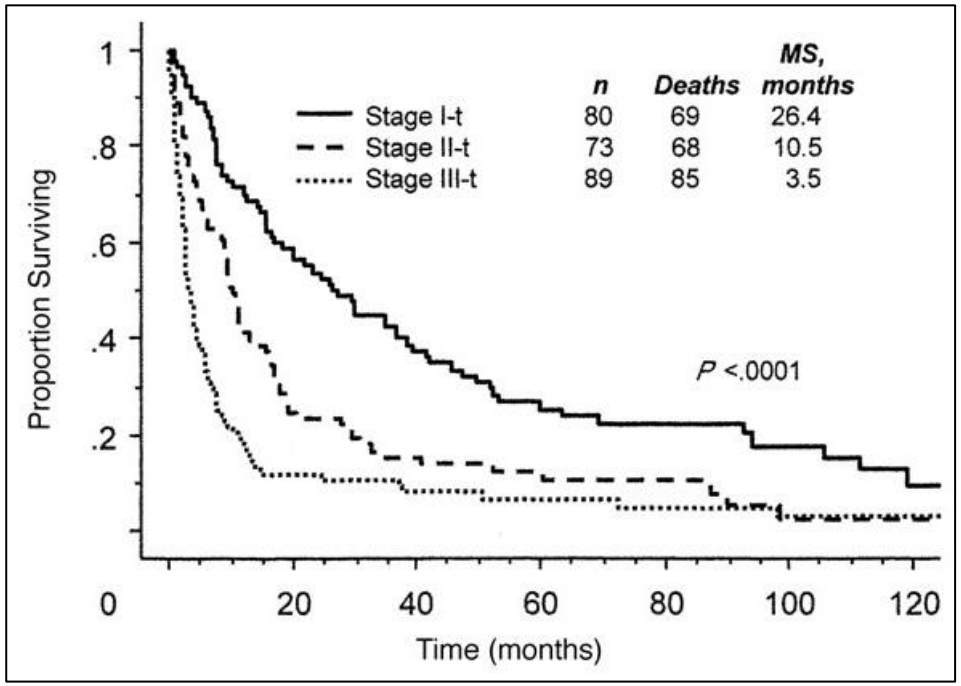
- **Epidemiology:**
  - Incidence: 9 to 12 cases/million/yr
  - Age at diagnosis: 65 yrs, slight male predominance
- **Renal disease :**
  - 60-70% at diagnosis
  - Proteinuria >1g/24h : >60% (median 5 g/d), nephrotic syndrome : >50%, decreased eGFR 45%
  - Hypertension and hematuria uncommon, slowly progressive CKD with polyuria possible
- **Cardiac disease (60%): prognostic factor ++**
  - NT-proBNP and troponin serum levels (Mayo Clinic staging)
- **Other common manifestations**: liver disease, peripheral/autonomic neuropathy, GI tract deposits
- **Underlying clonal disorder: usually plasmacytic and corresponding MGR(C)S (80%)**
  - Symptomatic MM <20%
  - Median bone marrow plasma cell infiltration 7%, t(11;14) ~ 50%
  - Waldenström or B-cell lymphoma rare (IgM monoclonal gammopathy)
  - Detectable serum/urine monoclonal gammopathy with abnormal FLCs (90%)
  - Over-representation of lambda LC (Vλ6 if renal disease)

Desport E, et al. Orphanet J Rare Dis 2012

Renal AL amyloidosis

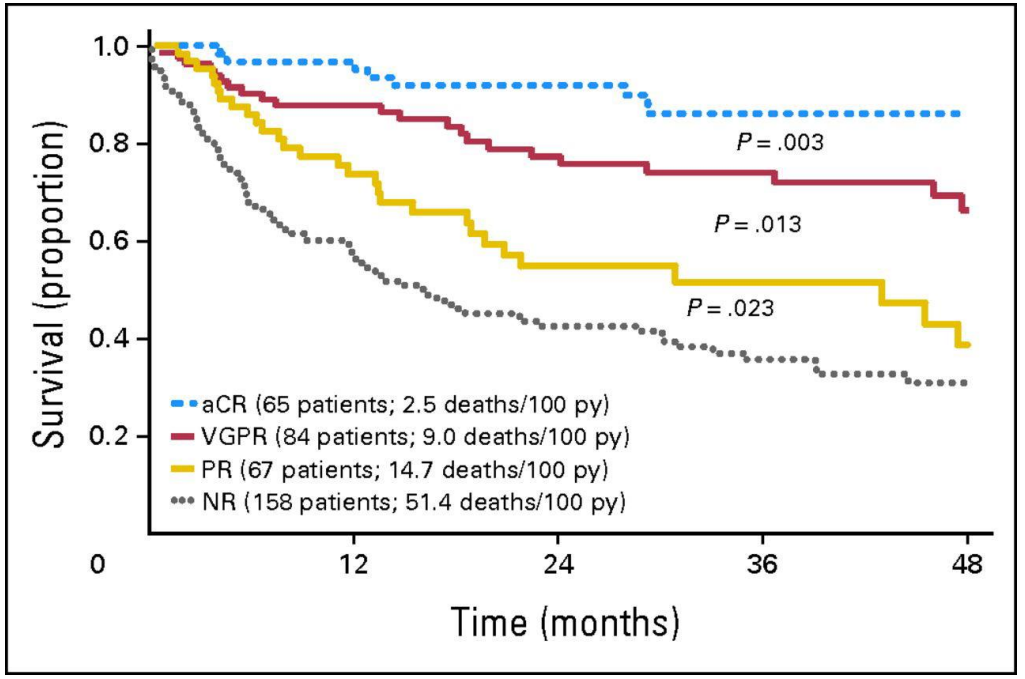


AL amyloidosis: prognostic factors



Severity of cardiac disease (Mayo Stage)

Dispenzieri A, et al. J Clin Oncol. 2004;22:3751-7



Quality and rapidity of hematological response

Palladini G, et al. J Clin Oncol. 2012;30:4541-9

Immunotactoid glomerulopathy/GOMMID

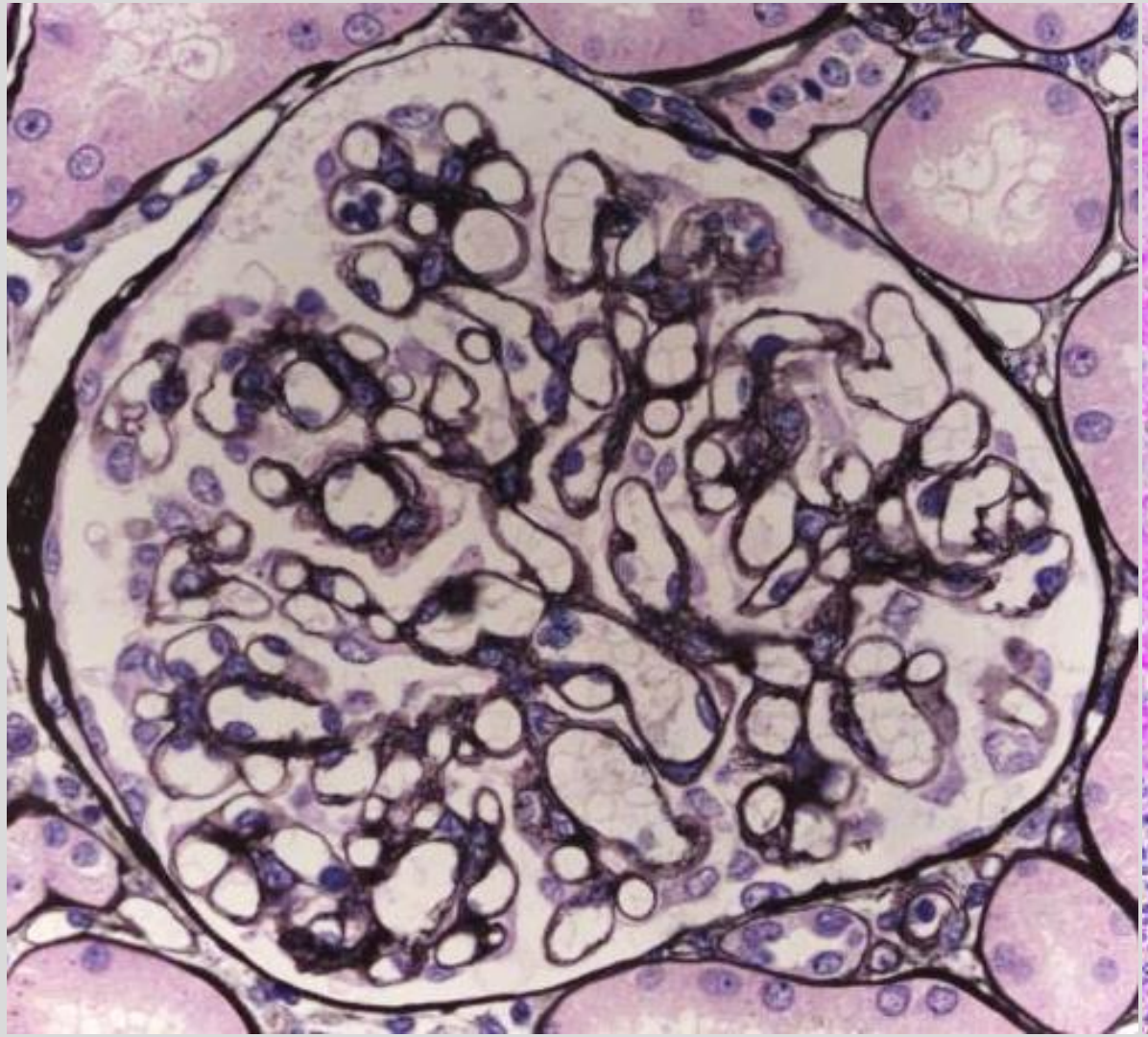
- Pathological definition:
  - monotypic IgG deposits
  - organized into microtubules (10-50 nm)
  - distinct central hollow core (magnification < 50.000)
  - cryoglobulins negative
- Extremely rare! Biopsy incidence <0.1%
- Clinicopathologic characteristics
  - Age at diagnosis ~ 60 yrs
  - Renal manifestations: chronic glomerular disease
    Proteinuria (>2 g/24h) : >90%
    Nephrotic syndrome, hematuria, renal insufficiency, hypertension > 50%
  - Extra-renal deposits exceptional: skin, peripheral nerve
- Hematological characteristics
  - Mostly lymphocytic clonal disorders
    (MGRS ~ 50%, CLL~ 50%)
  - Detectable monoclonal gammopathy >60%
  - Hypocomplementemia ~ 30%

Bridoux F. et al. Kidney Int 2002; 62: 1764-75
Rosenstock JL et al. Kidney Int 2003; 63: 1450-61
Javaugue V, et al. Kidney Int 2021; 99; 421-30

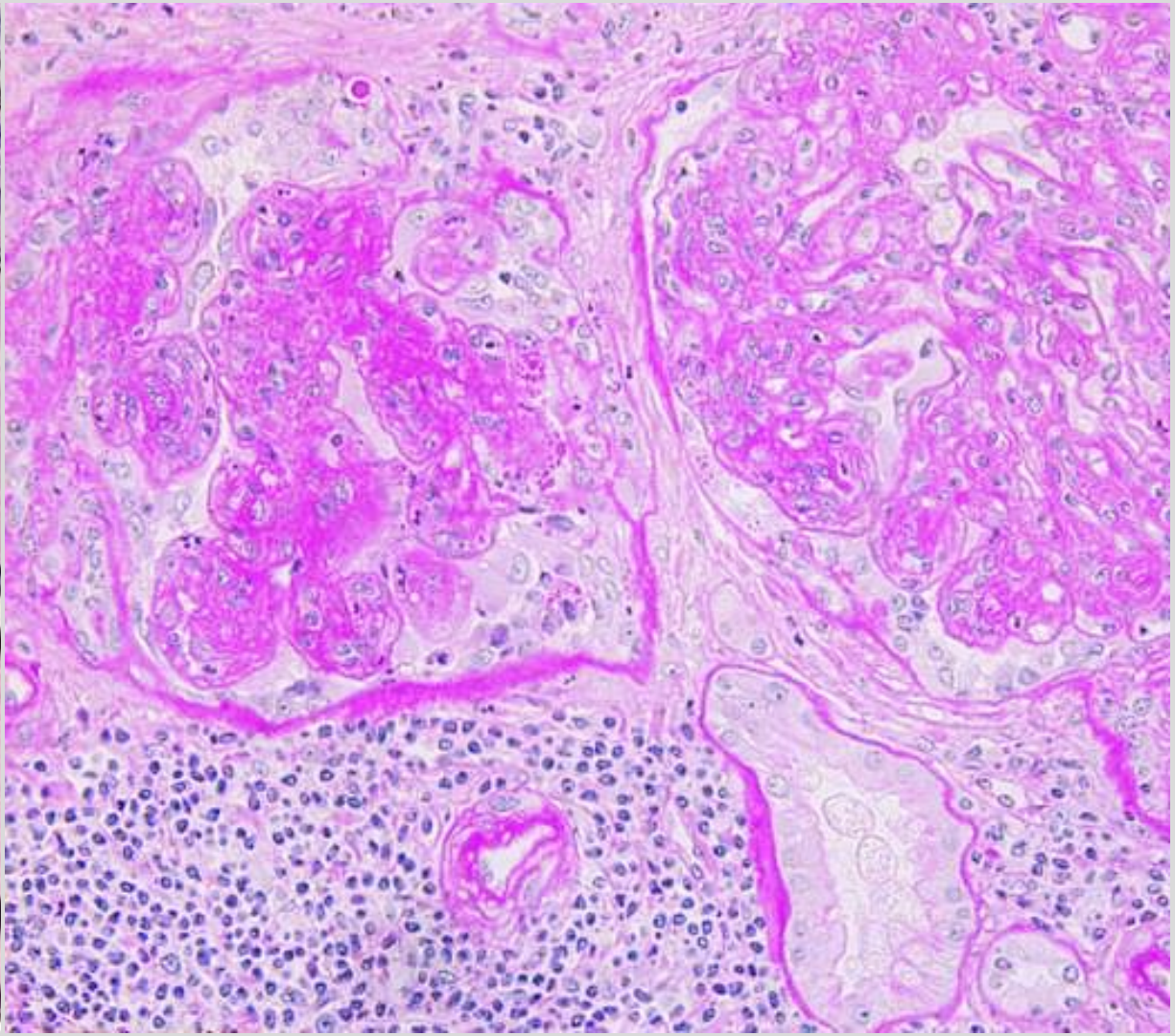
Table 1 | Baseline characteristics

Characteristics	No. of patients (N = 27)
Clinical characteristic	
Age, yr	61 (30–79)
Male sex	18 (67)
Hypertension	15 (56)
Proteinuria, g/d	6 (1–23)
Nephrotic syndrome	19 (70)
Microscopic hematuria	20 (74)
Serum creatinine, mg/d	1.5 (0.6–6.5)
eGFR, ml/min per 1.73 m^2	56 (11–108)
Chronic kidney disease ≥3	17 (63)
Extrarenal manifestations	1 (4)
Hematologic characteristics	
Measurable SPEP and/or UPEP monoclonal spike	4 (15)
Positive serum and/or urine immunofixation	19 (70)
Abnormal serum-free light chain ratio	3/16 (19)
IgG subclass by serum immunoblot analysis (n = 16)	
IgG1	9 (56)
IgG2	5 (31)
IgG3	2 (13)
IgG4	0
Diagnosis	
CLL[a]	10 (37)
Small lymphocytic lymphoma	3 (11)
MGRS	14 (52)
Underlying B-cell clone	
Lymphocytic	16 (60)
Plasmacytic	2 (7)
Unknown	9 (33)

Immunotactoid glomerulopathy/GOMMID



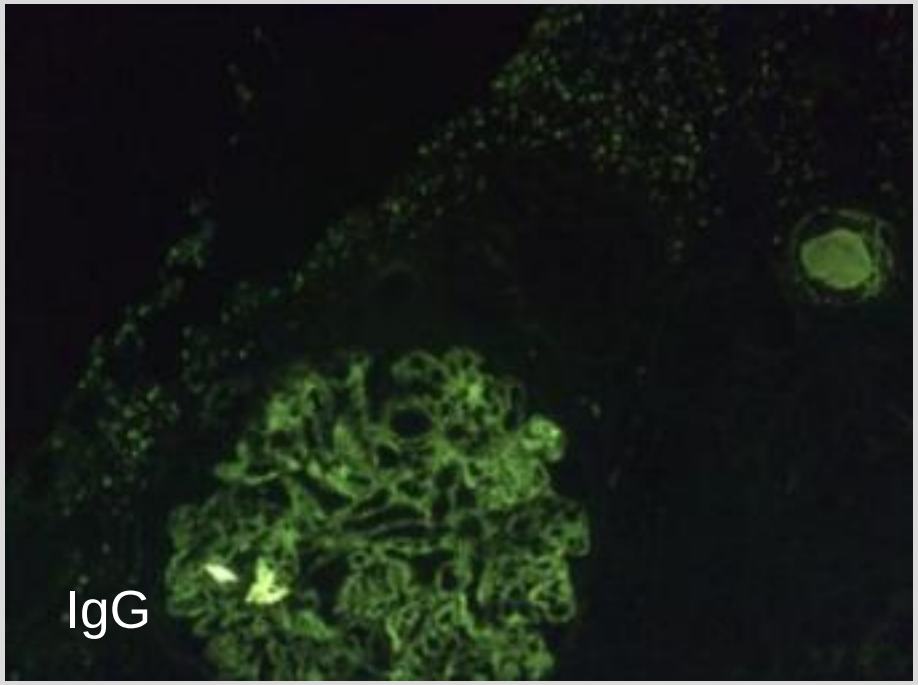
Atypical MGN

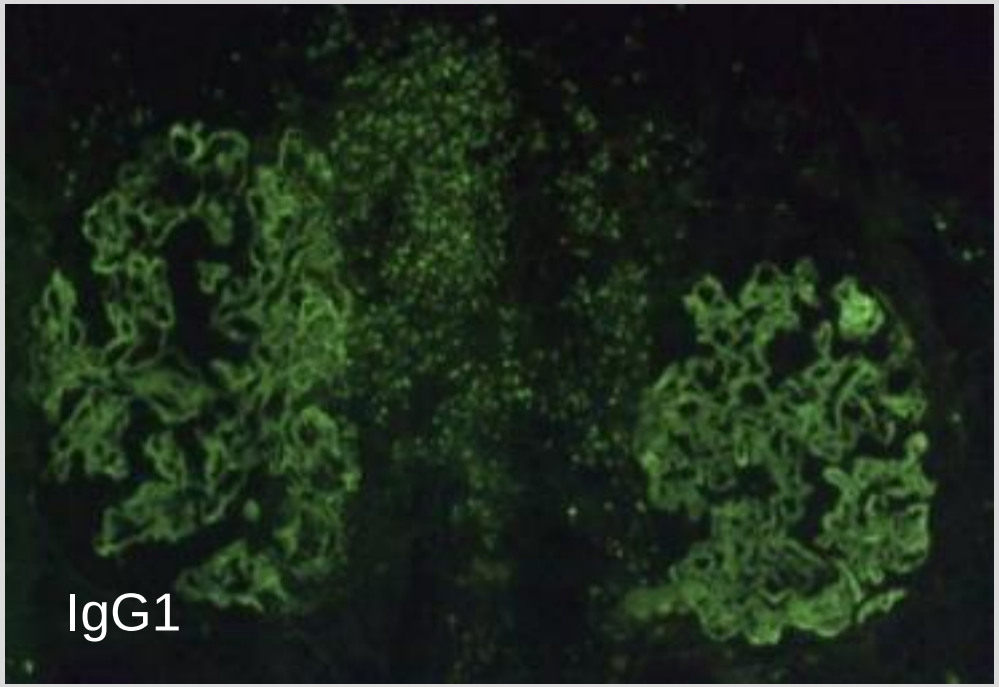


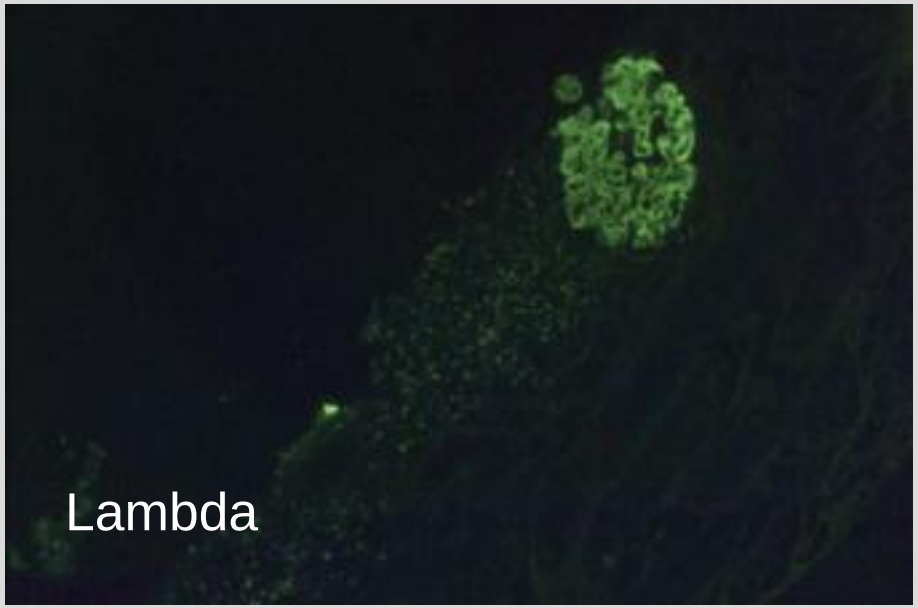
MPGN and malignant B-cell infiltration

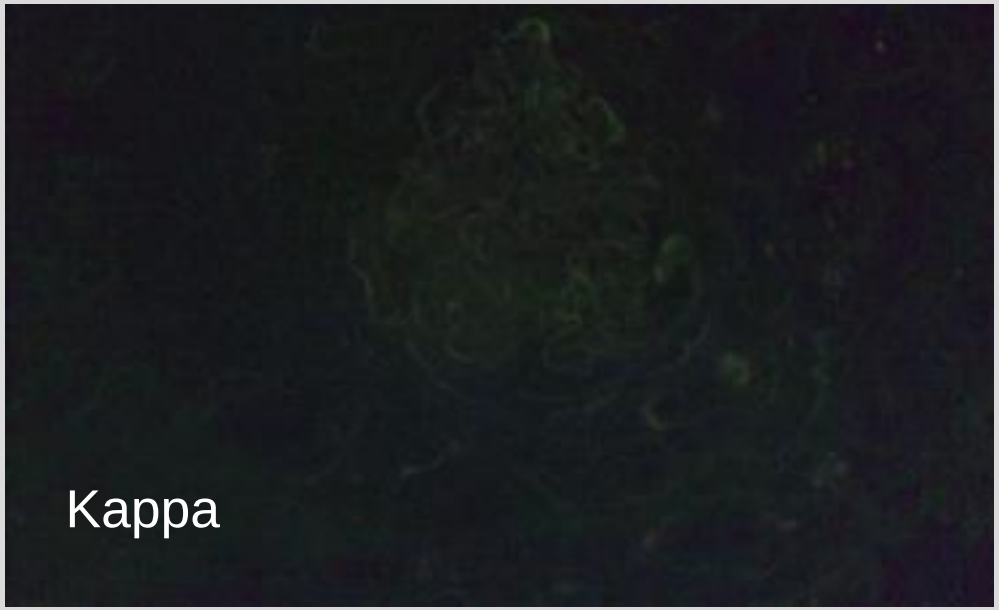
Javaugue V et al. Kidney Int 2021;99:421-30

Immunotactoid glomerulopathy/GOMMID

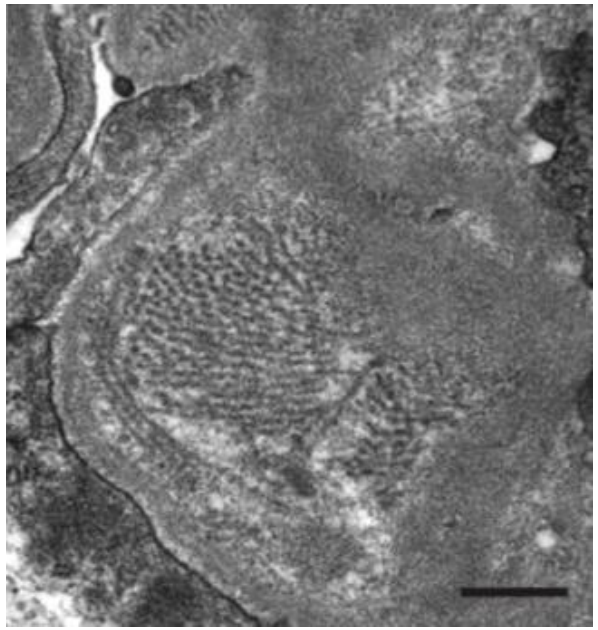


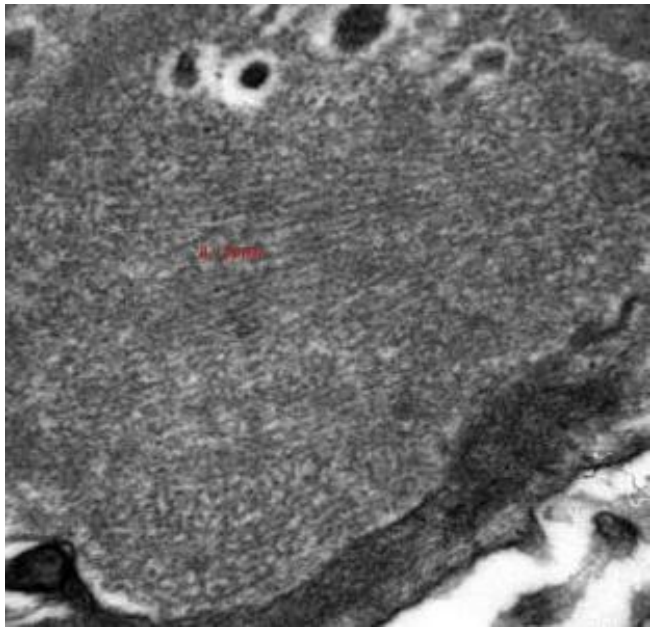


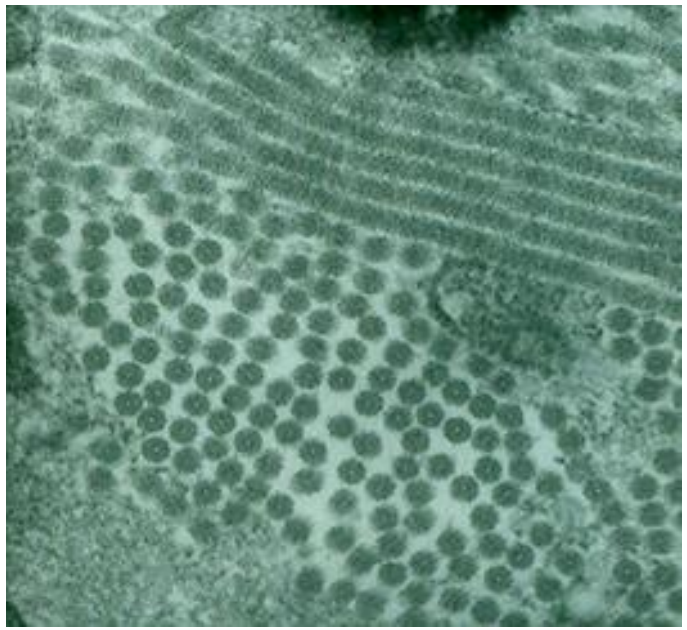




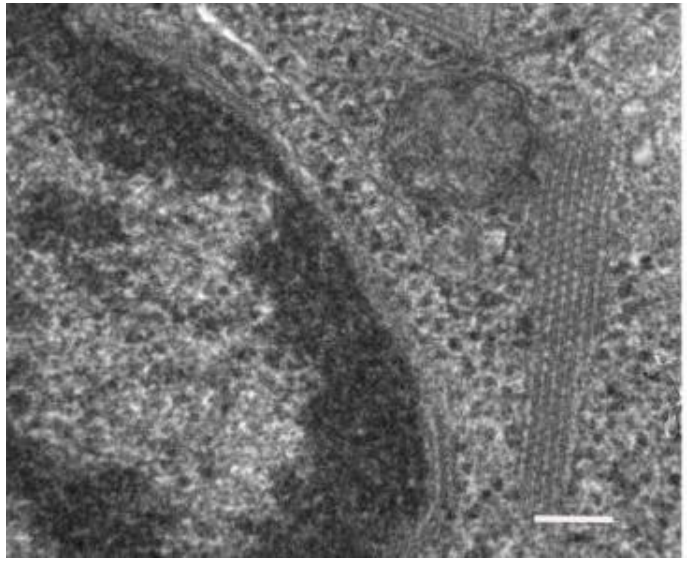
Immunotactoid glomerulopathy/GOMMID

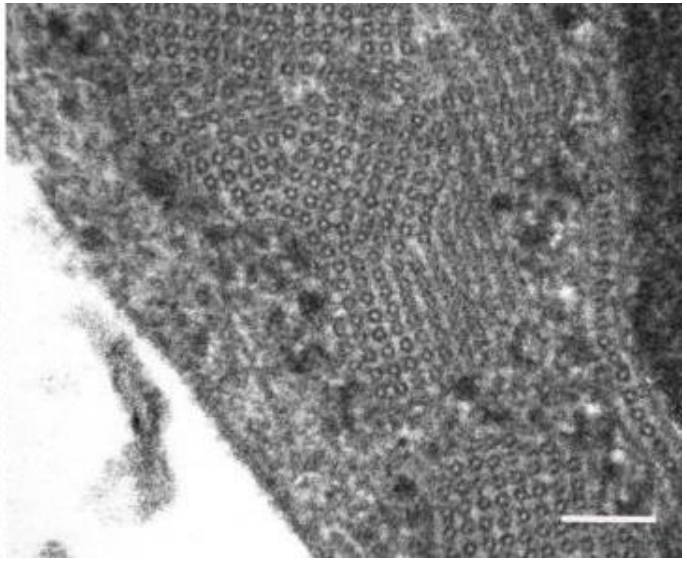






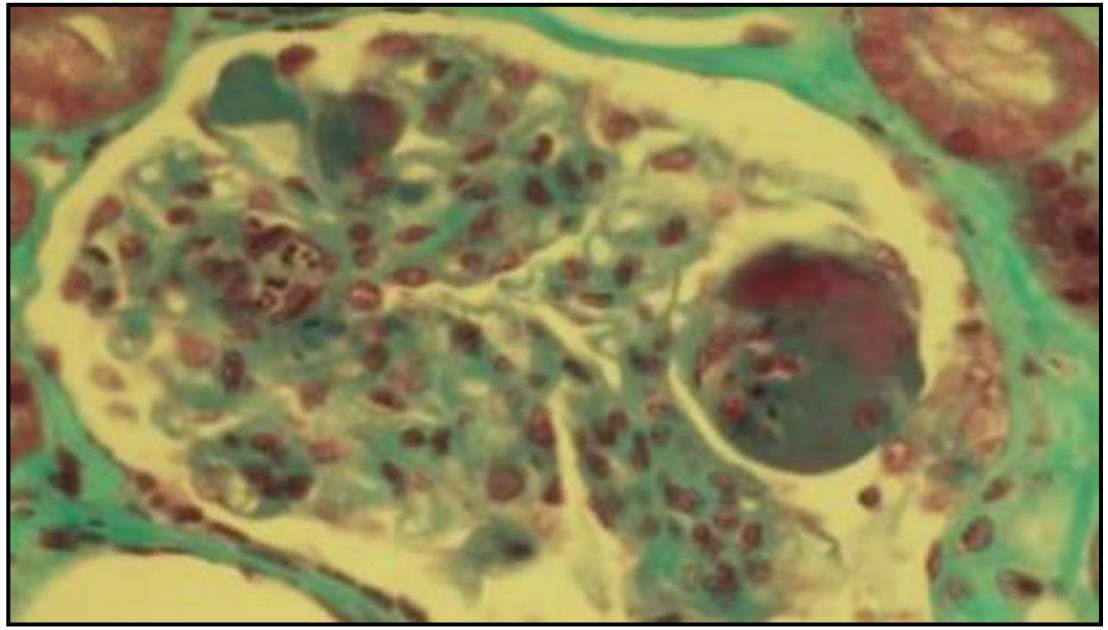
Glomerulus

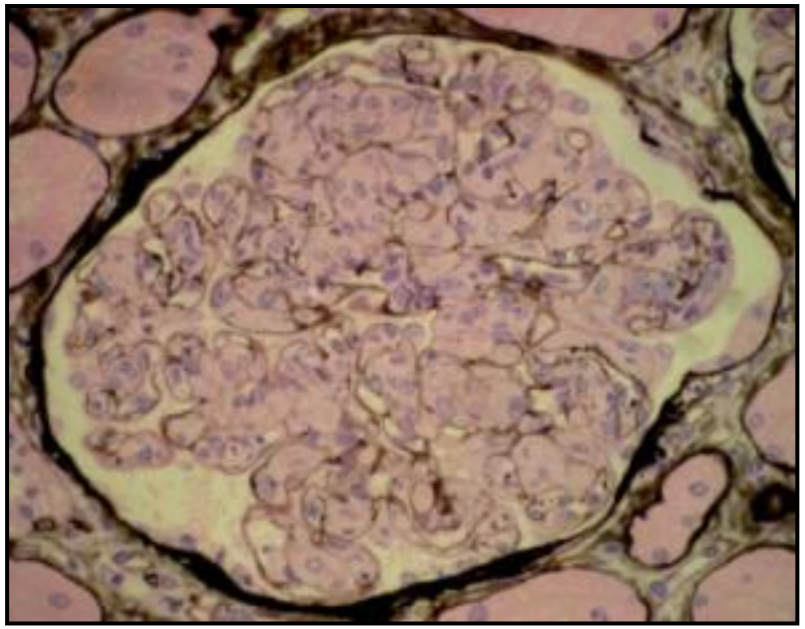


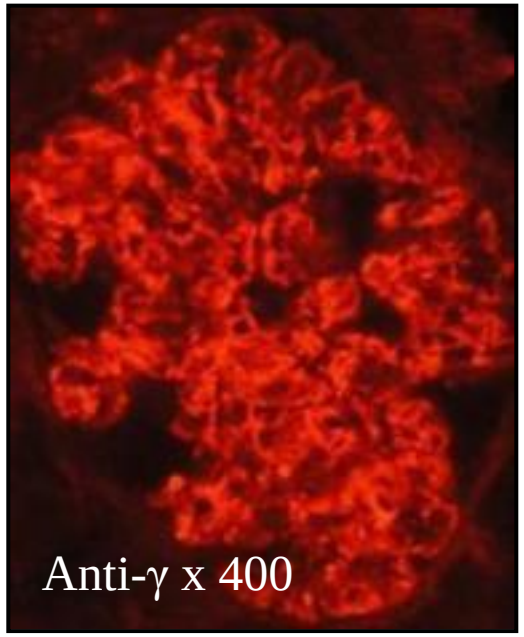


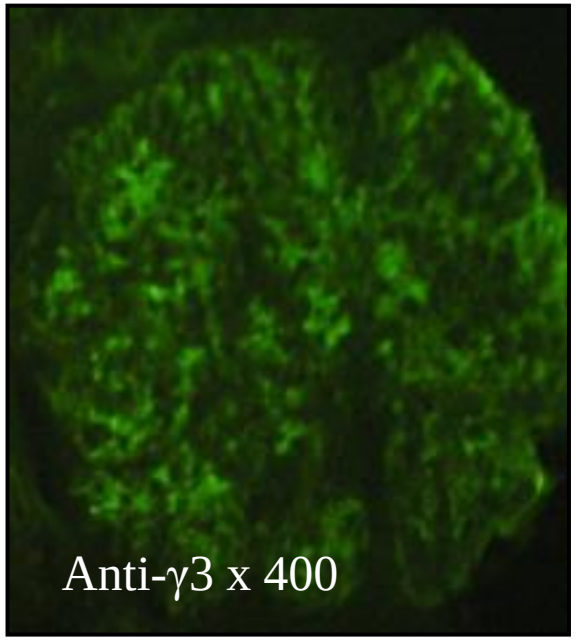
Clonal B-lymphocyte

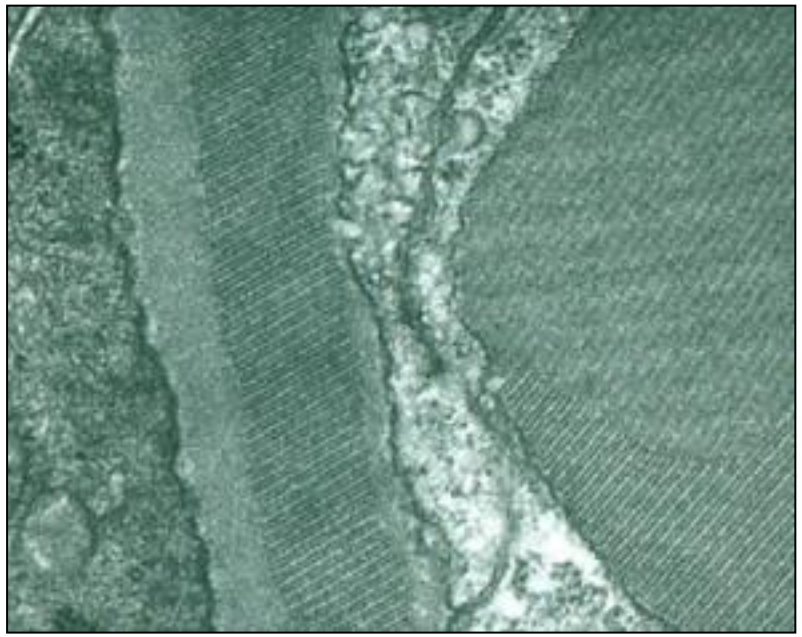
Type 1 cryoglobulinic glomerulonephritis











Type 1 cryoglobulinemia

- **Definitions**:
  - **Type 1: single monoclonal Ig**; type 2: monoclonal Ig (IgM) + polyclonal (IgG); type 3: polyclonal Igs

- **Renal disease in type 1 cryoglobulinemias**:
  - Prevalence: ~ 30%
  - **Chronic glomerular disease**: CKD, proteinuria, hematuria, (50-75%), hypertension +++ (80 %)
  - **Flares:** nephrotic syndrome, acute nephritic syndrome, severe AKI with oliguria

- **Extra-renal manifestations are common:**

  Purpura, skin ulcers, Raynaud phenomenon, polyarthralgias, peripheral neuropathy, Cardiomyopathy, pulmonary hemorrhage,…(type 1 < type 2)

Terrier B et al. Medicine 2013; 62: 61-8
Harel S et al. Br J Hematol 2015; 168(5):671-8

Type 1 cryoglobulinic glomerulonephritis

Immunologic and hematologic characteristics :

- **Hypocomplementemia** (50%), negative rheumatoid factor (≠ type 2 cryo)
- **Cryoglobulinemia**:
  - IgG (predominant if renal disease, mostly IgG3 and IgG1), IgM, IgA, + kappa LC (80%)
  - Inconstantly detected, particularly in crystalcryoglobulinemia
- **Hematological disease**:
  - MGRS (50%)
  - Symptomatic disease (50 %): Waldenström, CLL, lymphoplasmocytic lymphoma, MM (rare)

Treatment :

- High-dose corticosteroids
- Plasma exchanges in severe forms
- Clone targeted chemotherapy: bortezomib- or rituximab-based, HDM/ASCT

Fermand JP, et al. Blood 2013; 122: 3583-90
Harel S, et al. Br J Hematol 2015; 168(5):671-8

Monoclonal immunoglobulin deposition disease (Randall-type)

- **3 different subtypes:**

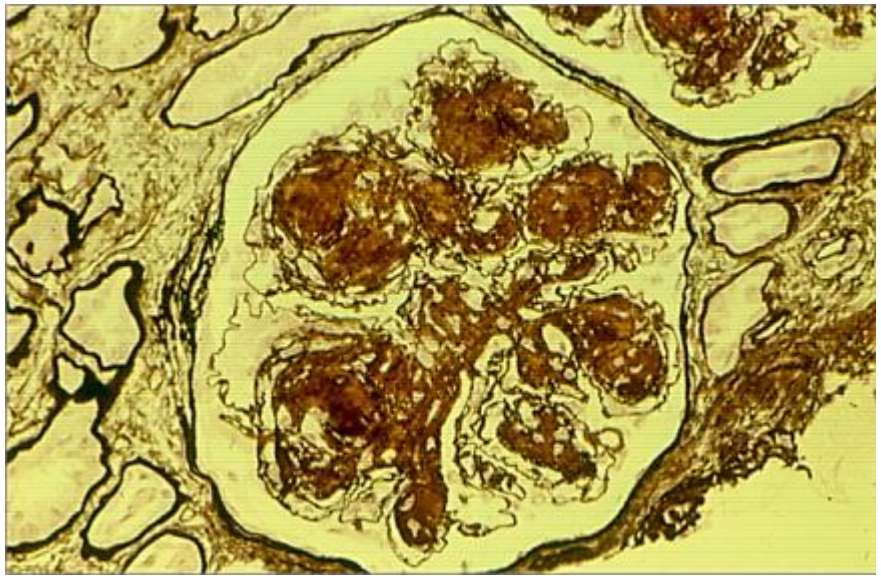
  LCDD (light chain only), **HCDD** (truncated heavy chain only), **LHCDD** (light chain + truncated heavy chain)

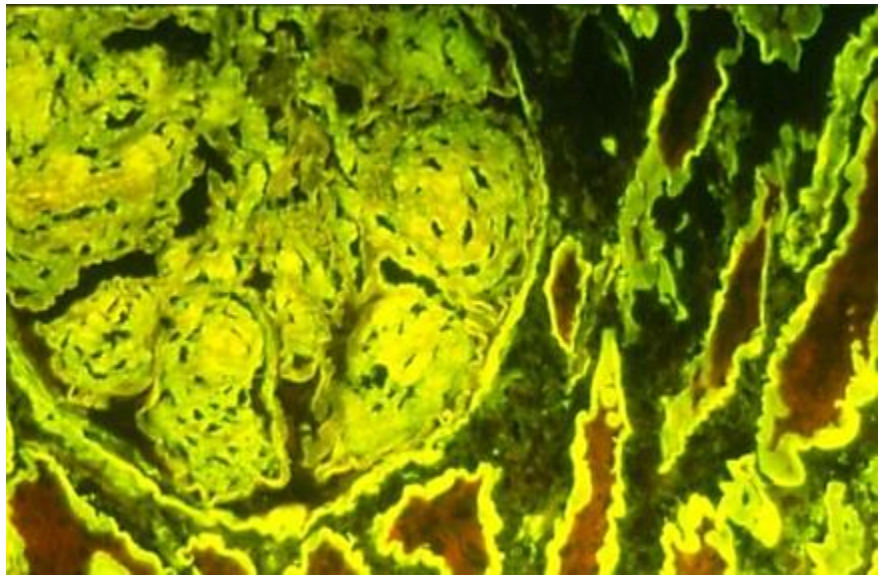
- **Epidemiology**: 0.33% of native kidney biopsies

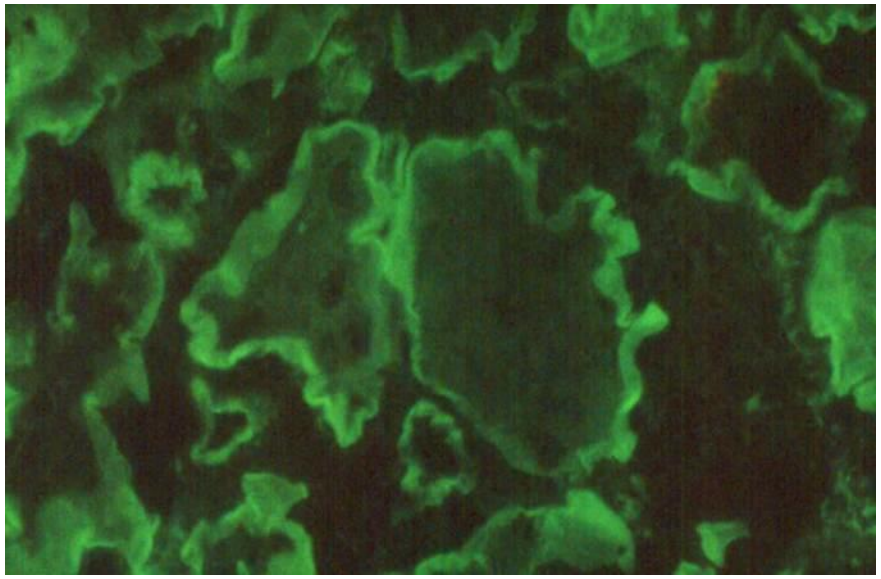
- **Clinical presentation**:
  - Median age: 64 yrs (53-75), slight male predominance
  - **Renal manifestations : ~ constant**
    - Proteinuria (90%) (median 1.8 g/d), nephrotic syndrome: 30-60 %, hematuria: 58 %, hypertension: 55 %
    - Renal insufficiency: 85-100 % (eGFR : 24 ml/min/1.73m^2, CKD≥ stage 4: 45%)
    - Uncommonly (10%): slowly progressive CKD with proteinuria < 0.5g/day
    - AKI: LCDD with concomitant myeloma cast nephropathy

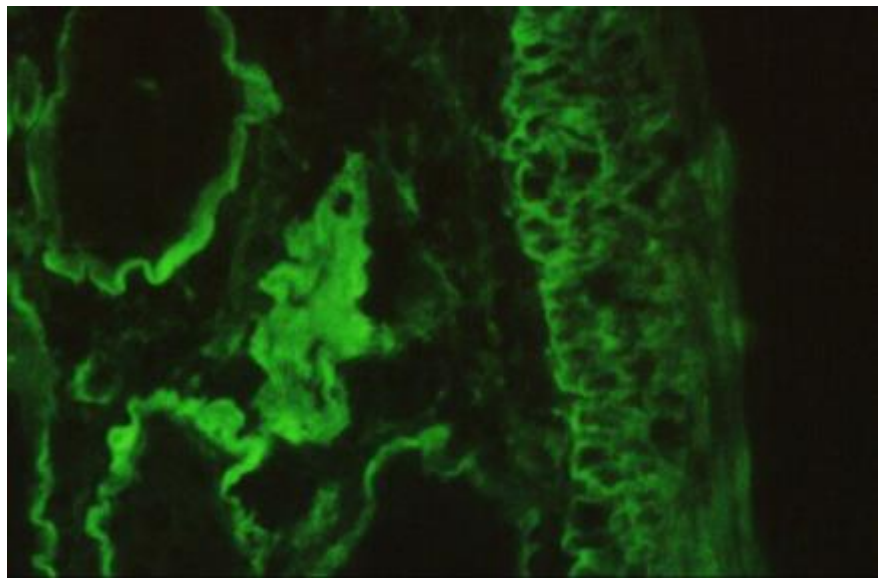
Nasr SH etal. Clin J Am Soc Nephrol 2012; 7: 231-9
Joly F et al. Blood 2019; 133: 576-87

Randall-type MIDD: renal pathology

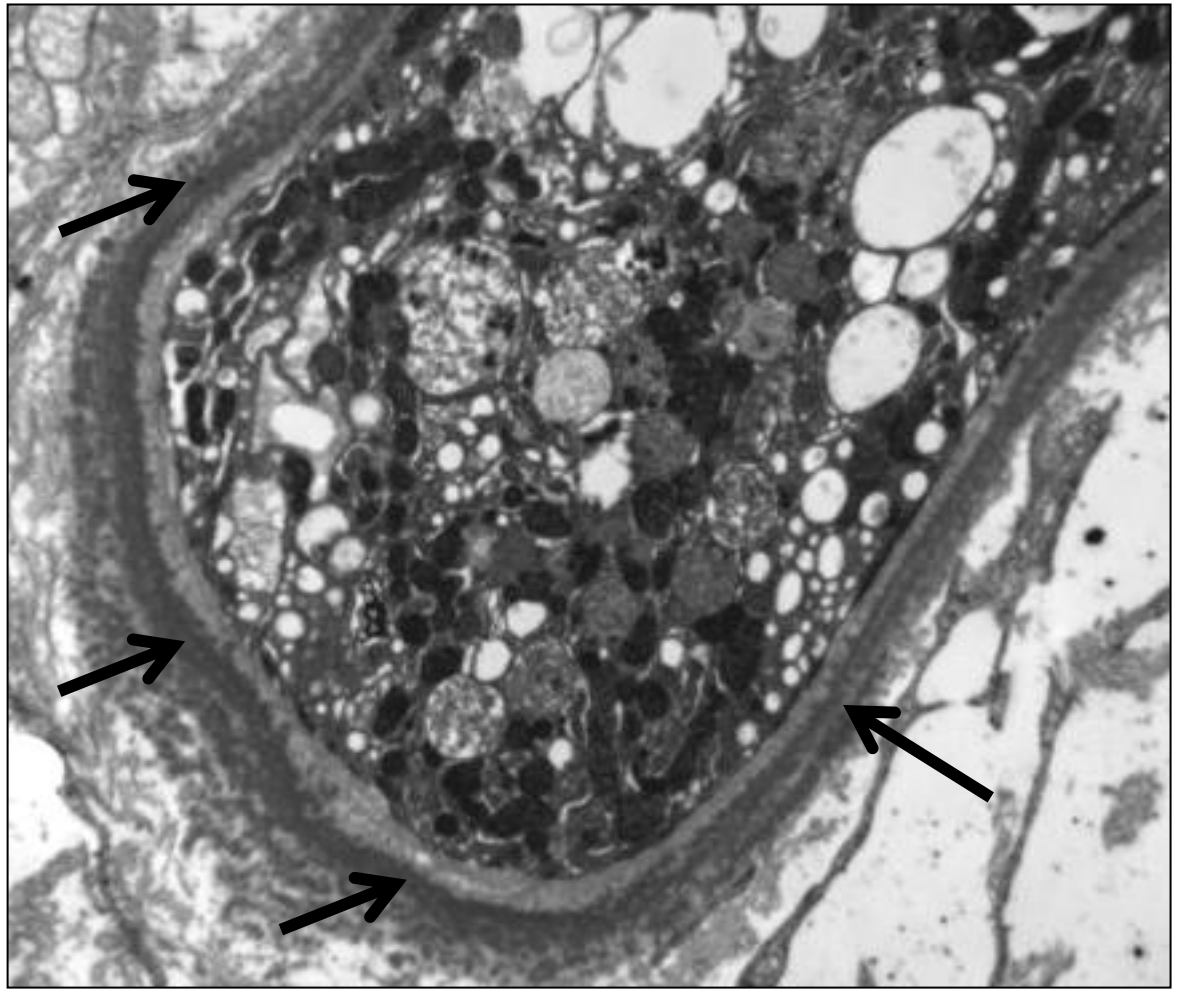


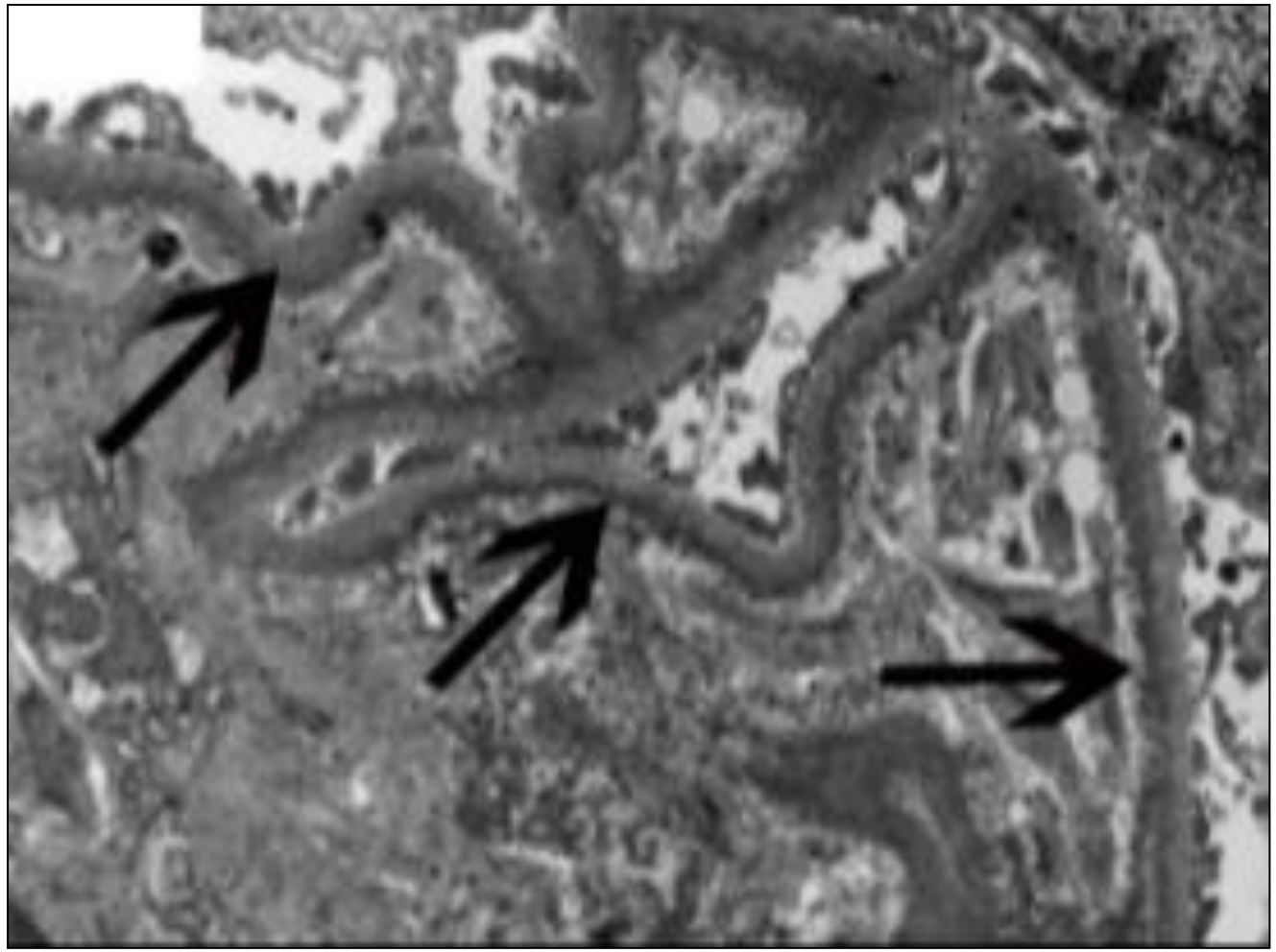






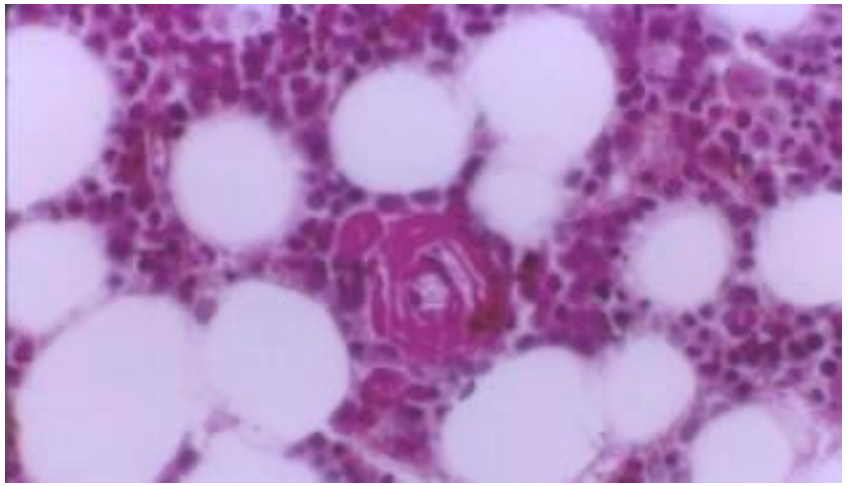
Randall-type MIDD: renal pathology





Joly F et al. Blood 2019; 133: 576-87

MIDD : extra-renal manifestations



- **MIDD = systemic disease**
  - At least 1 extra-renal involvement at diagnosis : 35%
  - Mostly in LCDD
  - Most common manifestations:
    - ➢Liver (17%) : hepatomegaly + cholestasis
    - ➢Heart (12%) : hypertrophic cardiomyopathy, diastolic dysfunction, raised Nt-proBNP and troponin levels
  - Other localizations: peripheral nerve, bone marrow, lung, thyroid, salivary glands, gastrointestinal tract, skin, spleen, pancreas, choroid plexus, cerebral arteries ….
  - Usually less symptomatic than in AL amyloidosis
  - May affect overall prognosis (heart disease)

Mohan M et al. Am J Hematol 2017; 92:739-45
Joly F et al. Blood 2019; 133: 576-87

MIDD : hematological characteristics

- Bone marrow plasma cell infiltration > 5 % : 50-95 %
- MGRS (60-65%), multiple myeloma (30-40 %), Waldenström/CLL (3-4%)
- Detectable serum and/or urine monoclonal gammopathy : 80-90%
- **Abnormal FLC level and ratio: ~ 100%**

- **LCDD :** **kappa LC** (80%), over-representation of the **Vκ4** subgroup
- **HCDD :** deposited and circulating truncated heavy chain
  (γ in most cases, uncommonly α and δ)
  CH1 deletion : 100%
  Complement activation (classical pathway) in γ1 and γ3 HCDD : low CH50, C3, C4

Nasr SH, et al. Clin J Am Soc Nephrol 2012; 7: 231-9
Bridoux F, et al Kidney Int 2017;91:423-34
Joly F, et al. Blood 2019; 133: 576-87

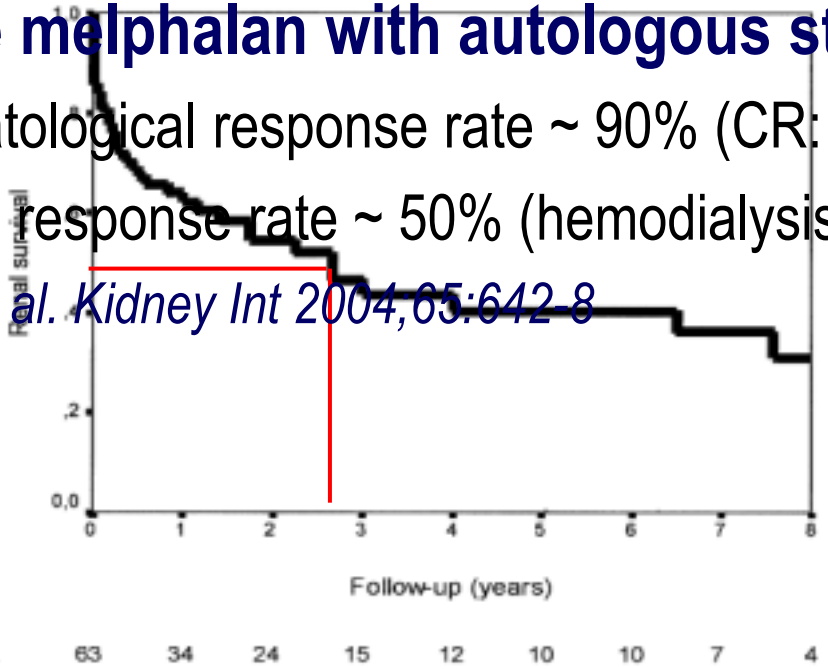
MIDD : treatment and outcomes

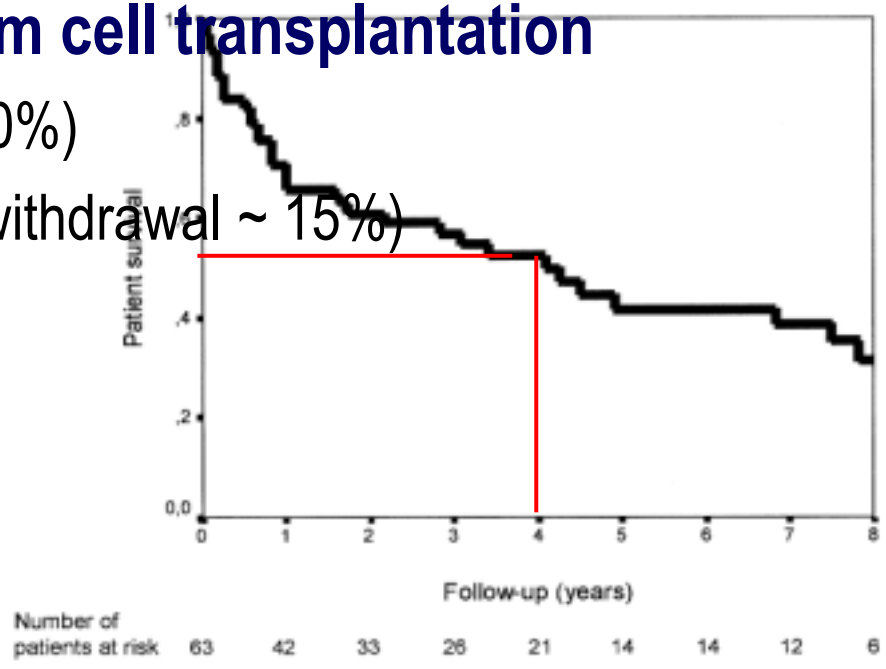
- **Conventional chemotherapy before novel-anti myeloma agents** (MP, VAD, VAMP)
  - ✓ Median renal survival ~ 2 yrs
  - ✓ Median overall survival~ 4 yrs

  Lin J, et al . J Am Soc Nephrol 2001;12:1482-92 *Pozzi C, et al. Am J Kidney Dis 2003;42:1154-63*

- **High-dose melphalan with autologous stem cell transplantation**
  - ✓ Hematological response rate ~ 90% (CR: 70%)
  - ✓ Renal response rate ~ 50% (hemodialysis withdrawal ~ 15%)

  Royer B, et al. Kidney Int 2004;65:642-8





MIDD : the impact of novel agents and FLC monitoring

- **Data from the French reference centre:**

49 patients (LCDD n= 35, L/HCDD n= 14)

Baseline S.Creat. 190 µmol/L, proteinuria : 1.5 g/d, hemodialysis at diagnostic : n= 8 (17%)
MGRS 62%, symptomatic MM 20%, abnormal FLCs : 100%

Bortezomib-based regimens (n=49):

BD (n=25), CyBorD (n=18), B+Imid (n=5)
First line : 77%, median number of cycles : 4.5

Hematological response rate (≥ PR): 82% (≥VGPR: 65%)
Renal response rate : 53% (final S. Creat 166 µmol/l, proteinuria 0.2g/d)
Renal and overall survival ~ 90% (median follow-up 54 months)

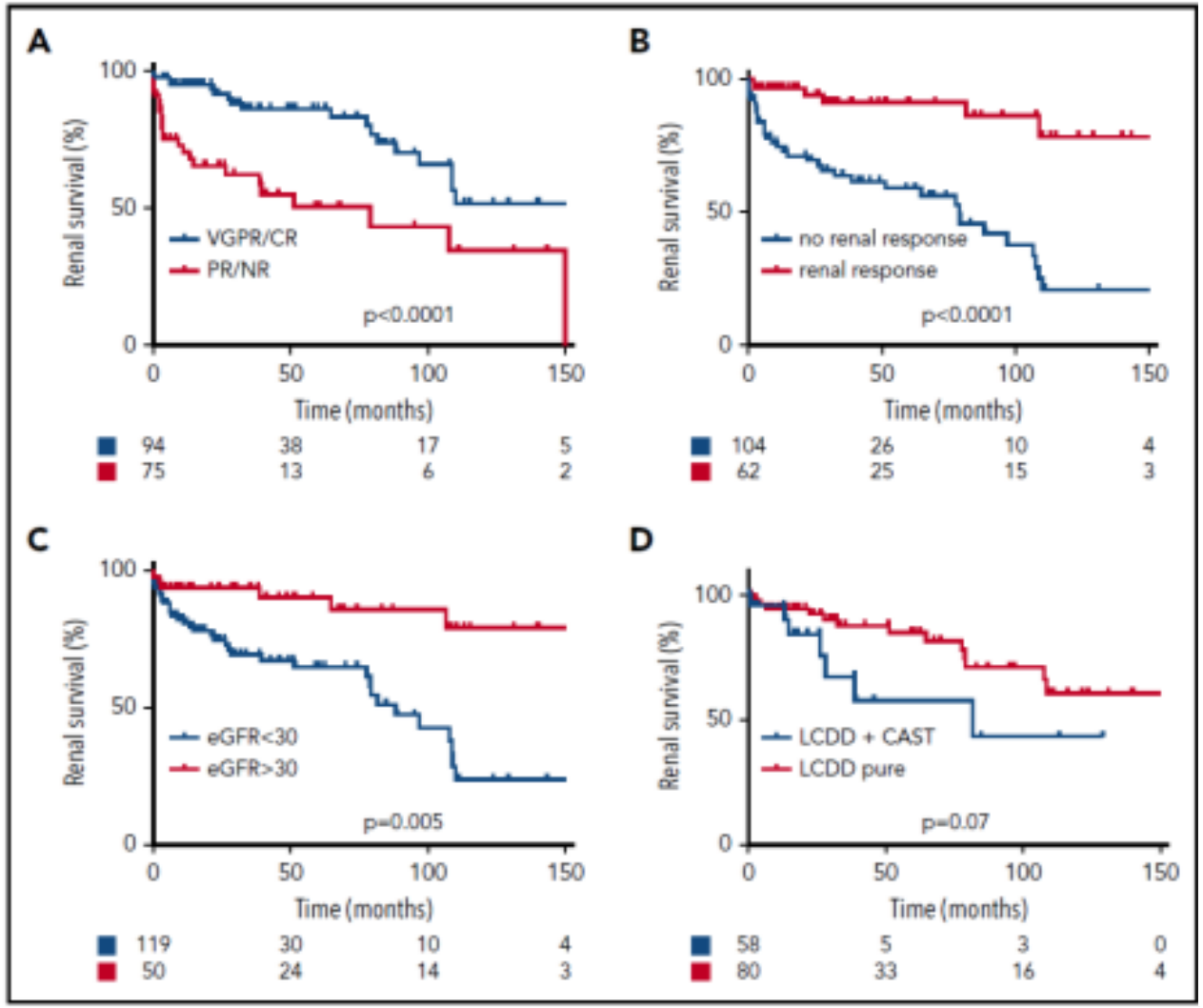
Predictors of renal response :

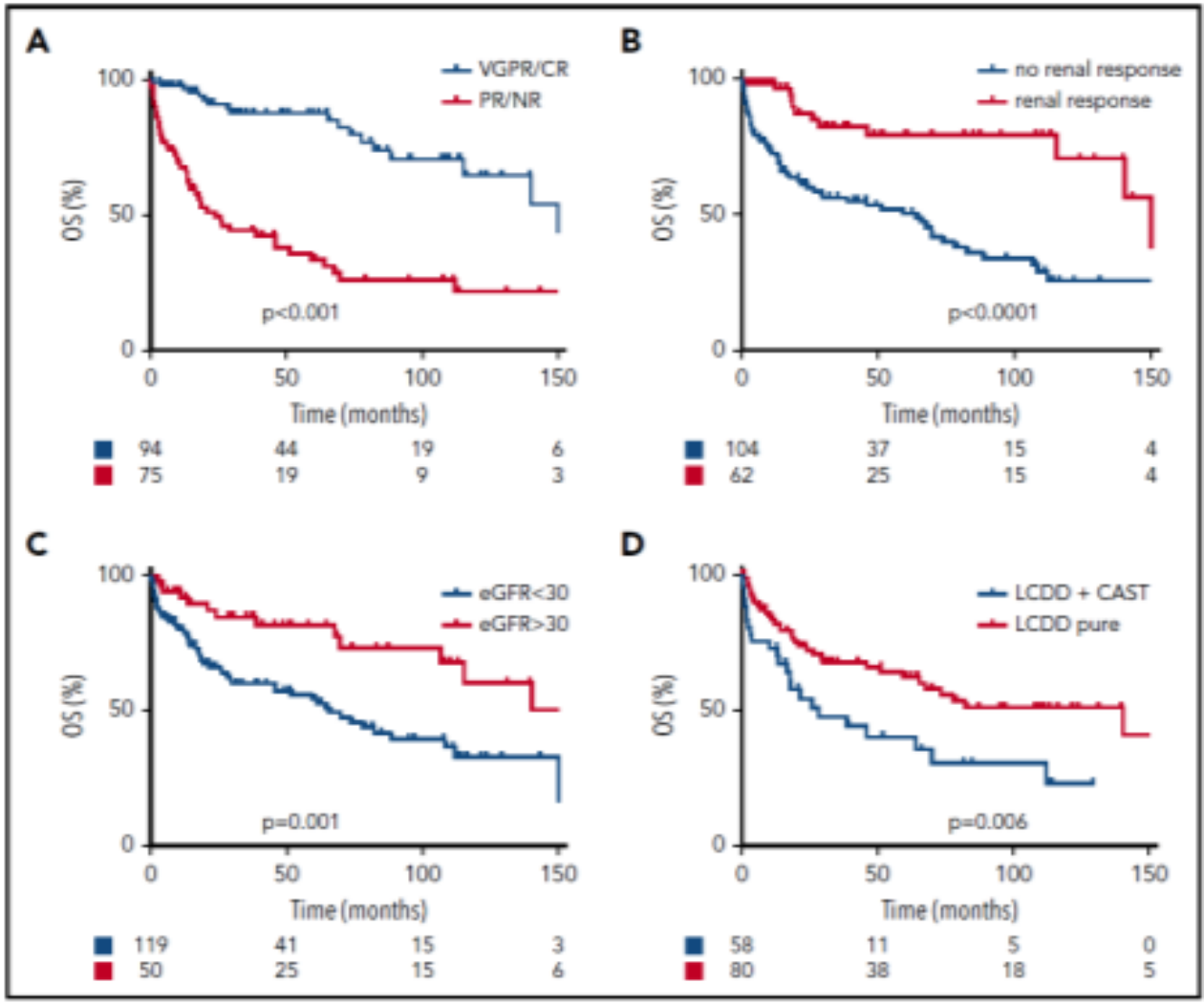
Univariate analysis : pre-treatment eGFR >30mL/min/1.73m^2, post treatment dFLC <40 mg/L
Multivariate analysis: post treatment dFLC <40 mg/L

Cohen C, et al. Kidney Int 2015; 88:1135-43

MIDD : factors associated with renal and patient survival

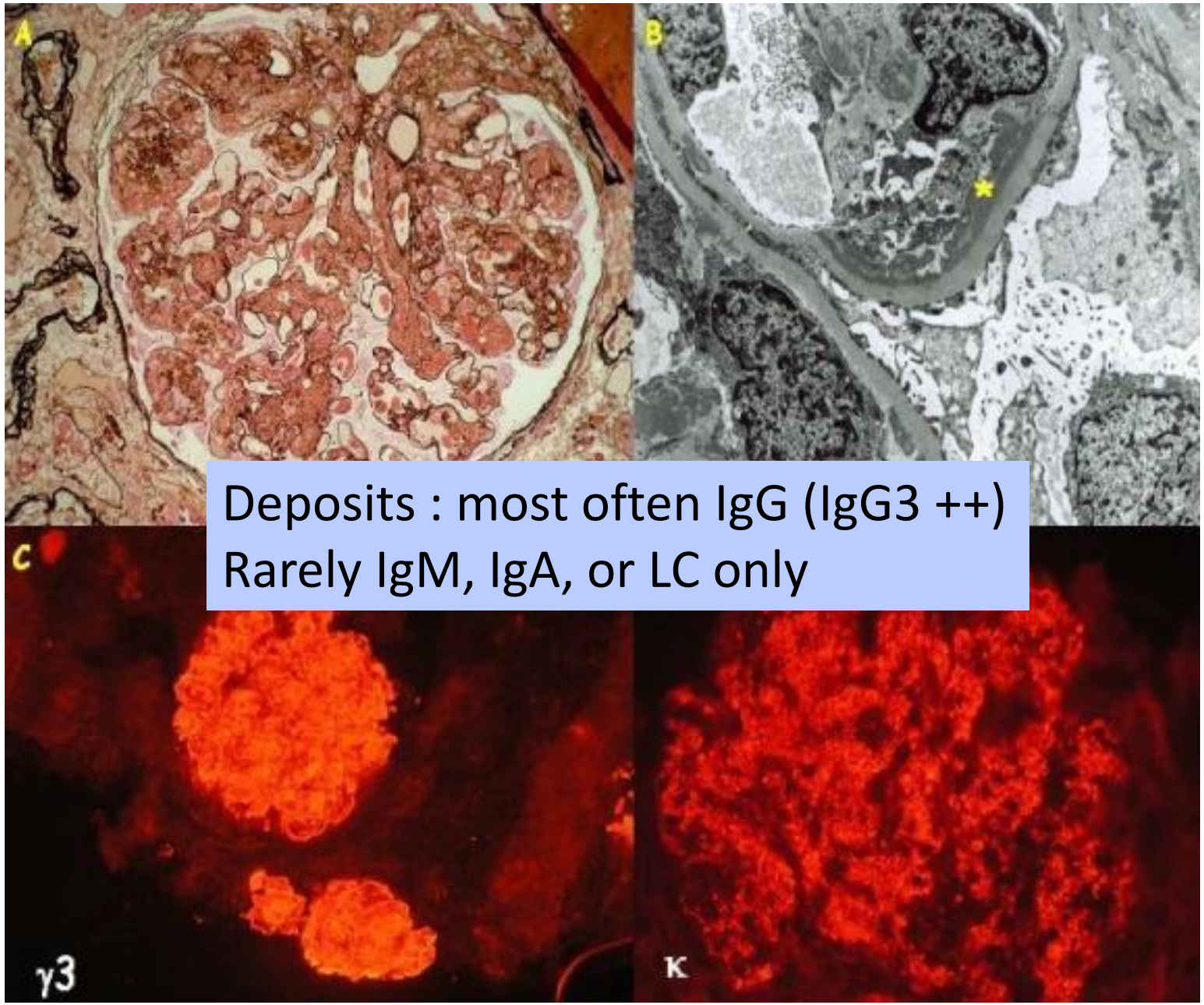
- The French series: 166 treated MIDD patients: LCDD (n=137), HCDD (n=18), LHCDD (n=11)





Joly F, et al. Blood 2019; 133: 576-87

Proliferative GN with monoclonal Ig deposits (PGNMID)



Deposits : most often IgG (IgG3 ++)
Rarely IgM, IgA, or LC only

Proliferative GN with monoclonal Ig deposits (PGNMID)

- Biopsy incidence 0.17% to 3.7% (3rd type of MGRS in frequency)
- Age at diagnosis: ~ 55 yrs, but may affect young adults (IgG3)
- Renal presentation :
  - Renal insufficiency 65%, (median eGFR 36 mL/min/1.73 m^2), <10% require dialysis
  - Proteinuria >1g/24h :100%, nephrotic syndrome: > 50%
  - Microscopic hematuria : 75%, hypertension : > 50%
  - Acute nephritic syndrome rare
  - Frequent and rapid relapse on the renal allograft

- **Absence of extra–renal manifestations**

Nasr SH, et al. J Am Soc Nephrol 2009; 20: 2055-64
Nasr SH, et al. Kideny Int 2020; 97: 589-601

Proliferative GN with monoclonal Ig deposits (PGNMID)

- **Hematologic characteristics**
  - Detectable bone marrow clonal population : **< 10%**
  - Detectable monoclonal gammopathy (immunofixation + FLCs): **30%** (60% with immunoblot)
  - Clonal detection rate: particularly low in PGNMID with IgG3 deposits
  - Hypocomplementemia : **10-25%**

- **Treatment**
  - If the clone is identified : anti-plasma cell agents (50%) or rituximab-based (50%)
  - If not identified : empirical regimens (bortezomib- or rituximab-based)
  - Improved renal prognosis after clone-targeted or empirical regimens *vs* symptomatic treatment

Nasr SH, et al. J Am Soc Nephrol 2009; 20: 2055
Gumber R, et al. Kidney Int 2018; 94:199-205
Bridoux F, et al. Nephrol Dial Transplant 2021;36:208-15

Question 2:

Regarding PGNMID, which of following proposals is false:

1. Glomerular monotypic Ig deposits are non-organized
2. PGNMID usually features linear Ig deposits along TBM
3. The rate of clonal B-cell detection is low
4. IgG3 is the most common involved isotype
5. PGNMID frequently recurrs on the renal allograft

Question 2:

Regarding PGNMID, which of following proposals is false:

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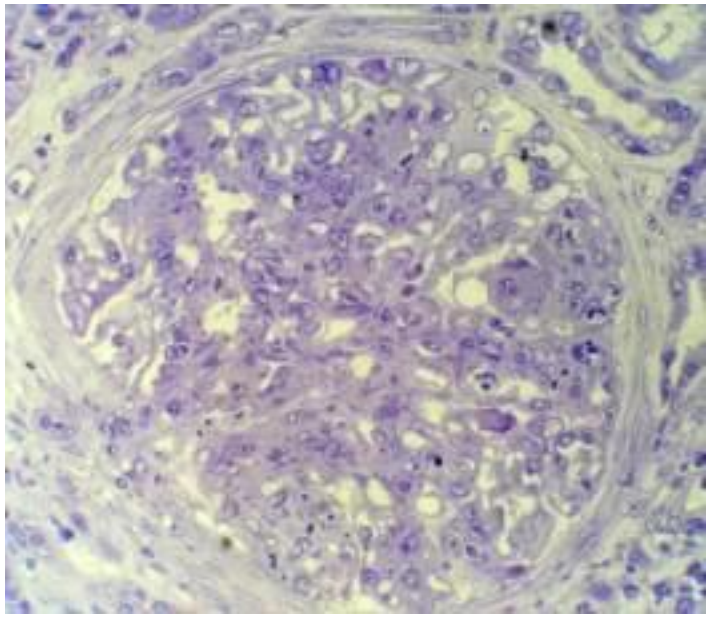
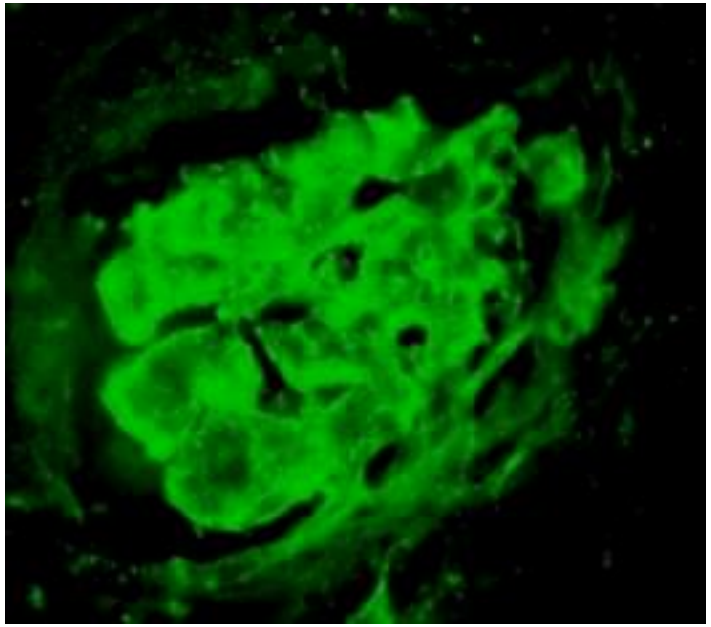
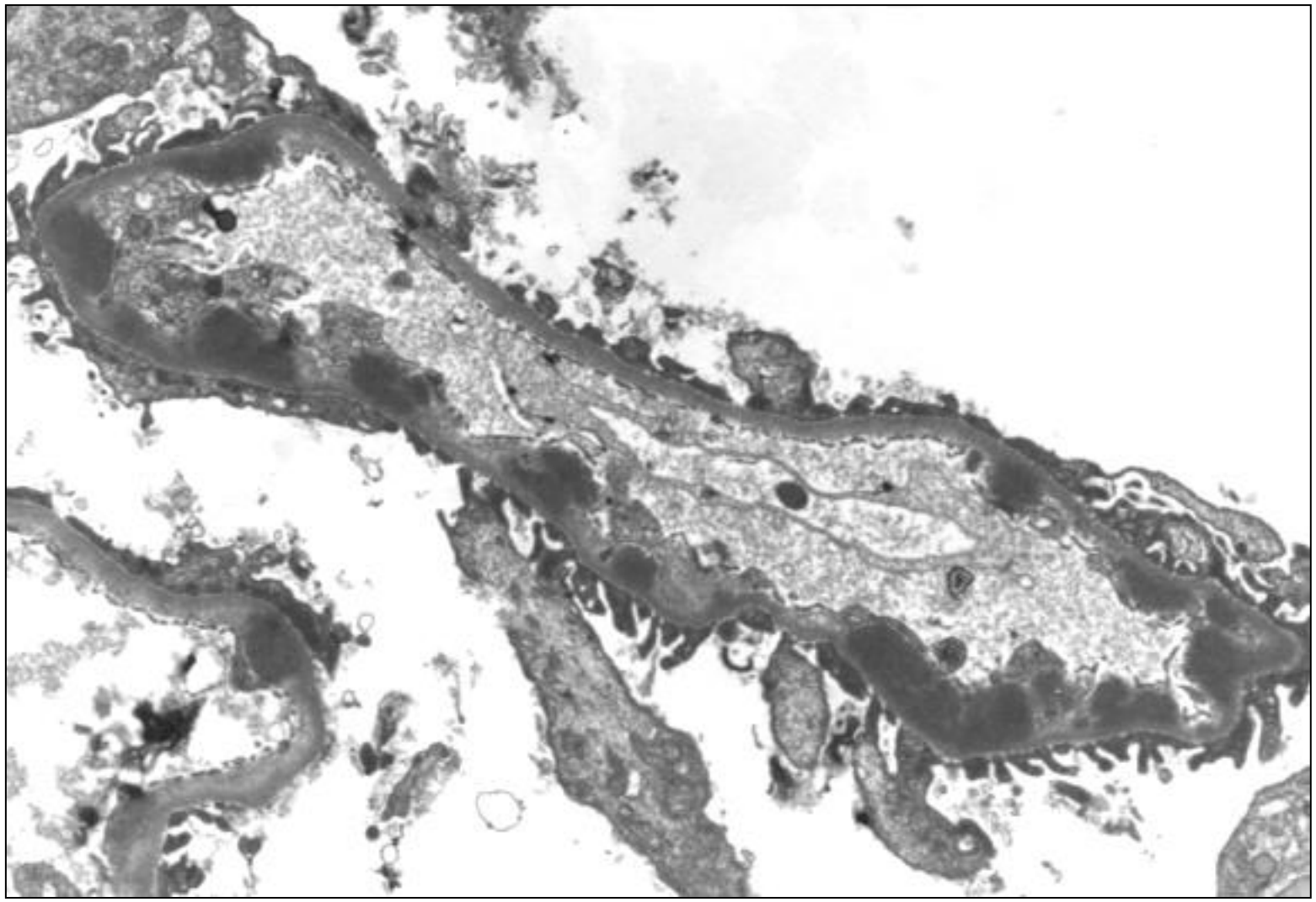
C3 glomerulonephritis and monoclonal gammopathy







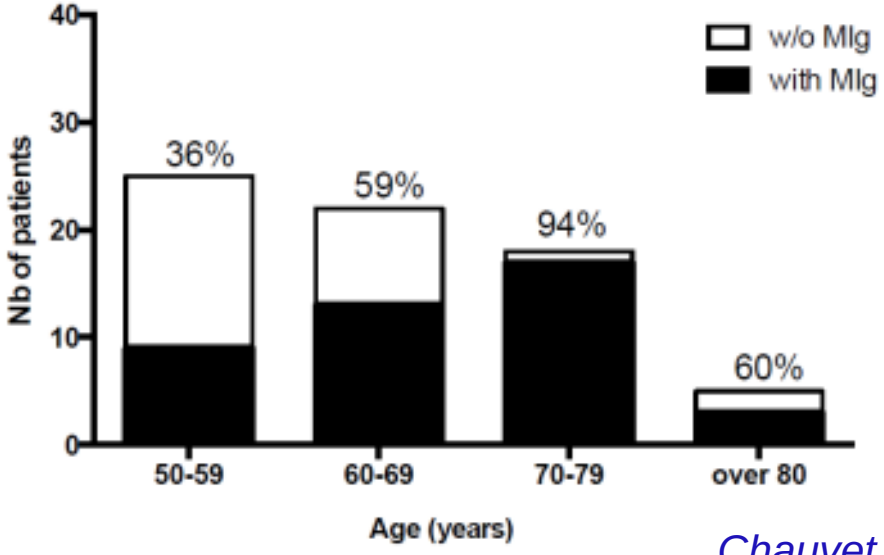
Sethi S, et al. Am J Kidney Dis 2010;56:977-82.
Bridoux F, et al. Clin J Am Soc Nephrol 2011; 6: 2165-74

C3 glomerulopathy and monoclonal gammopathy

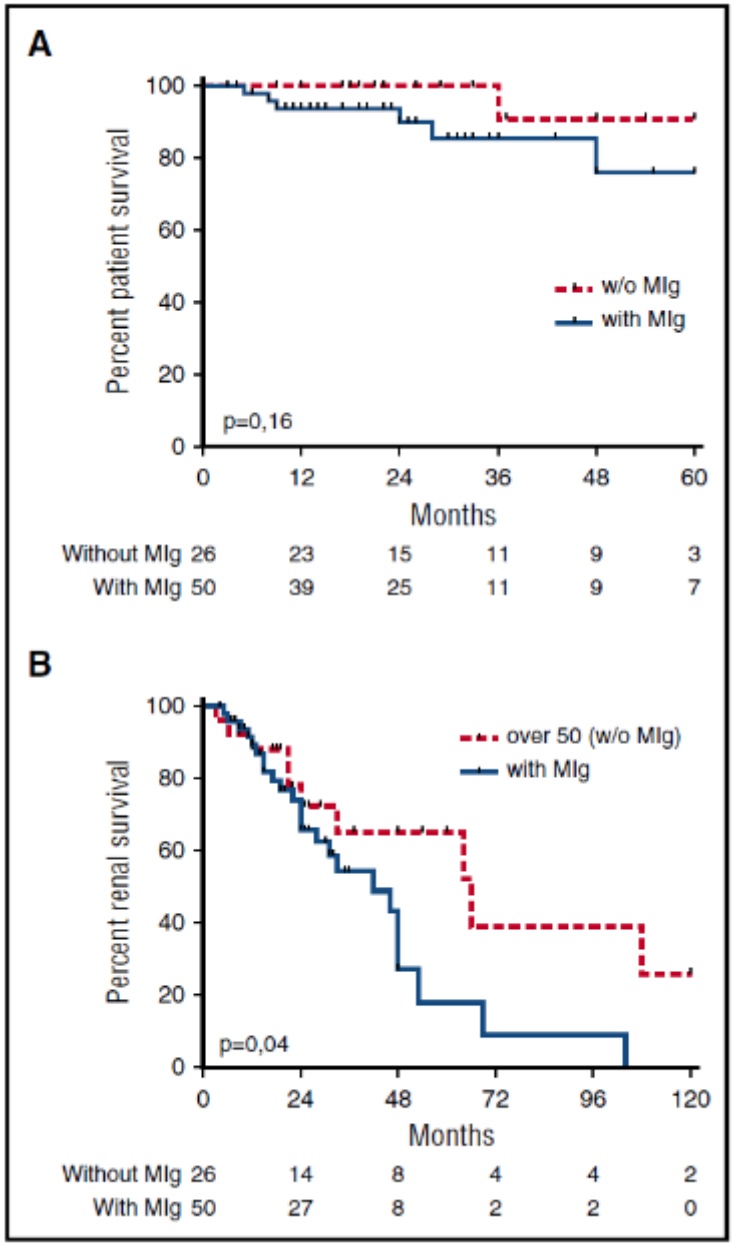
- **Conditions associated with C3GP vary with age :**

  < 50 yrs : C3Nef, C5Nef or anti-factor H autoantibodies
  Mutations in Factor H, Factor I, C3

  > 50yrs : Low prevalence of autoantibodies and mutations
  Monoclonal gammopathy is common
  Higher severity of renal disease and poor outcomes



Chauvet S, et al. Blood 2017; 129:1437-47
Ravindran A, et al. Kidney Int 2018; 94:178-86



C3G and monoclonal gammopathy : clinical presentation

At diagnosis	French series (n=50)	Mayo series (n=36)
Age (yrs)	65 (38-82)	60 (20-85)
Male (%)	33 (66%)	25 (69%)
Serum creatinine (mg/dl)	1.8 (0.8-11.2)	1.9 (0.8-14.7)
eGFR (ml/min/1.73m^2)	37 (3-100)	39.5 (3-60)
CKD stage 4-5 (%)	27 (55%)	11 (31%)
Nephrotic syndrome (%)	20 (43%)	Serum albumin 3.3 g/dl (2.4-4.6)
Proteinuria (g/24h)	3.15 (0.1-1.4)	3.0 (0.2-15.0)
Hematuria (%)	33/39 (84%)	32 (89%)
Extra-renal symptoms* (%)	5 (10%)	NA
Biologic markers of TMA (%)	3 (6%)	NA

*Digital ischemia (n=2), purpura (n=1), diffuse mucinosis (n=1), capillary leak syndrome (n=1)

Chauvet S, et al. Blood 2017; 129:1437-47
Ravindran A, et al. Kidney Int 2018; 94:178-86

C3G and monoclonal gammopathy : hematologic data

At diagnosis	French series (n=50)	Mayo series (n=36)
Serum monoclonal Ig		
IgG	47 (93%) **[IgGκ 71%]**	31 (89%) **[IgGκ 64%]**
IgA	2 (4%)	1 (3%)
IgM	0	3 (9%)
LC only	1 (2%)	1 (3%)
M-spike (g/l)	10.2 (2-38)	NA
Abnormal FLC (%)	20 (43%)	NA
dFLC (mg/l)	79 (2-20.800)	NA
Hematological diagnosis		
MGRS (%)	45 (**90%**) [SMM 30%]	28 (**78%**) [SMM 6%]
Symptomatic MM (%)	2 (4%)	2 (6%)
CLL (%)	3 (6%)	1 (3%)

Chauvet S, et al. Blood 2017; 129:1437-47
Ravindran A, et al. Kidney Int 2018; 94:178-86

C3 glomerulopathy and monoclonal gammopathy

- Complement abnormalities:
  - **Low serum C3 ± factor B: 44%** (C3 convertase activation)
  - C4, CFH, CFI, MCP = normal levels
  - **High sC5b-9 level: 78%** (C5 convertase activation)
  - Pathogenic variants: 7%

  - **Anticomplement autoantibodies: 49%**

    C3NeF: 7%
    anti-factor H: 17%
    anti-CR1: 27%
    anti-factor I: 5%
    Matched the serum Mlg in 23%
    Polyclonal in 77%

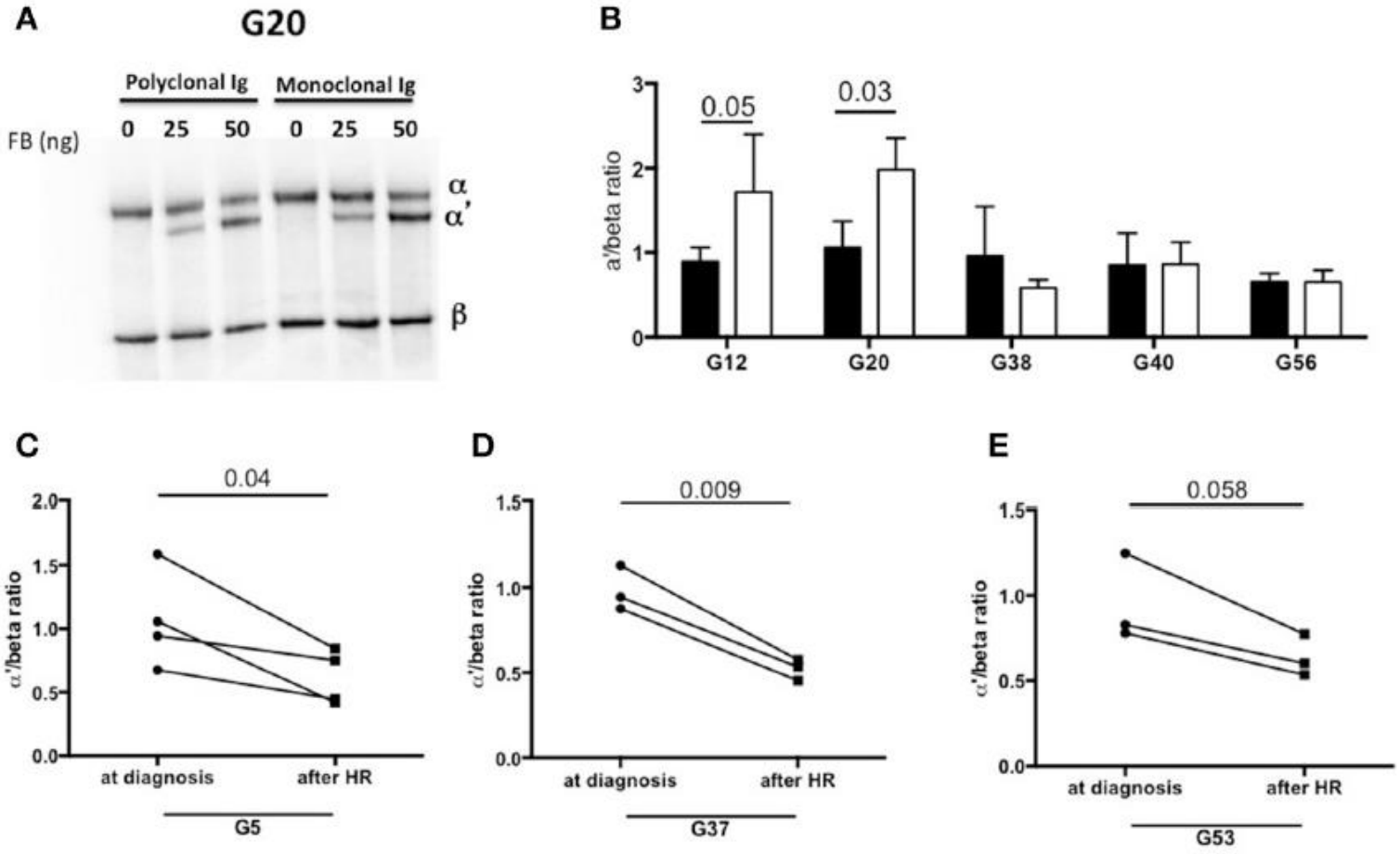
Chauvet S, et al. Front Immunol. 2018;9:2260

TABLE 1 | Comparison of immunological findings in 41 Mlg-C3G patients and 107 C3GN adults patients without Mlg.

	Mlg-C3G *N* = 41	Adults C3GN *N* = 107	*p*-value
IMMUNOLOGICAL FINDINGS			
C3 (mg/L)	703 (78-1220)	781 (67-1760)	0.86
Low C3 level, n(%)	18 (44%)	56 (40%)	0.71
C4 (mg/L)	250 (104-575)*	252 (94-751)*	1
sC5b-9 (ng/mL)	848 (164-2880)	478 (94-2582)	0.005
Elevated sC5b9 (upper 420ng/mL)	29/37 (78%)	47/76 (62%)	0.09
Elevated sC5b-9 (upper twice the normal)	15/37 (41%)	13/76 (17%)	0.01
C3NeF, n(%)	3 (7%)	44/98 (45%)	0.0001
C5NeF, n(%)	0/12 (0%)	11/21(52%)	0.002
Anti-FH Abs, n(%)	9 (17%)	10/91 (11%)	0.09
Anti-FI Abs, n(%)	2 (5%)	NA	-
Anti-CR1 Abs, n(%)	11 (27%)	3/84 (4%)	0.0001
GENETIC ANALYSIS			
Pathogenic variants	2/28(7%)	27/99 (27%)**	0.02

** C4 level was normal in all patients*

C3 glomerulopathy and monoclonal gammopathy



Purified monoclonal Ig

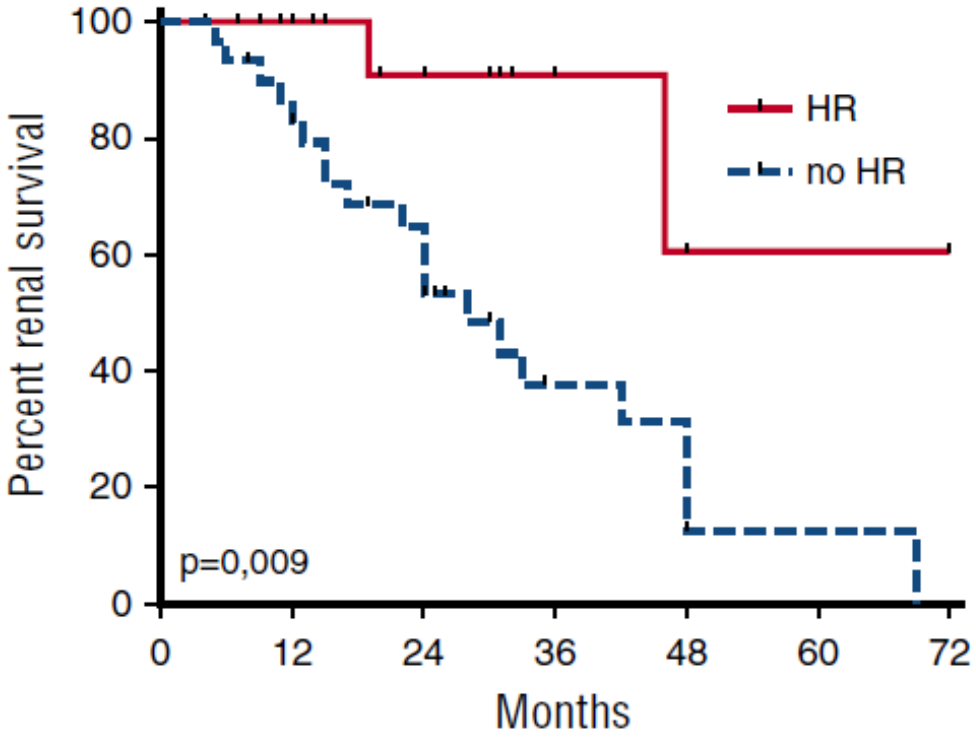
Polyclonal Igs from same patient

Most of the C3 convertase activity is borne by the MIg

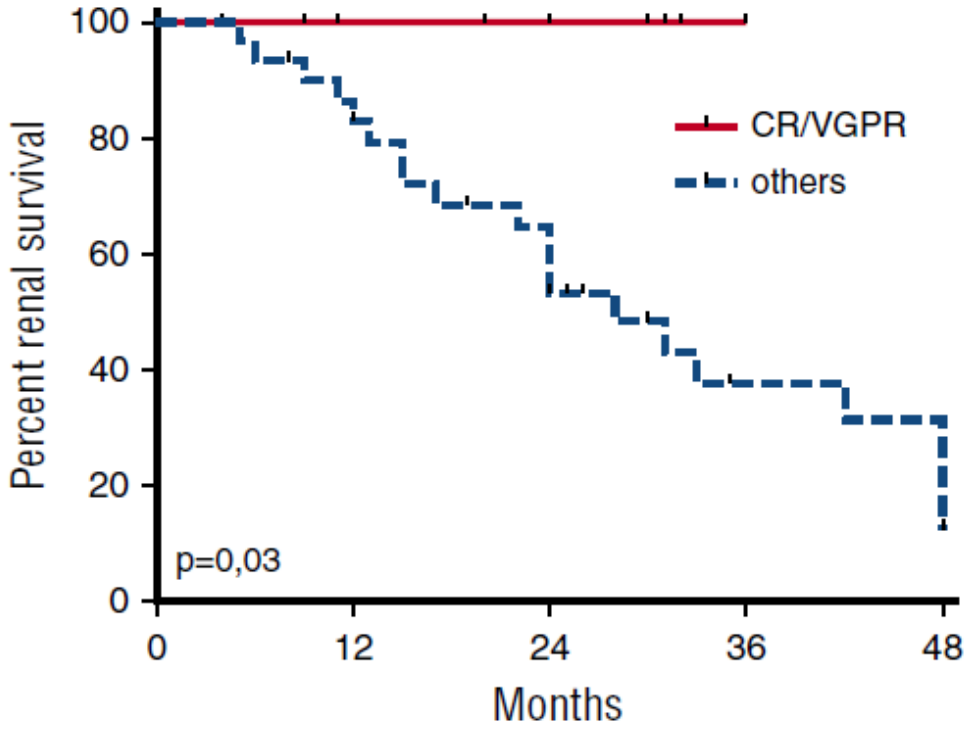
Hypothesis: MIg is a «platform» for the fixation of C3b and the assembly of C3 convertase

Chauvet S, et al. Front Immunol. 2018;9:2260

C3G and MGRS : effect of clone-targeted chemotherapy



HR	17	14	9	4	2	2	2
No HR	31	25	17	7	5	1	0

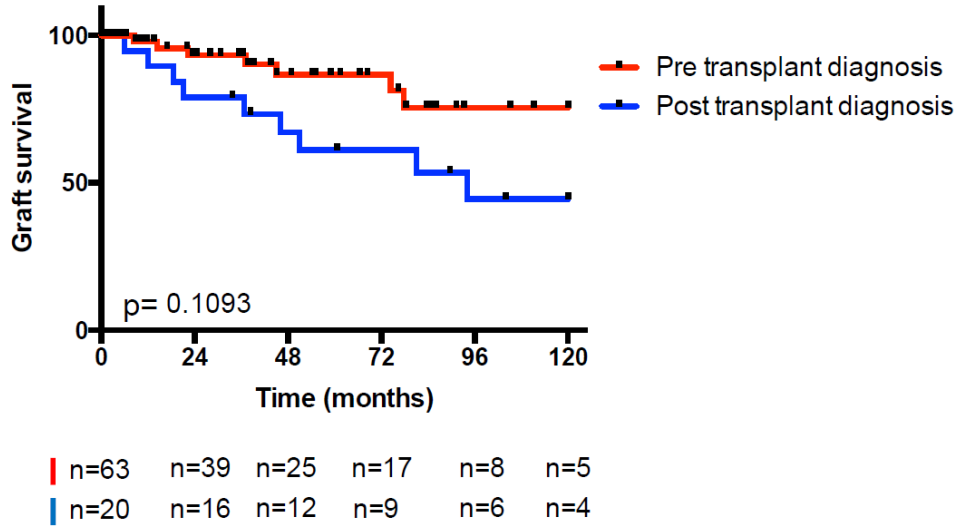


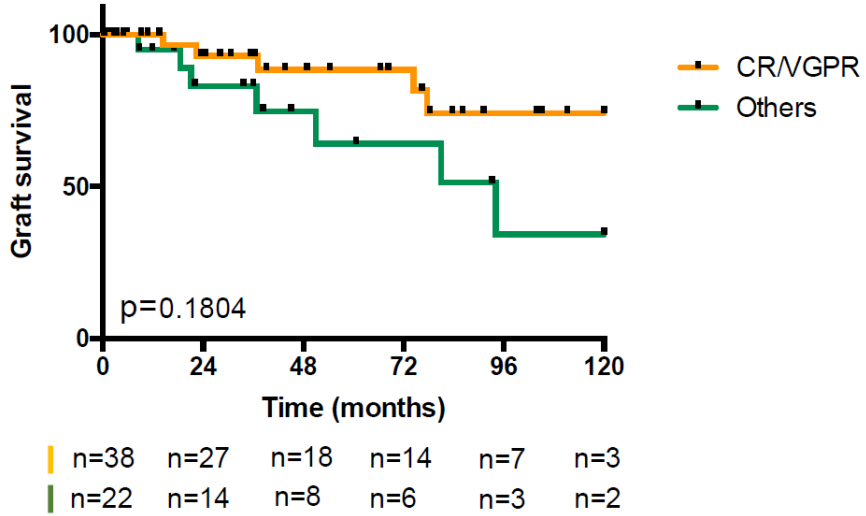
CR/VGPR	9	8	6	1	0
others	27	23	14	8	5

Chauvet S, et al. Blood 2017; 129:1437-47

Renal transplantation in MGRS

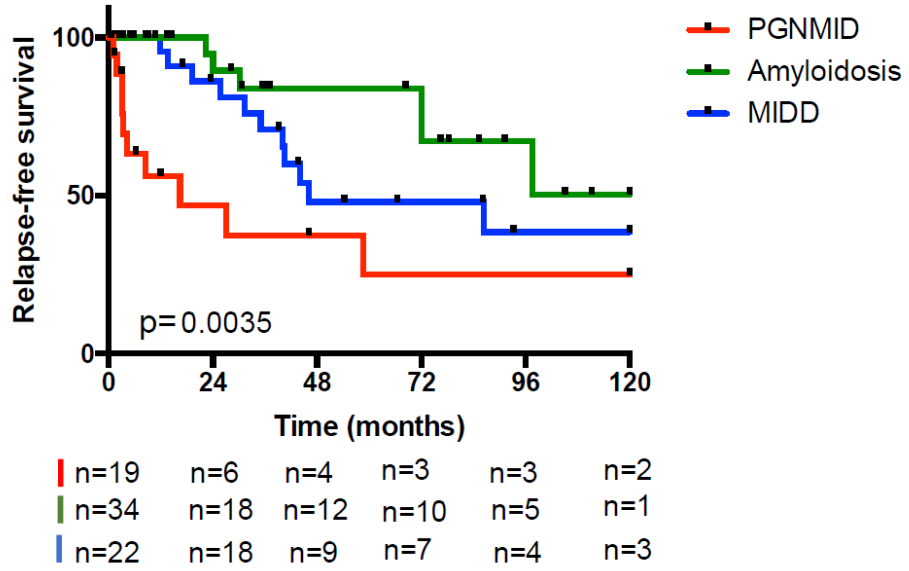
Data from the French reference centre





- Importance of establishing the diagnosis before Tx
- Importance of pre-Tx hematological response (CR/VGPR)
- Prognosis variable among MGRS-related renal diseases
- Increased risk of post-Tx infectious and neoplastic complications vs usual renal Tx recipients

Tassery M, et al. In preparation



Question 3:

Which of the following is the main factor determining renal outcomes in MGRS ?

1. Quality of the hematological response
2. eGFR at diagnosis
3. Proteinuria level at diagnosis
4. Serum level of the monoclonal Ig
5. Severity of interstitial fibrosis/tubular atrophy

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1. Quality of the hematological response
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3. Proteinuria level at diagnosis
4. Serum level of the monoclonal Ig
5. Severity of interstitial fibrosis/tubular atrophy

Conclusions: management of MGRS

1. **MGRS**: small B-cell clone + renal disease induced by the secreted monoclonal Ig
2. **Early diagnosis is mandatory**
   - Confrontation of clinical, immuno-hematologic and pathologic findings
   - Renal pathology: LM, detailed IF studies (L C+ IgG subclasses…), EM ± immuno EM, proteomics
3. **Renal and overall survival** depends on the rapid achievement of **deep hematological response** with chemotherapy adapted to the clone and to renal function
4. Careful and **repeated evaluation of hematological response** (FLCs, M-spike, IFPE) and tolerance
5. **Multidisciplinary management is required**

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