Membranous Nephropathy

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Membranous Nephropathy

Agenda

- Introduction
- Etiology
- Pathogenesis
- Pathology
- Diagnosis
- Management
- Recurrent vs. denovo MN

Introduction

- **Second most common cause of NS in adults after DN.1,2**
- **Circulating autoantibodies against podocyte antigens.**
- **Subepithelial IG deposits, damage in GBM, foot process effacement, and high-grade proteinuria.**
- **First described by Dr. Bell in 1946 as a thickened GBM and vacuolization.**

Introduction

- **Seen in all ethnic and racial groups and all sexes.**
- **Primary MN is more common in White males over 40 years.**
- **In young females ----suspicion of SLE.**
- **Less common in children----often associated with hepatitis B, autoimmune or thyroid disease.**

Primary/Idiopathic Membranous

Million Dollar Question!

We can see the antibodies….

So what are the antigens?

Introduction

Target antigens and autoantibodies

- **M-type phospholipase A2 receptor (PLA2R) detected in 2009 (70%)**
  - **PLA2R testing help in diagnosis, prognosis, therapeutic assessment and risk for recurrence post-transplant.**

Beck LH Jr*et al.* M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009;361:11-21.

Introduction

Anti-PLA2R antibodies.

-High sensitivity and specificity, 60–70% and 90–100% for PLA2R-MN.

-Anti-PLA2R antibodies for diagnosis --------**a gold standard.**

-Decreased specificity **(renal dysfunction , autoimmune diseases or diabetes**).

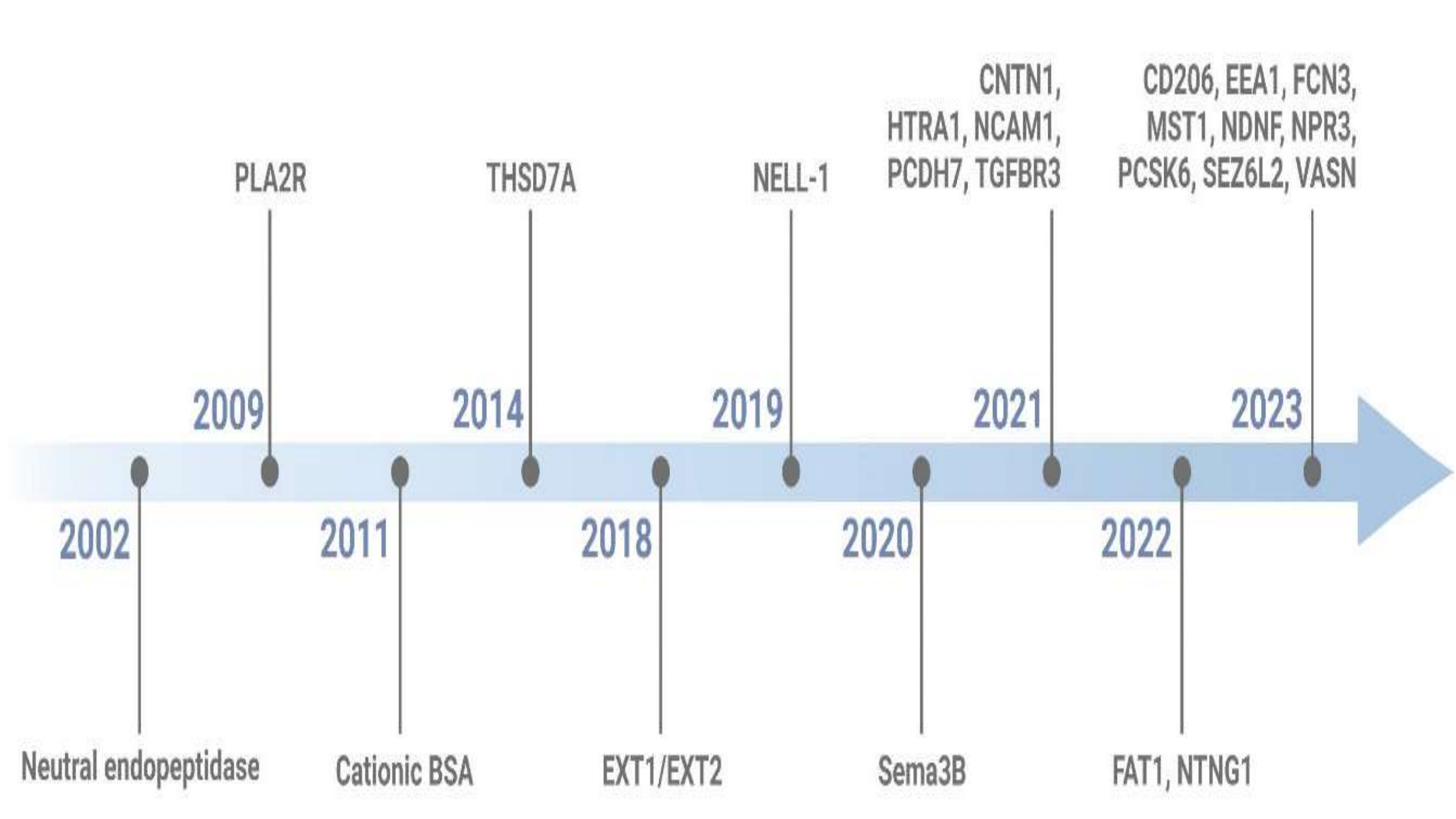
-Nephrotic patients without MN seldom have a positive anti-PLA2R antibody.

Dai H, Zhang H, He Y. Sci Rep 2015;5:8803.

Bobart SA, et al. Noninvasive diagnosis of PLA2R-associated membranous Clin J Am Soc Nephrol 2021;16:1833-9.

Introduction

- **Serum antibodies against diverse podocyte antigens:**
  - **Neural epidermal growth factor-like 1 (NELL1) (10% of 1ry cases)** Sethi S, et al. Kidney Int 2020;97: 163-74.
  - **Thrombospondin type 1 domain containing 7A (THSD7A) (3% of 1ry cases)** Tomas NM, et al.. N Engl J Med 2014;371:2277-87.
  - **Semaphorin 3B (Sema3B) young cases**
  - **Protocadherin 7 (PCDH7)**
  - **Exostosin 1 (EXT1)/exostosin 2 (EXT2) systemic autoimmune disease**
  - **Neural cell adhesion molecule 1 (NCAM1) systemic autoimmune disease**
  - **Type III transforming growth factor beta receptor (TGFBR3)**
  - **Proprotein convertase subtilisin/kexin type 6 (PCSK6) (NSAID abuse)** Sethi S. 2021;32:268-78. Sethi S, et al. J Am Soc Nephrol 2019;30:1123-36.
  - **Serine protease HTRA1 , Netrin G1 (NTNG1) , Protocadherin FAT1 (FAT1) , Neuron-derived neurotrophic factor (NDNF), Neutral endopeptidase (NEP), Cationic bovine serum albumin**


2002
Neutral endopeptidase
2009
PLA2R
2011
Cationic BSA
2014
THSD7A
2018
EXT1/EXT2
2019
NELL-1
2020
Sema3B
2021
CNTN1, HTRA1, NCAM1, PCDH7, TGFBR3
2022
FAT1, NTNG1
2023
CD206, EEA1, FCN3, MST1, NDNF, NPR3, PCSK6, SEZ6L2, VASN

Aetiology

- **Genetic risk factors**
- **Immune system : imbalance between the effector and regulatory arm**
- **Environmental factors**
- **Conventional risk factors: autoimmune diseases, infections, malignancy, and drugs.**

Aetiology

Genetics:

- **Familial MN were reported (case reports).**
- **Association with HLA-DR3, HLA-DQA, and HLA-DQ1.**
- **Genome wide association studies (GWAS) discovered the risk HLA loci of DQA1*0501 in Europeans, DRB1*1501 in East Asians, and DRB1*0301 in both ancestries.**
- **PLA2R risk alleles, positive PLA2R antibody and increased glomerular PLA2R expression were found in ~75% of the patients**

- Gupta S, et al. Nephrol Dial Transplant 2018;33:1493-502.
- Xie Jet al. Nat Commun 2020;11:1600.
- Freedman BI.Am J KidneyDis 1994;23:797-802.
- Stanescu HC, et al. N Engl J Med 2011;364:616-26.

Aetiology

Regulatory immune system:

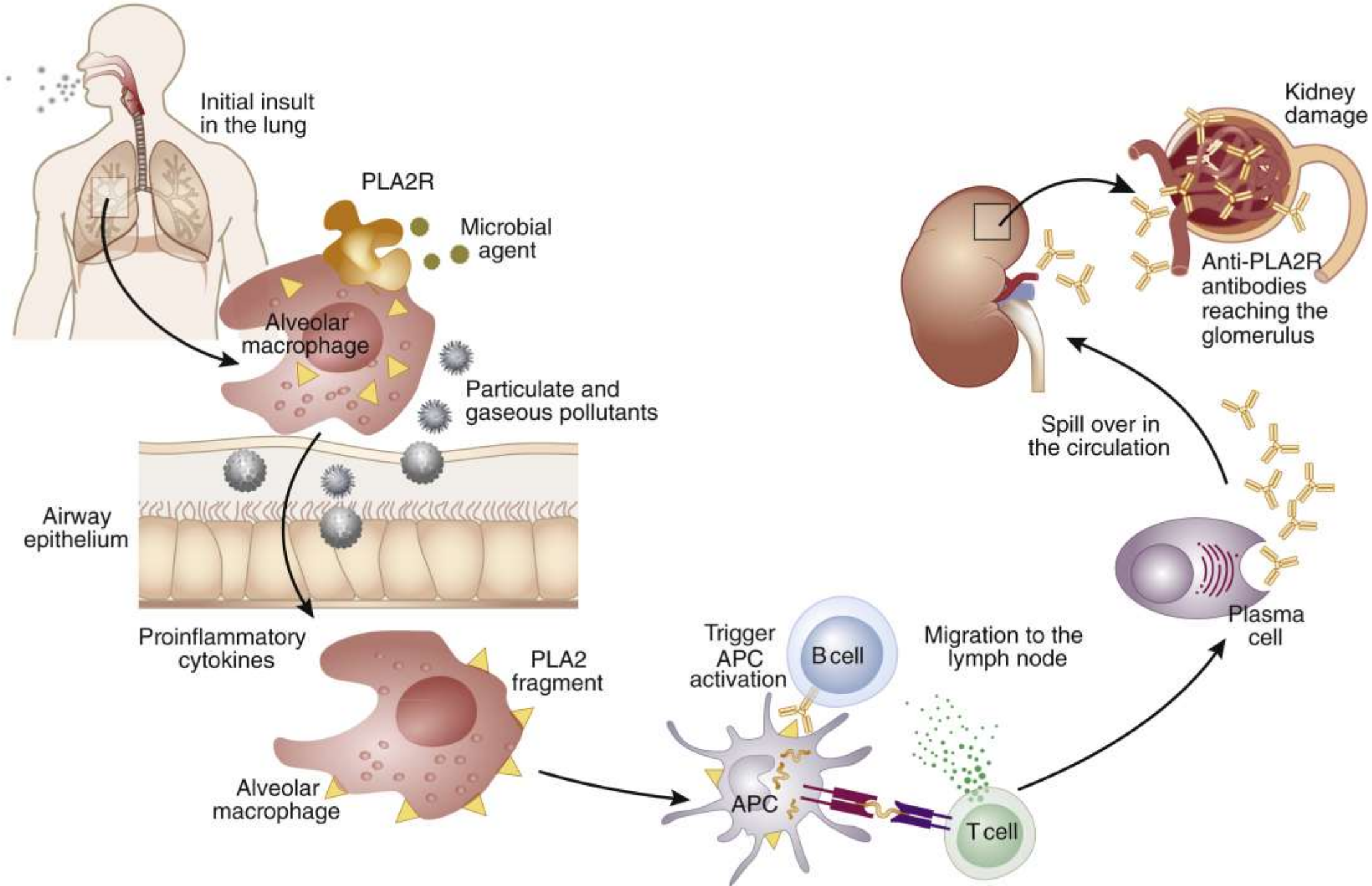
- Lower Treg frequency and function and lower levels of inhibitory cytokine (interleukin-35) than healthy controls, which improved after clinical remission post-immunosuppressive treatment.
- Autoimmune diseases were prevalent in 81% of EXT1/EXT2-associated MN

Aetiology

Environmental Toxins:

- **In China,** the frequency of MN **correlated with air pollution**.
- **In a French study,** MN patients were frequently exposed to toxic substances, such as **asbestos, lead, or organic solvents**, compared to the general population.

Xu X, et al. J Am Soc Nephrol 2016;27:3739-46.
Cremoni M, *et al.* Clin J Am Soc Nephrol 2022;17:1609-19.


Initial insult
in the lung
PLA2R
Microbial
agent
Alveolar
macrophage
Particulate and
gaseous pollutants
Airway
epithelium
Proinflammatory
cytokines
PLA2
fragment
Alveolar
macrophage
Trigger
APC
activation
B cell
APC
T cell
Migration to the
lymph node
Plasma
cell
Spill over in
the circulation
Kidney
damage
Anti-PLA2R
antibodies
reaching the
glomerulus

Aetiology

Target Antigens in Infection- and Medication Induced MN:

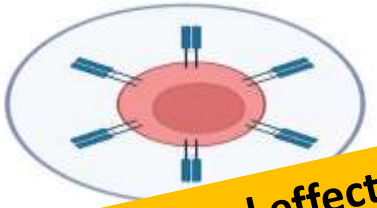
- **Viral infections (HBV, HCV, and HIV) ----PLA2R and THSD7A.** Levy JB, *et al.* Clin Kidney J 2021;14:876-83.
- **Schistosoma mansoni -------PLA2R staining.** Araújo SA, *et al.* Kidney Int 2019;96:793-4.
- **Syphilis-associated MN -----NDNF-3.** Sethi S, J Am Soc Nephrol 2023;34:374-84.
- **NSAID-associated MN ------positive PLA2R staining was found in 50–75%. and PCSK6 with prolonged use of NSAID.**
- **Supplemental drug, lipoic acid, and mercury-containing medicine were reported in NELL1-associated MN.** Spain RI, et al Kidney Int 2021;100:1208-13.

Pathogenesis

Proteinuria and nephrotic syndrome

Genetic susceptibility (risk alleles in *PLA2R1*, *NFKB1*, *IRF4* and *HLA-DR and HLA-DQ genes*)

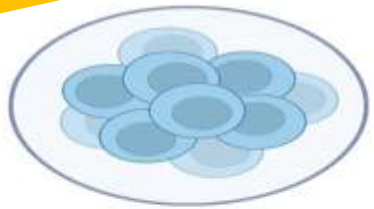
genetic polymorphisms



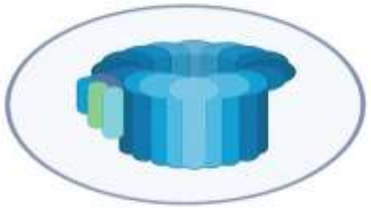
Enhanced effector T-cell responses

GBM and podocyte injury

Membranous Nephropathy

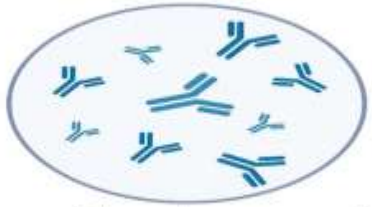


Decreased number and function of Tregs and Bregs

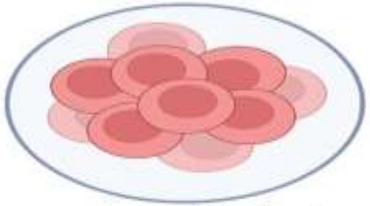


Activation of C3 and C5b-9

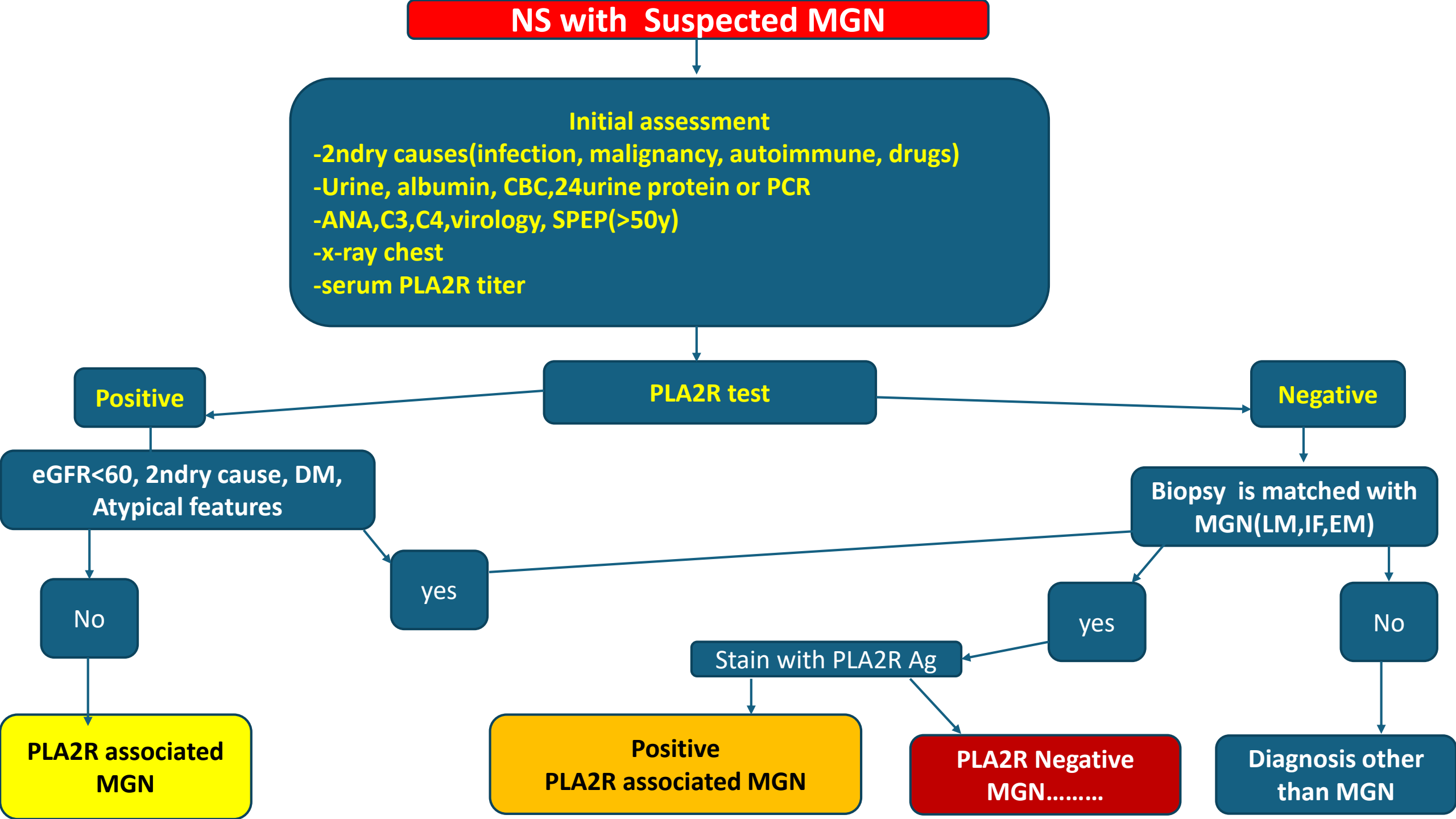
overexpression of podocyte Antigens (cancer, pollution)

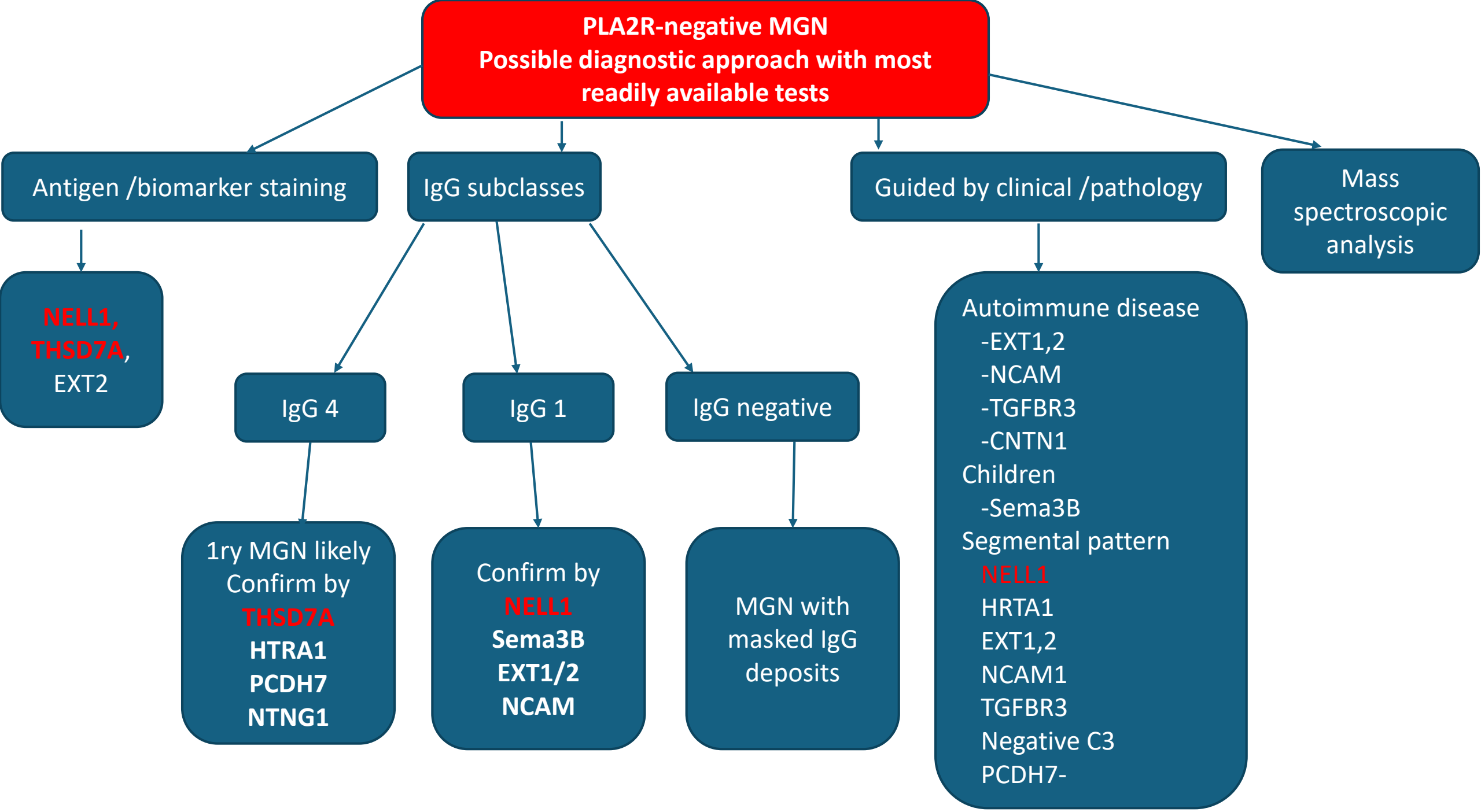


Autoantibody secretion by B cells against podocyte antigens



Increased T helper cells (Th2, Th17 and Tfh)


NS with Suspected MGN
Initial assessment
-2ndry causes(infection, malignancy, autoimmune, drugs)
-Urine, albumin, CBC,24urine protein or PCR
-ANA,C3,C4,virology, SPEP(>50y)
-x-ray chest
-serum PLA2R titer
PLA2R test
Positive
Negative
eGFR<60, 2ndry cause, DM, Atypical features
Biopsy is matched with MGN(LM,IF,EM)
No
yes
yes
No
Stain with PLA2R Ag
PLA2R associated MGN
Positive PLA2R associated MGN
PLA2R Negative MGN……
Diagnosis other than MGN

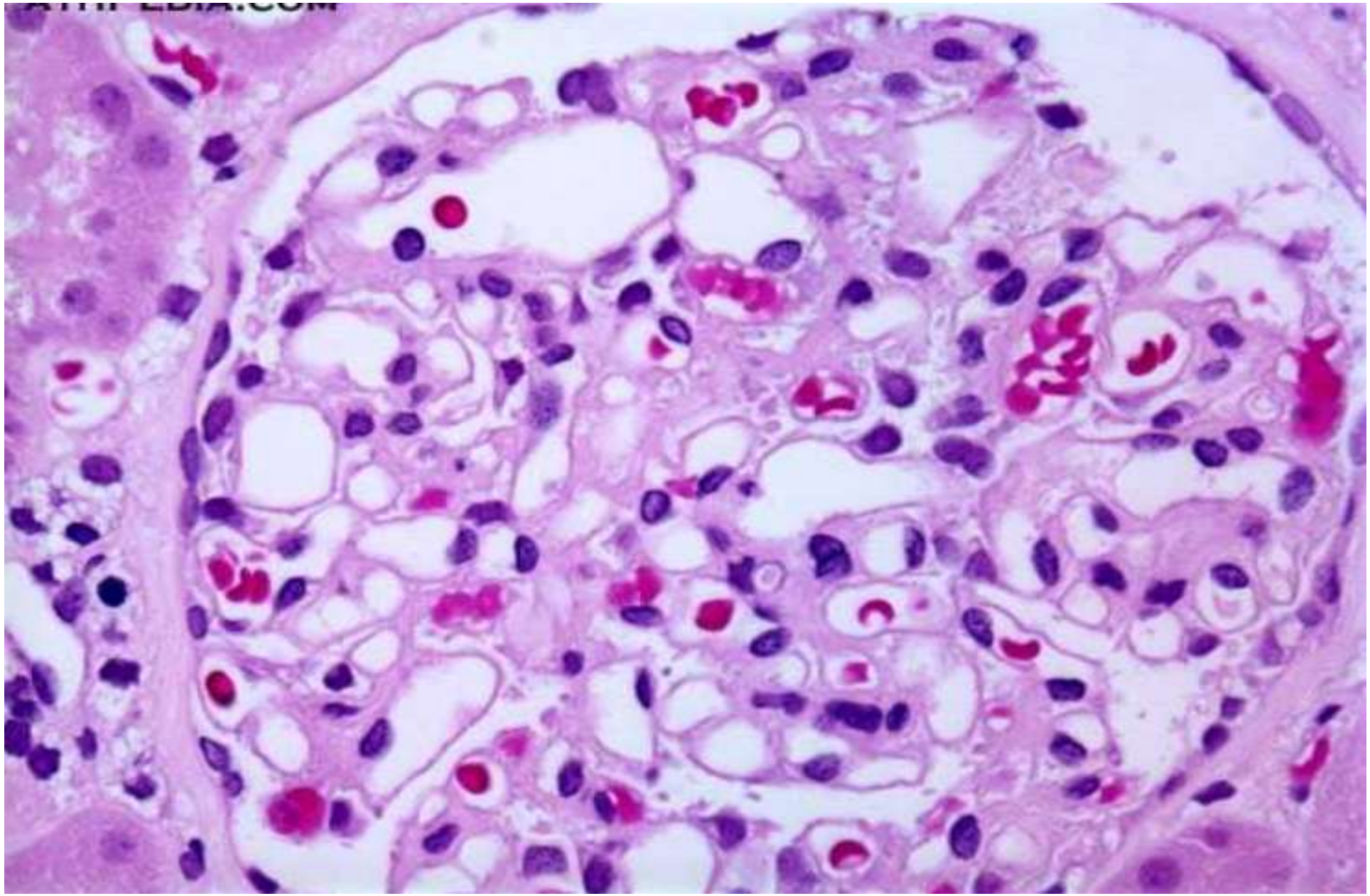

PLA2R-negative MGN
Possible diagnostic approach with most readily available tests
Antigen /biomarker staining
IgG subclasses
Guided by clinical /pathology
Mass spectroscopic analysis
NELL1, THSD7A, EXT2
IgG 4
IgG 1
IgG negative
Autoimmune disease
-EXT1,2
-NCAM
-TGFBR3
-CNTN1
Children
-Sema3B
Segmental pattern
NELL1
HRTA1
EXT1,2
NCAM1
TGFBR3
Negative C3
PCDH7-
1ry MGN likely
Confirm by
THSD7A
HTRA1
PCDH7
NTNG1
Confirm by
NELL1
Sema3B
EXT1/2
NCAM
MGN with masked IgG deposits

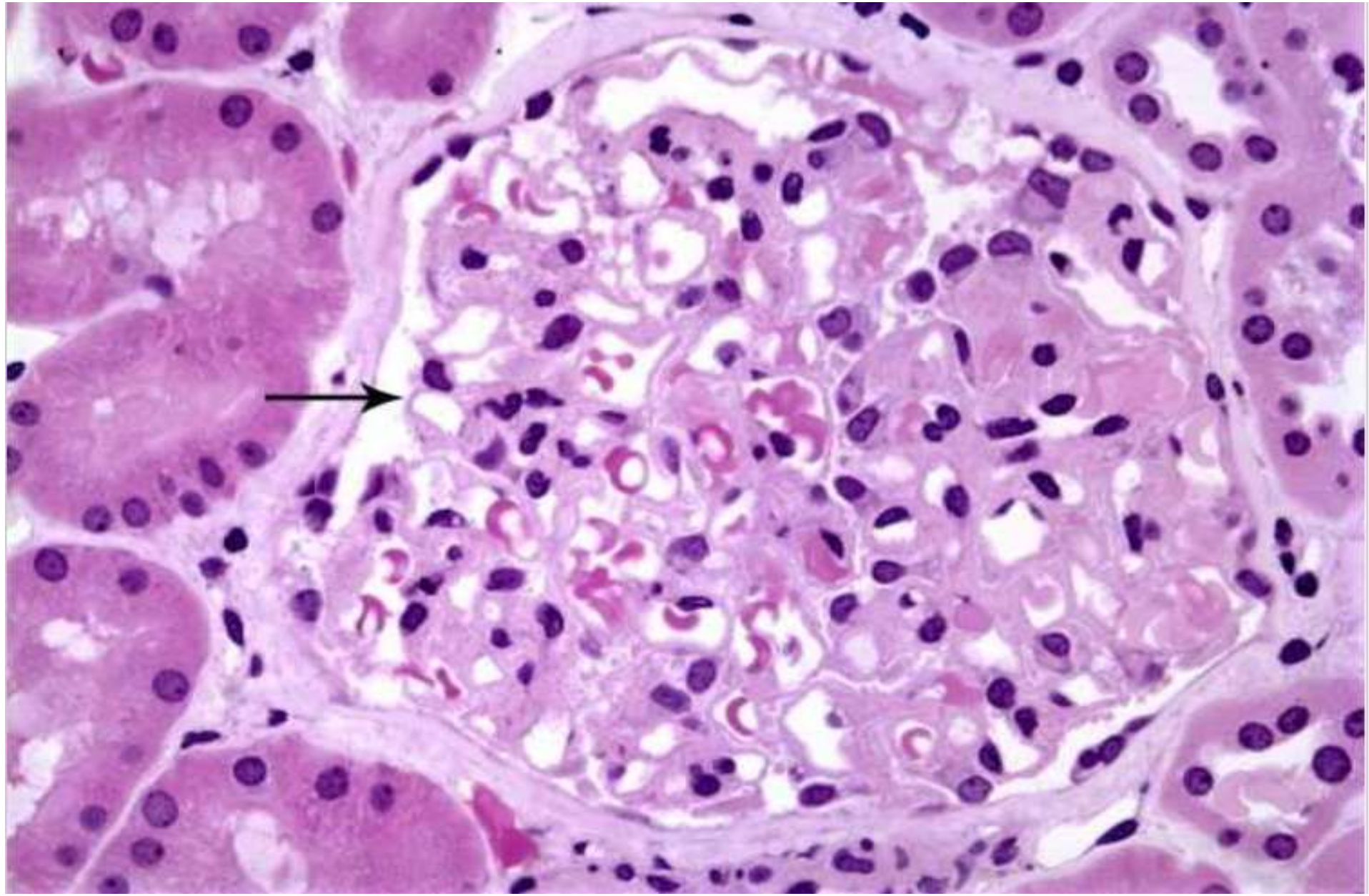
Pathology

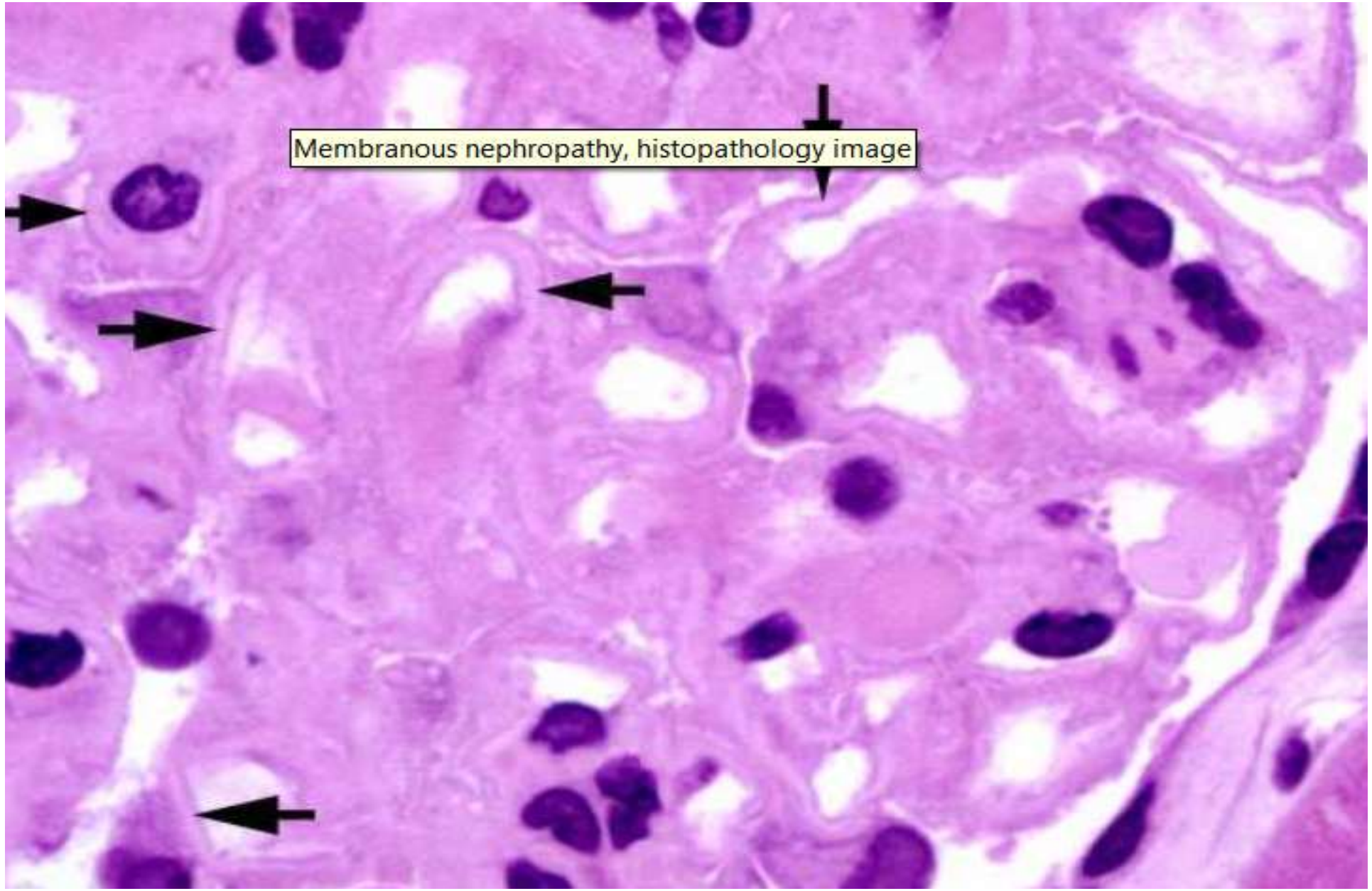
- **Global and diffuse GBM thickening and subepithelial deposits (**IgG)
  - (usually **IgG1 and IgG4**) , scant C3 deposition.
- **Presence of IgA, IgM, and C1q deposition and IgG1, IgG2, and IgG3**

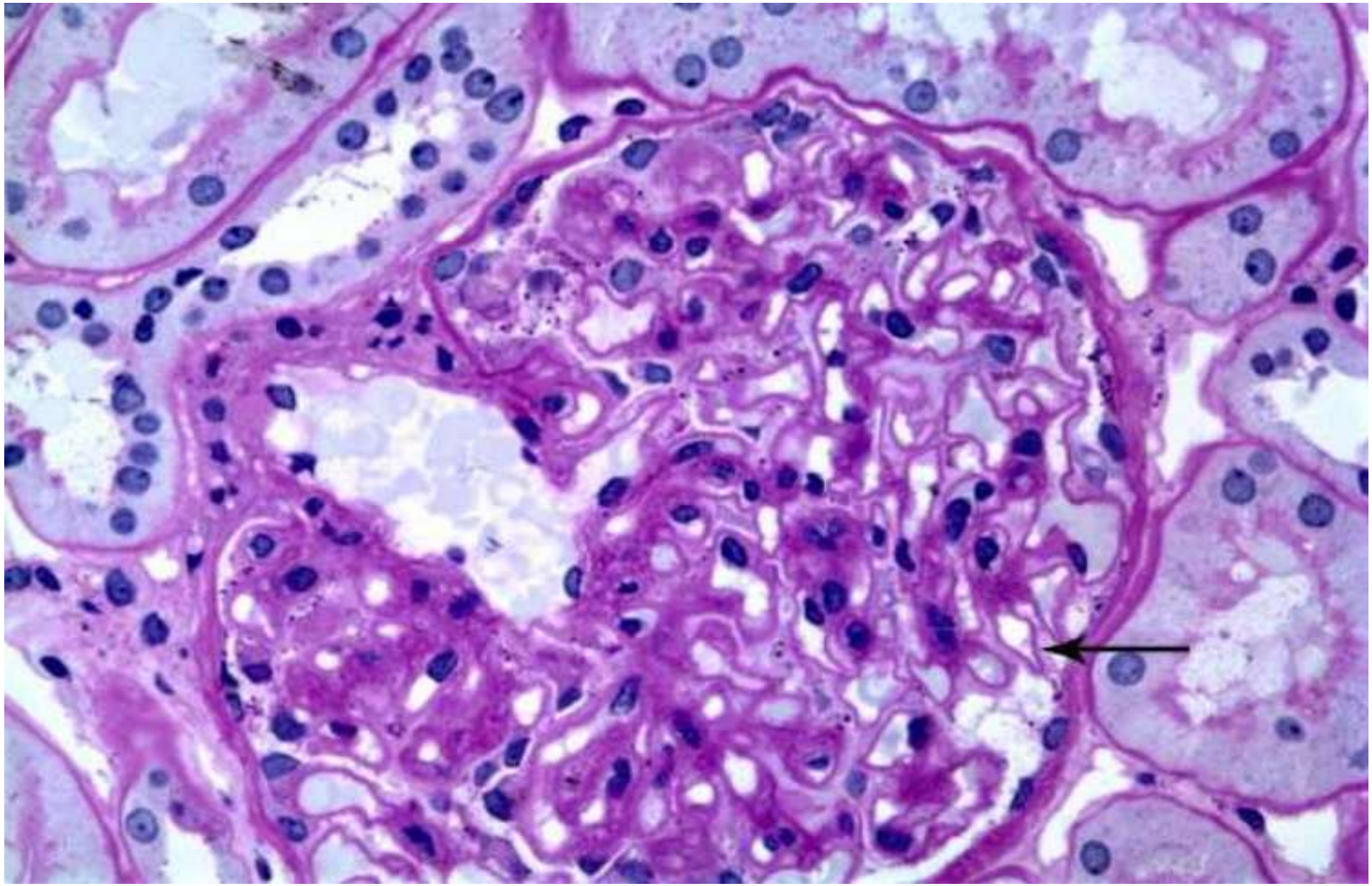
  autoimmune diseases-associated MN, mostly SLE .68

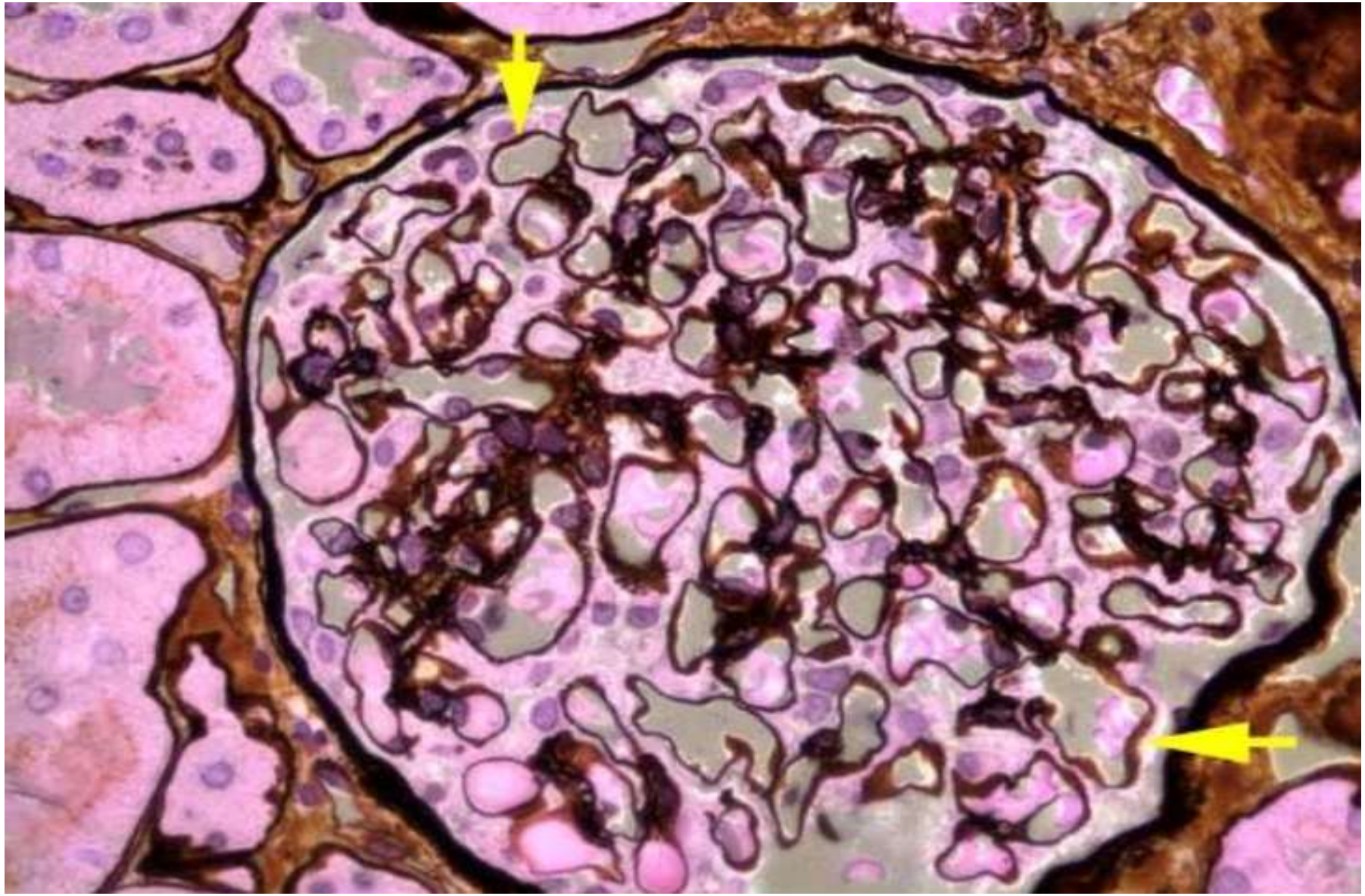
Tomas NMN Engl J Med 2014;371:2277-87.
Al-Rabadi LF, J Am Soc Nephrol 2021;32:1666-81.
Reinhard L, *et al.* J Am Soc Nephrol 2022;33:1823-31.

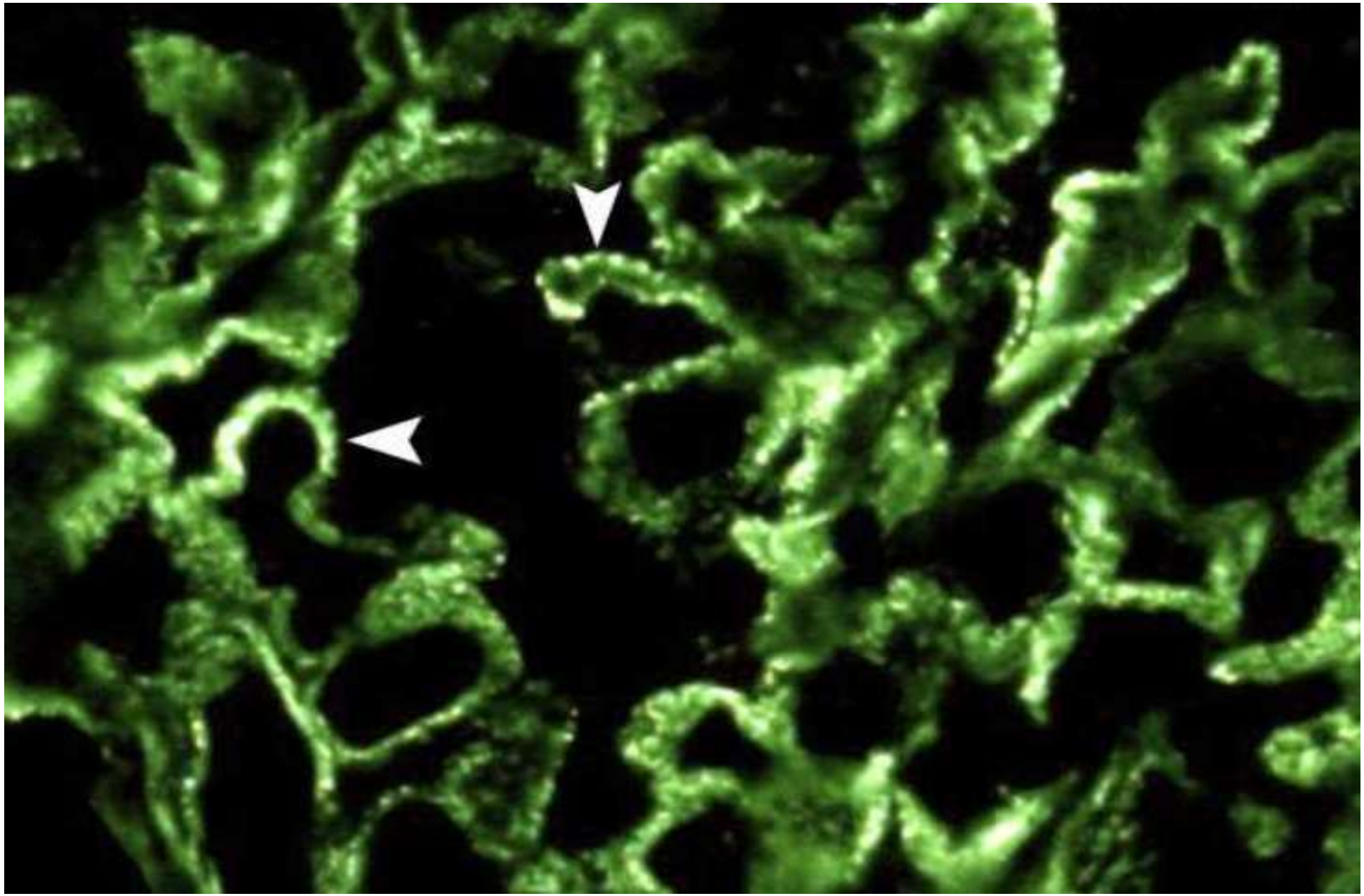


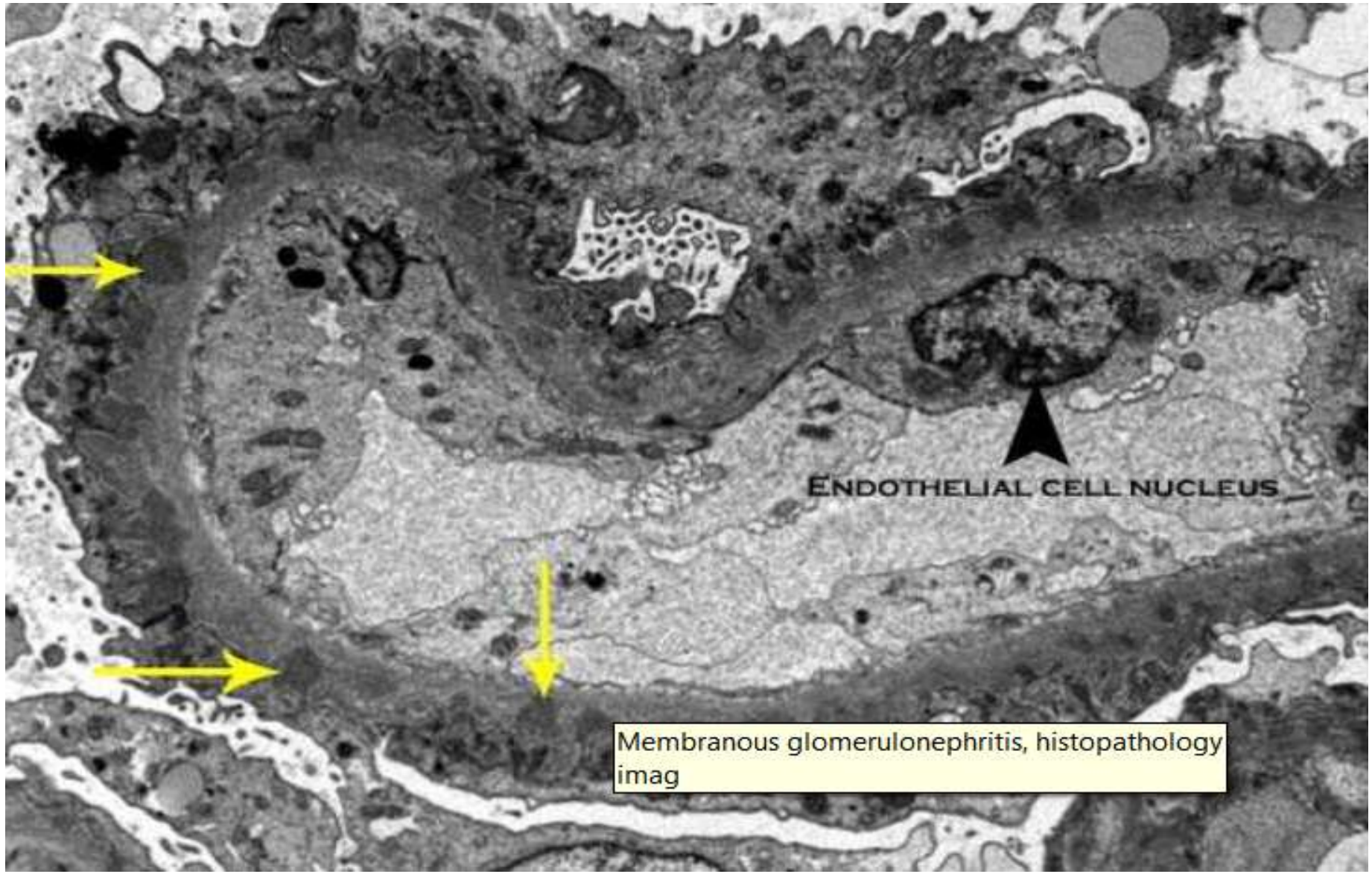



Membranous nephropathy, histopathology image

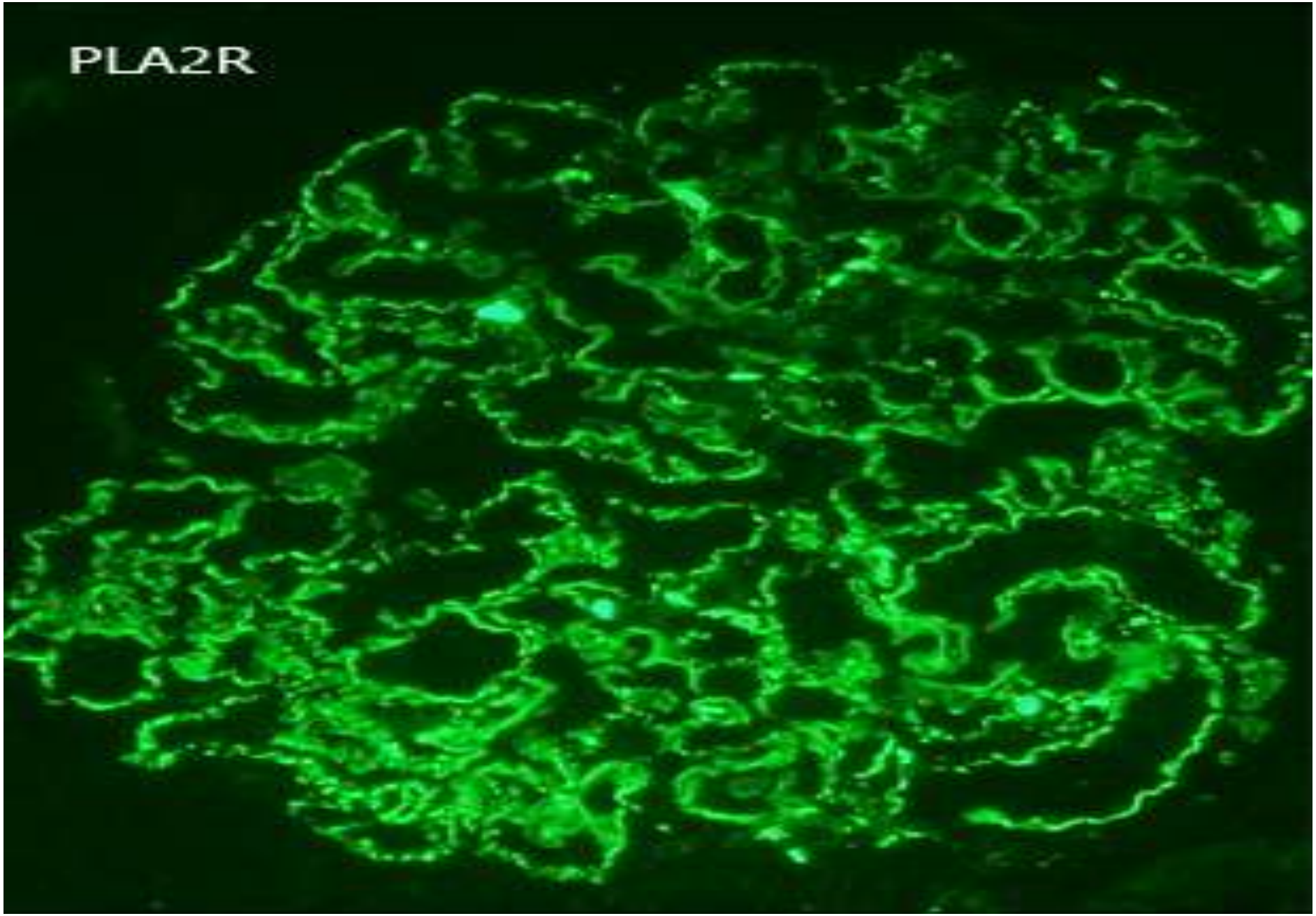








Membranous glomerulonephritis, histopathology imag


PLA2R

Pathology

- **NELL1-associated MN exhibits similar features to PLA2R-MN except for the segmental distribution of IgG.**

- **In EXT1/ EXT2-associated MN--------granular staining for EXT1 and EXT2 along GBM with all four IgG subclasses (IgG1 and IgG2).** + **staining of IgA, IgM, C3, and C1q** across the glomerulus, including subepithelial, subendothelial, and mesangium, and tubuloreticular inclusions.

- **NCAM1 50 and TGFBR3-associated** MN **exhibit features of membranous lupus nephritis**.

- **EXT1/EXT2 and NCAM1 can also be associated with mixed proliferative and membranous lupus nephritis.**

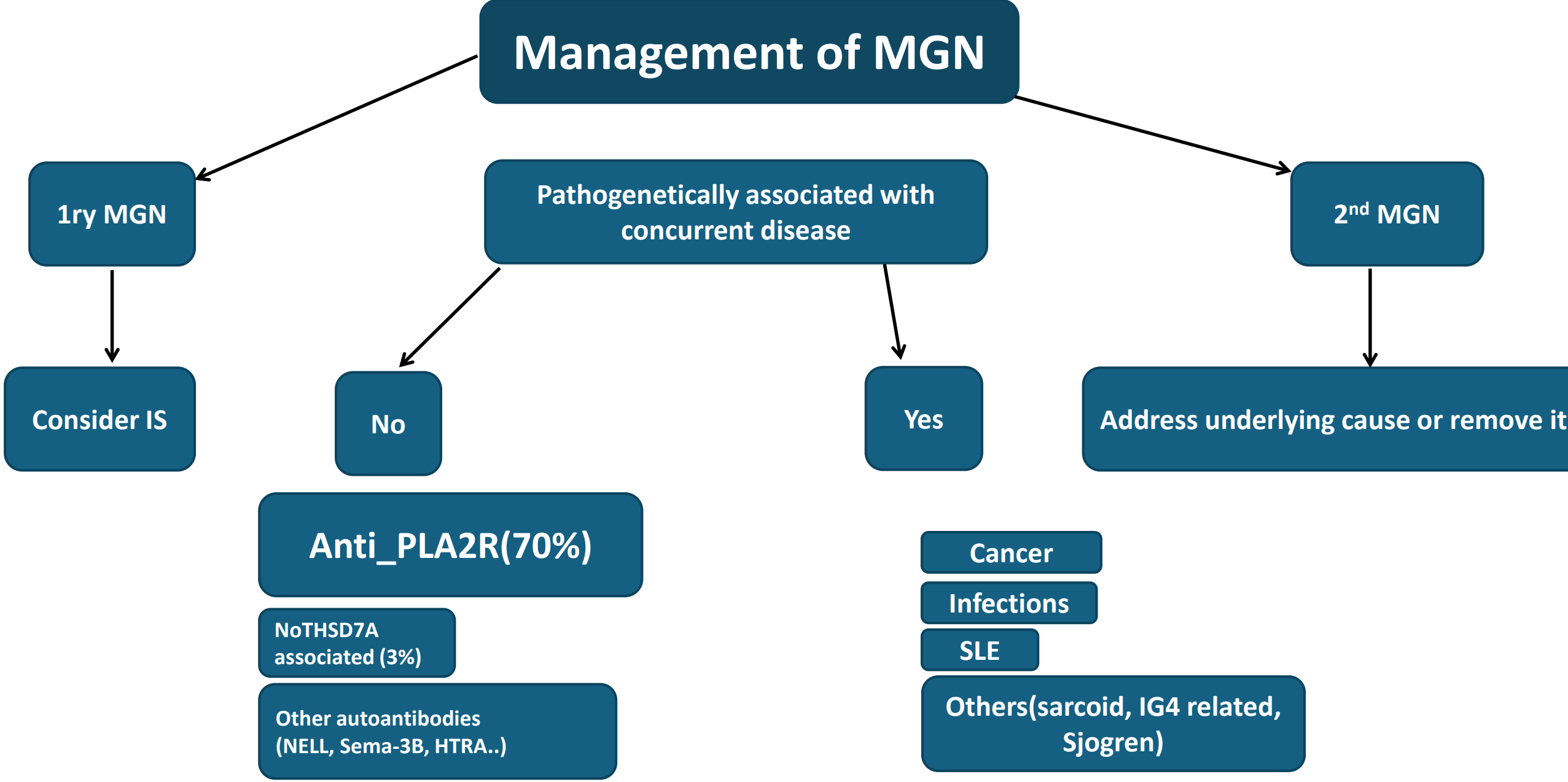
Management of MN

Aim:

-Prevent progression,
-decrease adverse effects of NS,
-Enhance quality of life by reducing symptoms.

Multifaceted approach:

- **Supportive +immunosuppressive therapy.**
- **Consider secondary causes (malignancies, autoimmune diseases, infections, and medications).**
  - **Renin-angiotensin system (RAS) blockers(ACEi or ARB).**
  - **SGLT2i (promising adjunctive therapy). 77,78**
  - **Diuretic therapies,**
  - **Lipid-lowering agents,**
  - **Anticoagulation**



Floege J et al Kid International 2019

Management of MN

- 30% ----------spontaneous complete remission within 6 months.
- 25 to 40% partial remission at five years

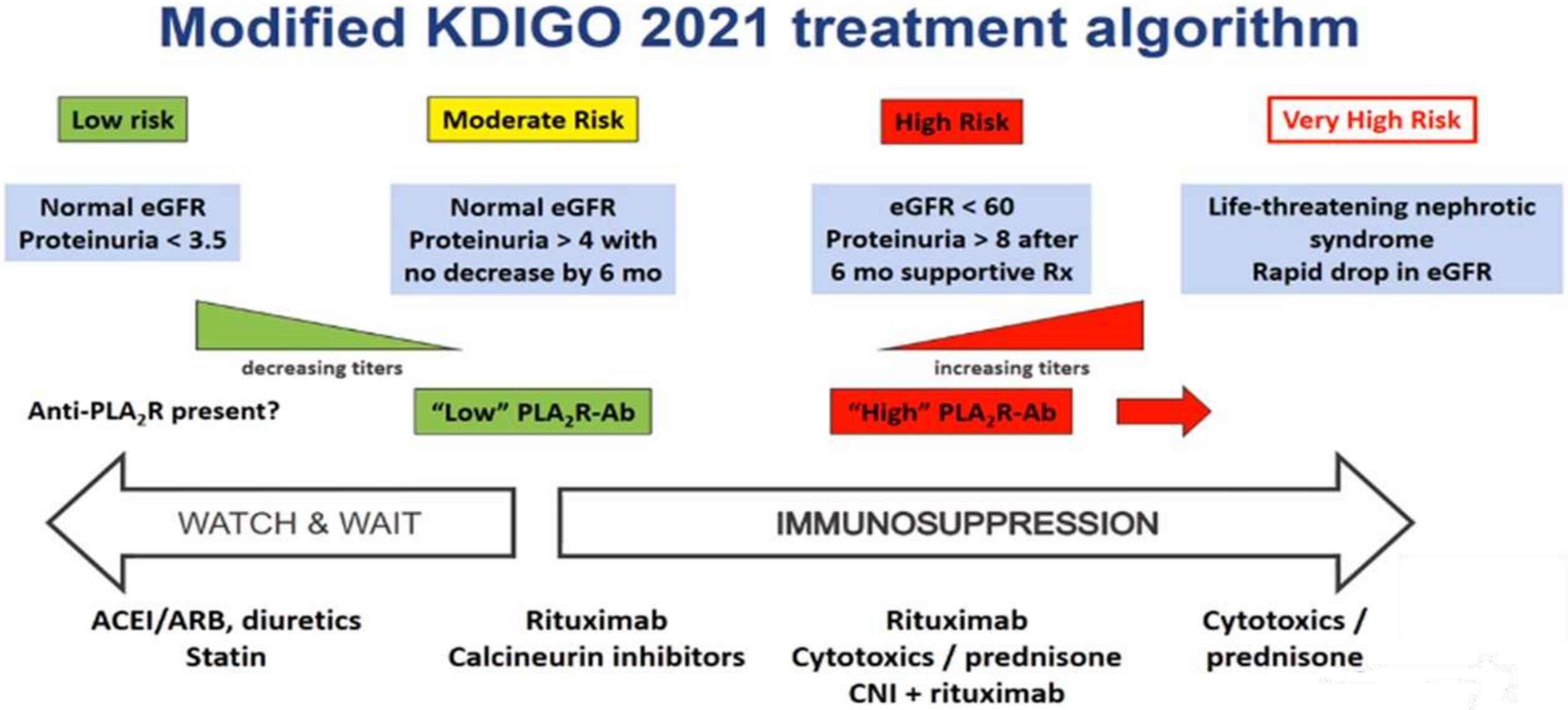
- At present, there are no standardized risk prediction tools.

- KDIGO categorizes patients into low, moderate, high, and very high risk based on clinical and biological markers

- The cyclical regimen is associated with toxicities such as infection, malignancy, and infertility.

- The standard of care shifted toward more targeted therapies, including B-cell depletion with rituximab and CNIs based on landmark clinical trials .

Management of MN



Modified from kdigo.org/wp-content/uploads/2017/02/KDIGO-GN-GL-Public-Review-Draft_1-June-2020.pdf

Management of MN

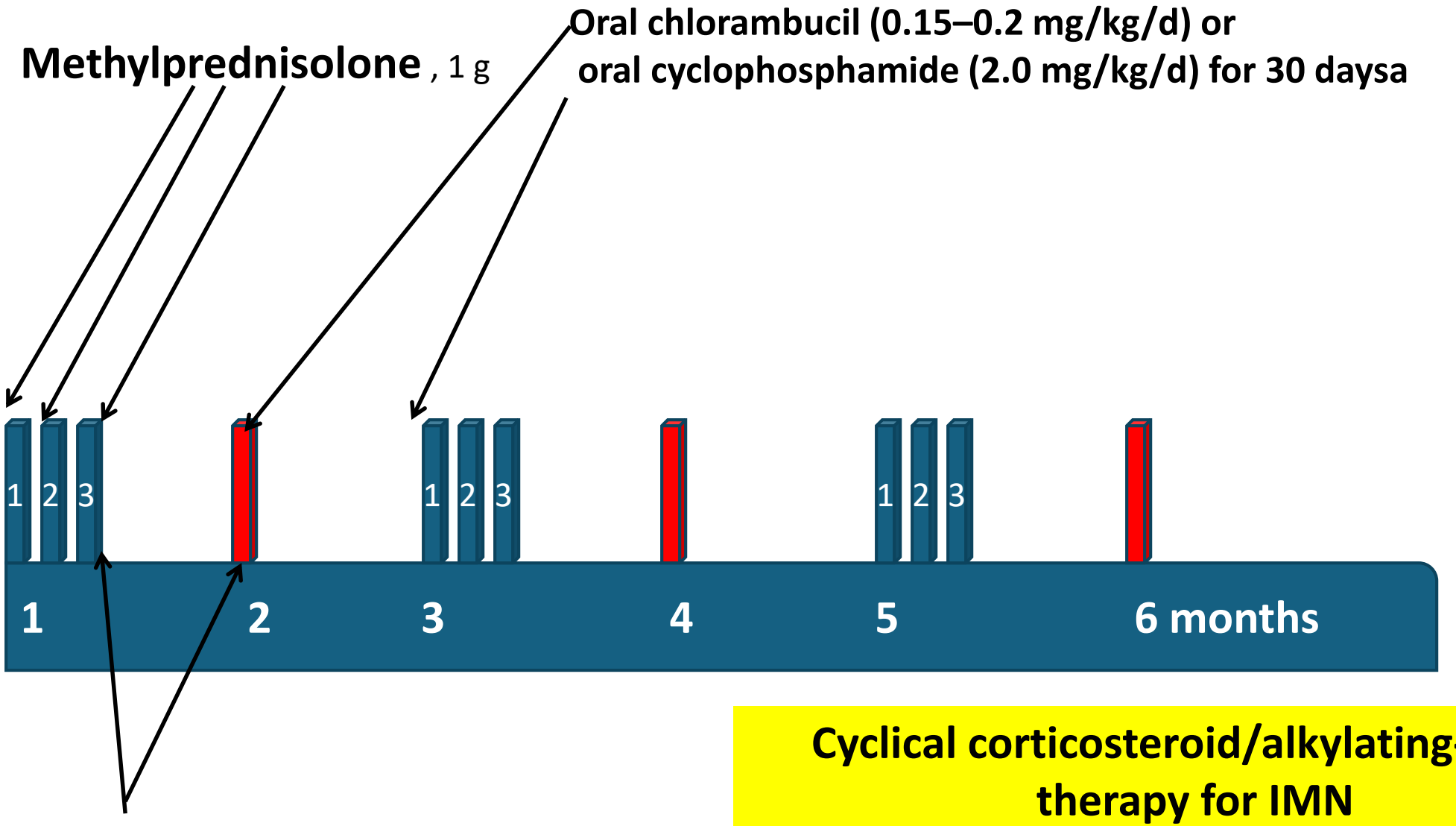
CNIs :

- **Inhibiting T-cells,**
- **Blocking T- and B-cell interactions,**
- **Stabilizing the podocyte cytoskeleton.**

Rituximab :

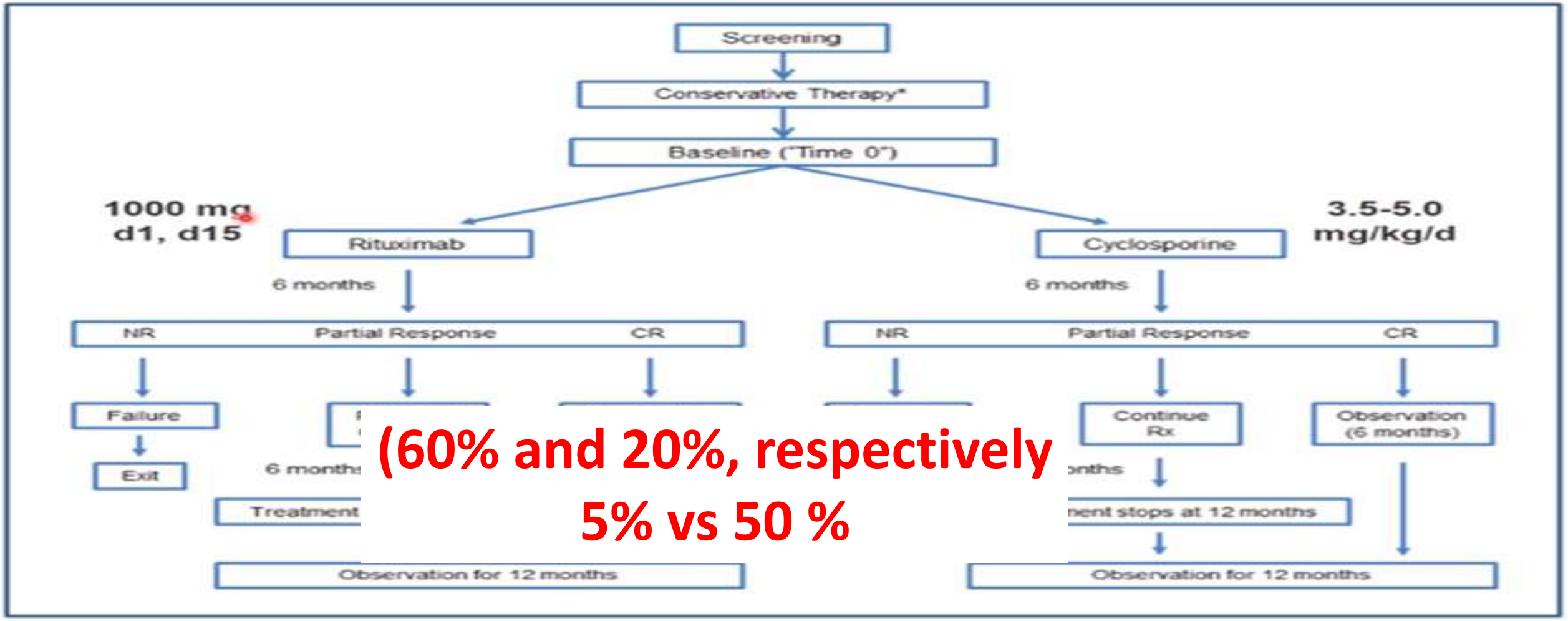
- Chimeric, monoclonal anti-CD20 IgG1 antibody that depletes B-cells for 6–8 months post infusion.
- Rituximab kills pro-B-cells to memory B-cells, which reduces serum PLA2R antibodies, (not plasmablasts or plasma cells) .

Fervenza FC, *et al.* N Engl J Med 2019;381:36-46.
Dörner T, Radbruch A, Burmester GR. B-cell-directed therapies for autoimmune disease. Nat Rev Rheumatol 2009;5:433-41.



Cyclical corticosteroid/alkylating-agent therapy for IMN
"Ponticelli Regimen"

MENTOR studv



(60% and 20%, respectively

5% vs 50 %

Fervenza FC et al. (2019) *N Engl J Med* 318: 36 – 46 (Supplement)

Superior sustained remission at 2 years in rituximab-treated patients compared to CsA therapy (60% and 20%, respectively).87

Rituximab monotherapy was associated with a 5% relapse rate after remission compared to a 50% relapse in the cyclosporin group at 2 years.87

Management of MN

GEMRITUX trial showed the efficacy of **rituximab compared to supportive therapy**, inducing ~**65%** partial or complete remission at 17 months.92

RI-CYCLO trial compared **rituximab with the Ponticelli cyclical regimen**.93
Although complete remission at 12 months was **higher in the cyclic regimen arm** (32% vs. 16%), the probabilities of complete or **partial remission were similar** at 2 years (82% vs. 83%).
The serious adverse effects were similar in both groups.

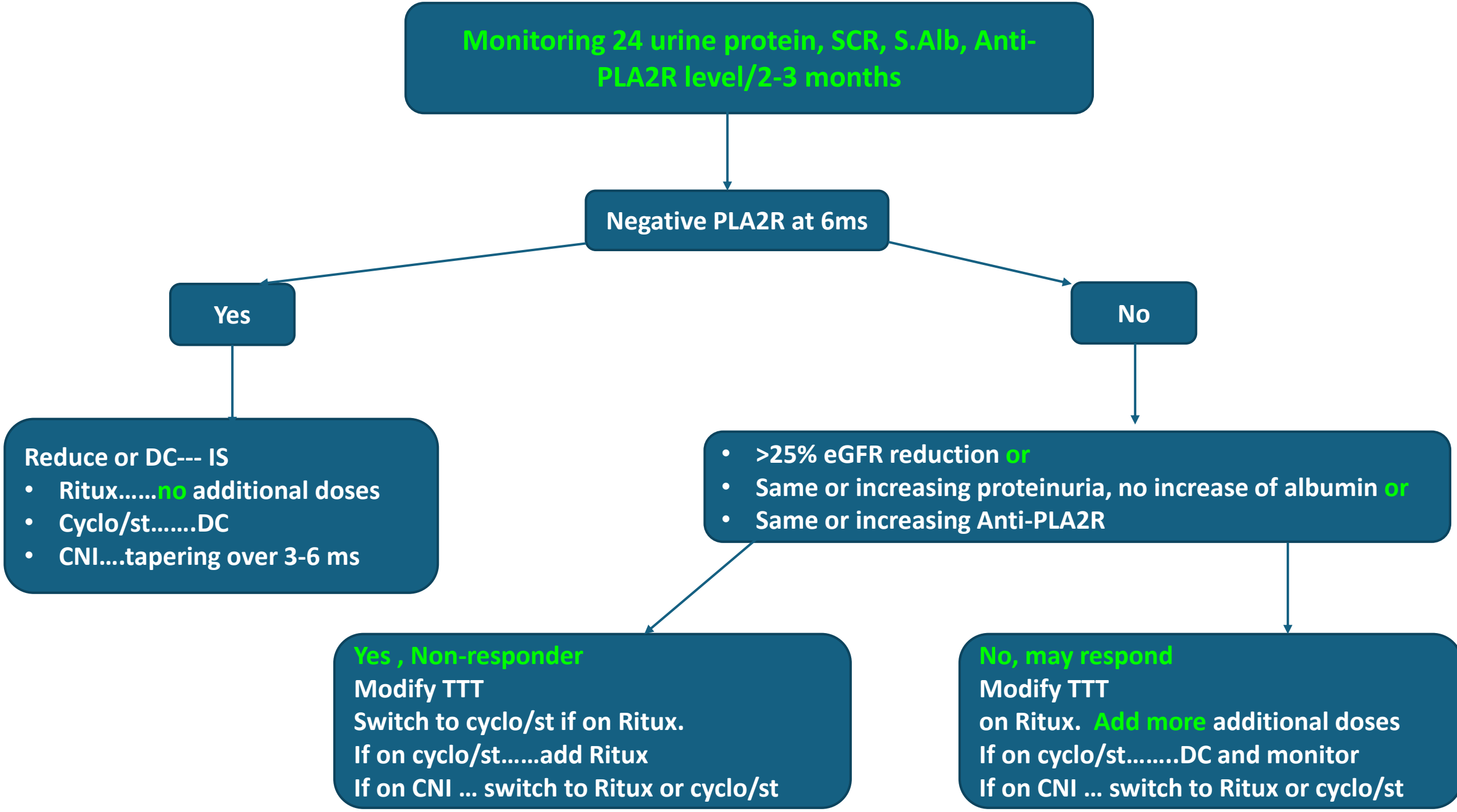
Zonozi et al. showed 100% remission rate with the combination of rituximab with low-dose cyclophosphamide for 2 months and (2.5 mg/ kg oral daily for 1 week, then 1.5 mg/kg oral daily at weeks 2–8) and a rapid prednisone taper.94
On the other hand, addition of an upfront tacrolimus before rituximab infusion at 6 months was found inferior to the cyclical regimen for remission induction at 2 years in the STARMEN trial.95 H

Rituximab-resistant cases:

- **20–30% of MN patients have resistance to treatment.**
- **Anti-rituximab antibody formation and ineffective B-cell killing, respectively.97**
- **Fully humanized and more potent anti-CD20 agents (obinituzumab and ofatumumab)**

Obinutuzumab versus rituximab for the treatment of refractory primary membranous nephropathy.
Mingyue Xu , Yifeng Wang , Meihe Wu , Ruiying Chen , Wenqian Zhao , Mingxin Li , Chuan-Ming Hao , Qionghong Xie
NDT, Volume 40, Issue 5, May 2025, Pages 978–986, https://doi.org/10.1093/ndt/gfae230Conclusion

This retrospective study suggests that obinutuzumab is an effective treatment option for patients with primary membranous nephropathy refractory to GC + CTX, CNI and rituximab regimens.


Monitoring 24 urine protein, SCR, S.Alb, Anti-PLA2R level/2-3 months
Negative PLA2R at 6ms
Yes
No
Reduce or DC--- IS
• Ritux……no additional doses
• Cyclo/st…….DC
• CNI….tapering over 3-6 ms
• >25% eGFR reduction or
• Same or increasing proteinuria, no increase of albumin or
• Same or increasing Anti-PLA2R
Yes , Non-responder
Modify TTT
Switch to cyclo/st if on Ritux.
If on cyclo/st……add Ritux
If on CNI … switch to Ritux or cyclo/st
No, may respond
Modify TTT
on Ritux. Add more additional doses
If on cyclo/st……..DC and monitor
If on CNI … switch to Ritux or cyclo/st

Recurrent MN

Epidemiology:

- 10 and 45 % Beck LH JrN Engl J Med 2009; 361:11.

Diagnosis (only by biopsy), Protocol biopsies---increases prevalence

Pathogenesis and risk factors :

- **PLA2R antibodies (mainly IgG4** were colocalized in glomerular deposits)
  - **Circulating anti-PLA2R** antibodies at or after transplant is risk factor
  - **High titers** earlier onset of recurrence
  - **Persistence or reappearance** after transplant predicts a worsening clinical course
- Antibodies to THSD7A and anti-semaphorin 3B antibodies associated with recurrence
- **Genetic factors**
  - Genetic polymorphisms of PLA2R gene and HLA-A3 antigen.
  - polymorphisms in donor *PLA2R1* and *HLA-D*.
- **Living, related donor transplant increases risk of recurrence** Zaghrini CKidney Int 2019; 95:666.

Recurrent MN

Clinical presentation:

- Usually recur after **13 to 15 months**. Reinhard L, et al J Am Soc Nephrol 2020; 31:197.
- **Progression of proteinuria** is common. Hoxha E, N Engl J Med 2016; 374:1995.
- **GFR** is often normal or only mildly decreased on initial presentation.

Recurrent MN-surveillance

All patients

Monitoring
Scr, UPCR/month for 6-12 m

PLA2R associated MN

Monitoring
Scr, UPCR, and PLA2Rab/m for 6-12 m

- **Rising biomarkers ------Biopsy**
- **No need for protocol biopsy to monitor for recurrence**
- IgG4 is the dominant IgG subclass in recurrent MN. **Hanset N, et al. Am J Kidney Dis 2020; 76:624.**

Treatment if recurrent MN

Mild
Prot.<1g
Normal eGFR
Protocol biopsy

Moderate to severe
Prot. >1g
Deteriorating eGFR

No I.S.
Supportive TTT
RASi,BP control, Statin
Monitoring
Scr, UPCR, PlA2R ab

Rituximab, redoes if:
pro.t.>1g CD19>1%

Supportive TTT
RASi,BP control, Statin
Monitoring
Scr, UPCR, PlA2R ab ,CD19

Rituximab resistant (2 courses)
pro.t.>1g PLA2Rab
Cycloph. 2mg/kg/d for 8-12 wks
instead of antiproliferative

Recurrent MN-prognosis

- **Incidence of graft loss at 10 years due to recurrent disease was 12.5 % [48].**
- **5-year graft survival was only 59 %. Greater than 60 % graft loss due to the recurrent MN [13].**
- **10-year graft survival was similar between patients ± recurrent MN (87 vs. 90 %, respectively) [14].**

DE NOVO MEMBRANOUS NEPHROPATHY

	Recurrent MN	Denovo MN
Incidence	10 and 45 %	1.5-2%, Paediatric Tx 9%
Association		ABMR, DSA
Target antigens	• PLA2R • THSD7A • semaphorin 3B	Protocadherin FAT1 • PLA2R (Covid-18 vaccinated)
clinically	Asymptomatic Proteinuria , eGFR At 13-15 months	Asymptomatic (30%) Proteinuria , eGFR At 63-102 months
Diagnosis	Biopsy IgG4 mainly	Biopsy IgG1 mainly(with ABMR)
TTT	As mentioned, Mild , moderate to severe	TTT of rejection
Prognosis (G loss)	12.5%	Worse than recurrent (50%)

Measures to be considered before transplant

- Diagnose the type of MN(1ry or 2ndry), PLA2R ab related or non- PLA2R ab related .
- If Anti-PLA2R ab negative-------- No further testing is needed (low risk)
- If Anti-PLA2R ab positive ------Test annually, if > 150u/ml preemptive TTT till decrease by 50%
- Non-PLA2R ab positive ----------No need to test for PLA2R
- Choice of donor : living has better outcome than deceased


Thank you