Membranous nephropathy

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Membranous nephropathy

- Definition:

- Immune complex glomerular disease in which immune deposits of IgG and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall.

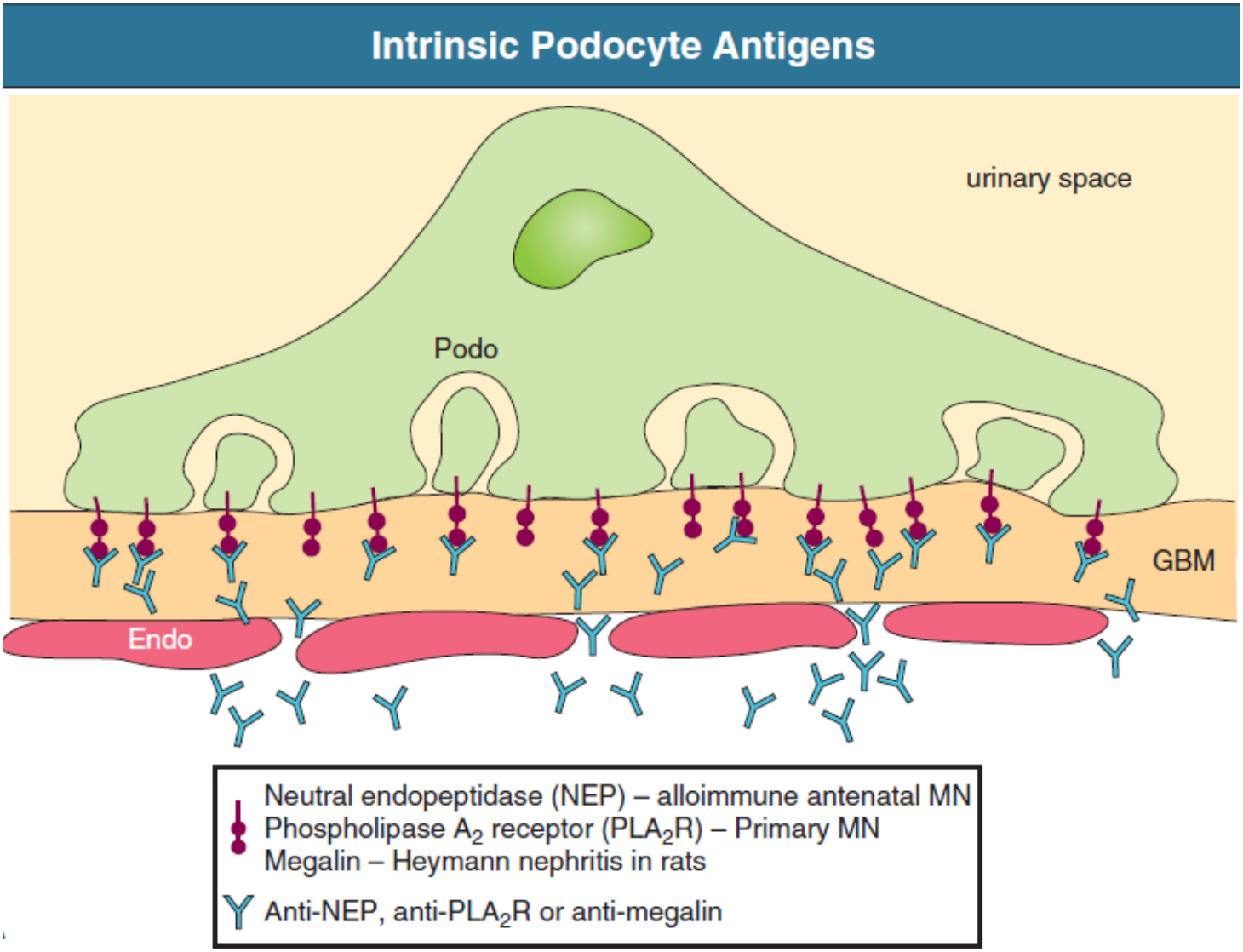
- Epidemiology:

- Most common cause of primary nephrotic syndrome in older (>60 years) Caucasian adults
  - 25 - 35% of cases
  - 20% progress to ESRD

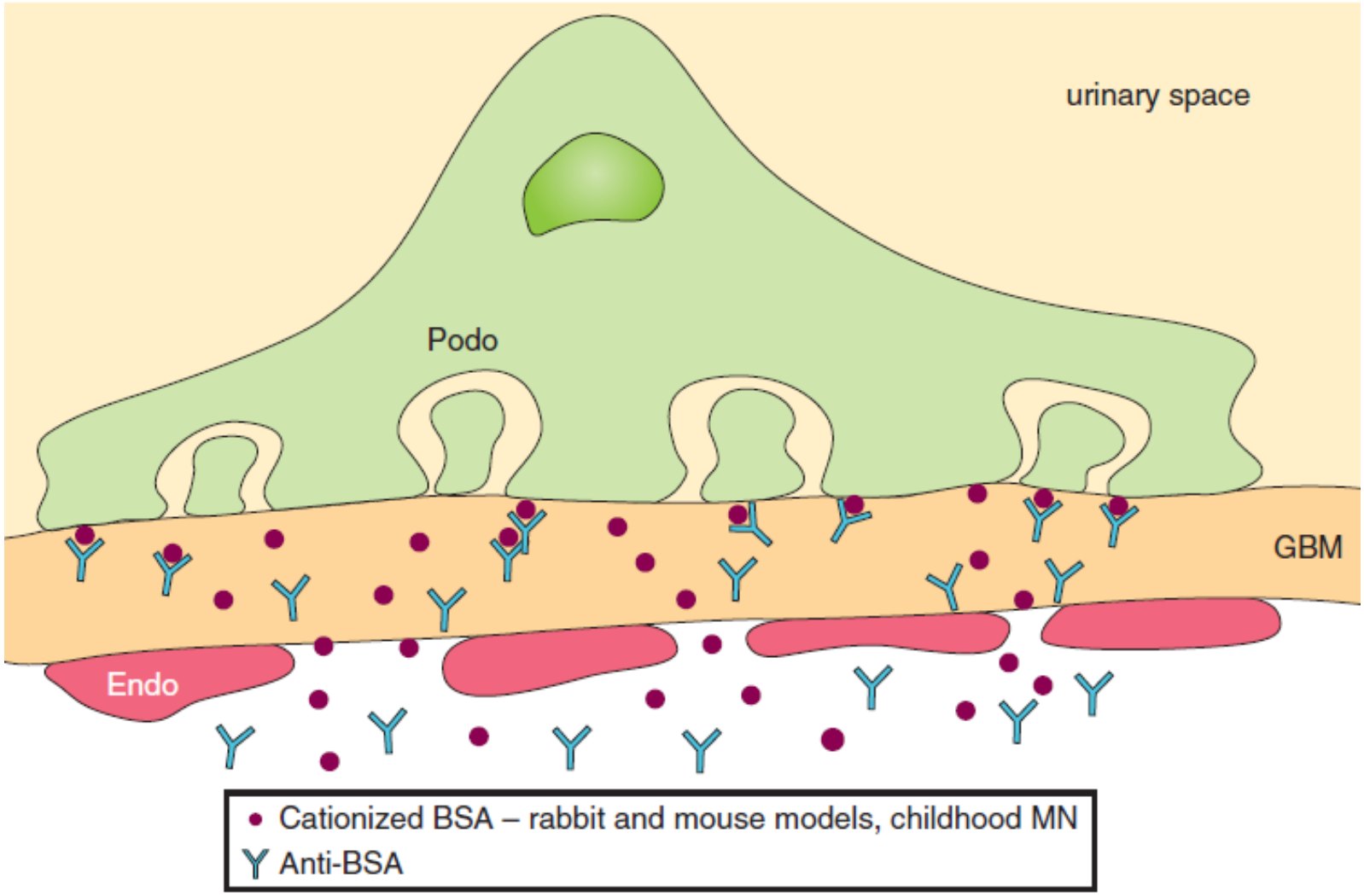
Etiology

Primary		
Anti-PLA_2R associated (70%-80%) Idiopathic (20%-30%)		
Secondary	**Common**	**Uncommon**
Autoimmune diseases	Class V lupus nephritis	Rheumatoid arthritis Autoimmune thyroid disease IgG4-related systemic disease Anti-GBM and ANCA-associated crescentic glomerulonephritis
Infections	Hepatitis B	Hepatitis C virus (HCV) Human immunodeficiency virus (HIV) Syphilis Schistosomiasis
Malignancy	Solid tumors (colon, stomach, lung, prostate)	Non-Hodgkin lymphoma Chronic lymphocytic leukemia (CLL) Melanoma
Drugs or toxins	Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors	Mercury-containing compounds Gold salts D-Penicillamine, bucillamine
Miscellaneous		Sarcoidosis Anticationic bovine serum albumin
Alloimmune		
Graft-versus-host disease following hematopoietic stem cell transplantation *De novo* membranous nephropathy in renal allograft Fetomaternal alloimmunization to neutral endopeptidase		

Pathogenesis
1. Antigens



Extrinsic Planted Antigens



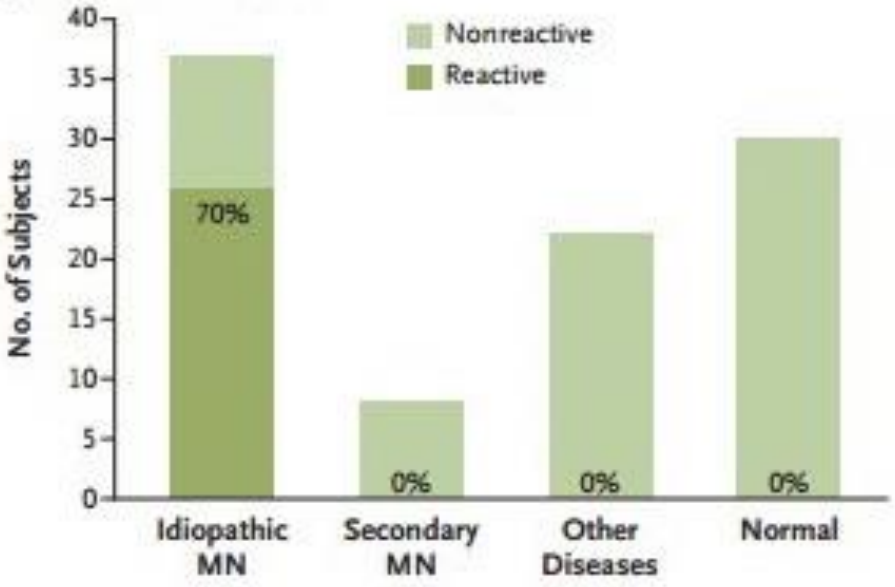
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

B Reactivity to the 185-kD Protein



No. of Subjects	Idiopathic MN	Secondary MN	Other Diseases	Normal
Reactive serum	26	0	0	0
Nonreactive serum	11	8	22	30

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CORRESPONDENCE

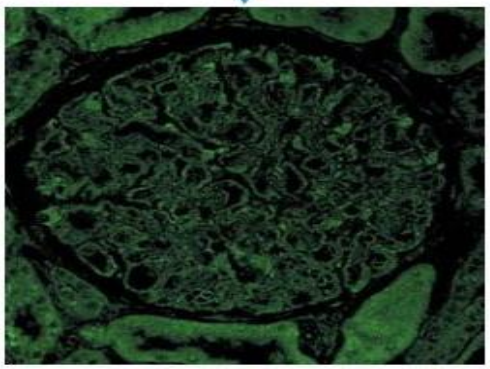
PLA_2R Autoantibodies and PLA_2R Glomerular Deposits in Membranous Nephropathy

N Engl J Med 2011; 364:689-690 | February 17, 2011 | DOI: 10.1056/NEJMc1011678

autoantibodies against PLA_2R were found in 70 to 80% of patients with idiopathic membranous nephropathy but not in those with secondary membranous nephropathy or other renal diseases. It has been suggested that the serum level of PLA_2R autoantibody could be used for the diagnosis of and therapeutic implications. The absence of circulating PLA_2R autoantibody at the time of kidney biopsy does not rule out a diagnosis of PLA_2R-related membranous nephropathy.

Hanna Debiec, Ph.D.
Pierre Ronco, M.D., Ph.D.

Serum anti-PLA_2R positive | Serum anti-PLA_2R negative | Serum anti-PLA_2R negative



N=3

PLA_2R		
No. of Patients	Serum Reactivity	Biopsy
21	+	+
3	+	–
8	–	–
10	–	+
42	+24	+31
	57%	74%

Anti-PLA2R Titers Clinical Significance (1)

Serum PLA2R auto antibodies test is a good +ve but not good -ve marker for MN.

Anti-PLA2R Titers Clinical Significance (2)

- anti-PLA2R titers strongly correlated with clinical status
- lower anti-PLA2R titers were associated with a higher rate of spontaneous remission
- a decline in anti-PLA2R predicted the clinical response to immunosuppressive therapy

Hofstra JM et al. Clin J Am Soc Nephrol 2011; 6:1286.
Hofstra JM et al. J Am Soc Nephrol 2012; 23:1735.
Ruggenenti P et al. J Am Soc Nephrol 2015; 26:2545.

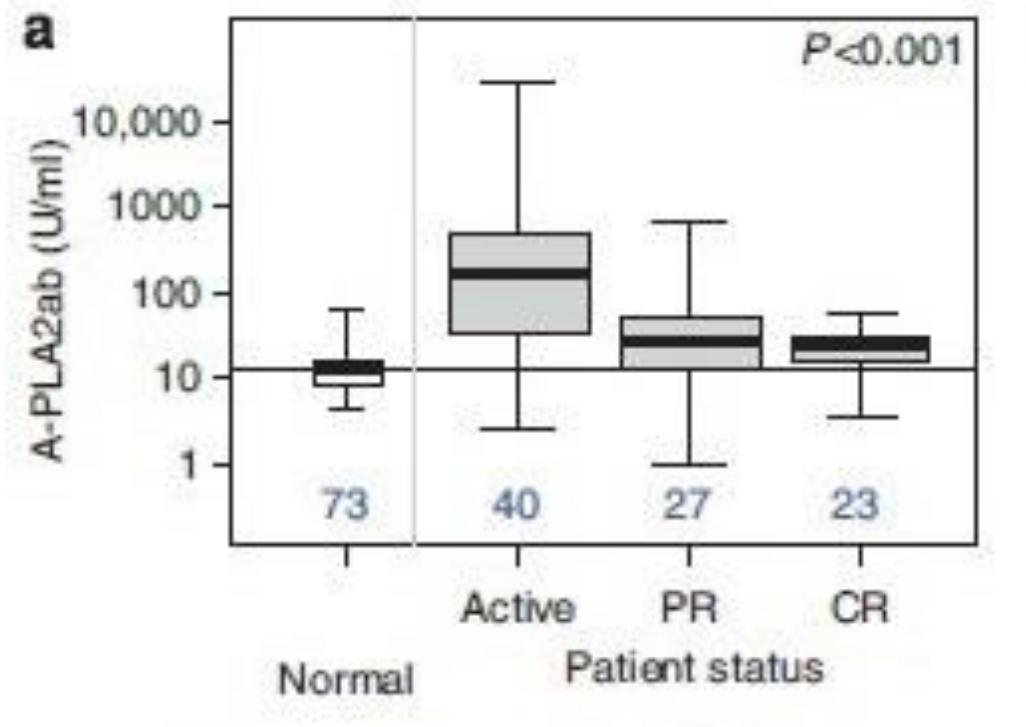
http://www.kidney-international.org

kidney INTERNATIONAL ISN

clinical investigation

Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy

Durga Kanigicherla[1], Jennet Gummadova[2], Edward A. McKenzie[2], Stephen A. Roberts[3], Shelley Harris[1], Milind Nikam[1], Kay Poulton[1], Lorna McWilliam[1], Colin D. Short[1], Michael Venning[1] and Paul E. Brenchley[1,4]

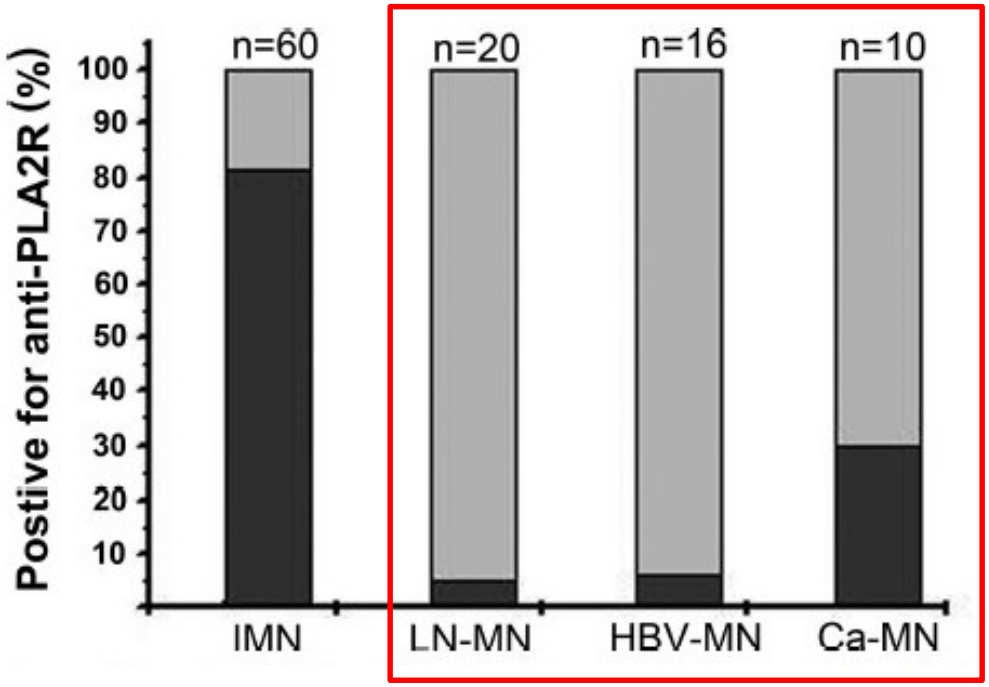


Anti-PLA2R

Is it only related to Idiopathic MN?

Anti-Phospholipase A2 Receptor Antibody in Membranous Nephropathy

Weisong Qin,* Laurence H. Beck, Jr.,† Caihong Zeng,* Zhaohong Chen,* Shijun Li,* Ke Zuo,* David J. Salant,† and Zhihong Liu*



J Am Soc Nephrol 22: 1137–1143, 2011.

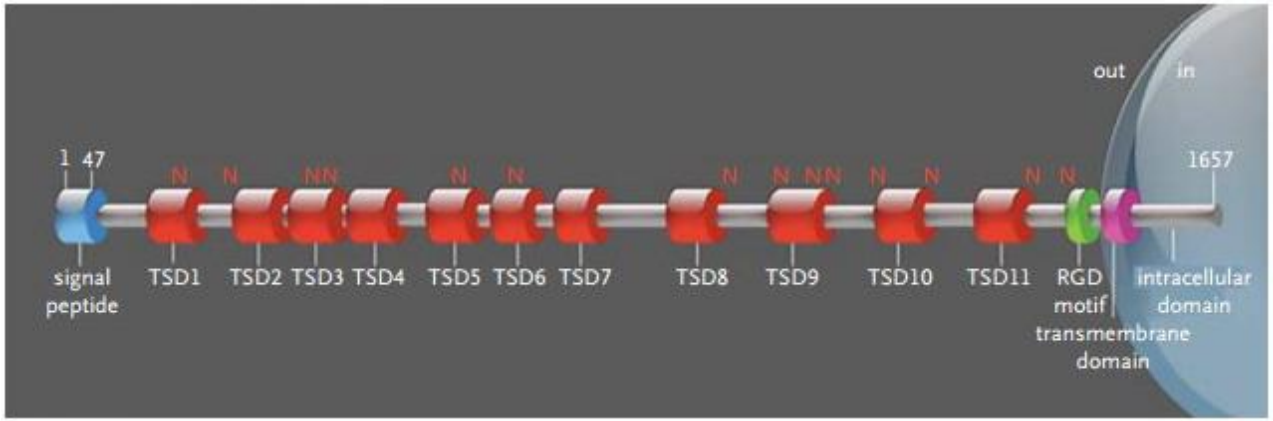
Anti-PLA2R Titers Clinical Significance (3)

- Highly suggestive of primary MN
- But does not exclude the coexistence of:
  - hepatitis virus infection,
  - malignancy,
  - another associated rheumatologic or inflammatory disease.

J Am Soc Nephrol 22: 1137–1143, 2011.

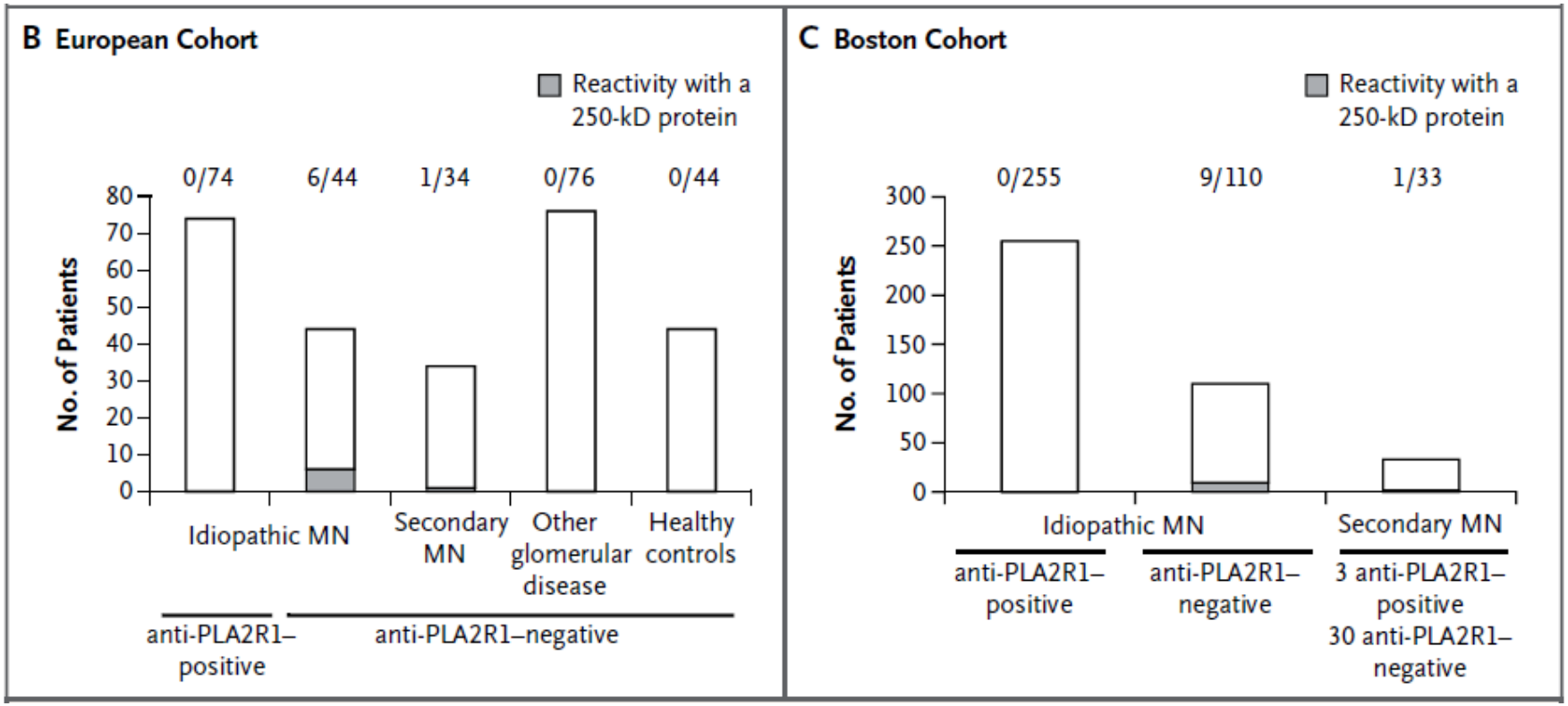
Thrombospondin type-1 domain-containing 7A (THSD7A)

- A transmembrane protein expressed on podocytes.
- Responsible Ab in 10% of idiopathic MN with negative anti-PLA2R Ab.



ORIGINAL ARTICLE

Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy



2. Antibodies

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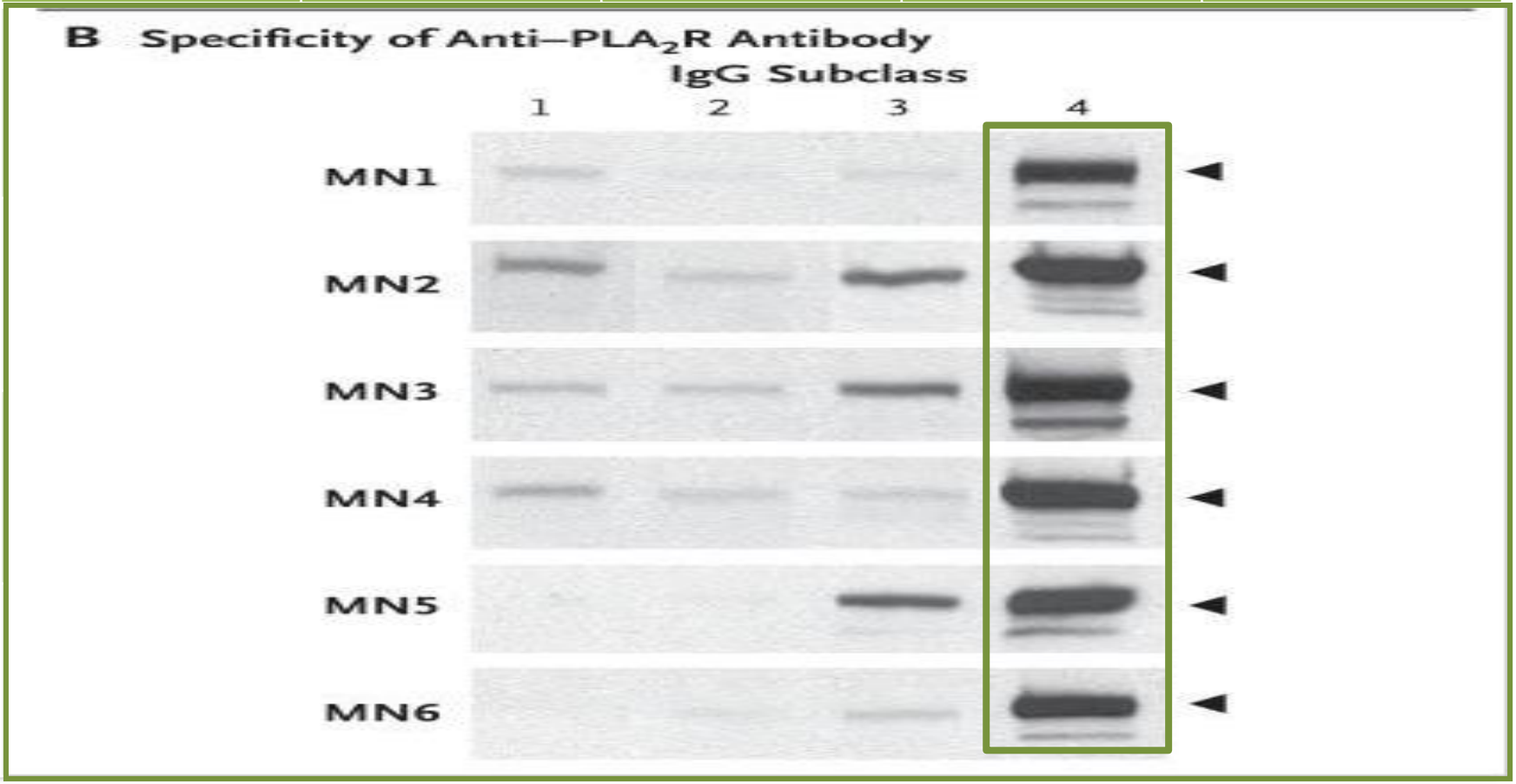
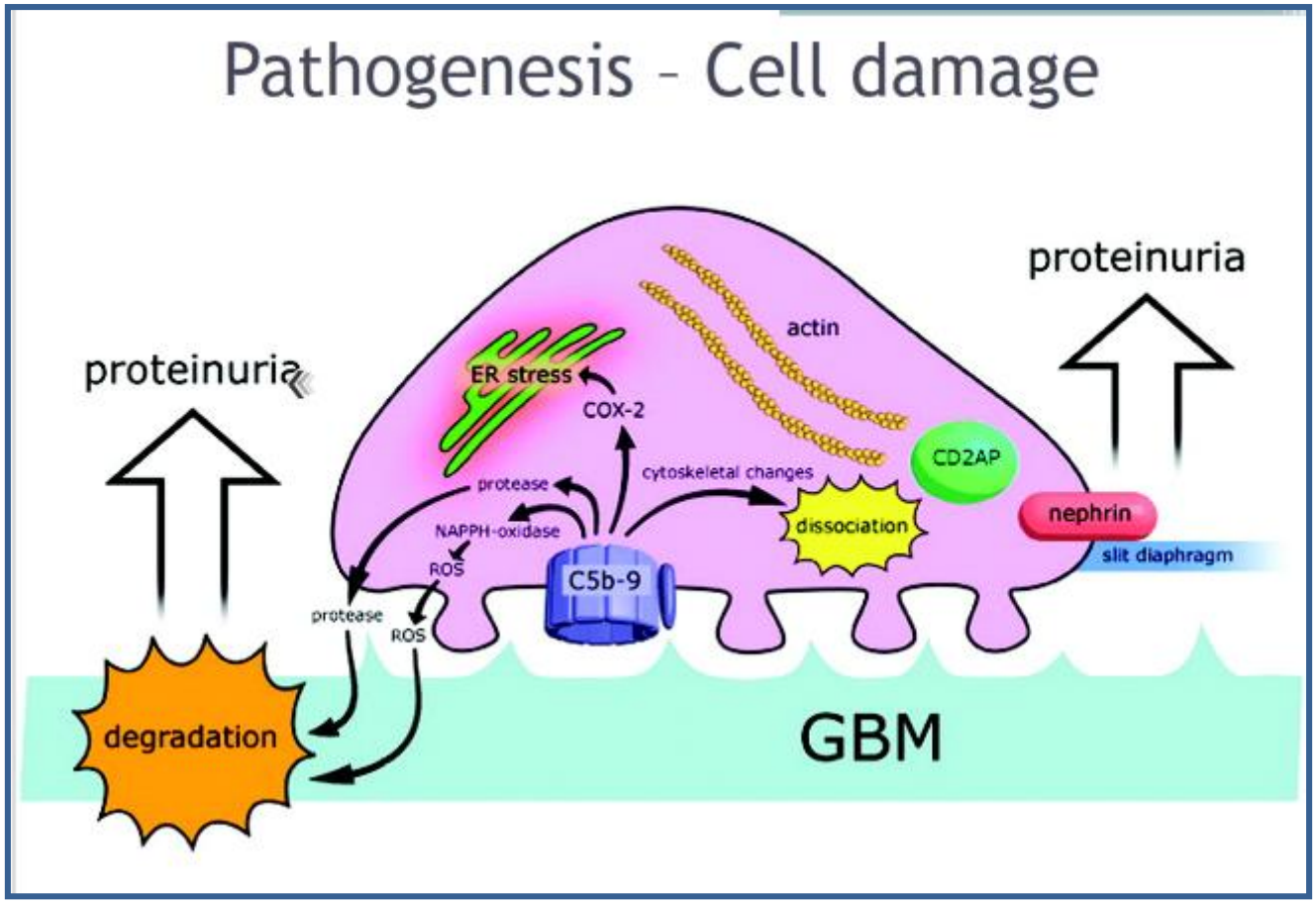
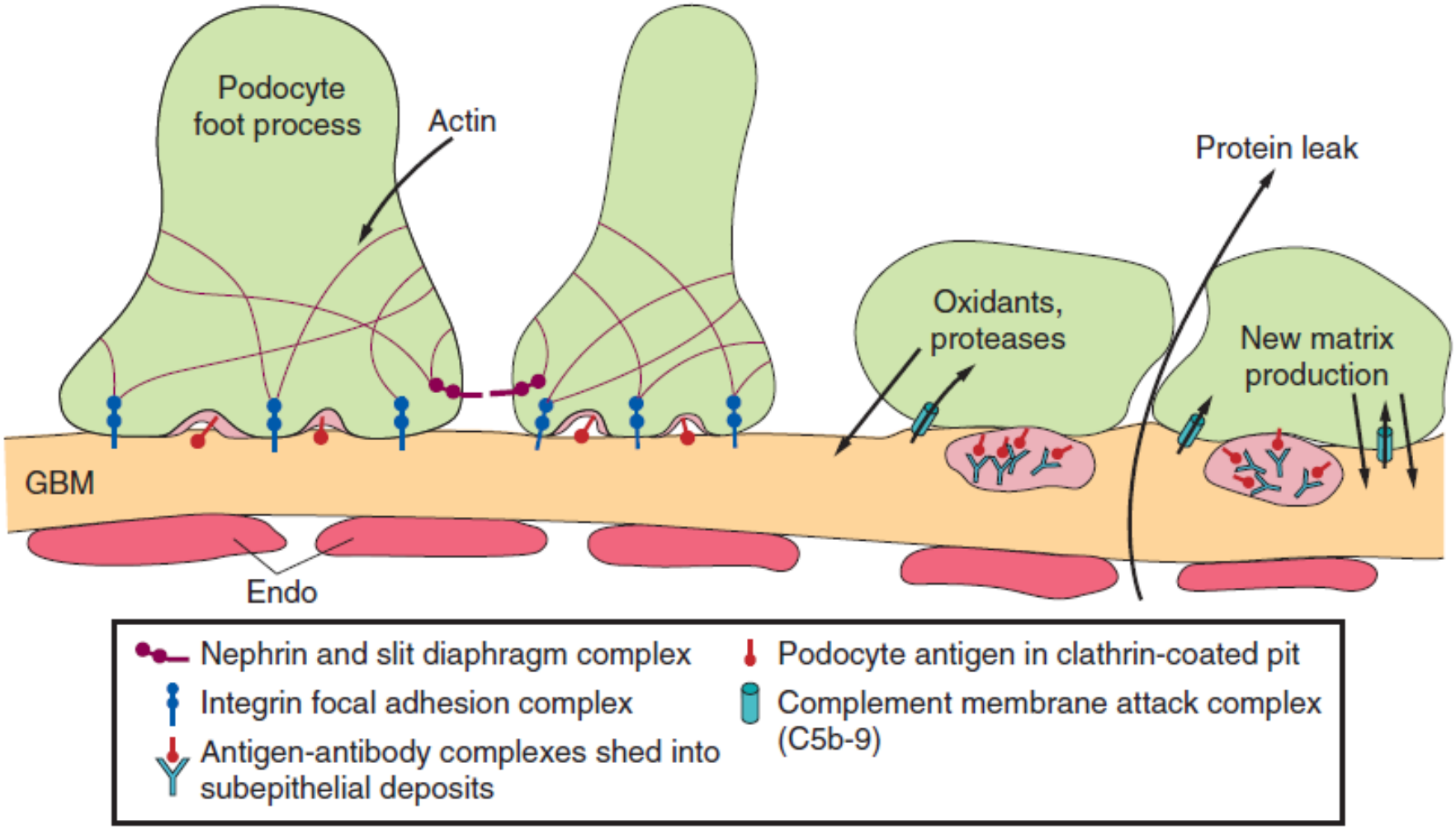
	IGg1	IGg2	IGg3	IGg4



3. Podocyte damage



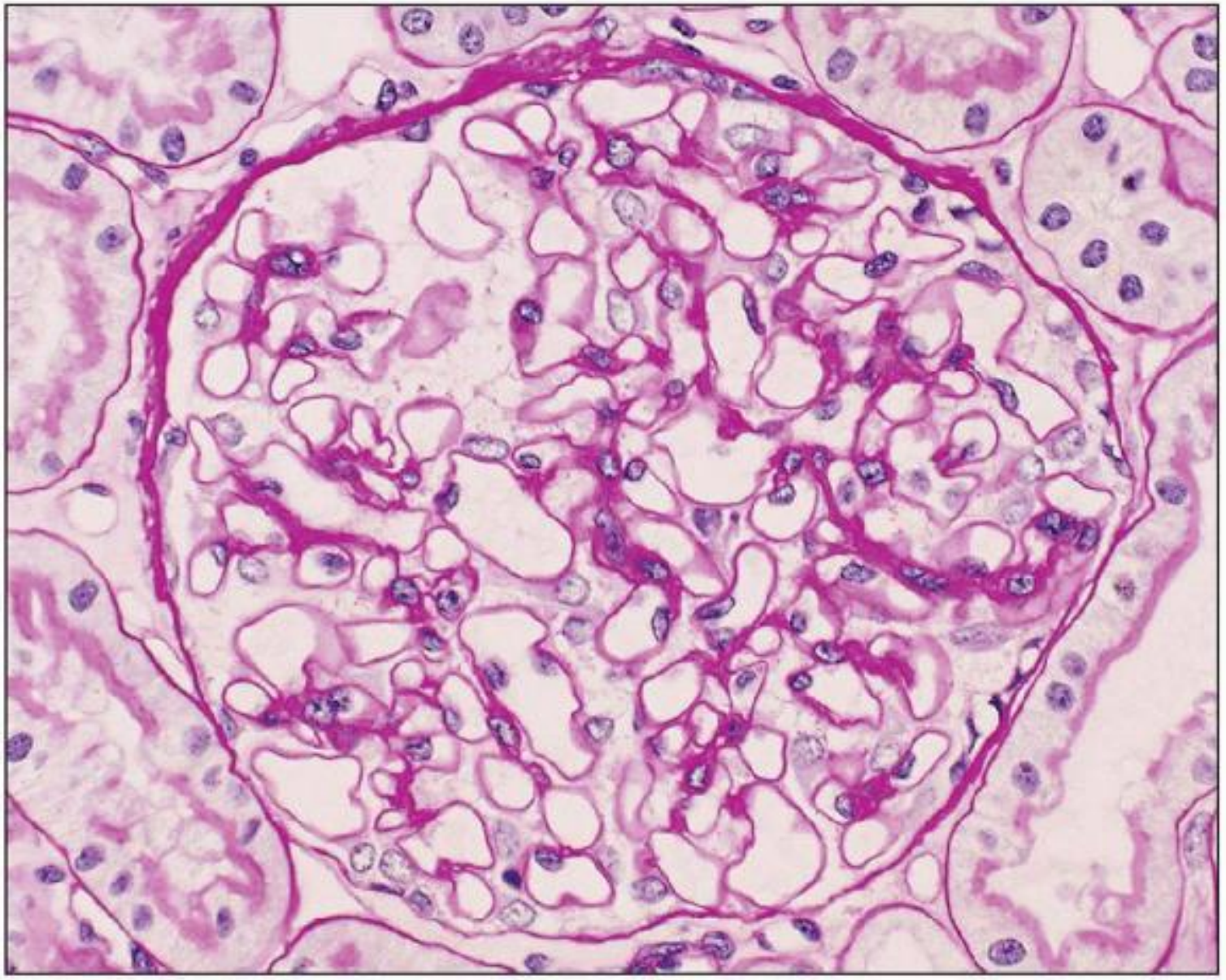
4. New ECM formation

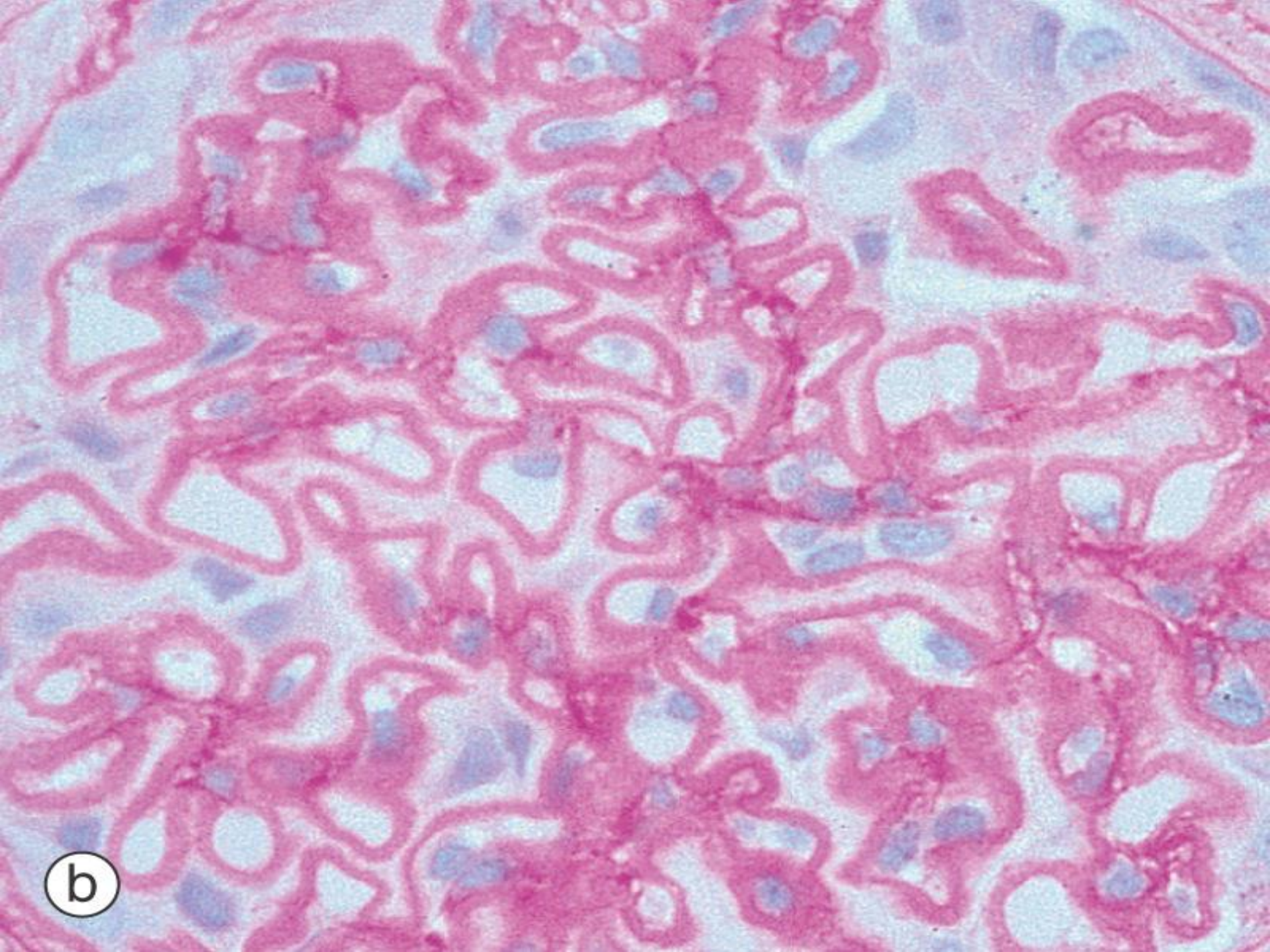


Clinical features

- Proteinuria:
  - Subnephrotic (20 – 30%)
  - Nephrotic range proteinuria (70 – 80%)
  - Non selective
- Microscopic hematuria (30 – 40%)
- Normal complement level
- In primary MN, serologic tests for anti-PLA2R are positive in 75% to 80% of cases
- Other autoantibodies (ANA, ANCA, RF) –ve
- Hypertension (10 – 20%)
- Normal renal functions (90%)
- Thromboemolic disease (DVT, RVT, PE)

Pathology

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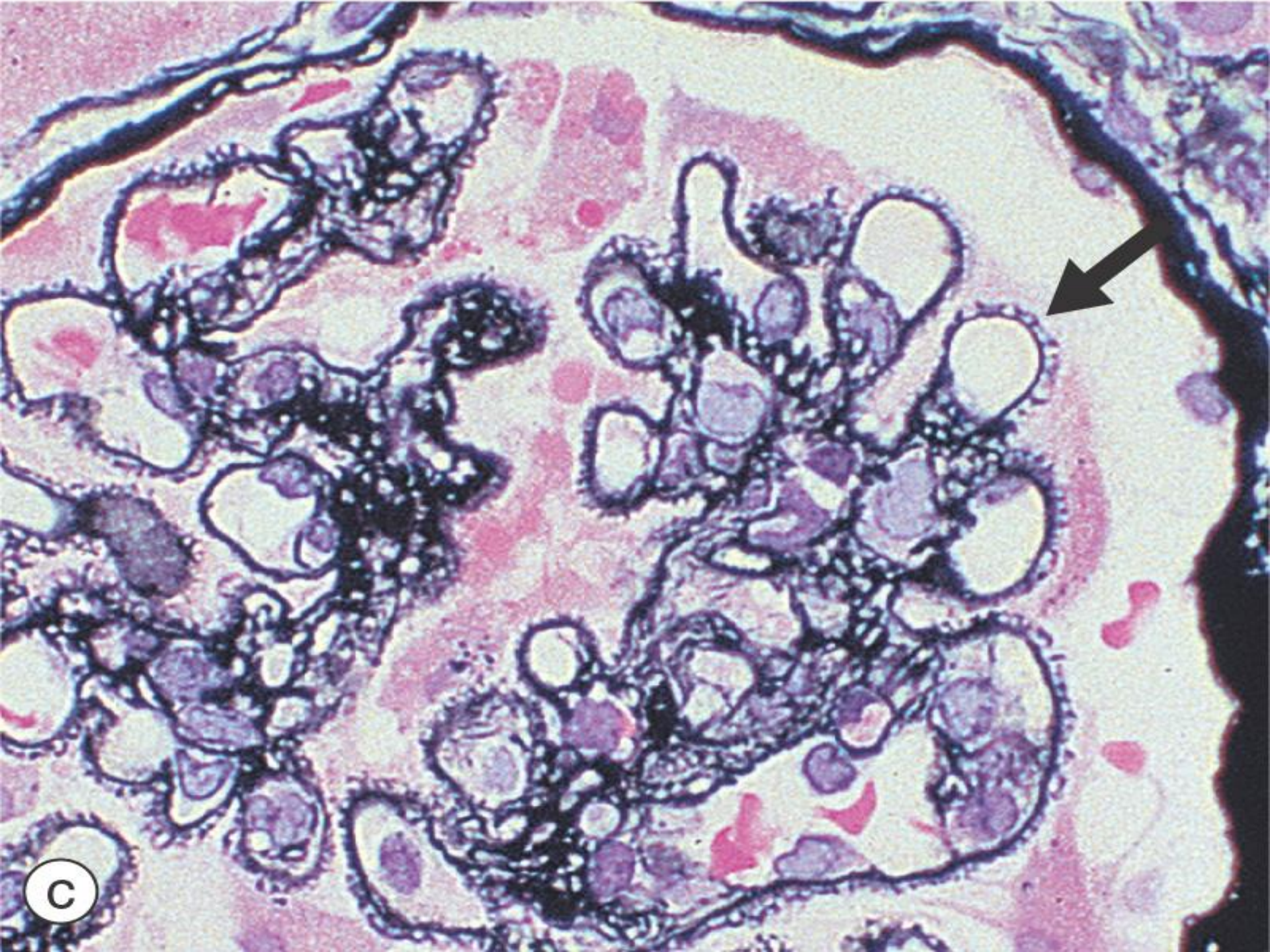
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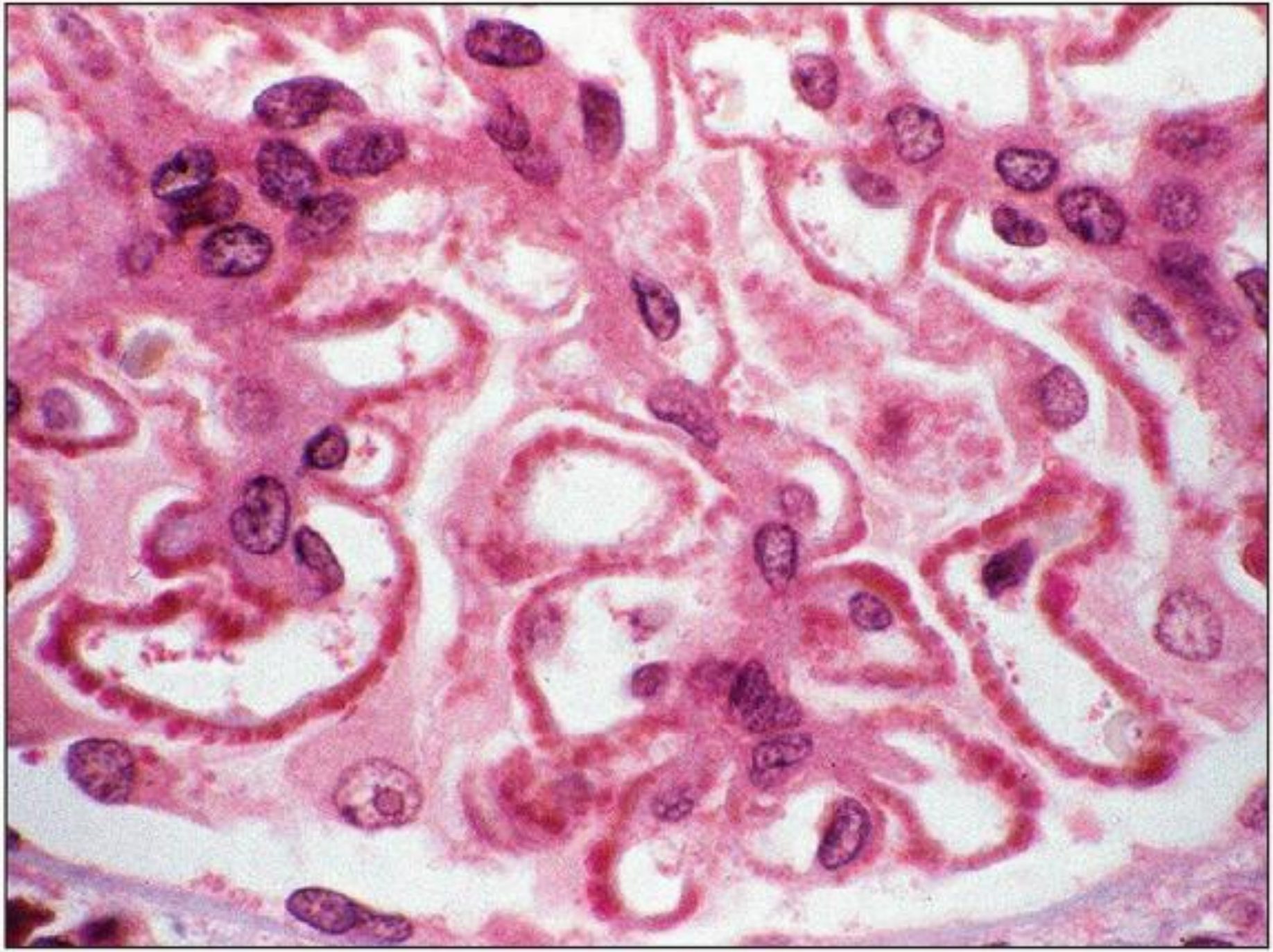

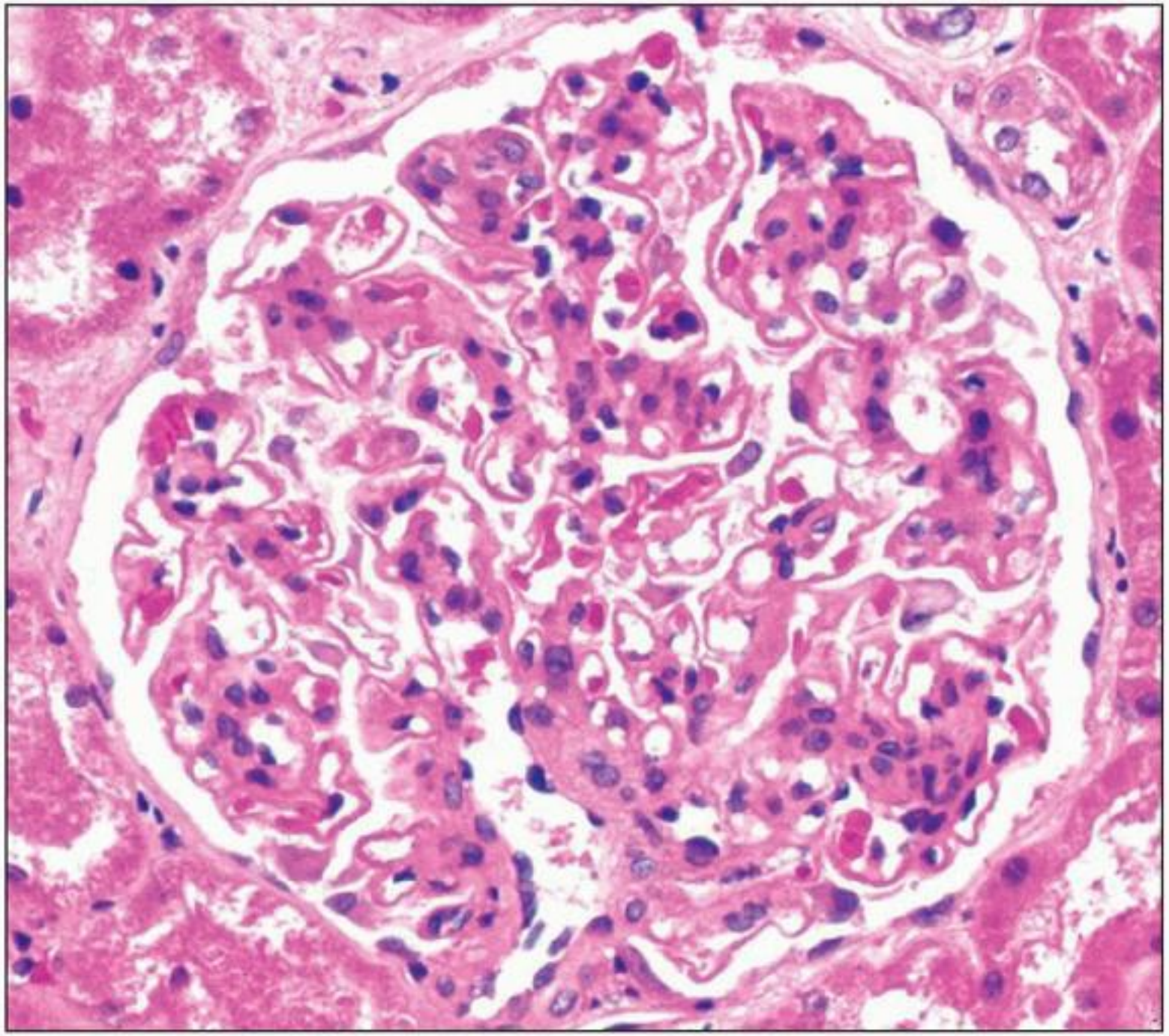

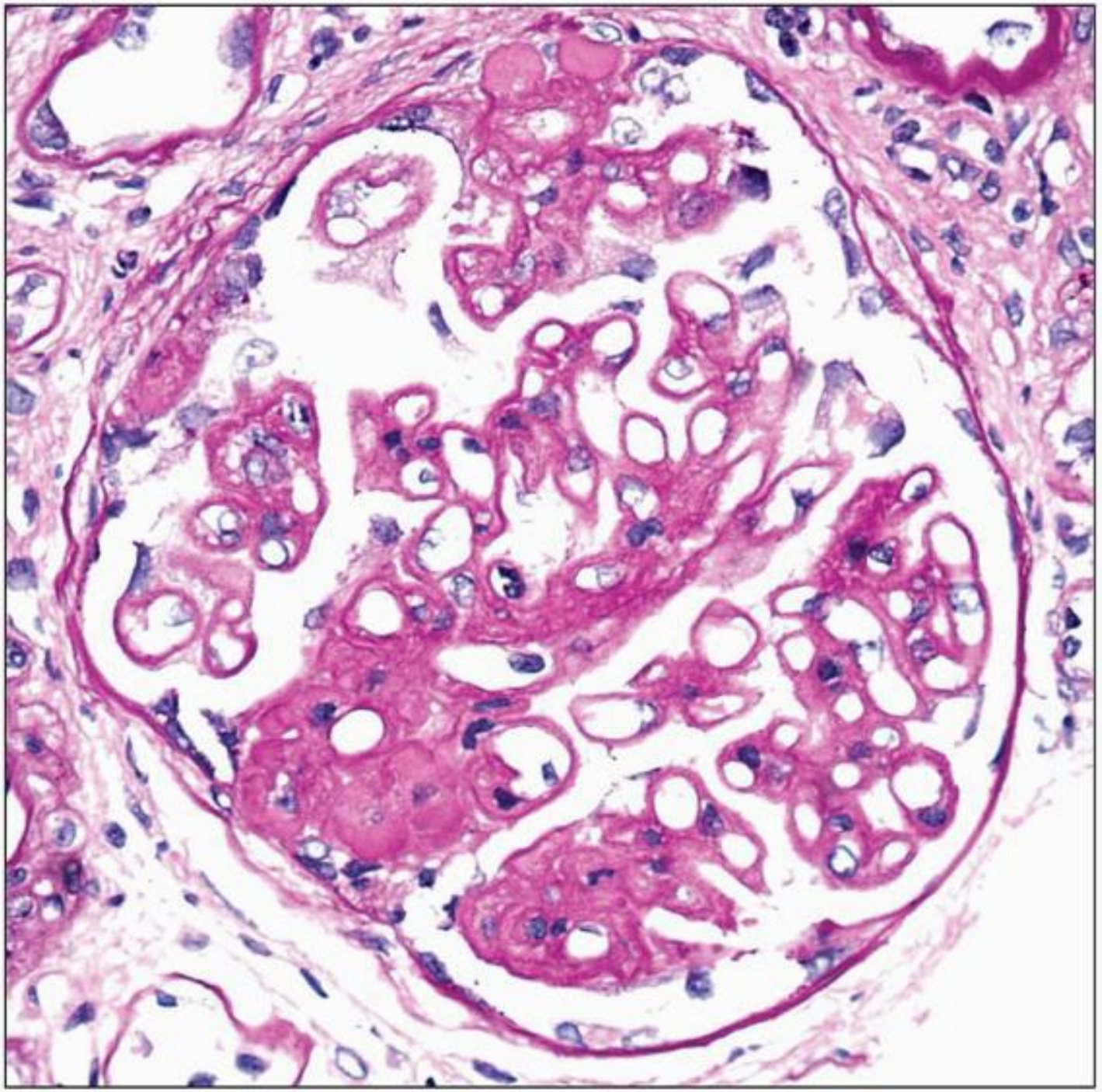

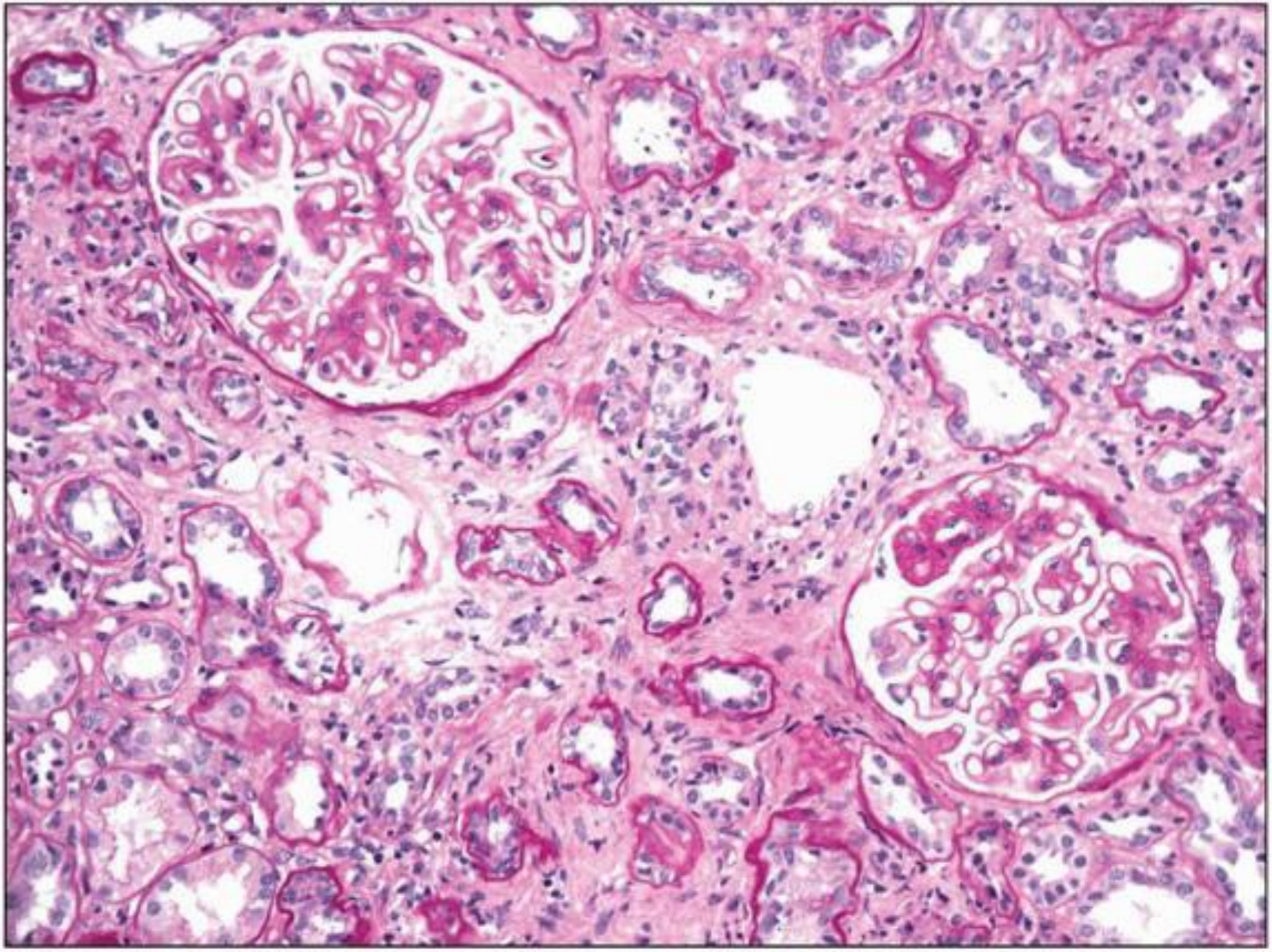

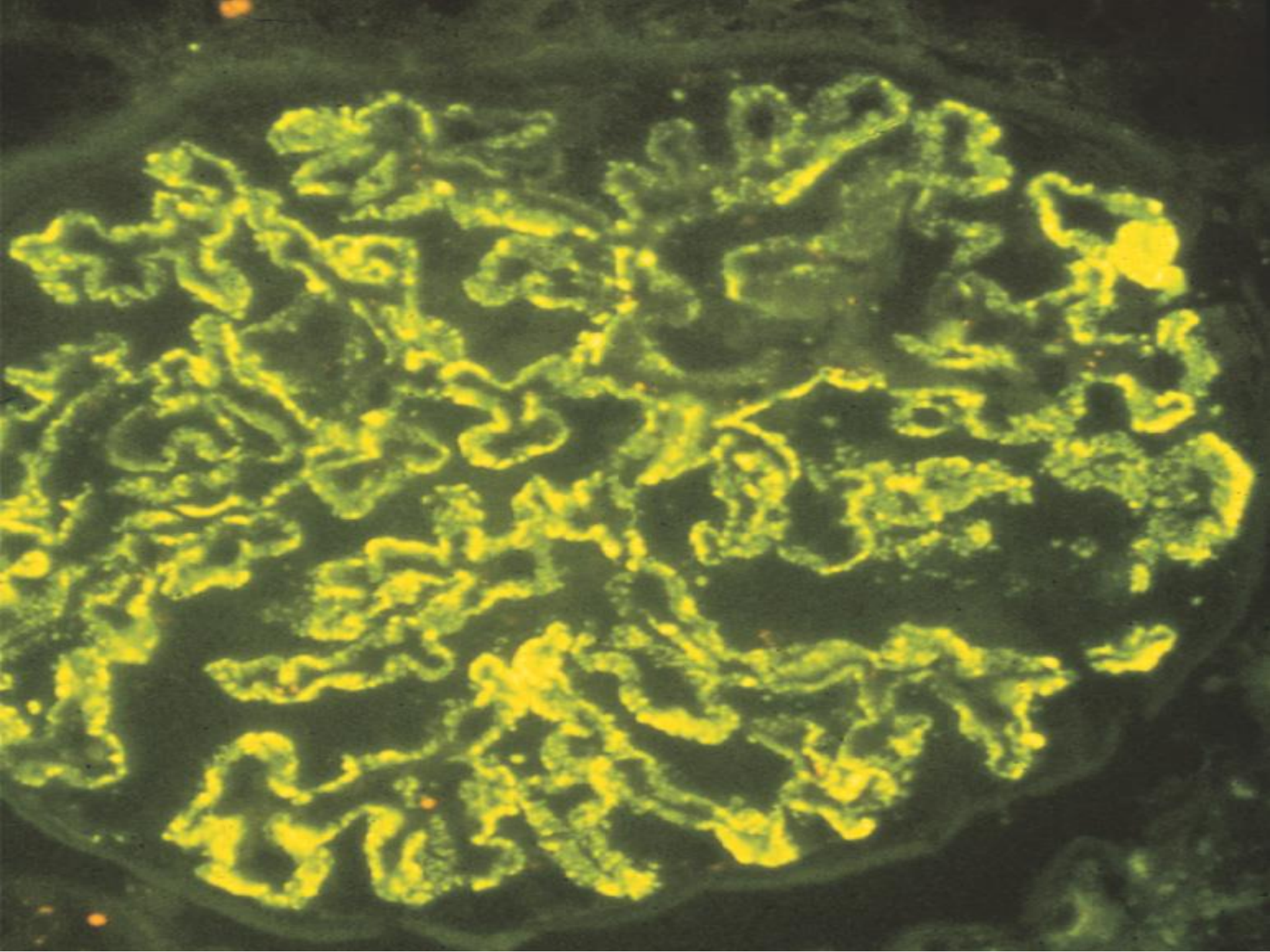

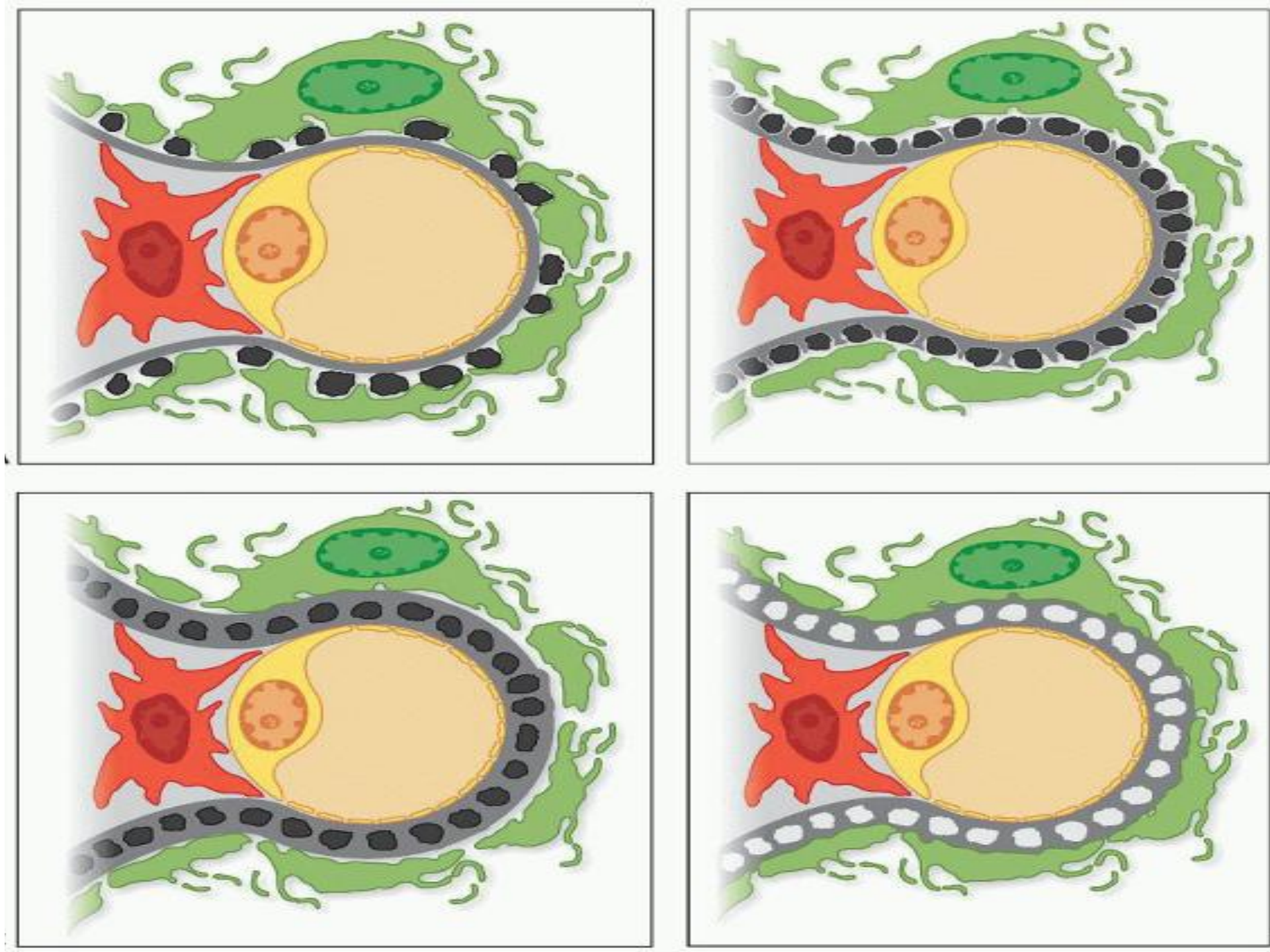

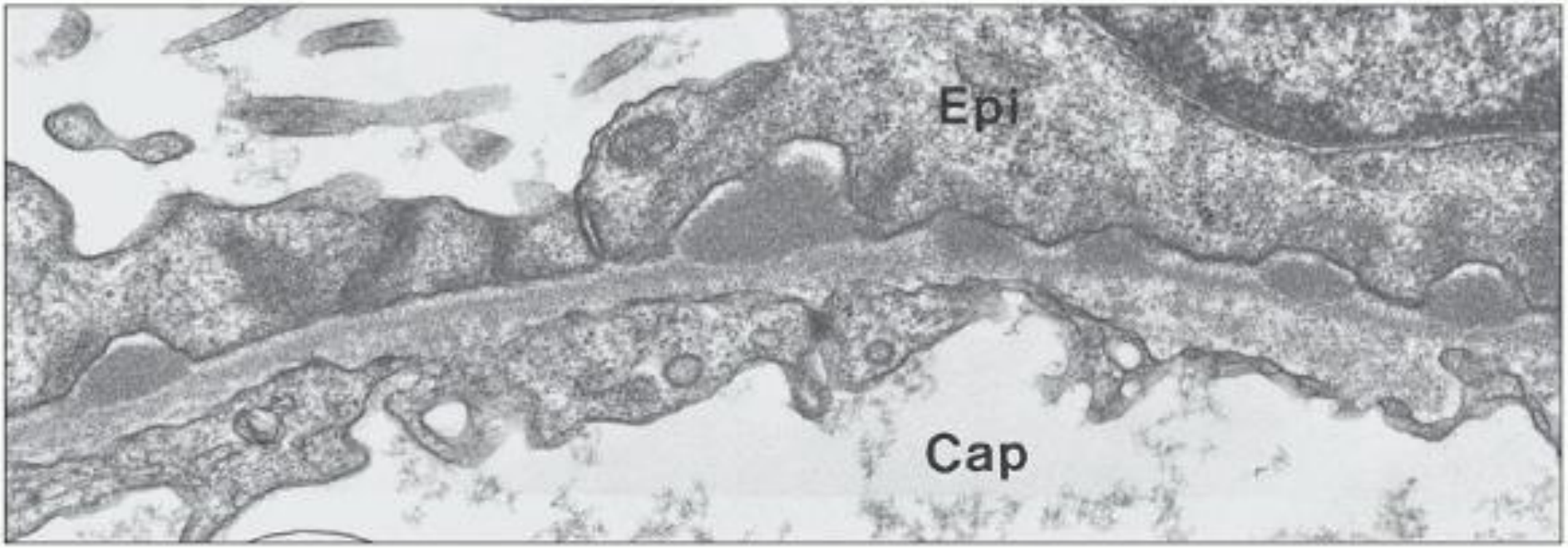
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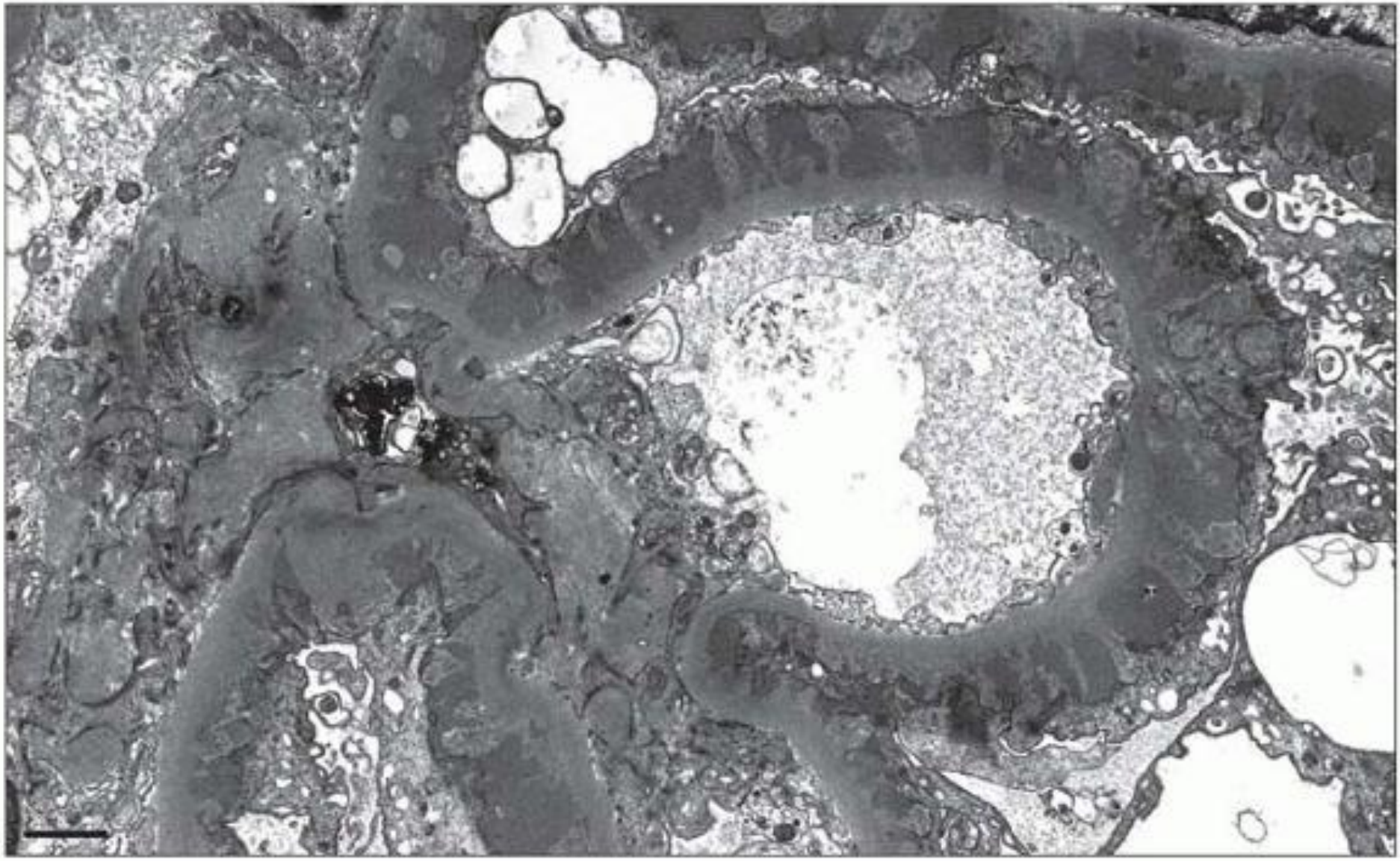
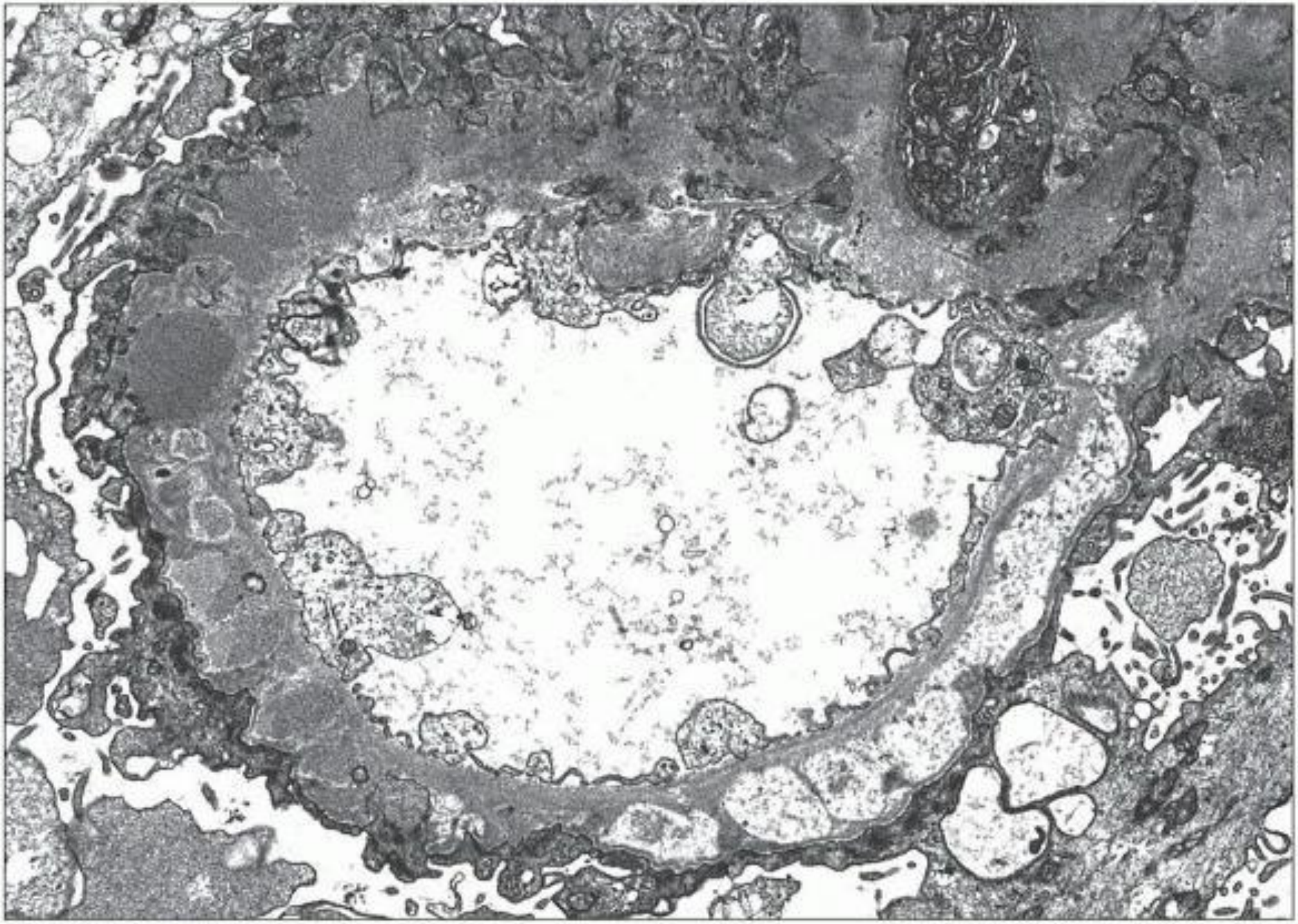
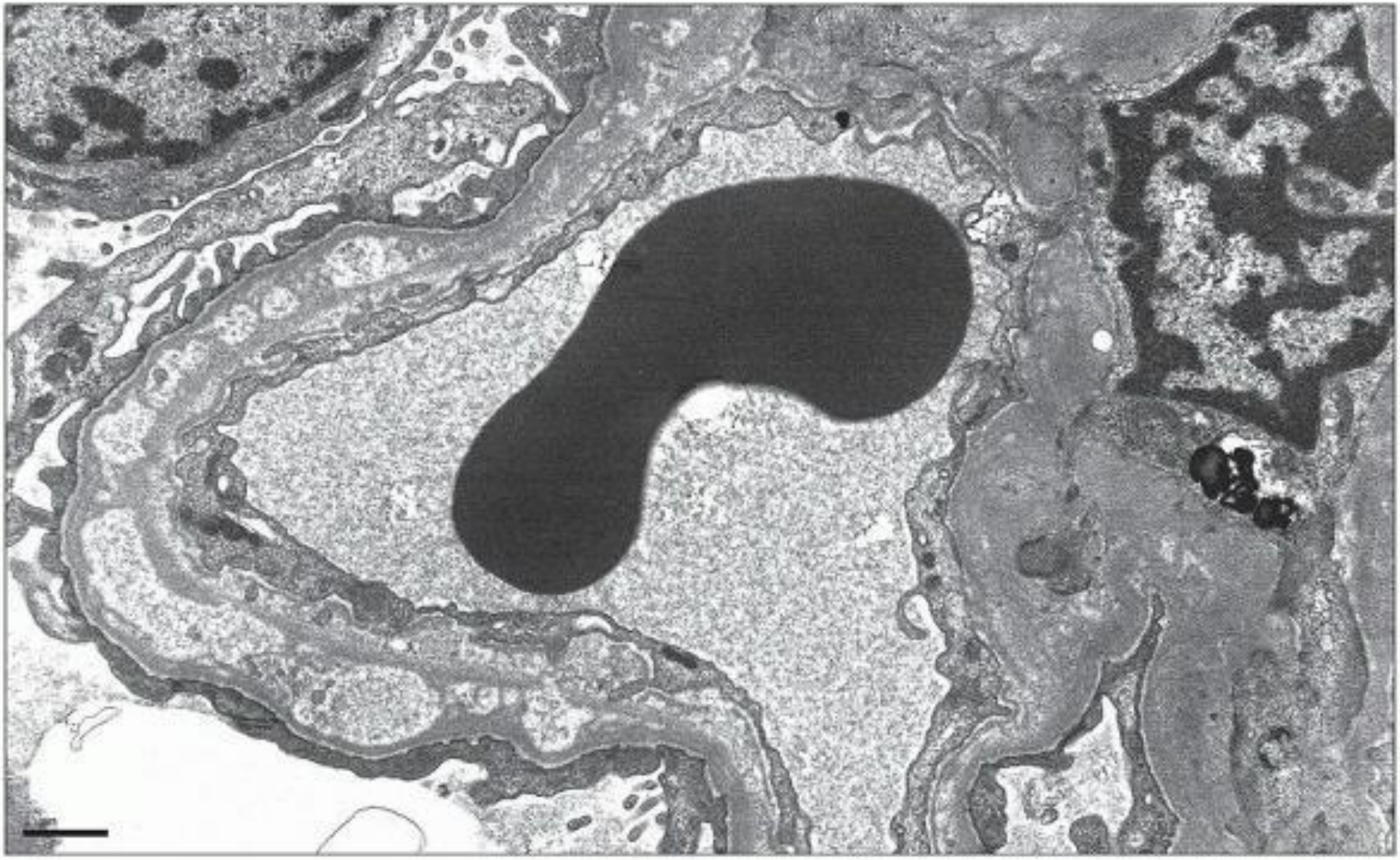






Diagnosis

Patient Groups	Test
All patients	Blood pressure Renal function (serum creatinine and creatinine clearance) Urine protein excretion (24-hour urine or urine protein-creatinine ratio) Serum albumin Serum cholesterol, including LDL-HDL ratio Urinalysis Renal biopsy Anti-PLA_2R
Associated disease	Hepatitis B (HBs antigen) Hepatitis C (HCV antibody) Antinuclear antibody (ANA), anti–double-stranded DNA (hallmark of systemic lupus erythematosus) Complement C3, C4 (usually normal in idiopathic MN)
Select Patients	
With suspected thromboembolic events, flank pain, hematuria, acute renal failure	Renal venous Doppler ultrasound Contrast CT, MRI
With sudden decrease in renal function, development of active urine sediment	Anti-GBM antibody Antineutrophil cytoplasmic antibody (ANCA) Assess for interstitial nephritis
Suggestive symptoms or age >50 years	Cancer screening (see text)

Distinguishing Histopathologic Features of Primary Versus Secondary Membranous Nephropathy

Primary	Secondary
Immunofluorescence Microscopy	
IgG4 > IgG1, IgG3	IgG1, IgG3 > IgG4
IgA, IgM absent	IgA, IgM may be present.
Mesangial Ig staining absent	Mesangial Ig staining may be present.
C1q negative or weak	C1q positive
PLA_2R positive and co-localizes with IgG	PLA_2R negative
Electron Microscopy	
Subepithelial deposits only ± mesangial deposits rarely	Subepithelial deposits ± mesangial and subendothelial deposits

Malignancy Screening
When to screen?

If the anti-PLA2R antibody test is negative

+ the kidney histology is consistent with secondary MN

+ there is no other clear cause of secondary MN

+ risk factors or alarm signs:
    - extensive smoking history,
    - guaiac-positive stools,
    - unexplained anemia or weight loss

Laurence H Beck, Richard J Glassock. UpTodate. Oct 21, 2015.

Malignancy Screening
How to screen?

Investigations suggested to detect/exclude an underlying cancer in a patient with apparently idiopathic (primary) MN and repeatedly negative serologic tests for anti-PLA2R1 autoantibody and/or absence of PLA2R1 or IgG4 in glomerular deposits

Cancer Type	Young Adult	Older Patient
Lung	Chest x-ray	Computed tomography
Kidney	Ultrasonography, malignant cells in the urine	Ultrasonography, malignant cells in the urine
Breast	Physical examination	Mammography
Stomach	Fecal occult blood?	Gastroscopy
Colon	Fecal occult blood?	Colonoscopy
Prostate	Rectal digital examination, percentage PSA	Ultrasonography, prostate biopsy
Uterus	Gynecologic examination	Colposcopy

In young patients, fecal occult blood is usually searched for only in the case of anemia. MN, membranous nephropathy; PLA2R1, phospholipase A2 receptor 1; PSA, prostate specific antigen.

Claudio Ponticelli, Richard J. Glassock. CJASN. 2014 Mar;9(3):609-16.

Malignancy Screening

How to screen?

Examination:

- LN.

- Systemic exam for any mass.

Malignancy Screening
Frequency of screening

Cancer screening should continue for a period of **five to ten years** after the diagnosis of MN

(since cancers associated with MN are typically diagnosed within this time frame.)

Laurence H Beck, Richard J Glassock. UpTodate. Oct 21, 2015.

Clinical course

- Spontaneous remission in up to 30%
- 25% ESRD after 8 years

Factors	Predictor	PPV (%)
Clinical Features		
Age	Older > younger	43
Gender	Male > female	30
HLA type	HLA/B18/DR 3/Bffl present	71
Hypertension	Present	39
Serum Levels		
Albumin	<1.5 g/dL	56
Creatinine	Above normal	61
Urine Protein		
Nephrotic syndrome	Present	32
Proteinuria	>8 g for >6 months	66
IgG excretion	>250 mg/day	80
β_2-Microglobulin excretion	>54 μg/mmol creatinine <54	79
C5b-9 excretion	>7 mg/mg creatinine	67
Biopsy Changes		
Glomerular focal sclerosis	Present	34
Tubulointerstitial disease	Present	48

Management
Renal Disease Risk Categories

Low Risk	Medium Risk	High Risk
Normal serum creatinine and creatinine clearance plus proteinuria <4 g/day over 6 months of observation	Normal or near-normal creatinine clearance and persistent proteinuria >4 g/day to <8 g/day over 6 months despite maximum conservative treatment	Deteriorating renal function and/or persistent proteinuria >8 g/day for 3 (up to 6) months of observation

Definitions

Complete Remission: Urinary protein excretion <0.3 g/d (uPCR <300 mg/g or <30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

Partial Remission: Urinary protein excretion <3.5 g/d (uPCR <3500 mg/g or <350 mg/mmol) *and* a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.

7.1: Evaluation of MN

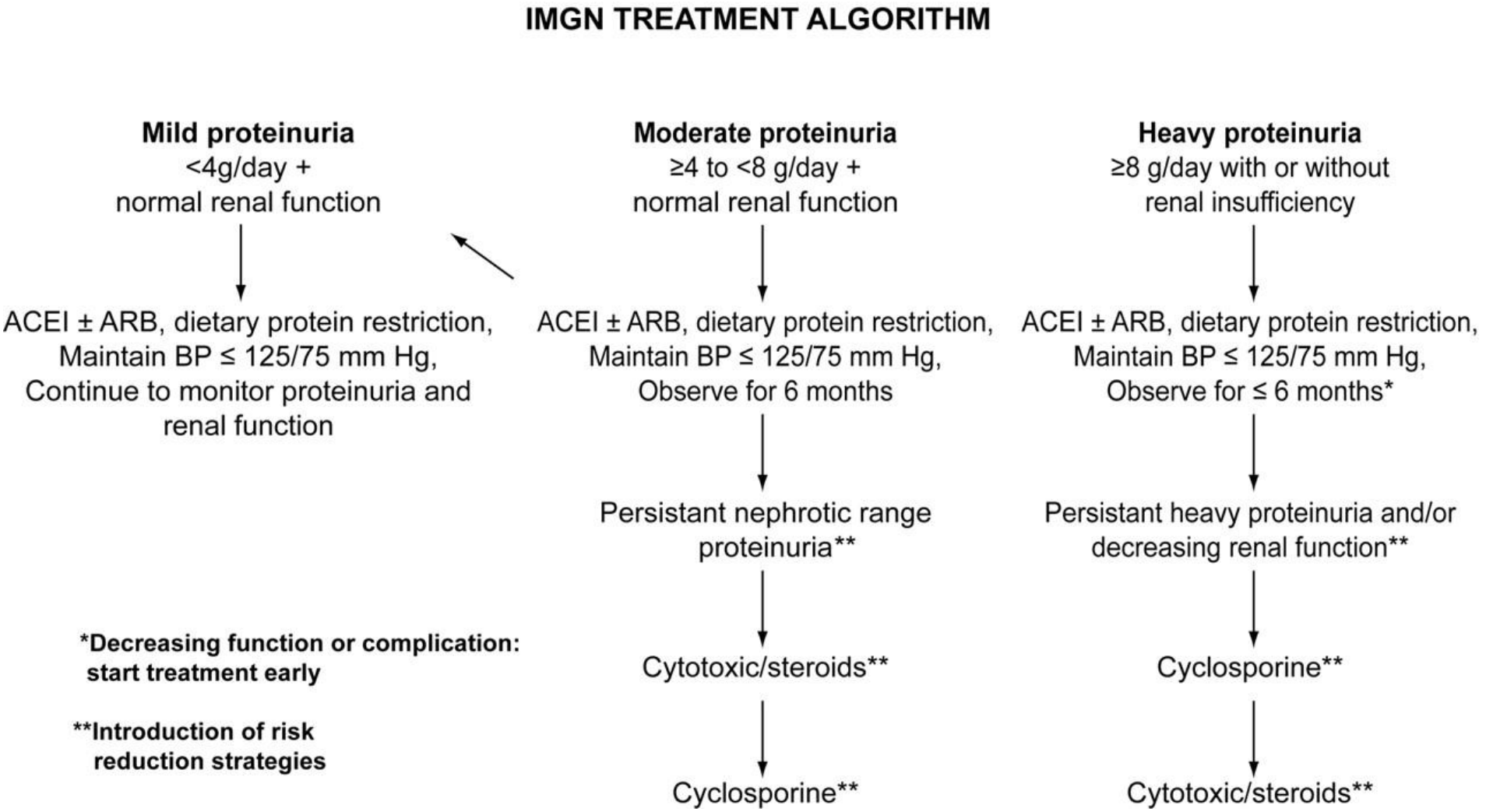
7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (*Not Graded*)

7.2: Selection of adult patients with IMN to be considered for treatment with immunosuppressive agents (see 7.8 for recommendations for children with IMN)

7.2.1: We recommend that initial therapy be started only in patients with nephrotic syndrome *AND* when at least one of the following conditions is met:

- urinary protein excretion persistently exceeds 4 g/d *AND* remains at over 50% of the baseline value, *AND* does not show progressive decline, during antihypertensive and antiproteinuric therapy (see Chapter 1) during an observation period of at least 6 months; (*1B*)
- the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (*1C*)
- SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min per 1.73 m^2 *AND* this change is not explained by superimposed complications. (*2C*)

Treatment



Cattran D JASN 2005;16:1188-1194

JASN

"Ponticelli Regimen"

Table 15 | Cyclical corticosteroid/alkylating-agent therapy for IMN (the "Ponticelli Regimen")

Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methyprednisolone (0.5 mg/kg/d) for 27 days
Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days[a]
Month 3: Repeat Month 1
Month 4: Repeat Month 2
Month 5: Repeat Month 1
Month 6: Repeat Month 2

IMN, idiopathic membranous nephropathy.

[a]Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to $<3500/mm^3$, then hold chlorambucil or cyclophosphamide until recovery to $>4000/mm^3$.

CNI-based regimens

Cyclosporine: 3.5–5.0 mg/kg/d given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity (Sandimmune®, Neoral®, and generic cyclosporin considered equivalent).

Tacrolimus: 0.05–0.075 mg/kg/d given orally in two divided doses 12 hours apart, without prednisone, for 6–12 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity.

Table 2. Possible treatment choices in patients with idiopathic (primary) membranous nephropathy

Treatment	Results	Notes
Steroids alone	No benefit	Although ineffective, frequently used by practitioner
Steroids-alkylating agents	Can significantly increase the probability of complete or partial remission. Protect renal function in the long term	The results are confirmed by randomized controlled trials. Risk of side effects (infection, leucopenia). Avoid frequent repetitions (risk of oncogenic or gonadotoxic effects)
CNI	Can significantly reduce the amount of proteinuria and increase the probability of complete or partial remission. Little information about their effects on renal function	Relapse of proteinuria is frequent after CNI withdrawal. Risk of hypertension, nephrotoxicity. Little information about long-term safety
Mycophenolate salts	Ineffective when given alone. Can reduce proteinuria when given together with steroids	Only small-sized studies with short-term follow-up are available. High relapse rate. No information about the long-term safety and efficacy
ACTH	Can reduce proteinuria	Only few small-sized studies with short-term follow-up are available. A randomized controlled trial is in progress
Rituximab	Can reduce proteinuria	Large observational studies available. No head-to- head comparison with other treatments

CNI, calcineurin inhibitors; ACTH, adrenocorticotropic hormone.

Claudio Ponticelli, Richard J. Glassock. CJASN. 2014 Mar;9(3):609-16.

Resistant IMN

7.6: Treatment of IMN resistant to recommended initial therapy

7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)

7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)

Relapsing IMN

7.7: Treatment for relapses of nephrotic syndrome in adults with IMN

7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)

7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see Recommendation 7.3.1), the regimen be repeated only once for treatment of a relapse. (*2B*)

ANTI-PLA2R ANTIBODY and TREATMENT DECISIONS

- ***Absent or low-titer*** **anti-PLA2R portends spontaneous remission, and is a reason to delay introduction of IS therapy**

- ***Elevated*** **Anti-PLA2R antibody titer does not predict the initial response to a specific treatment modality, regardless of choice of regimen**

- ***Declining*** **anti-PLA2R antibody titers (>50% of BL) during treatment predict remission or a decline in proteinuria in next 1-3 months**

- ***Persistently*** **positive anti-PLA2R at end of a course of therapy or *re-appearance* after a remission portend a subsequent relapse**

Primary Membranous Nephropathy:

A proposal for personalized care-2016

- **Patients with NS need *only be tested* for anti-PLA2R antibody if MN is suspected- If positive then a diagnosis of a lesion of MN is established (without renal biopsy)- but may be 1º or 2º**

- **All patients with a biopsy lesion of MN should be tested for anti-PLA2R antibody (ELISA preferred) and PLA2R Ag in glomeruli prior to treatment. Negative tests indicate an evaluation for 2º MN is needed or that a SR is likely**

- **In suspected 1º MN initial tests for anti-PLA2R antibody results do not greatly influence the choice of drug for initial treatment but low titres suggest likely SR**

Primary Membranous Nephropathy:

A proposal for personalized care-2016

- **Testing for anti-PLA2R antibody (ELISA preferred) should occur in all 1º MN patients at 1-2 month intervals during therapy and at the end of therapy. A 50% decline in titer predicts a 50% decline in proteinuria 3-6 months later**

- **After a remission, a rising titer predicts relapse- but monitoring may not be required during prolonged remission**

- **All patients with ESRD due to 1º MN should be tested pre-transplant. Recurrence of MN expected in 75-80% , if positive, and <25% if negative**

Thank You