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Gen. Org. مؤسسة عامة

Glomerular Diseases Causing Nephrotic Syndrome (MCD, FSGS, MN)

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30 November 2023

وزارة الصحـــــة العامـــــة
Ministry of Public Health
State of Qatar • دولـــة قطـــر

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Disclosure Statement

I make the following declaration in relation to this CPD Activity :

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- There is no plagiarism or copyright infringement.
- The content is balanced and free of bias, either commercial or non-commercial.

Nephrotic Syndrome

- Edema
- Heavy proteinuria (> 3g/24hrs)
- Hypoalbuminemia (< 2.5g/dL in children, < 3.5g/dL in adult)
- Hyperlipidemia
- Lipiduria (oval fat bodies)

Major causes of nephrotic syndrome

➢Primary renal diseases:

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous glomerulopathy
- Membranoproliferative glomerulonephritis

➢Secondary renal diseases:

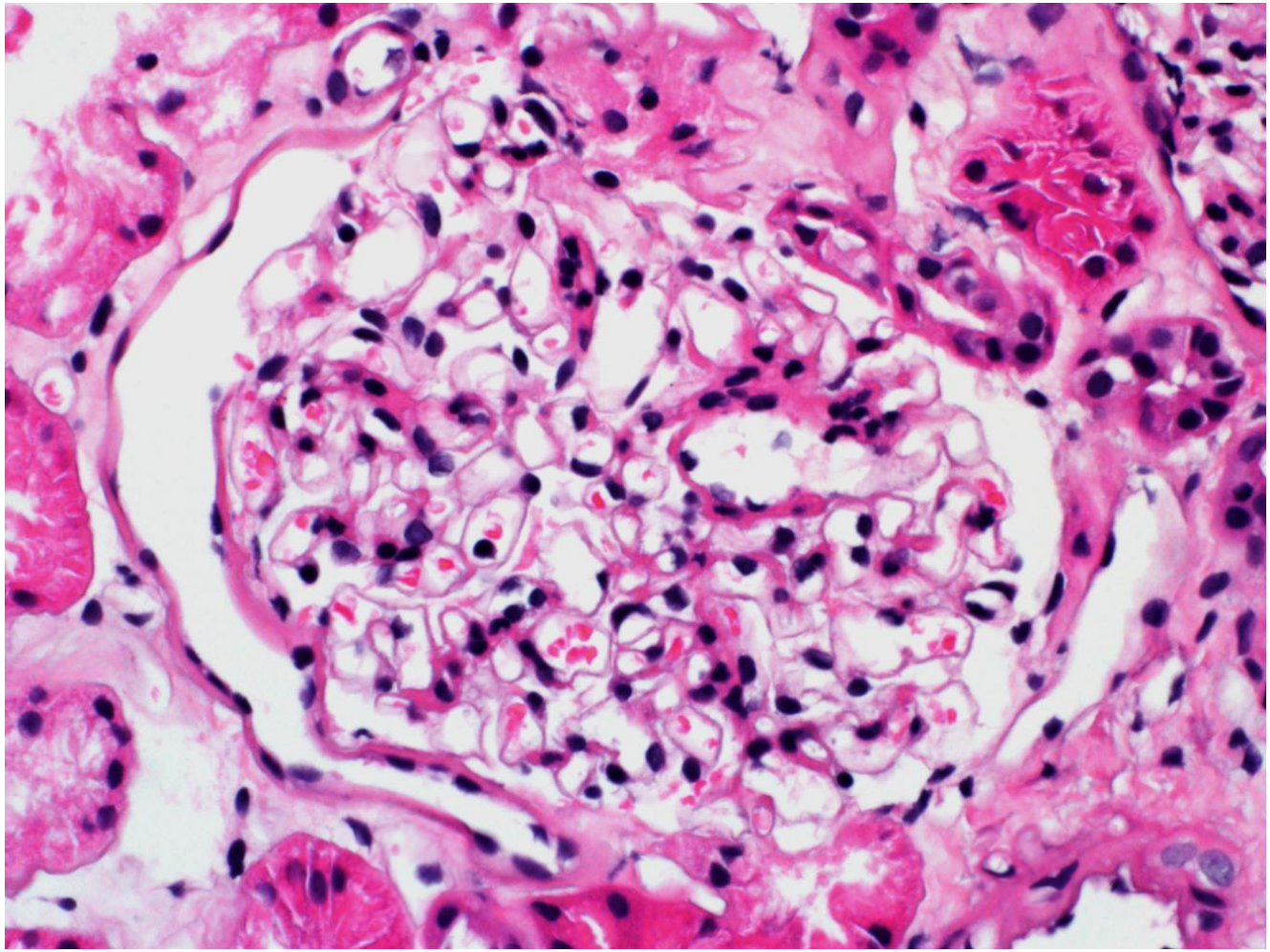
- Diabetic nephropathy/glomerulosclerosis
- Amyloidosis
- Lupus nephritis

Minimal Change Disease

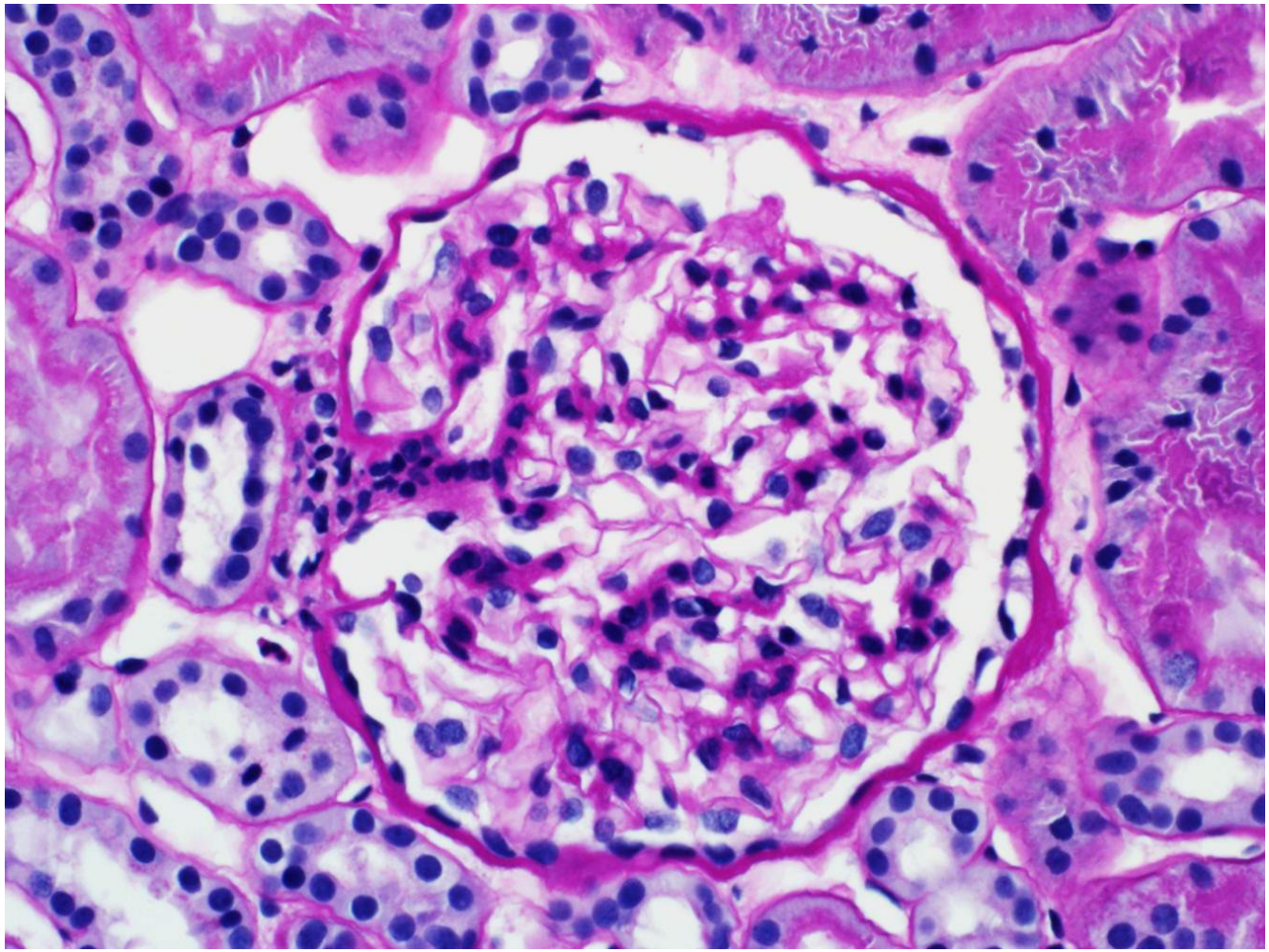
- Glomerular disease with minimal or no glomerular alterations, no glomerular immune deposits, and extensive effacement of foot processes.

- Most common in children
- Children: median age of onset is 2.5 years
- Adult: higher incidence in elderly

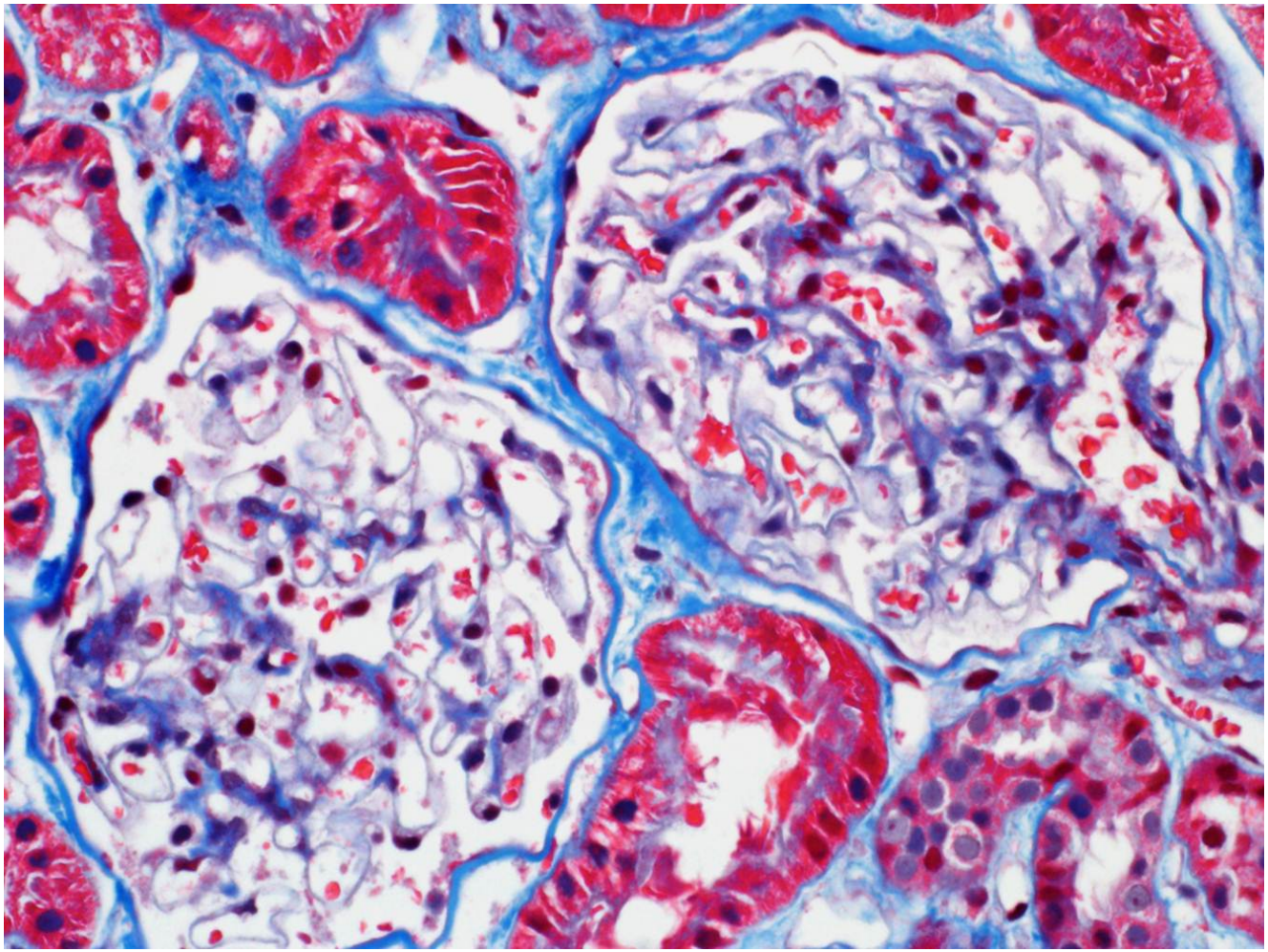
Minimal Change Disease



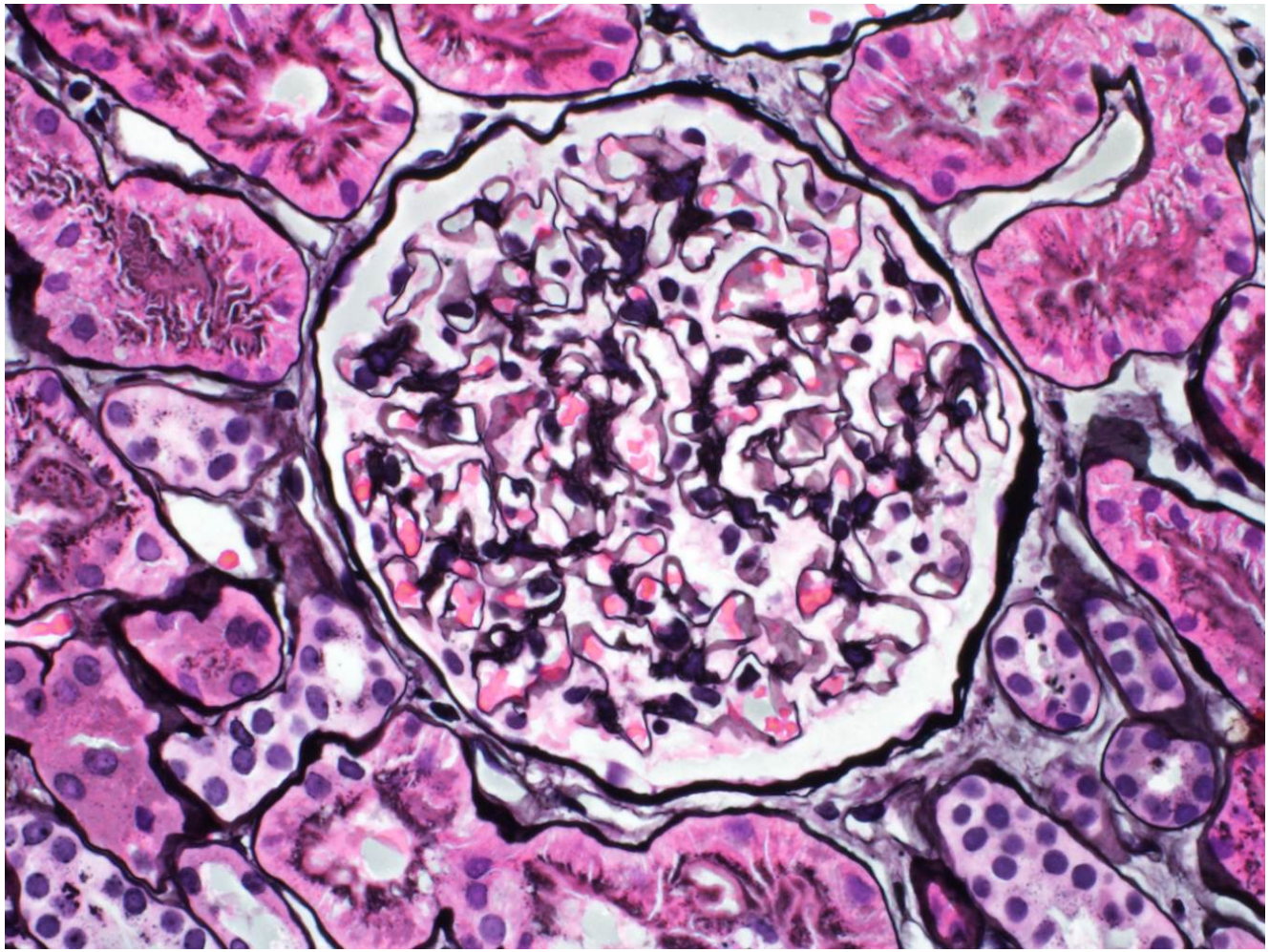
Minimal Change Disease

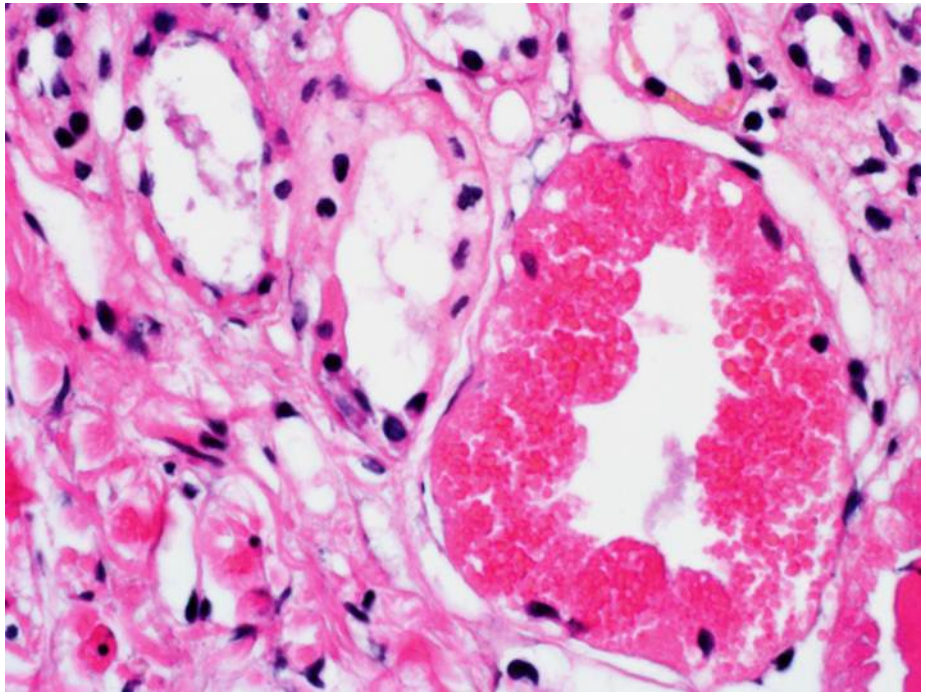


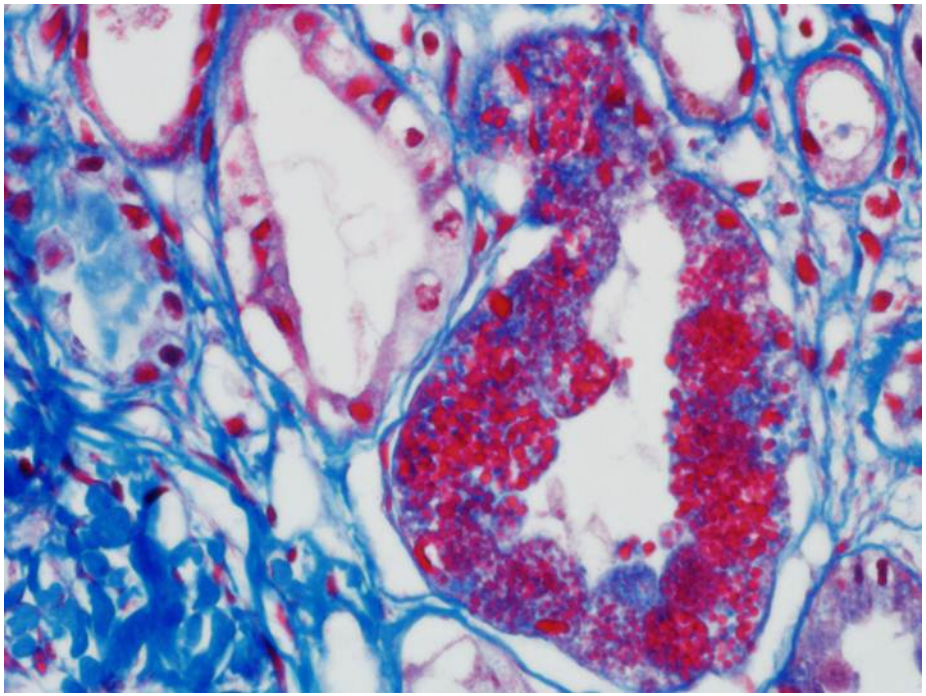
Minimal Change Disease

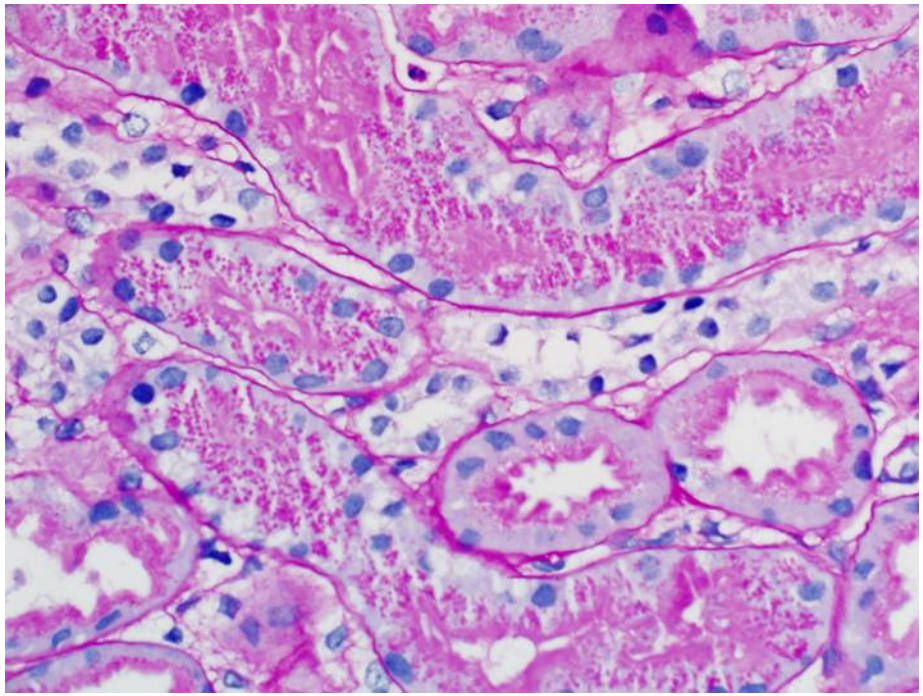


Minimal Change Disease







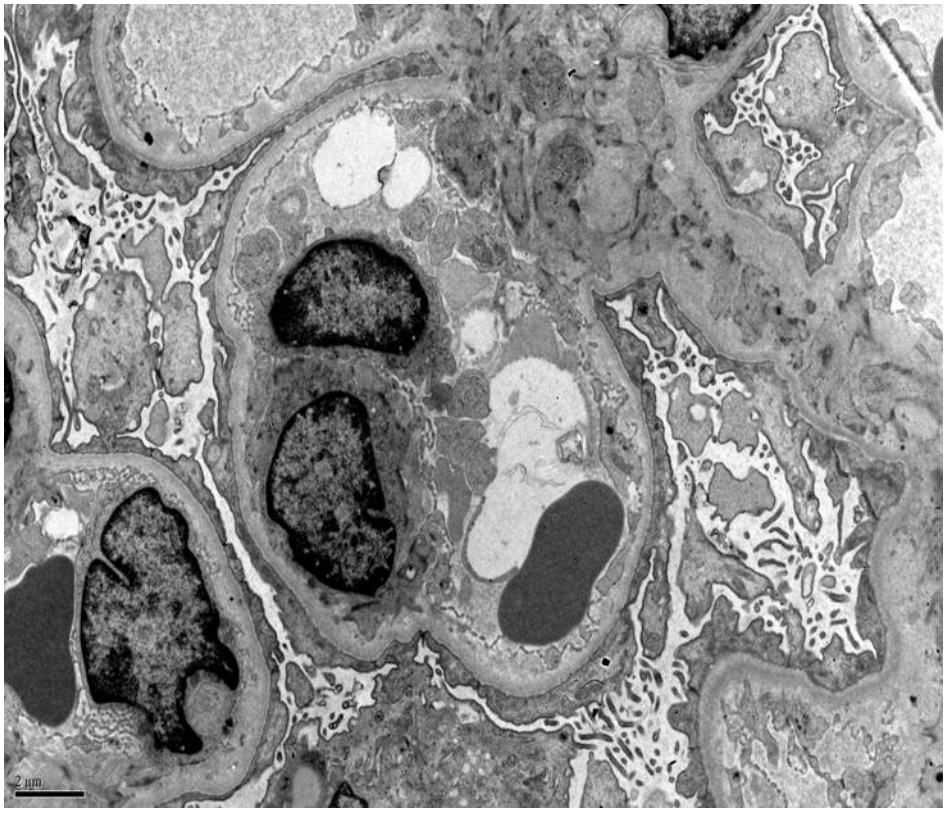


Protein resorption droplets

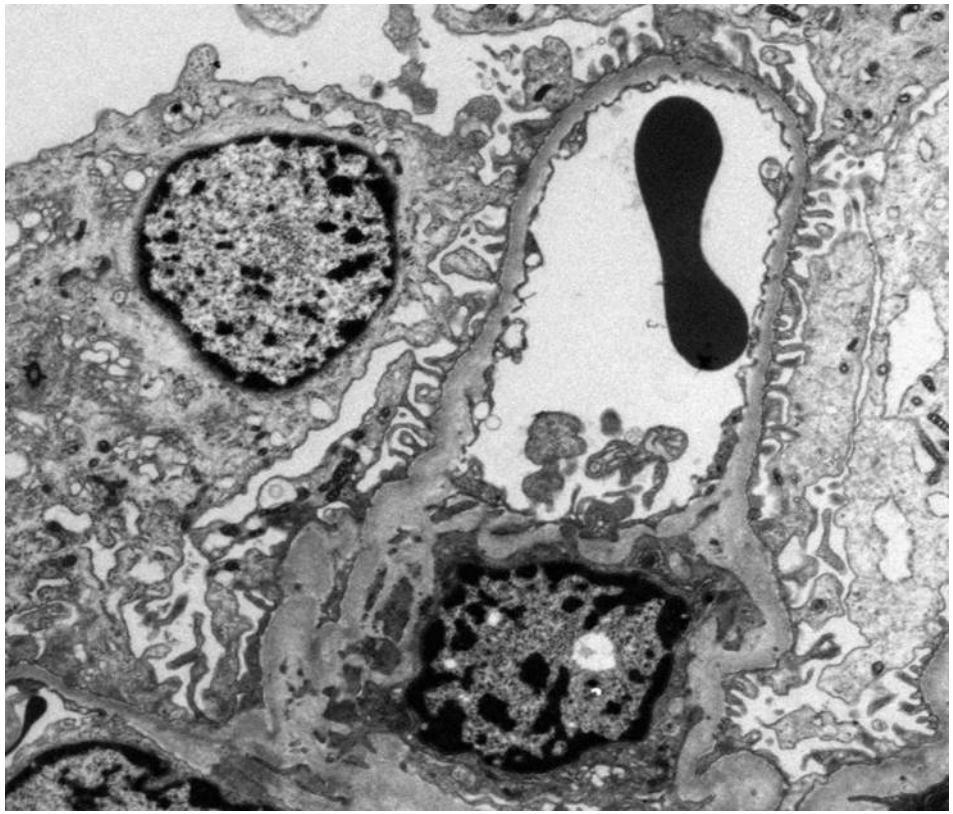
Immunofluorescence Findings

- Typically no staining for Immunoglobulins and complements.
- IgM

Electron Microscopic Findings

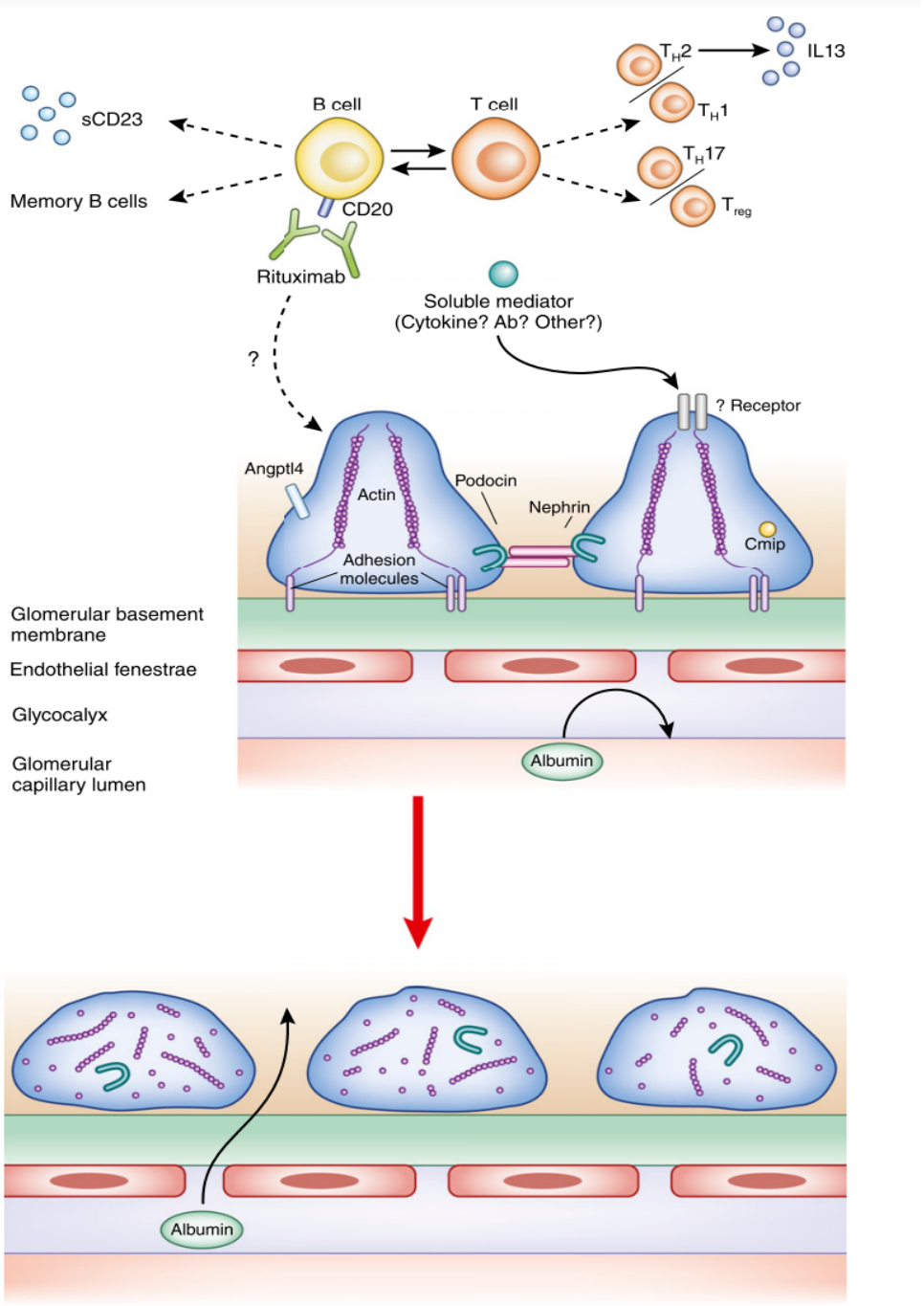


Minimal change disease



Normal

Pathogenesis of minimal change disease



Minimal Change Disease, Vivarelli et al. Clin J Am Soc Nephrol 2017

CLINICAL RESEARCH www.jasn.org

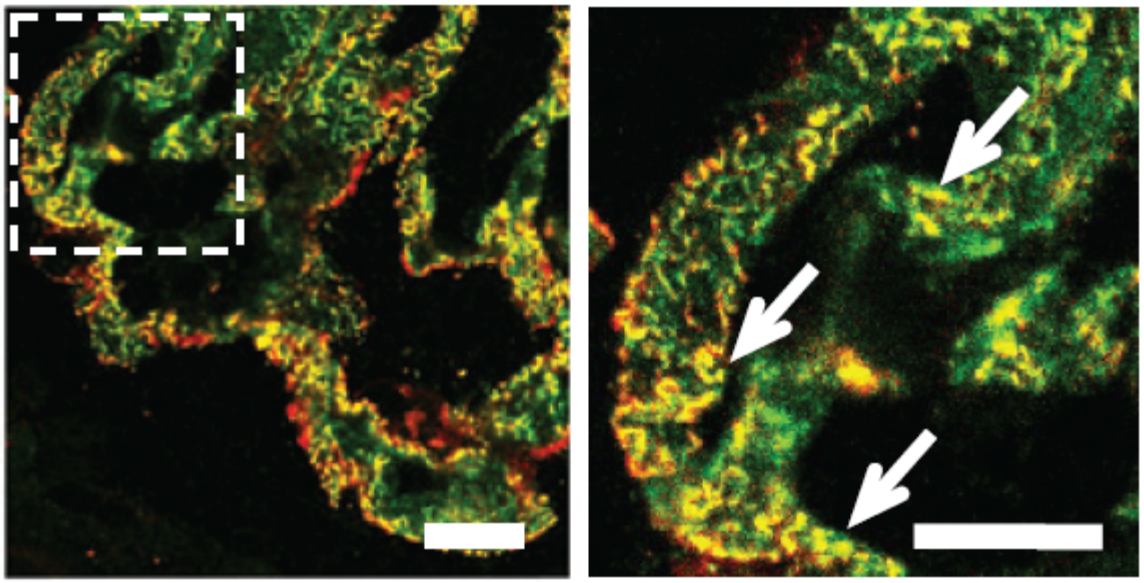
JASN 33: 238–252, 2022

Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology

Andrew J.B. Watts,[1,2] Keith H. Keller,[1] Gabriel Lerner,[3,4] Ivy Rosales,[5] A. Bernard Collins,[5] Miroslav Sekulic,[1,6] Sushrut S. Waikar,[2,4] Anil Chandraker,[2] Leonardo V. Riella,[7] Mariam P. Alexander,[8] Jonathan P. Troost,[9] Junbo Chen,[3] Damian Fermin,[10] Jennifer L. Yee,[10] Matthew G. Sampson,[11,12] Laurence H. Beck, Jr.,[4] Joel M. Henderson,[3] Anna Greka,[2,12] Helmut G. Rennke,[1] and Astrid Weins[1,2]

- This study describes the novel discovery in both adults and children with MCD of autoantibodies targeting nephrin, a critical component of the podocyte slit diaphragm that ensures integrity of the glomerular filtration barrier. This observation aligns with the established proteinuric effect of antinephrin antibodies demonstrated in animal models. These findings identify an important autoimmune mechanism in a subset of patients with MCD and provide a framework for the application and development of precision medicine strategies in this condition.

Punctate IgG present in a subset of MCD renal biopsies colocalizes with the critical podocyte slit diaphragm protein nephrin.



JASN **33**: 238–252, 2022

CLASSIFICATION OF MINIMAL CHANGE DISEASE AND VARIANTS

➢ Idiopathic Forms

- Minimal change disease (MCD)
- Histologic variants of MCD:
  - *Diffuse mesangial hypercellularity*
  - *IgM nephropathy*
- Minimal change disease with acute renal failure
- Dual glomerulopathies
  - *Minimal change disease and IgA nephropathy*
  - *Minimal change disease and lupus nephritis*

➢ Secondary Forms

- Secondary to therapeutic agents *(NSAIDs, Lithium)*
- Secondary to malignancies (*Lymphoma, Leukemia)*
- Other associations

    Bee stings

    Food allergies

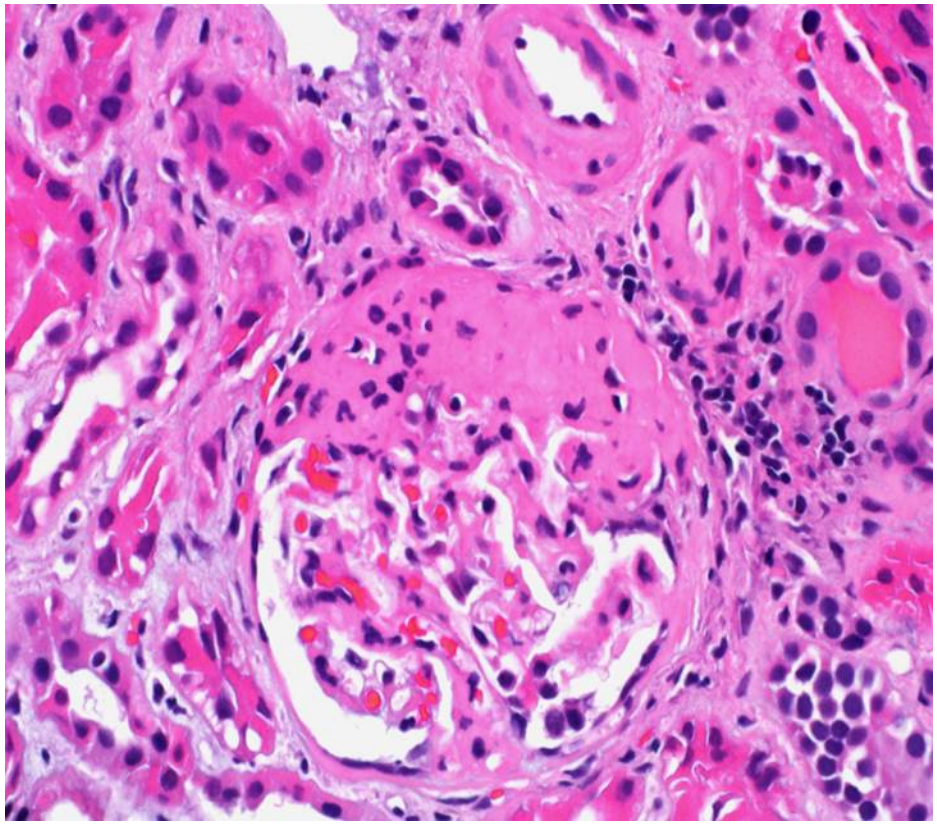
    EBV, HIV

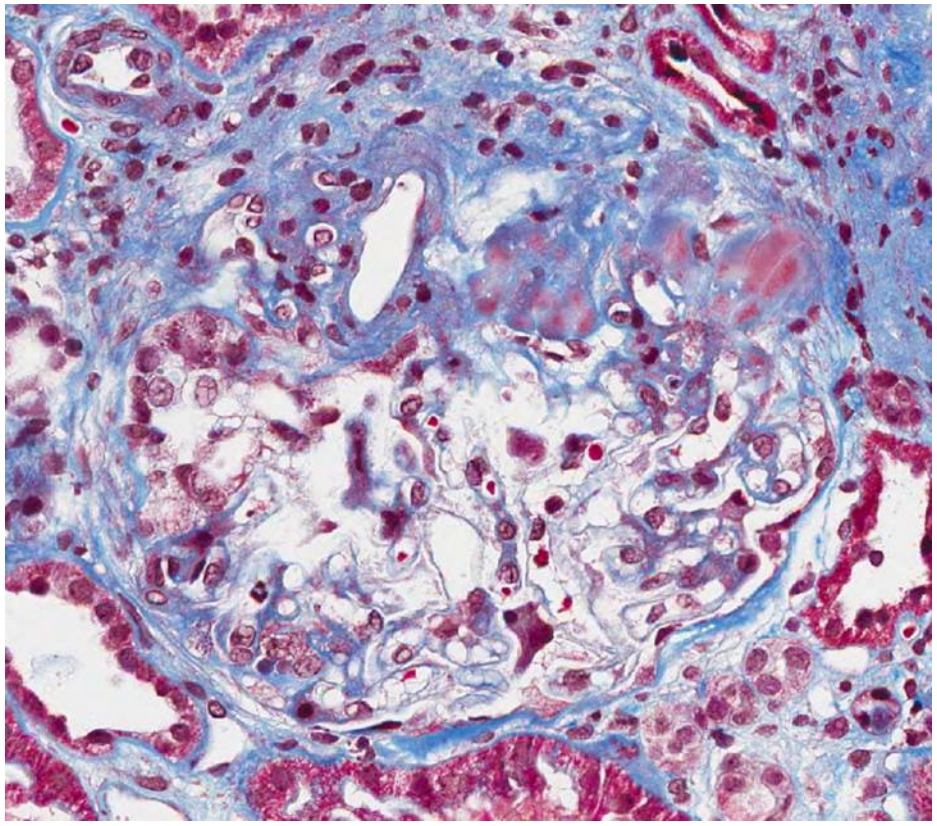
Focal Segmental Glomerulosclerosis

- Slightly more common in males.
- The most common cause of nephrotic syndrome in adults.
- Comprises 10-20% of the cases of idiopathic nephrotic syndrome in children.

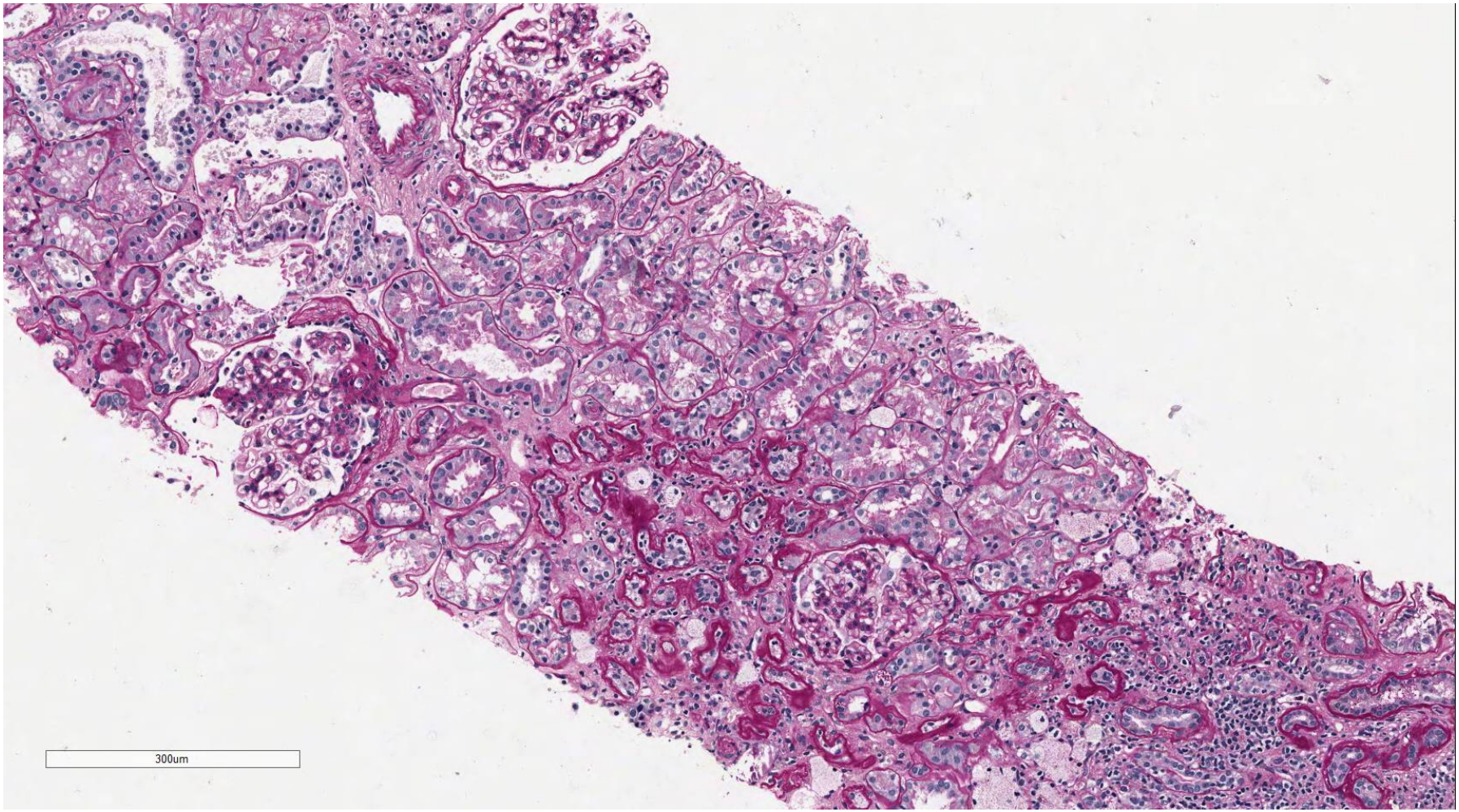
Focal Segmental Glomerulosclerosis

Focal segmental consolidation of the glomerular tufts by increased extracellular matrix. (Not secondary to glomerulonephritis or vascular disease)

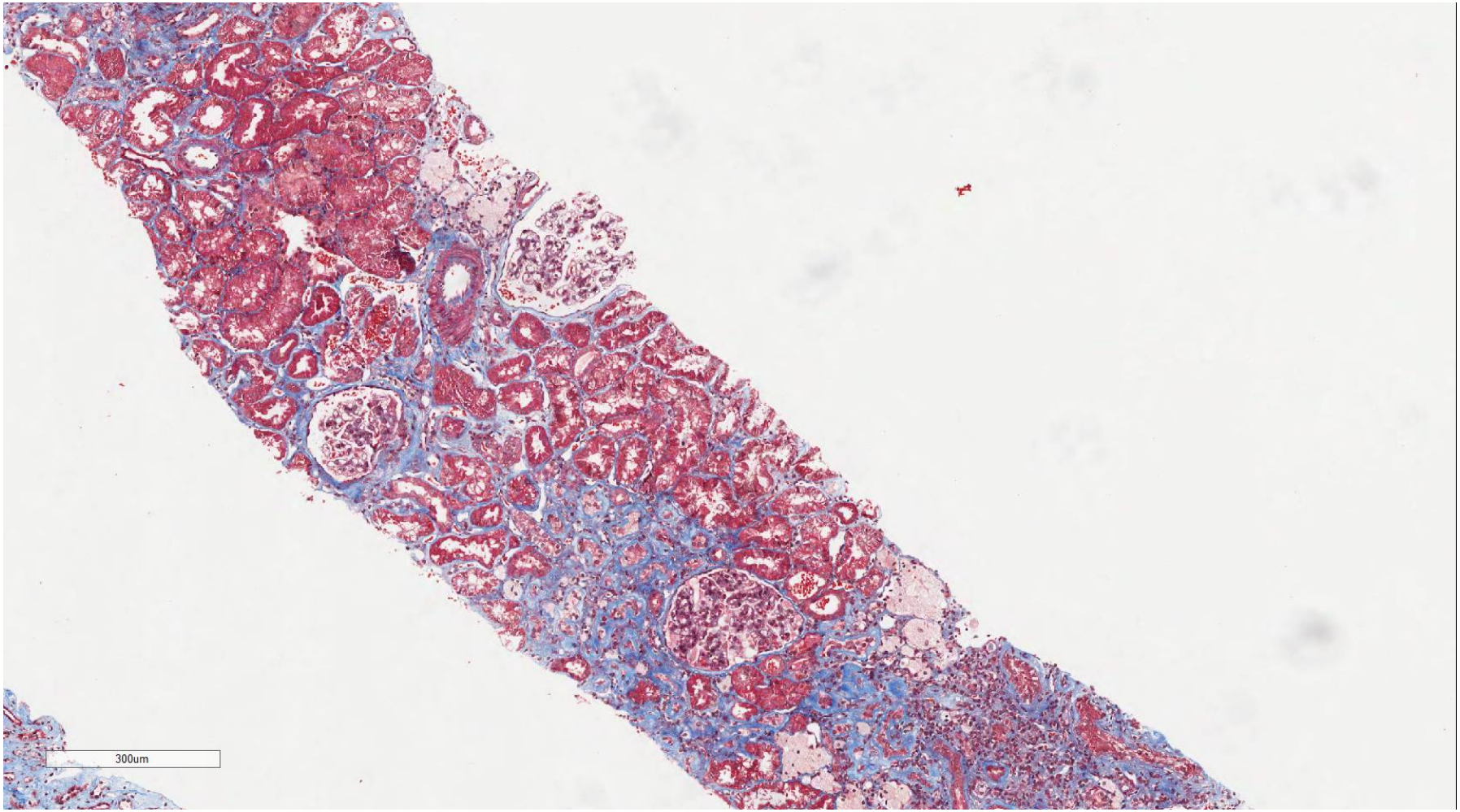




PAS (Periodic acid-Schiff) stain

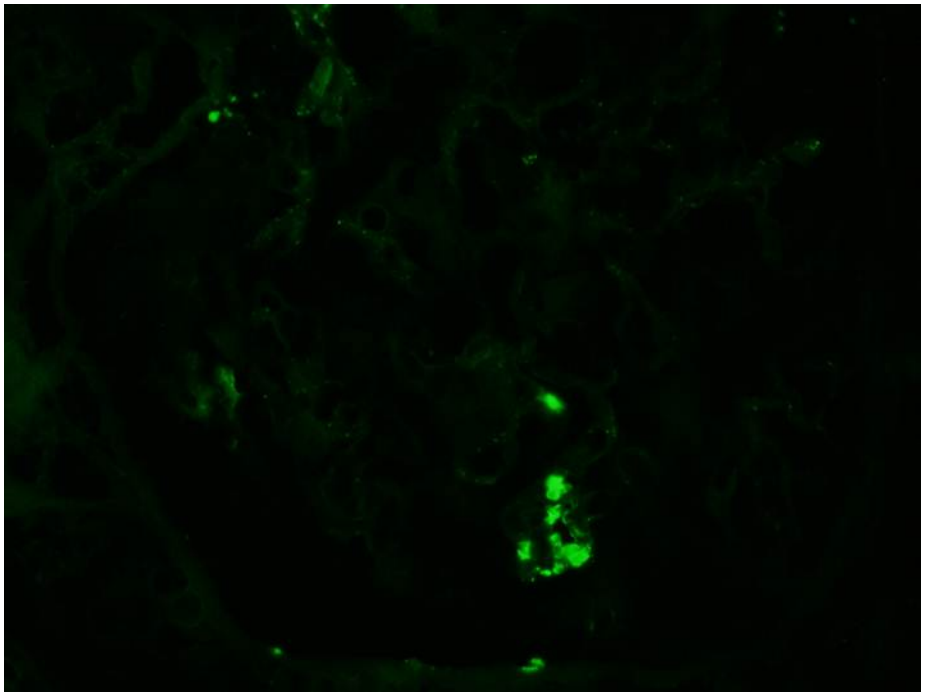


Masson’s trichrome stain

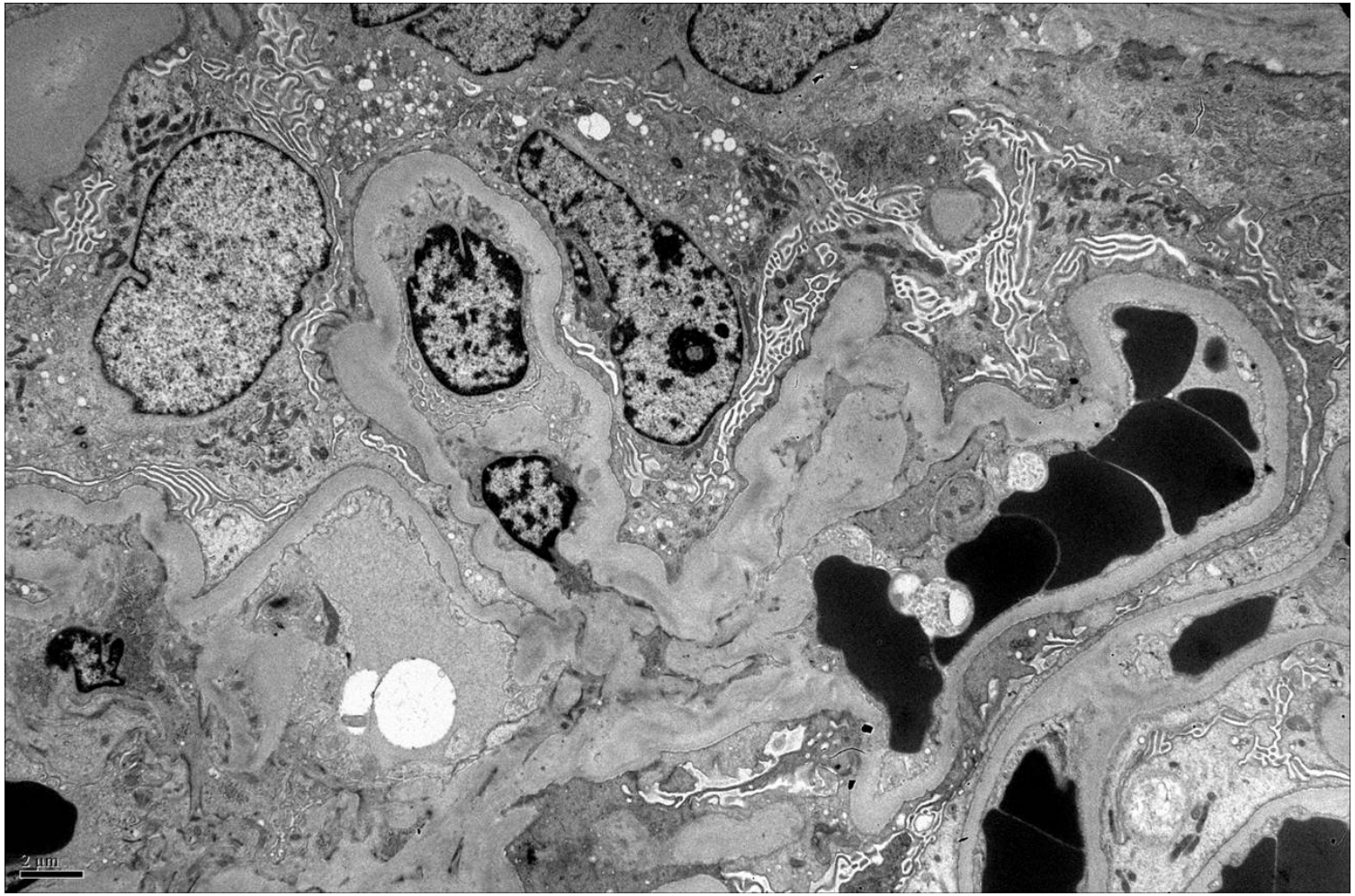


Immunoflourescence findings

- Usually negative
- There may be focal and segmental granular deposition of IgM and C3 in the distribution of segmental glomerular sclerosis.



Electron microscopic findings



Histologic variants
(Columbia classification)

- FSGS, not otherwise specified (NOS)
- FSGS, perihilar variant
- FSGS, cellular variant
- FSGS, tip variant
- FSGS, collapsing variant

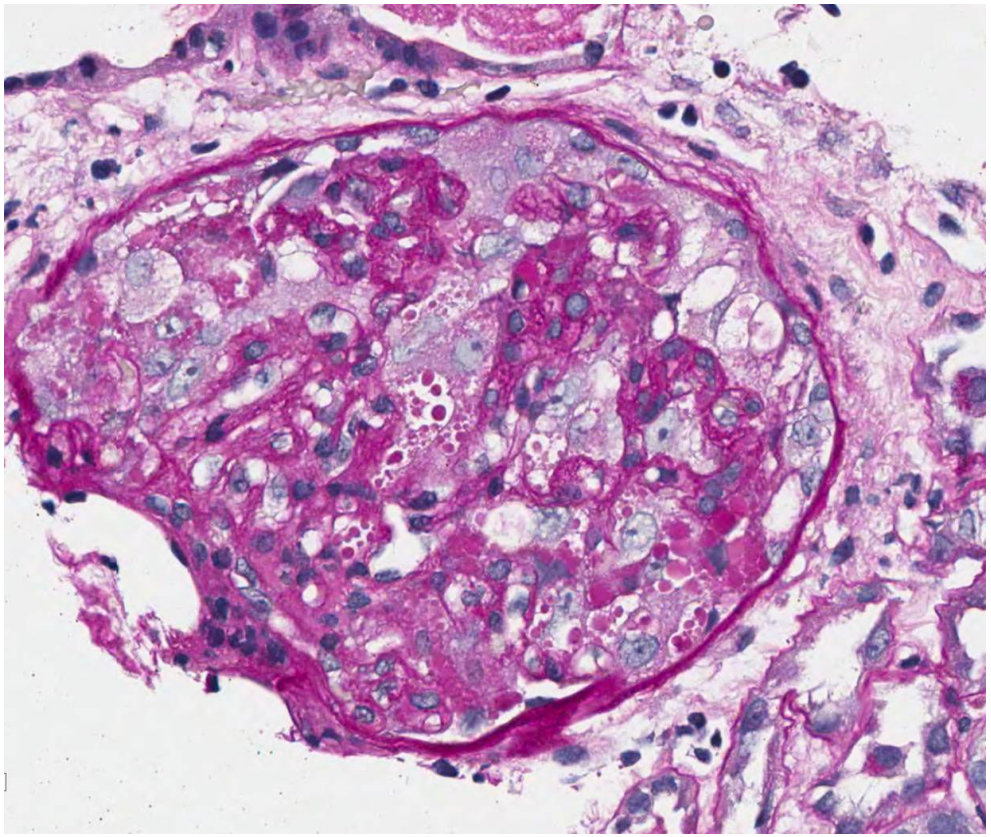
D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004 43:368-82.

Stokes MB, D'Agati VD. Morphologic variants of focal segmental glomerulosclerosis and their significance. Adv Chronic Kidney Dis. 2014;21(5):400-7.

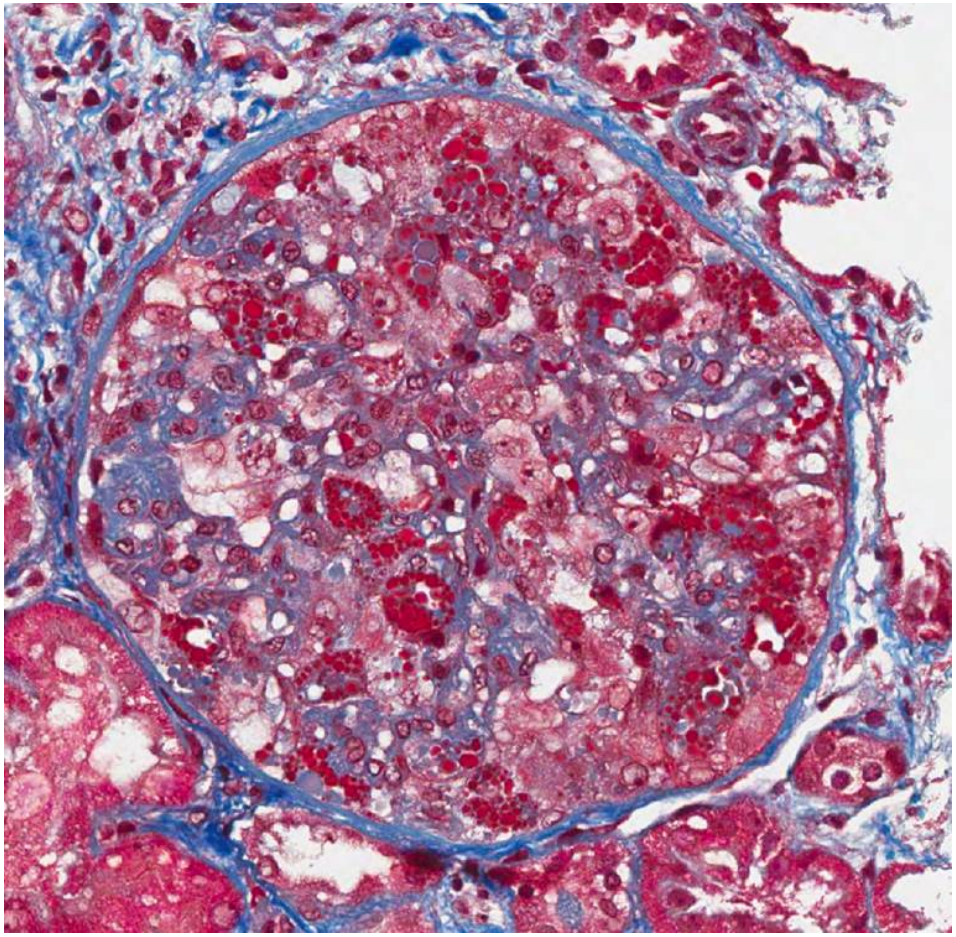
FSGS, collapsing variant

*• At least one glomerulus with defining features.

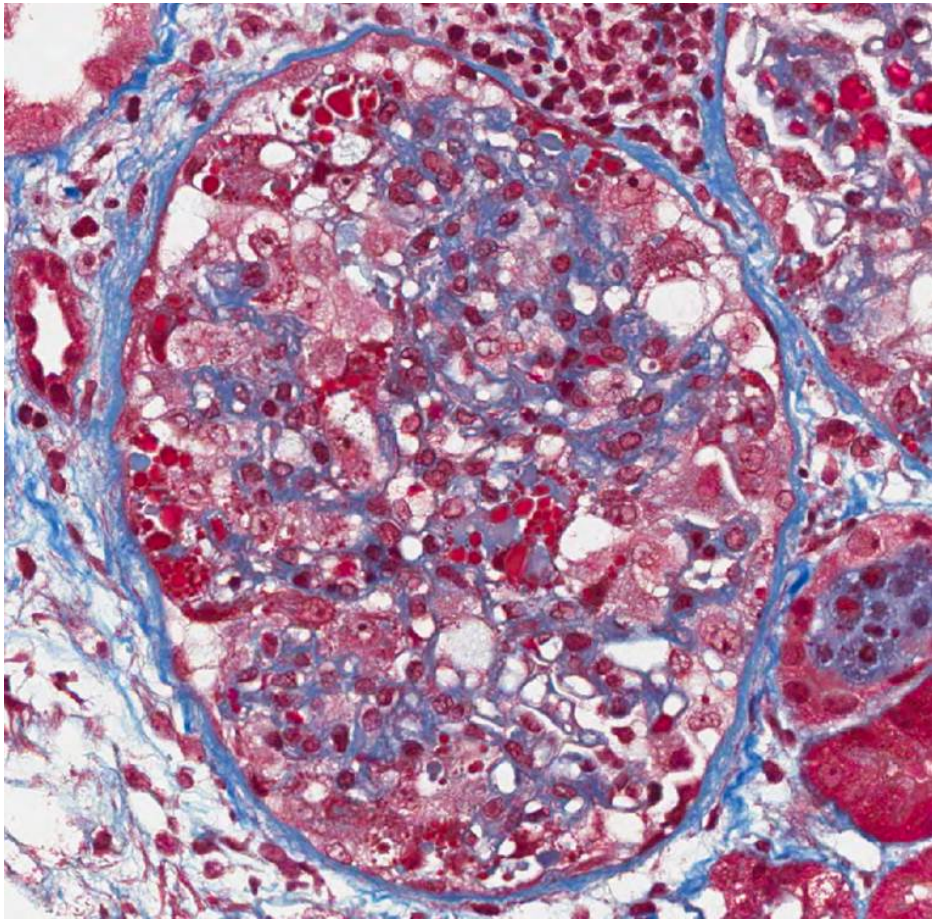
• Other glomeruli may have segmental lesions of any subclass.



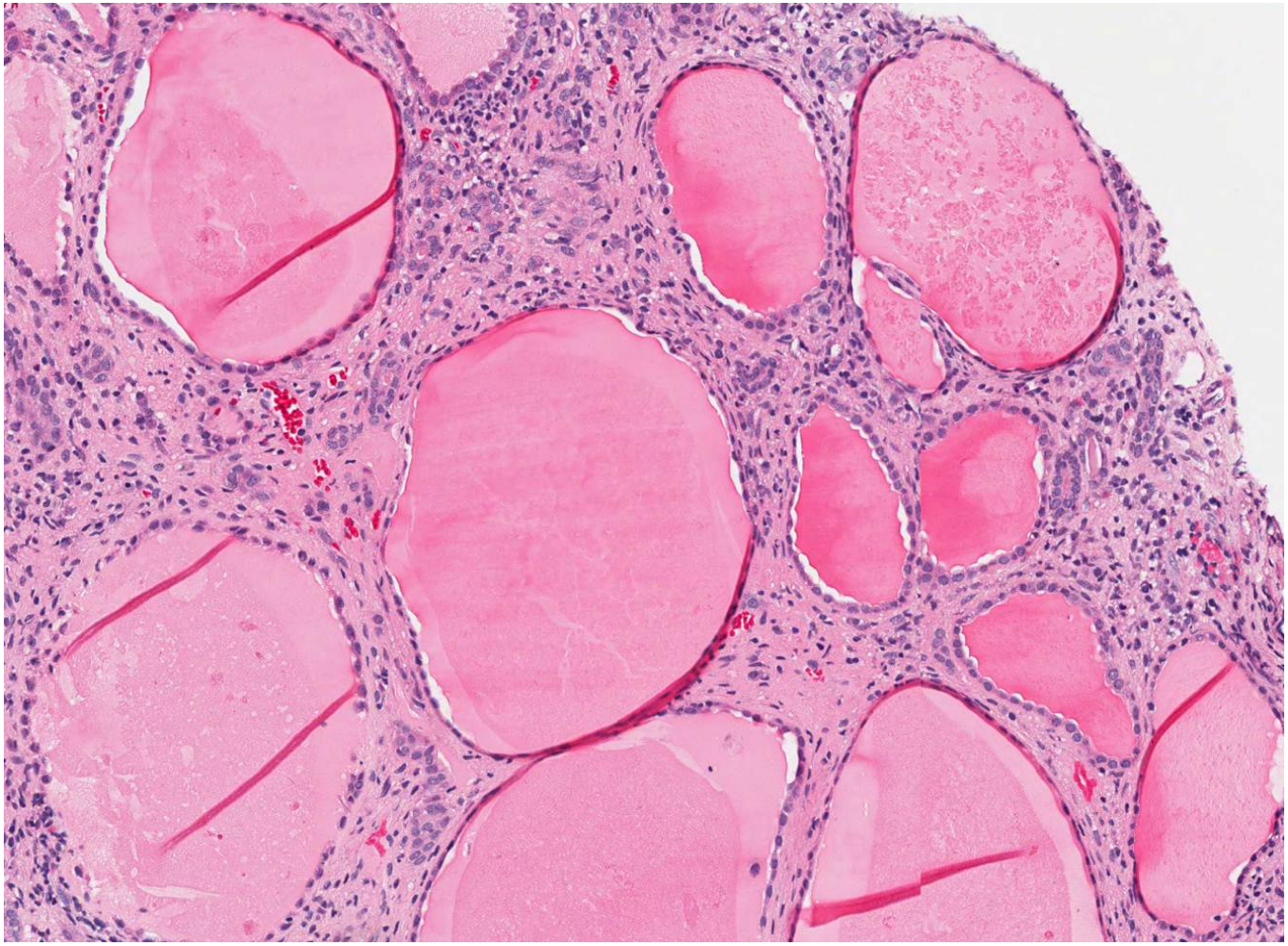
*Thomas DB, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int. 2006; 69:920-6.



Collapsing FSGS



Tubular microcysts



FSGS, tip variant

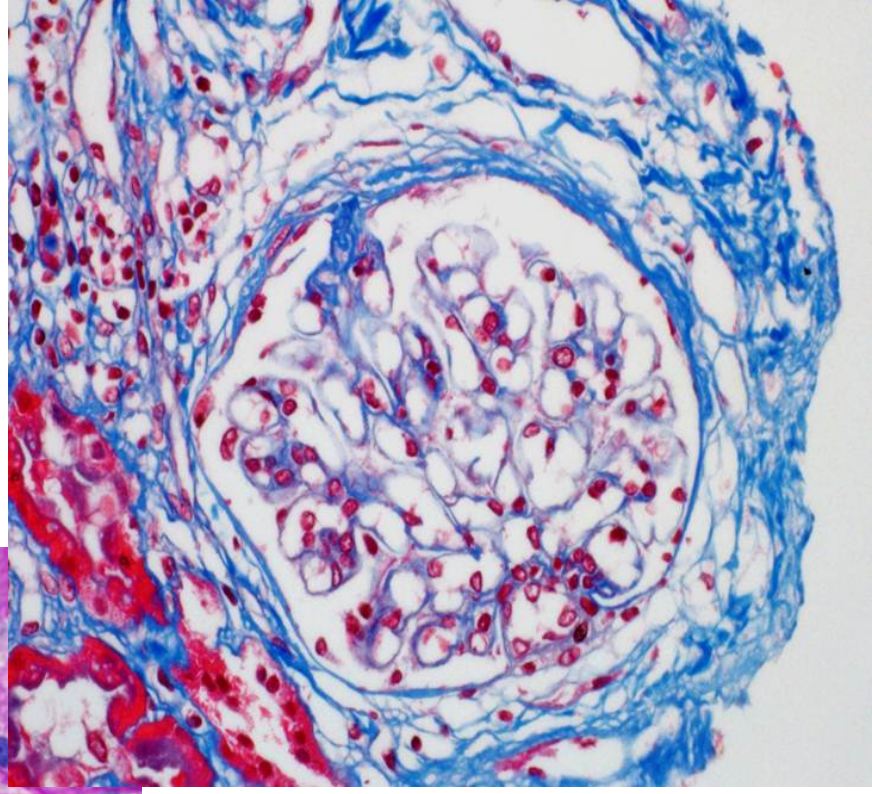
- At least 1 segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule)
- The tubular pole must be identified in the defining lesion
- The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck
- The tip lesion may be cellular or sclerosing

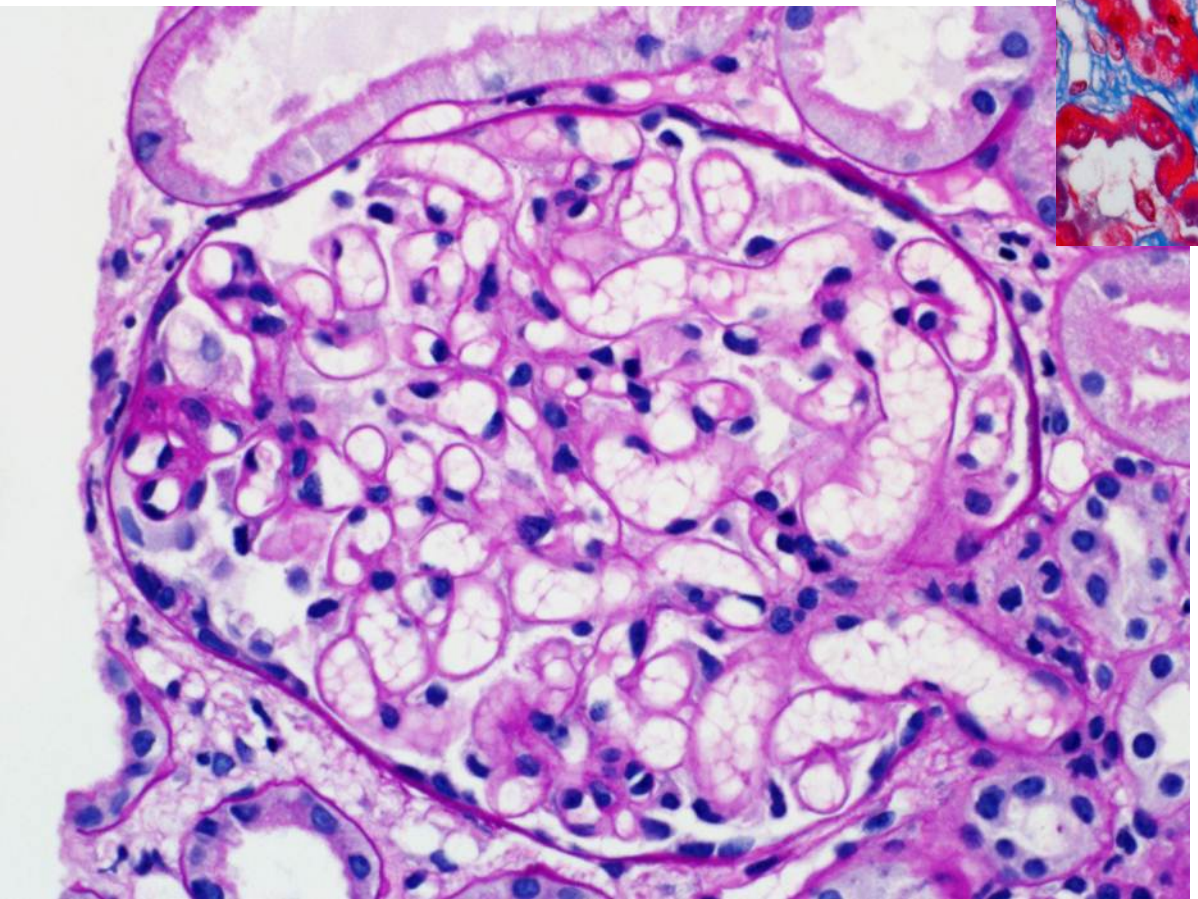
➢Exclude collapsing variant

➢Exclude any perihilar sclerosis

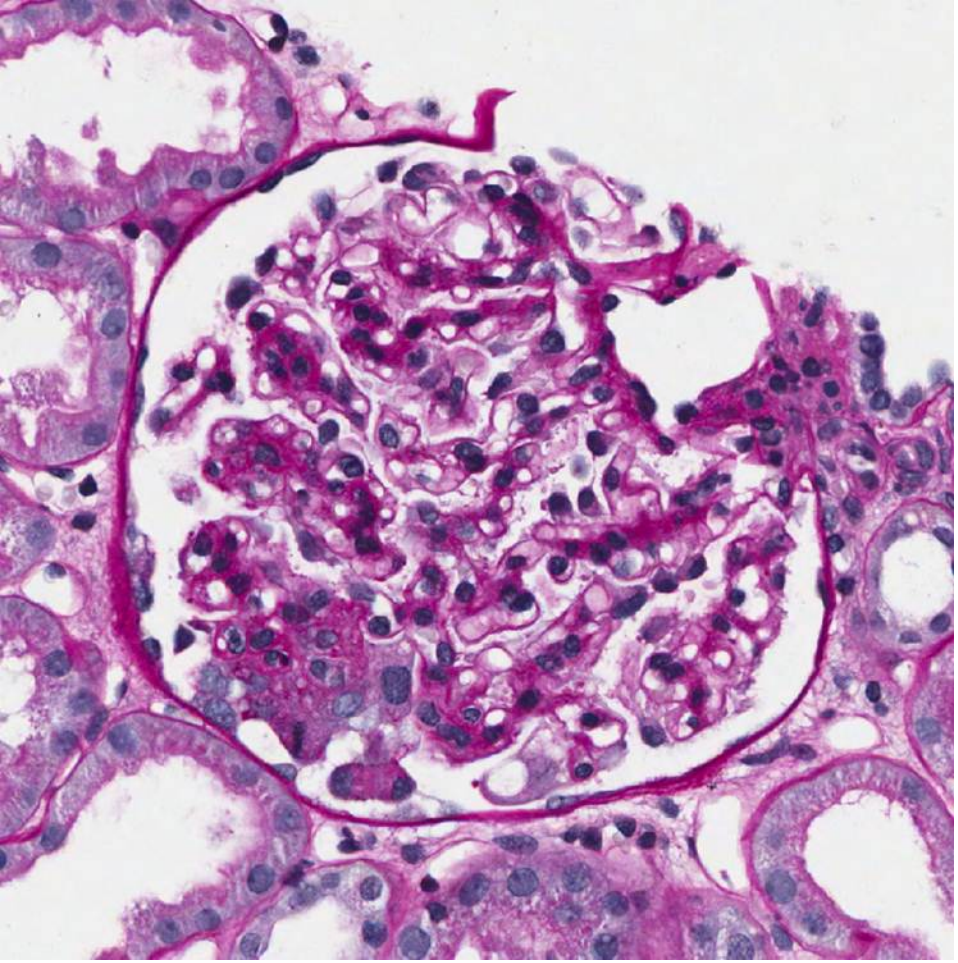
D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004 43:368-82.

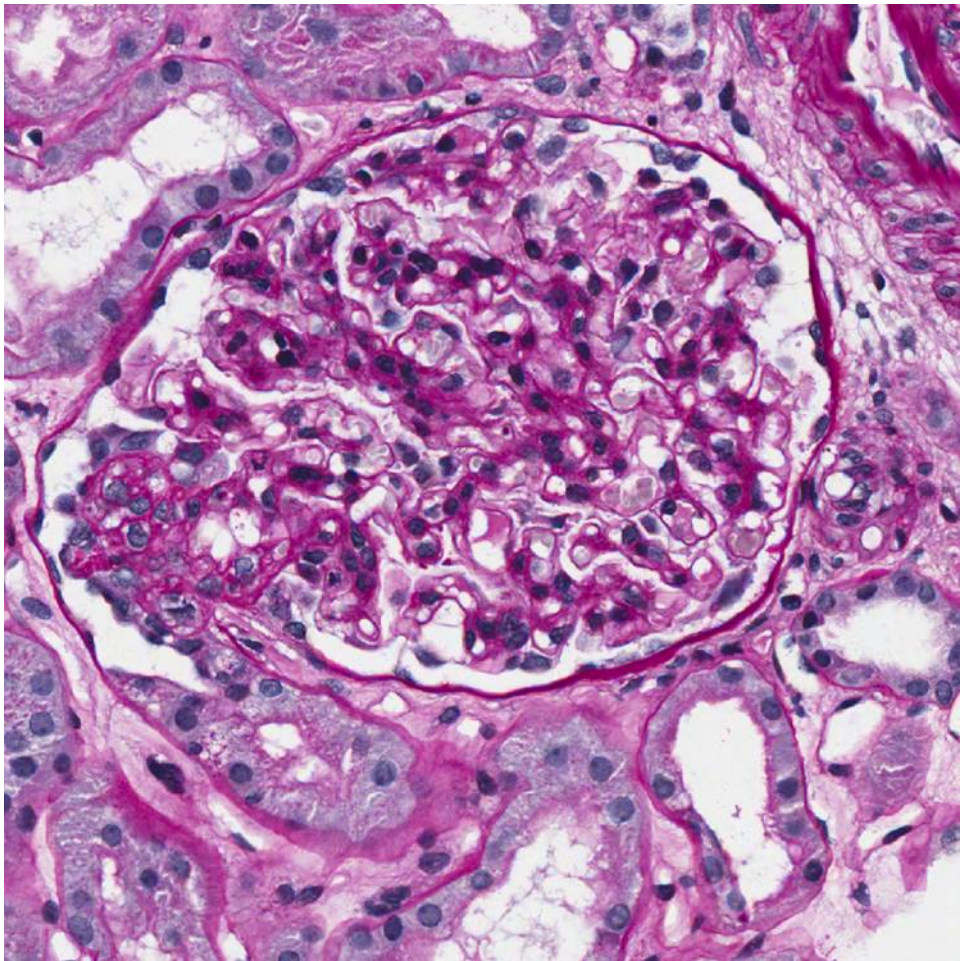
FSGS, tip variant





FSGS, tip variant





FSGS, cellular variant

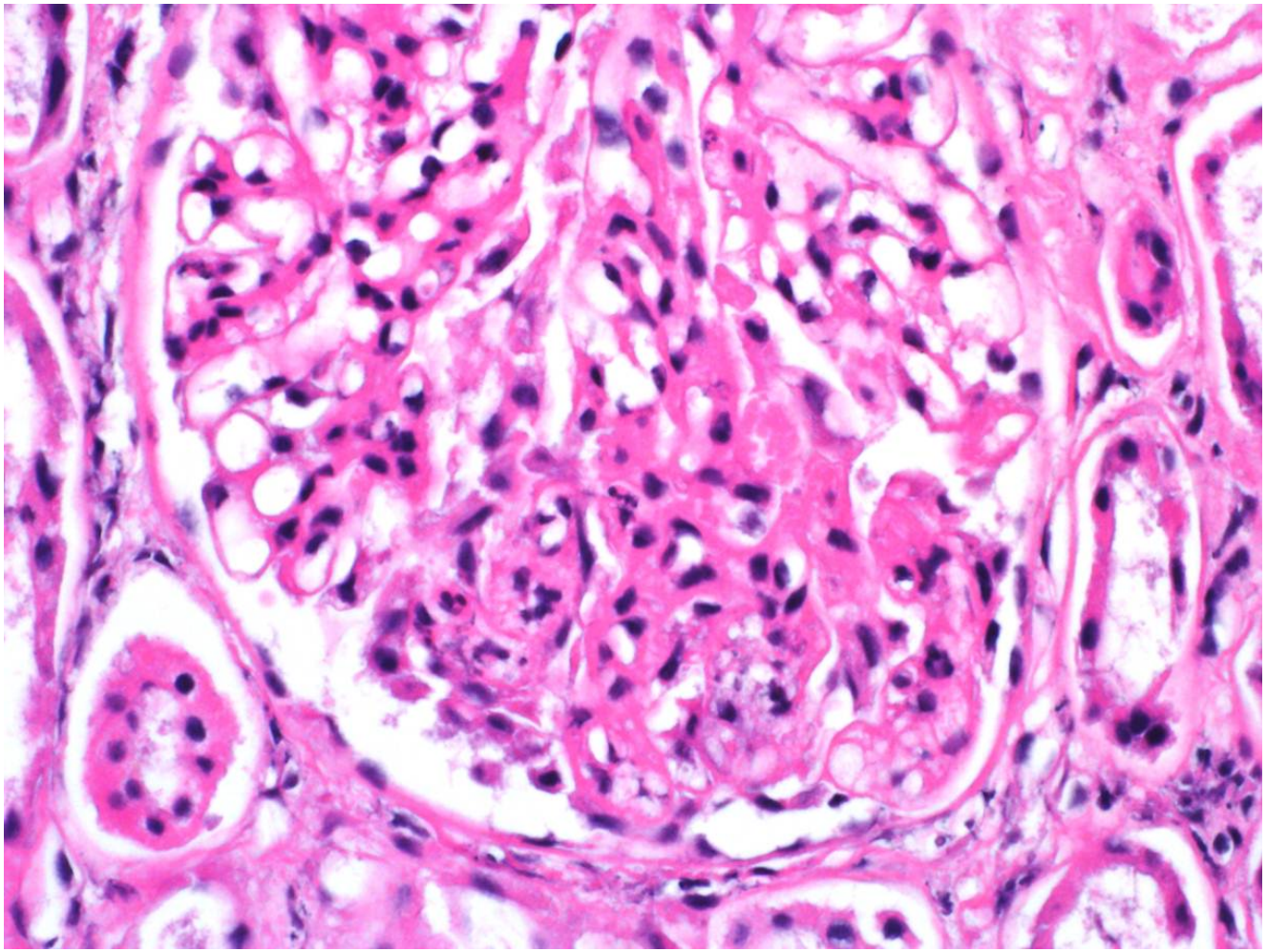
- Exclude collapsing and tip variants.
- At least one glomerulus with defining features:

1- Endocapillary hypercellularity, typically expansive and foam cells, in any segment of glomerular capillary tuft (at least 25%), with capillary lumen occlusion.

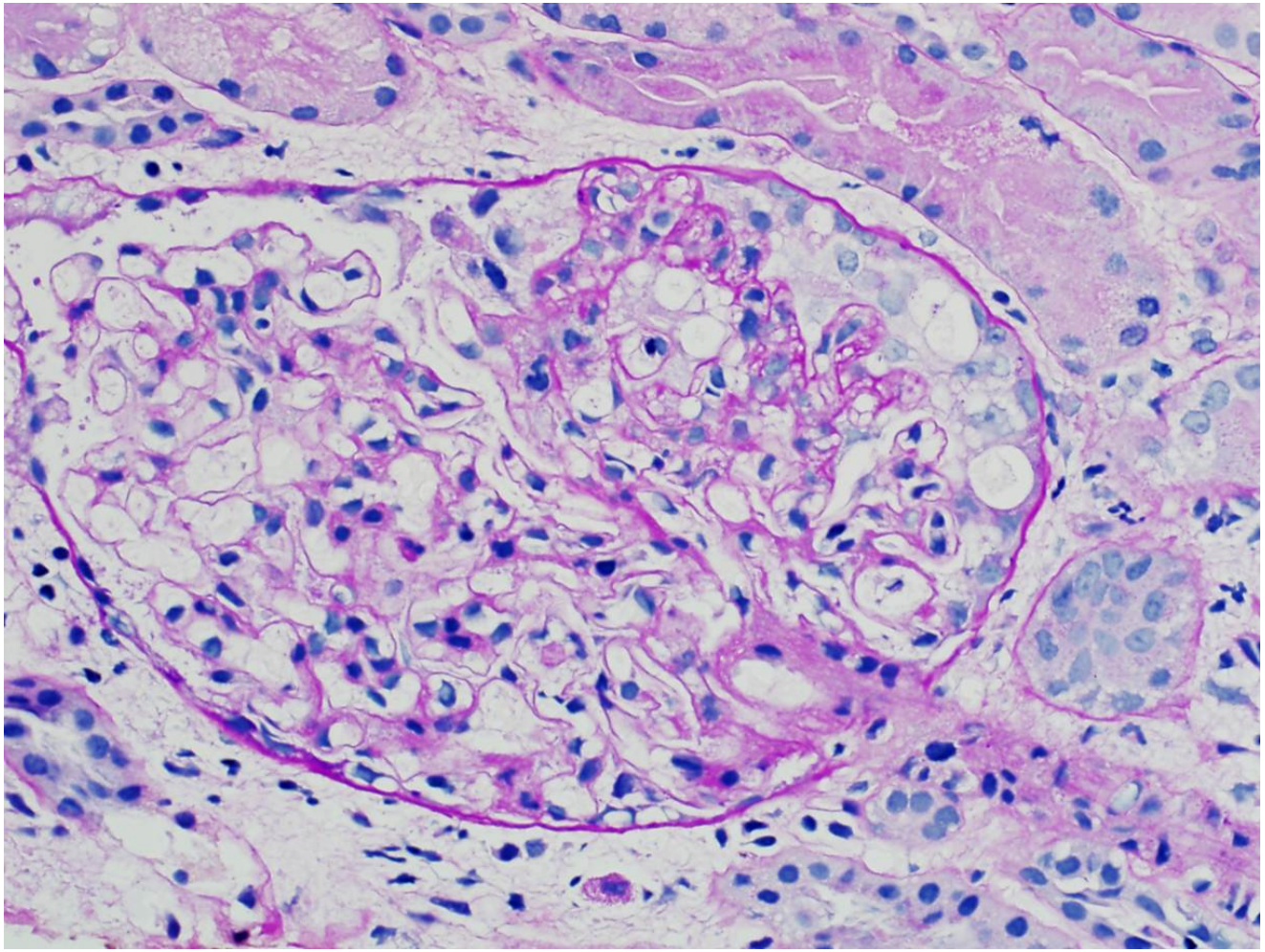
2- Other glomeruli may have segmental sclerosing lesions.

*Thomas DB, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int. 2006; 69:920-6.

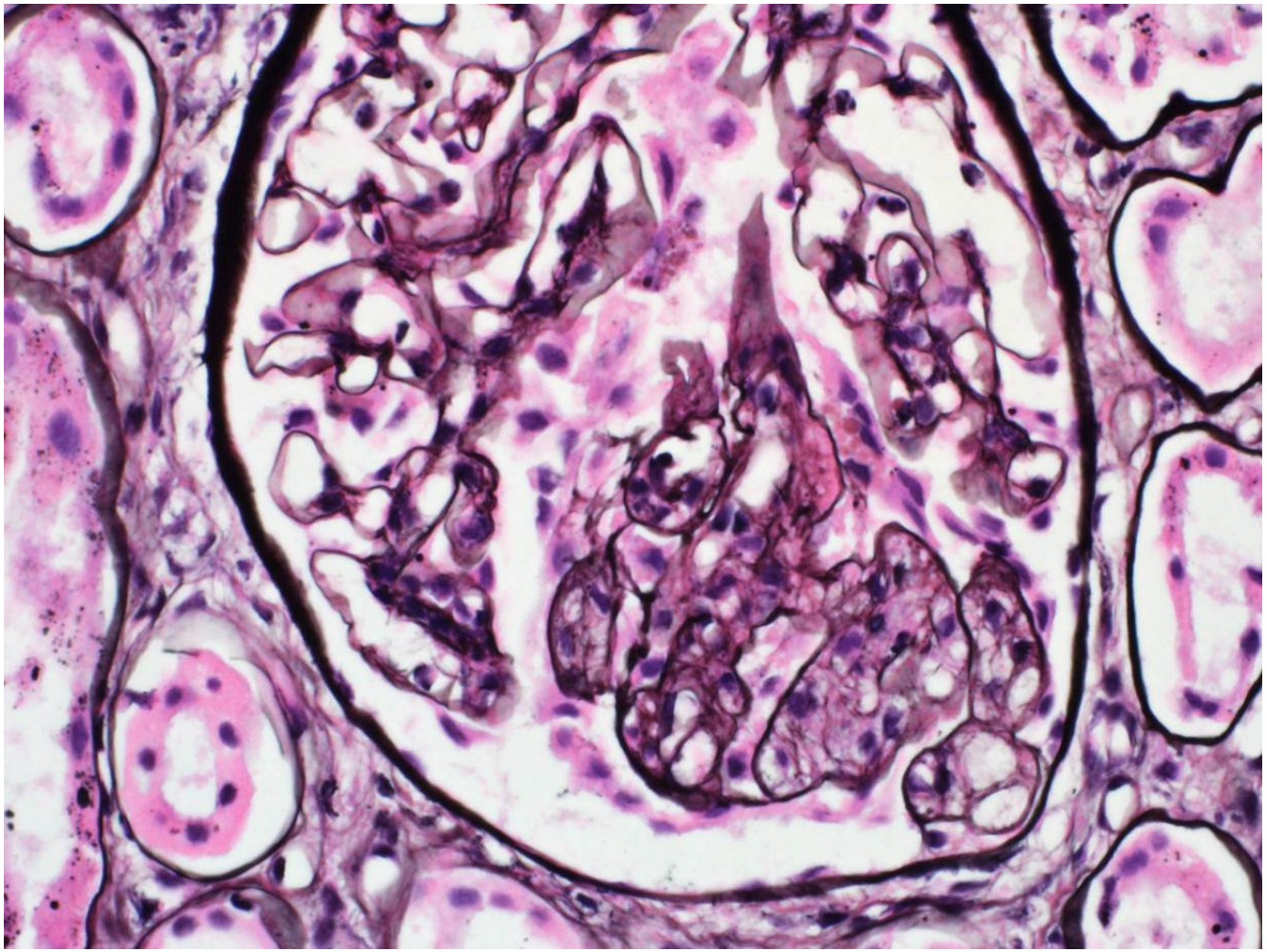
FSGS, cellular variant



FSGS, cellular variant



FSGS, cellular variant



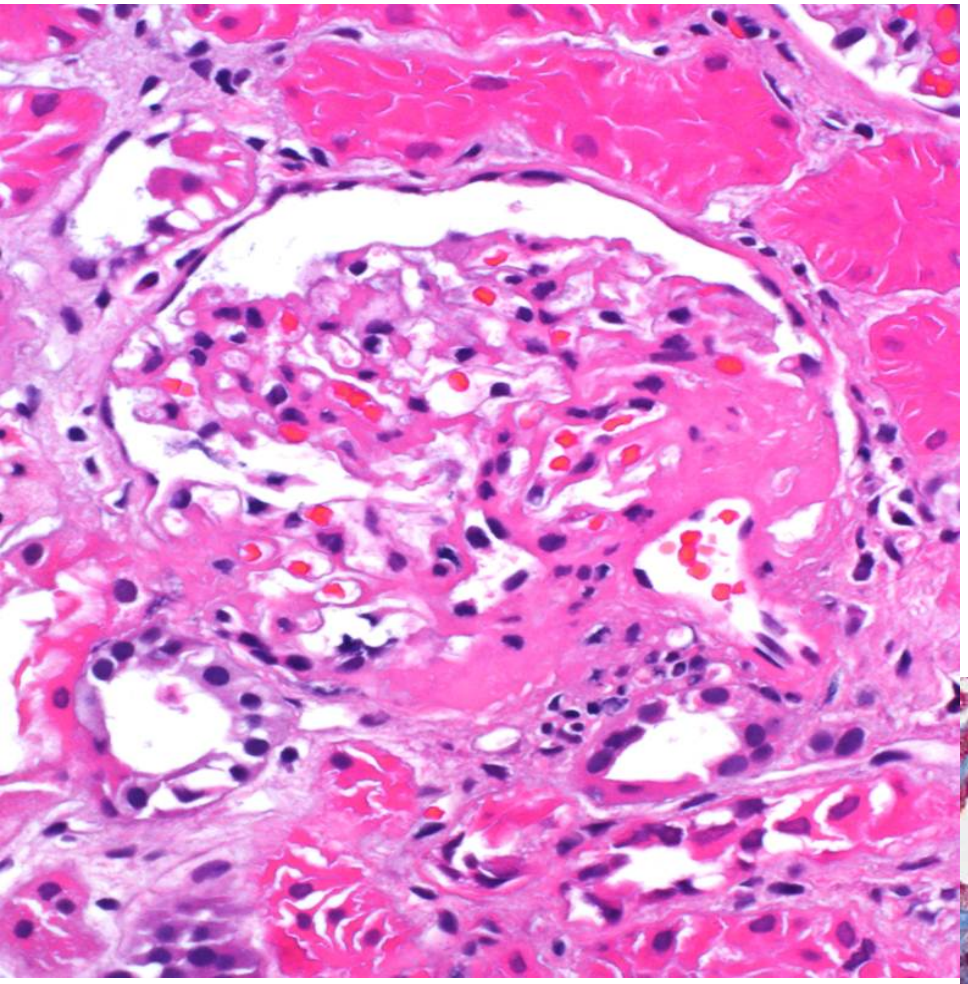
FSGS, perihilar variant

- Exclude collapsing, tip, and cellular variants.
- More than 50% of glomeruli must have the defining features:

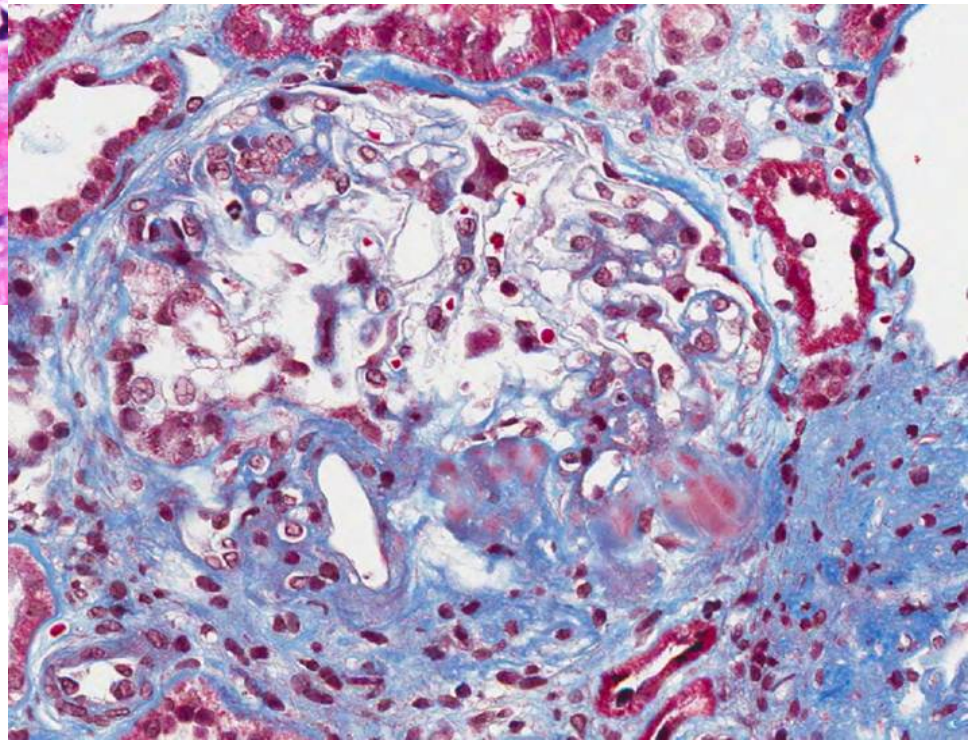
1- At least one glomerulus must have perihilar hyalinosis.

2- More than 50% of glomeruli with segmental lesions must have perihilar sclerosis.

*Thomas DB, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int. 2006; 69:920-6.



FSGS, perihilar variant



FSGS, not otherwise specified (NOS)

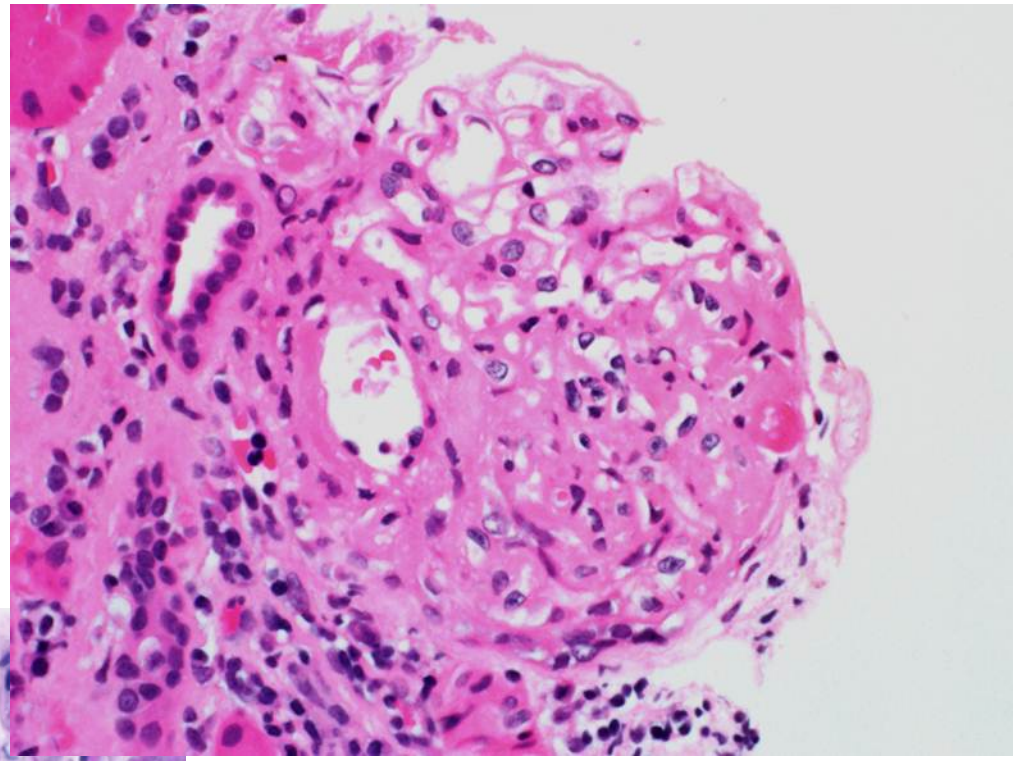
- Exclude other variants

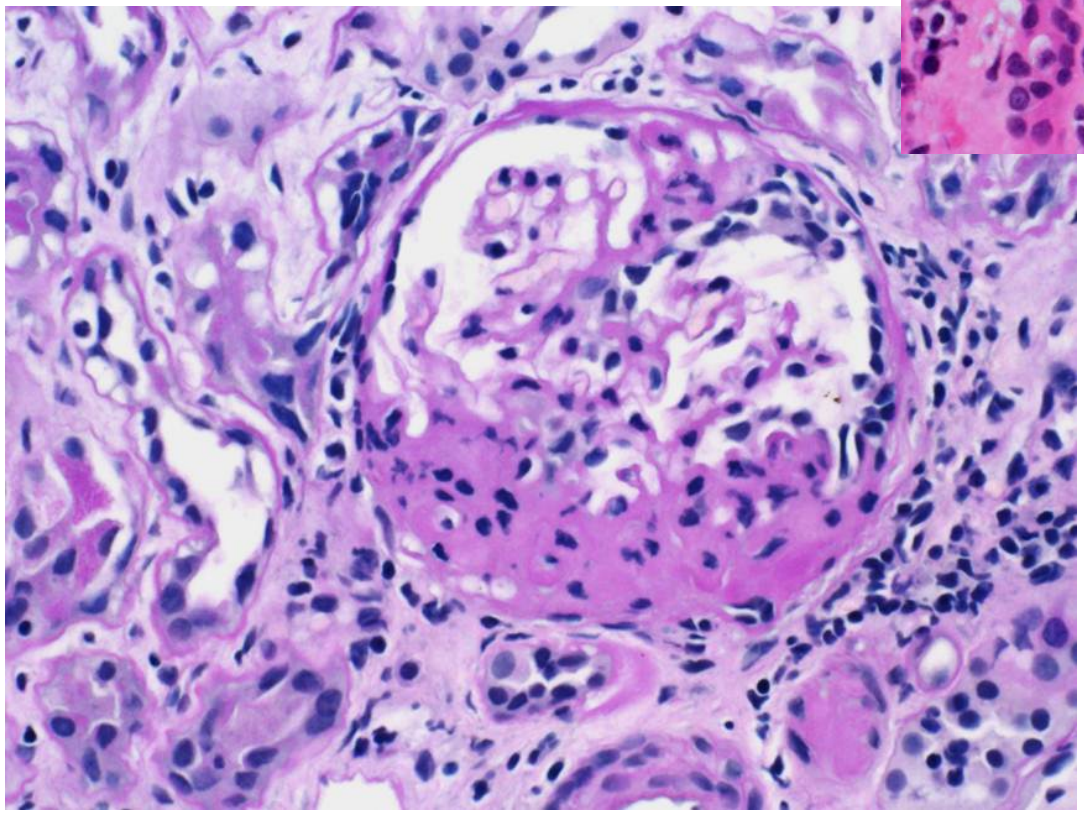
  - At least 1 glomerulus with segmental increase in matrix obliterating the capillary lumina.

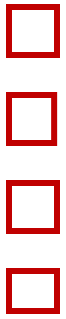
  - There may be segmental glomerular capillary wall collapse without overlying podocyte hyperplasia.

D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004 43:368-82.

FSGS, not otherwise specified (NOS)







Stokes MB, D'Agati VD. Morphologic variants of focal segmental glomerulosclerosis and their significance. Adv Chronic Kidney Dis. 2014;21(5):400-7.

Etiologic Classification of FSGS

- Idiopathic
- HIV-Associated Nephropathy
- Heroin Nephropathy
- Familial FSGS
  - *Mutations in alpha-actinin-4 (AD)*
  - *Mutations in podocin (AR)*
  - *Others*
- Drug Toxicity
  - *Pamidronate*
  - *Lithium*
  - *Interferon*

Etiologic Classification of FSGS

- Secondary FSGS Mediated by Adaptive Structural - Functional Responses

- Reduced renal mass

Oligomeganephronia

Unilateral renal agenesis

Reflux nephropathy

Surgical renal ablation

- Initially normal renal mass

Diabetes mellitus

Hypertension

Obesity

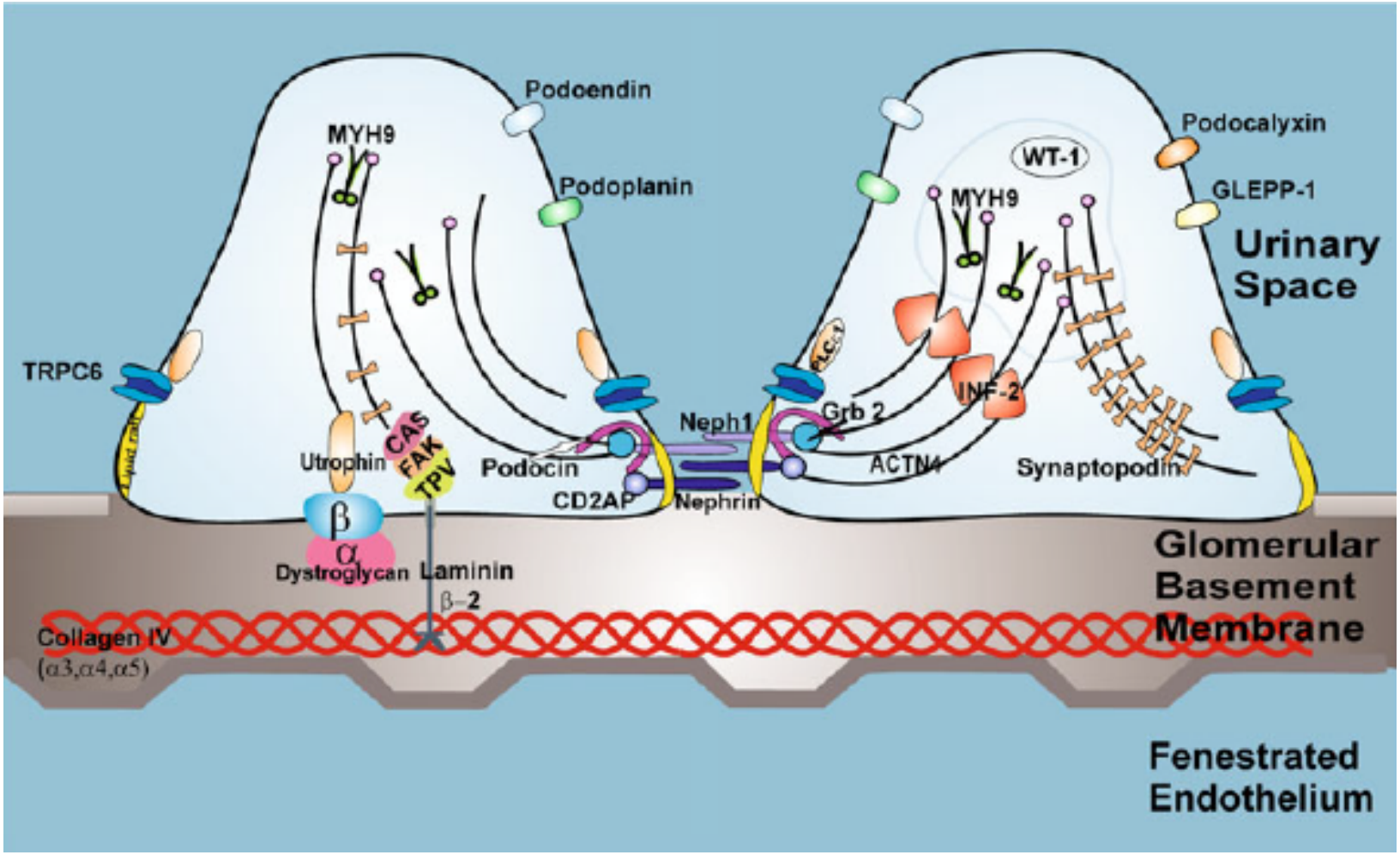
Sickle cell disease

Pathogenesis

Table 2 Genetic causes of FSGS and nephrotic syndrome

Genes (inheritance)	Protein localization	Locus	Phenotype
NPHS1/nephrin (AR)	Podocyte and slit diaphragm	19q13.1	Congenital nephrotic syndrome
NPHS2/podocin (AR)	Podocyte and slit diaphragm	1q25-q31	Early onset FSGS
CD2AP (AD)	Podocyte and slit diaphragm	6p12.3	Adult onset FSGS
WT1 (AD)	Podocyte	11p13	Syndromic DMS, syndromic and isolated FSGS
ACTN4/α-actinin 4 (AD)	Podocyte	19q13	Adult onset FSGS
TRPC6 (AD)	Podocyte	11q21-q22	Adult onset FSGS
PLCE1 (AR)	Podocyte	10q23-q24	Non-syndromic DMS, FSGS
LMX1B (AD) [76]	Podocyte	9q34.1	Syndromic NS and skeletal dysplasia
SMARCAL1 (AR) [77]	Podocyte	2q34-q36	Syndromic immune complex nephritis and skeletal defect
LAMB2 (AR)	Glomerular basement membrane	3p21	Syndromic DMS, isolated FSGS
SCARB2 (AR) [78]	Lysosome	4q21.1	Syndromic FSGS
MYH9 (Complex)	Podocyte	22p	Idiopathic FSGS
INF2 (AD)	Podocyte	14q32	Adult onset FSGS
Unknown	Unknown	Unknown	Galloway–Mowat syndrome
Multiple	Unknown	Multiple	Charcot–Marie–Tooth disease

Pathogenesis and therapy of focal segmental glomerulosclerosis: an update. Gbadegesin R, Lavin P, Foreman J, Winn M. Pediatr Nephrol. 2011;26(7):1001-15.



Pathogenesis and therapy of focal segmental glomerulosclerosis: an update. Gbadegesin R, Lavin P, Foreman J, Winn M. Pediatr Nephrol. 2011;26(7):1001-15.

caveats

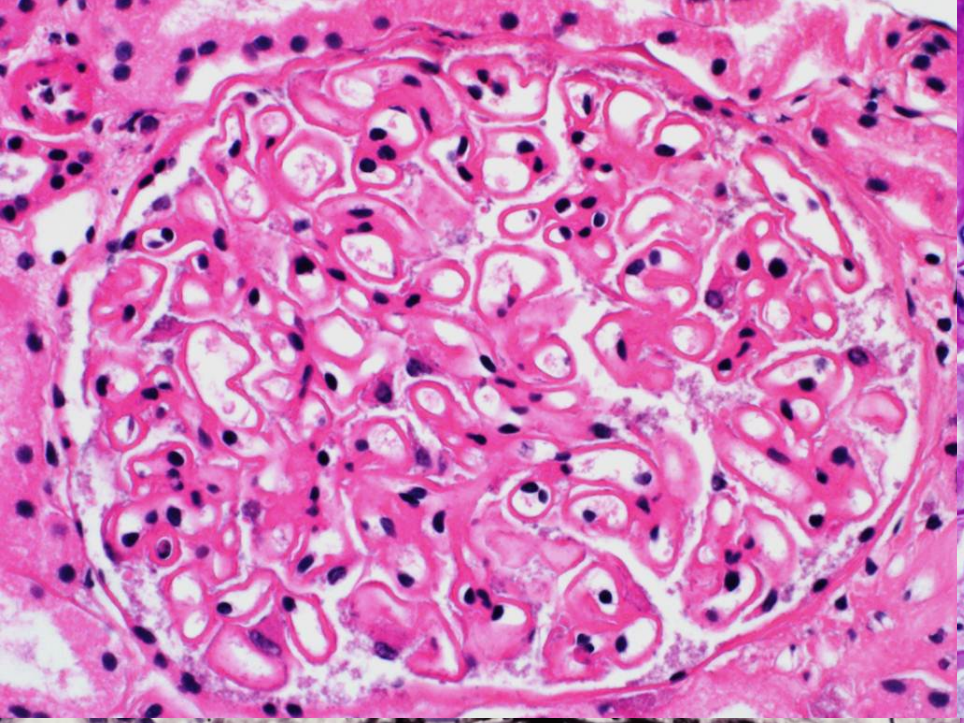
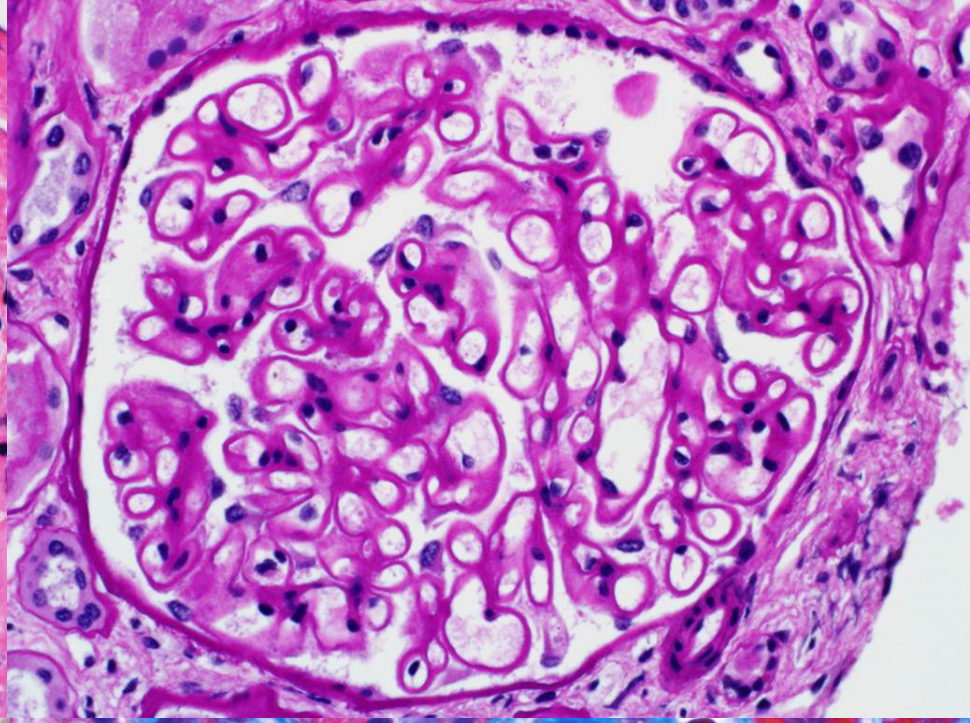
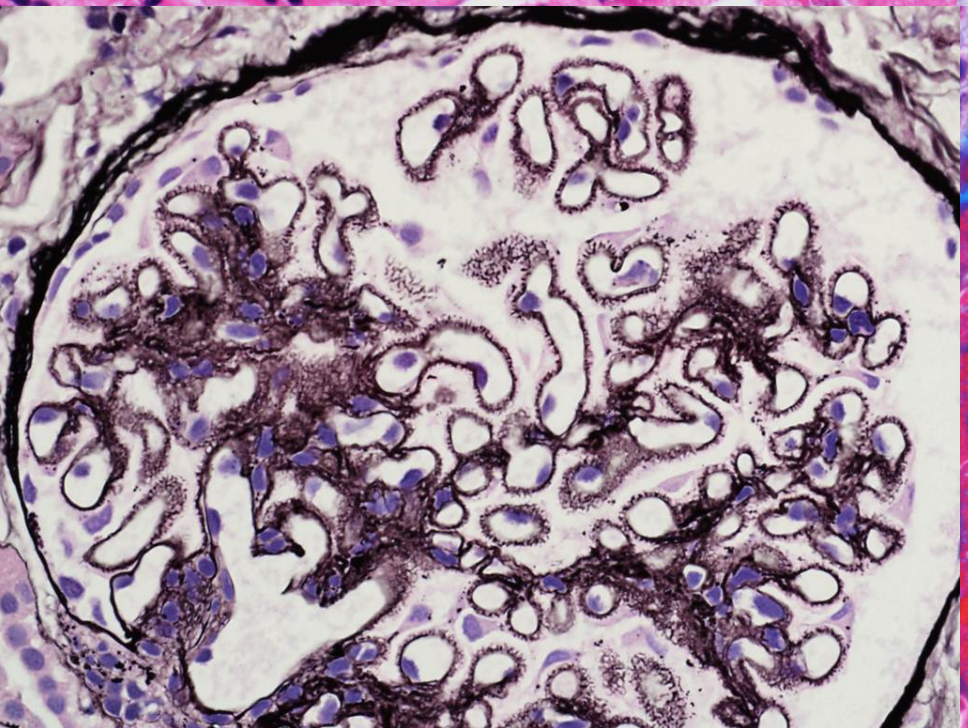
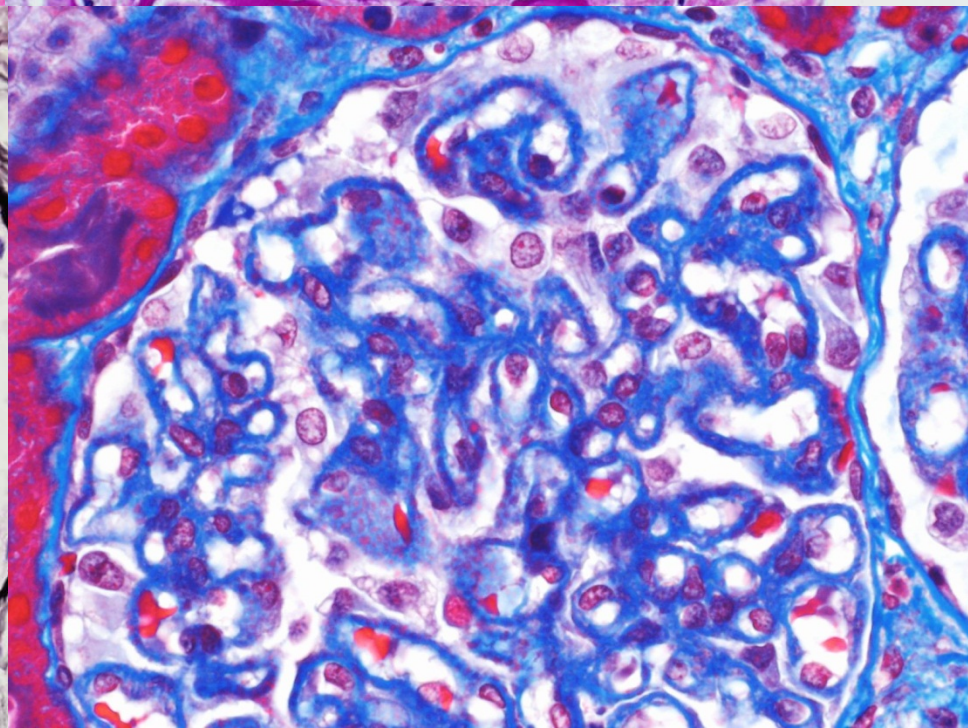
- The possibility of unsampled FSGS should be suspected if there is patchy IFTA or inadequate biopsy.
- More extensive sectioning of the paraffin block may reveal the diagnostic lesion.
- Reexamine IF and EM tissue.
- Primary FSGS is distinguished from secondary FSGS by careful clinical-pathologic correlation.
- Nonspecific glomerular scaring can be seen in other glomerulonephritis.

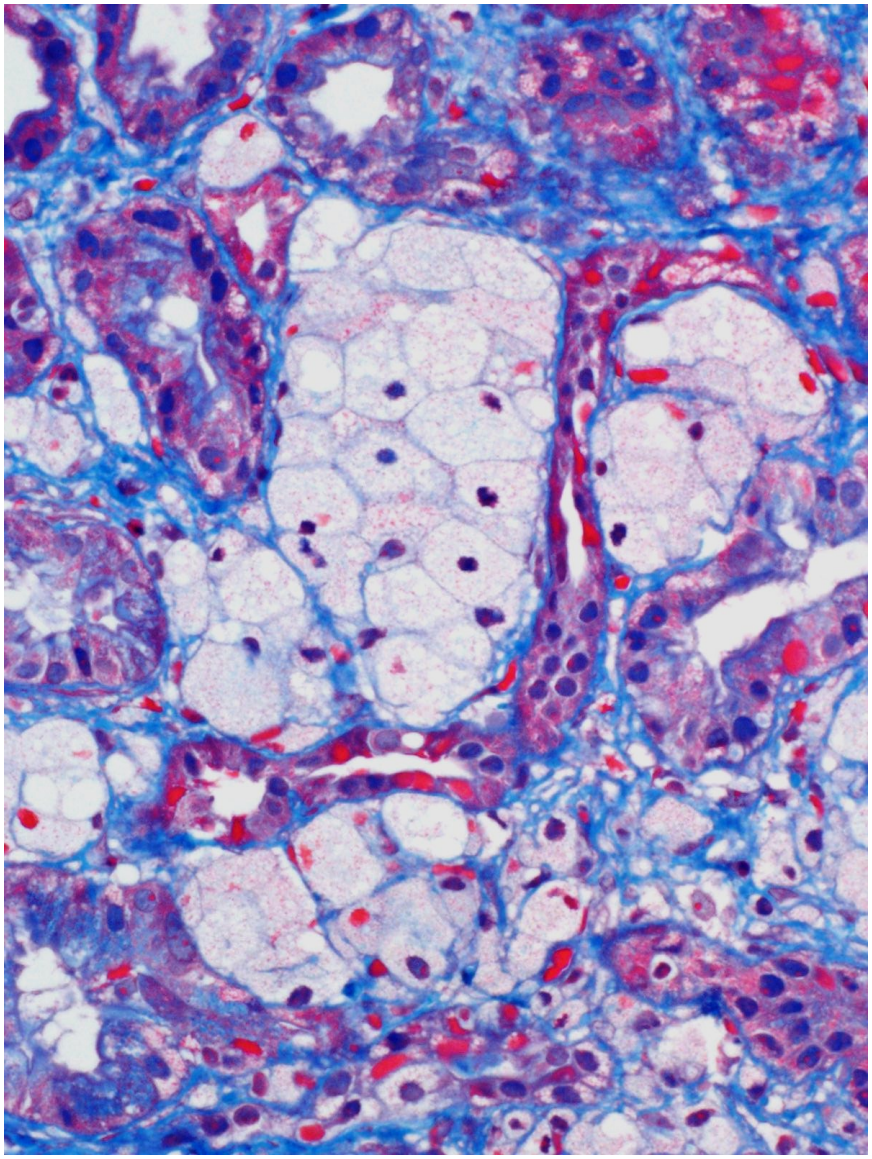
Membranous Glomerulopathy

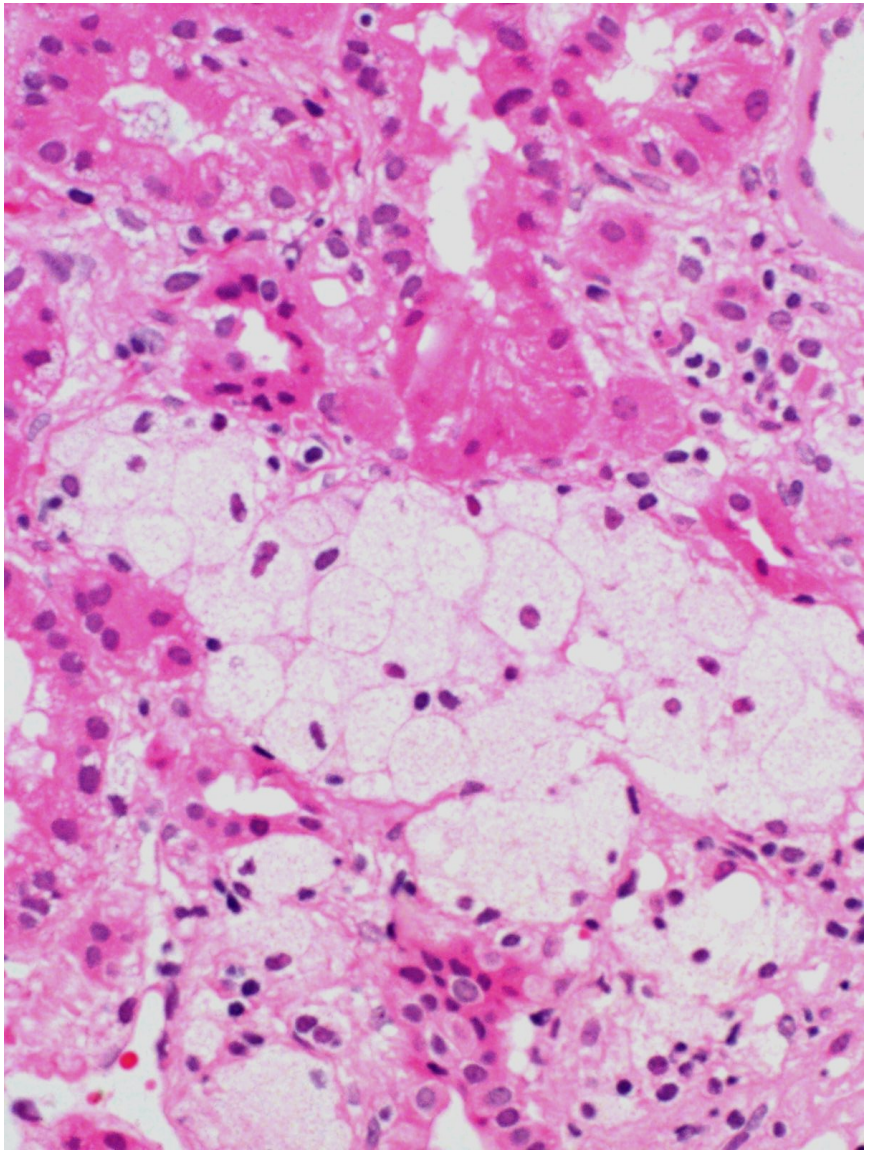
- It is defined pathologically as a spectrum of glomerular capillary wall abnormalities resulting from the formation of subepithelial immune deposits.
- Glomerulopathy VS glomerulonephritis.

Clinical Features

- Occurs at all ages BUT much more common in adults than children. (4^{th} & 5^{th} decades)
- Proteinuria: nephrotic range (3.5 g/day)> subnephrotic.
- Microhematuria (up to half pts at presentation)
- Renal vein thrombosis is a common complication.

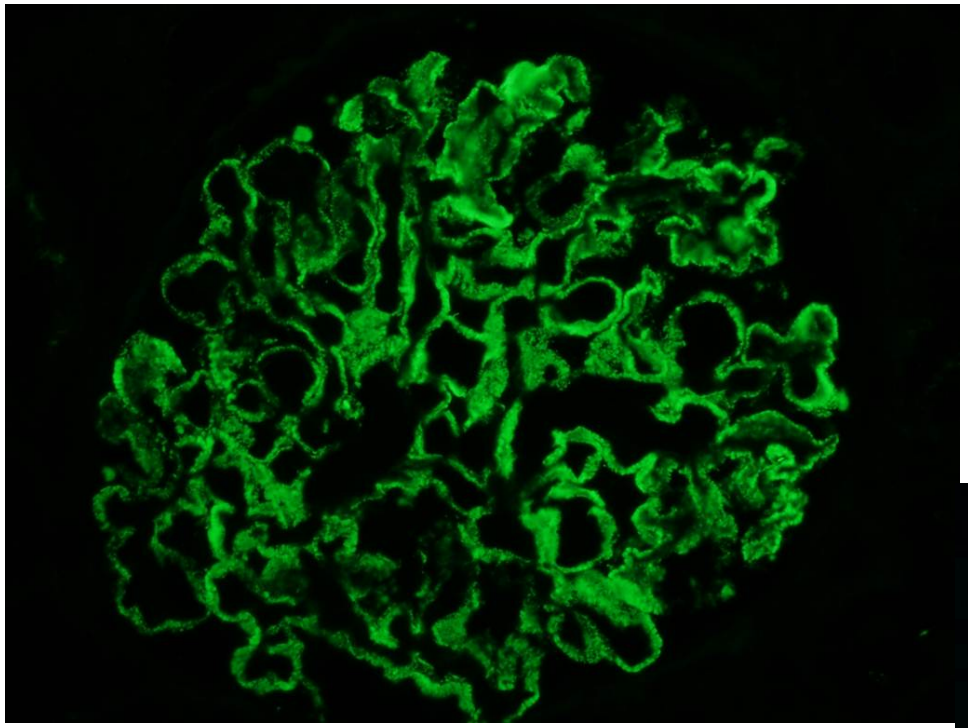





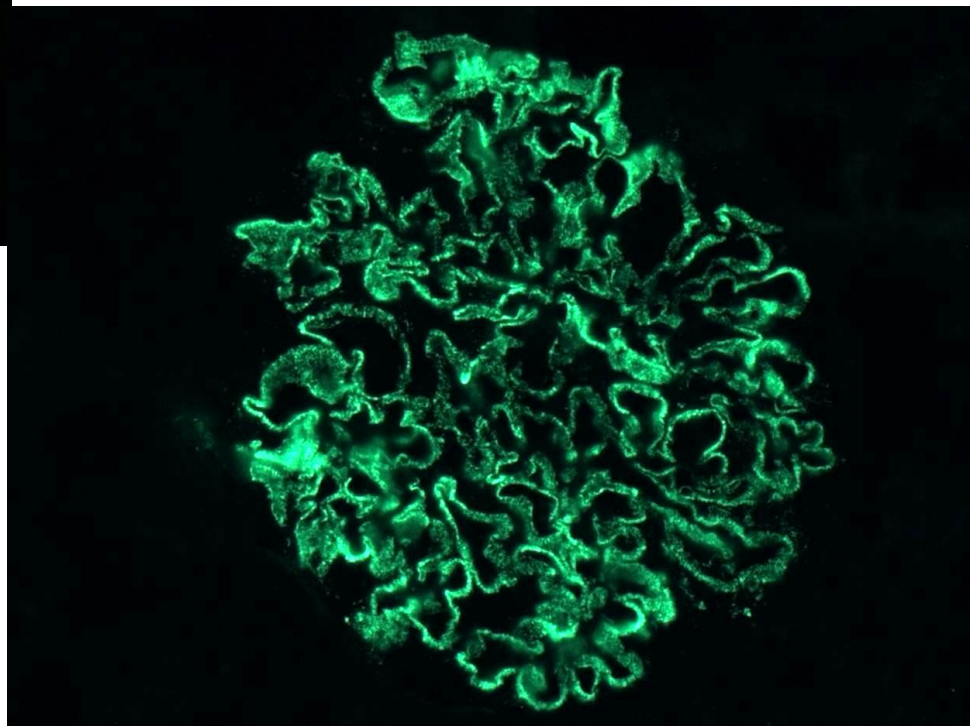




Interstitial foam cells

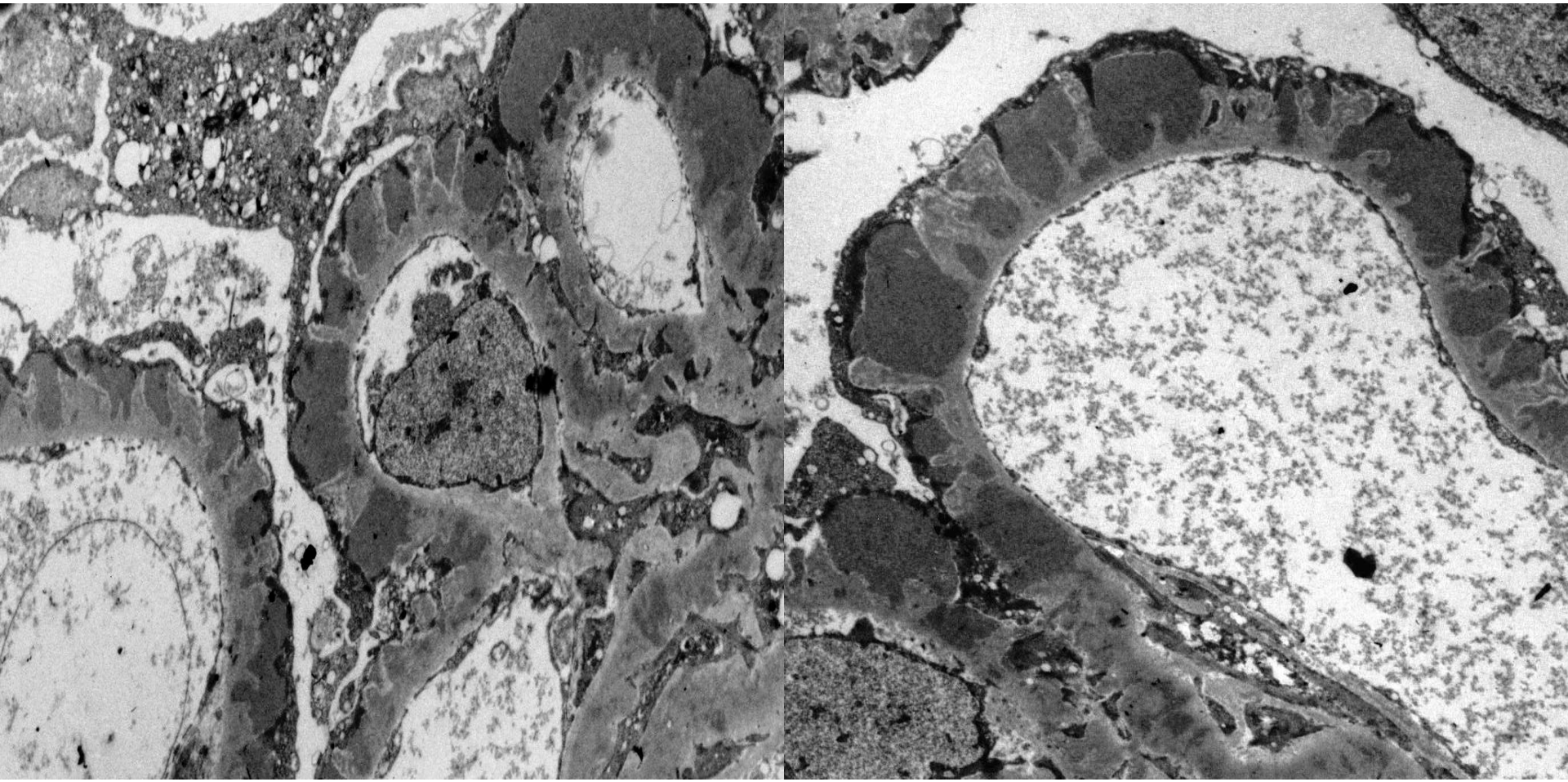
Immunoflourescence findings





IgG, C3, Kappa, Lambda

MGN



Stages

Four stages have been defined by Ehrenreich and Churg (1968):

Stage 1:

LM: GBM normal thickness or slightly thickened, slight GBM vacuolization.

EM: small focal subepithelial deposits, no spikes, focal foot process effacement

Stage 2:

LM: GBM moderately thickened, spikes, vacuolization.

EM: diffuse subepithelial deposits, well-developed spikes, diffuse foot process effacement.

Stages

Stage 3:

LM: GBM markedly thickened, chain-like appearance, residual spikes, vacuoles.

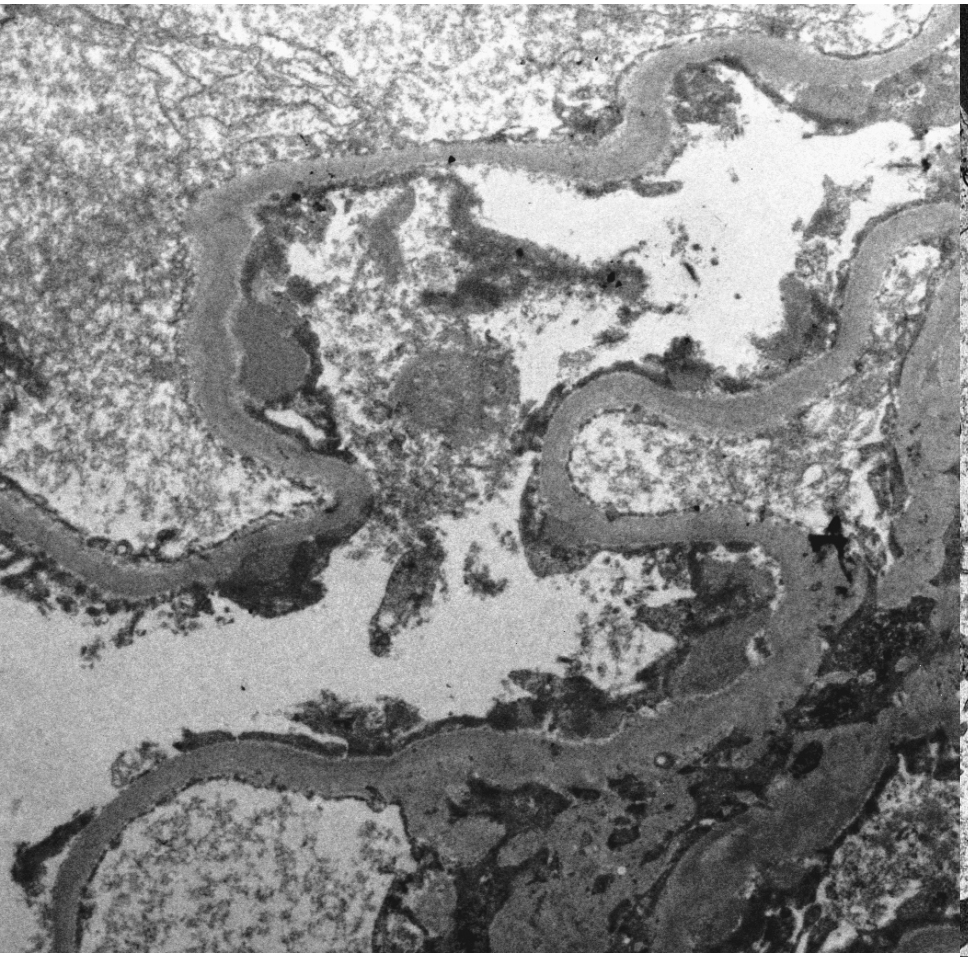
EM: intramembranous deposits, resorbed deposits, lacunae, spikes, neomembrane, diffuse foot process effacement

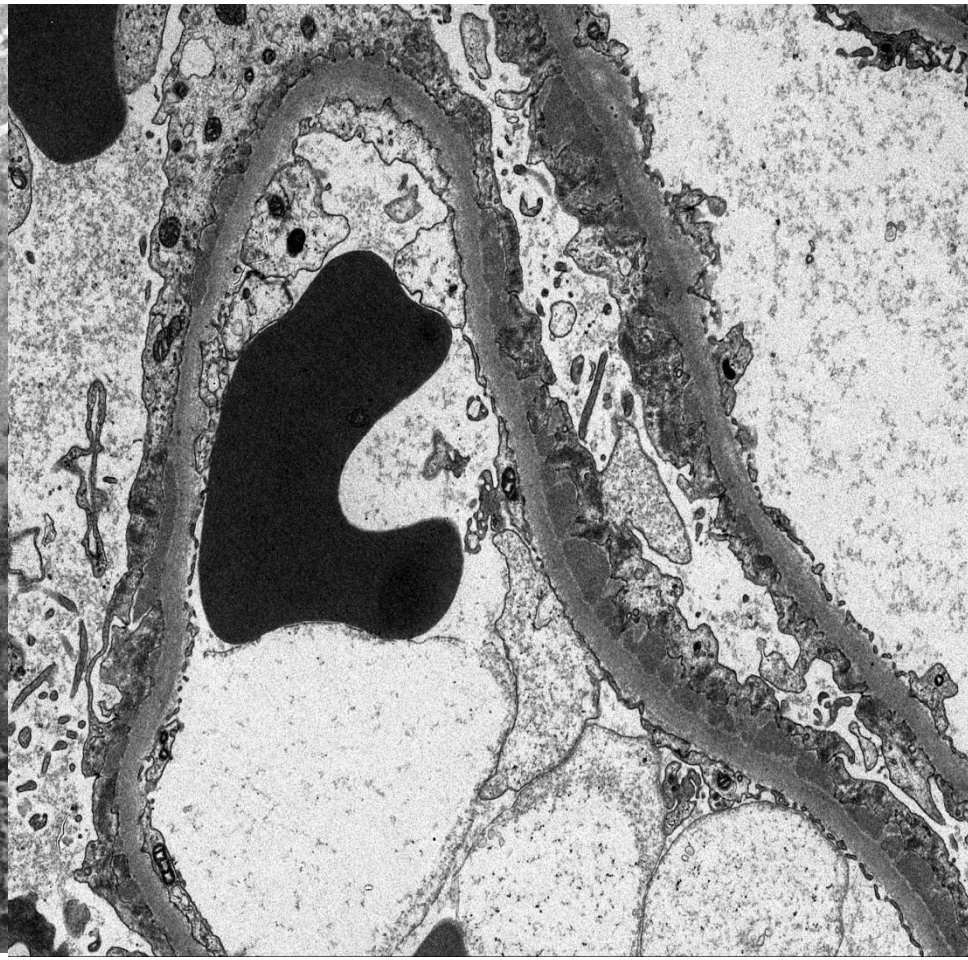
Stage 4:

LM: GBM markedly thickened, few spikes, vacuoles, sclerotic glomeruli.

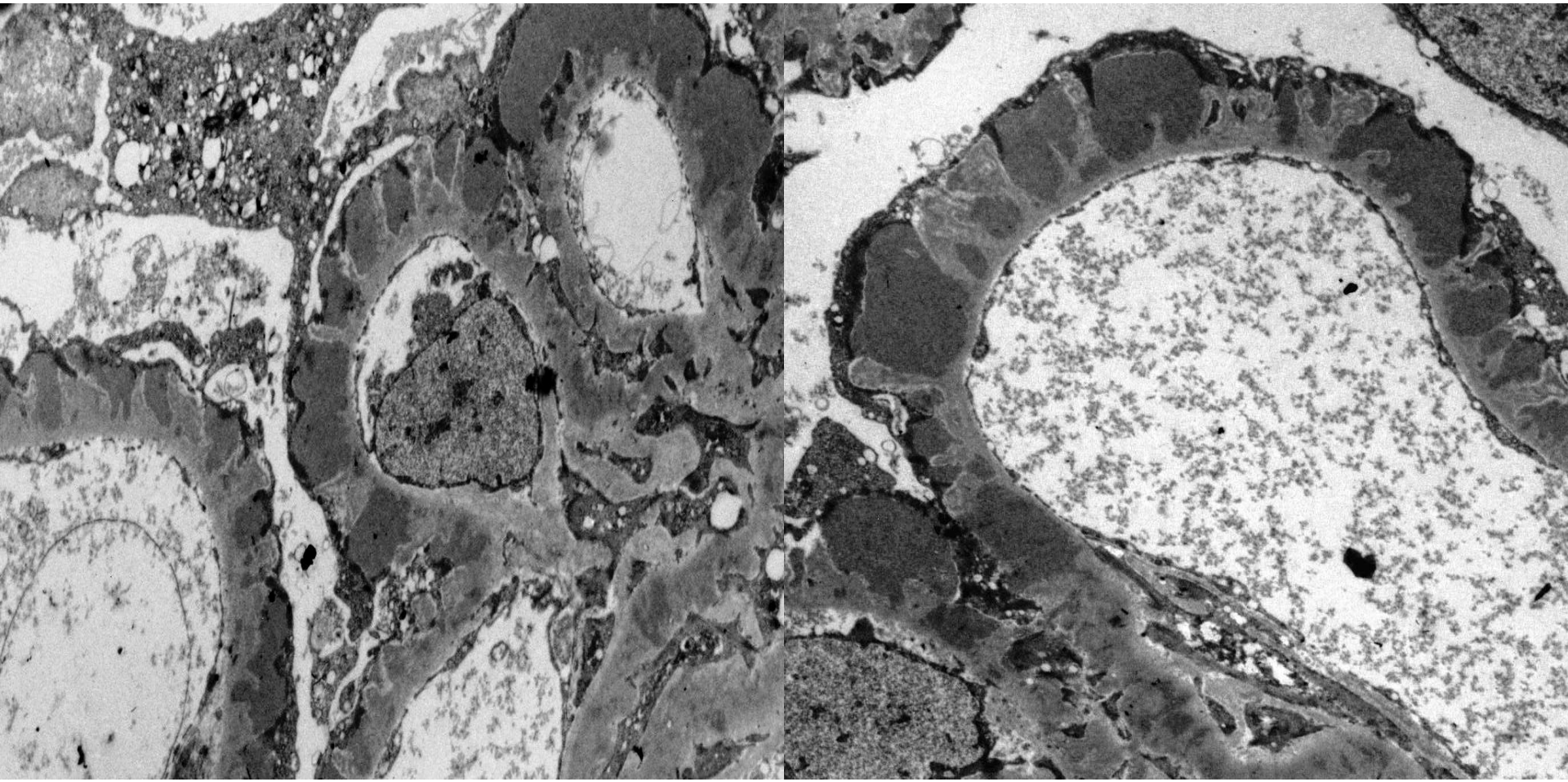
EM: few deposits, lacunae, thickened sclerotic GBM, some restored foot process.

MGN Stage 1

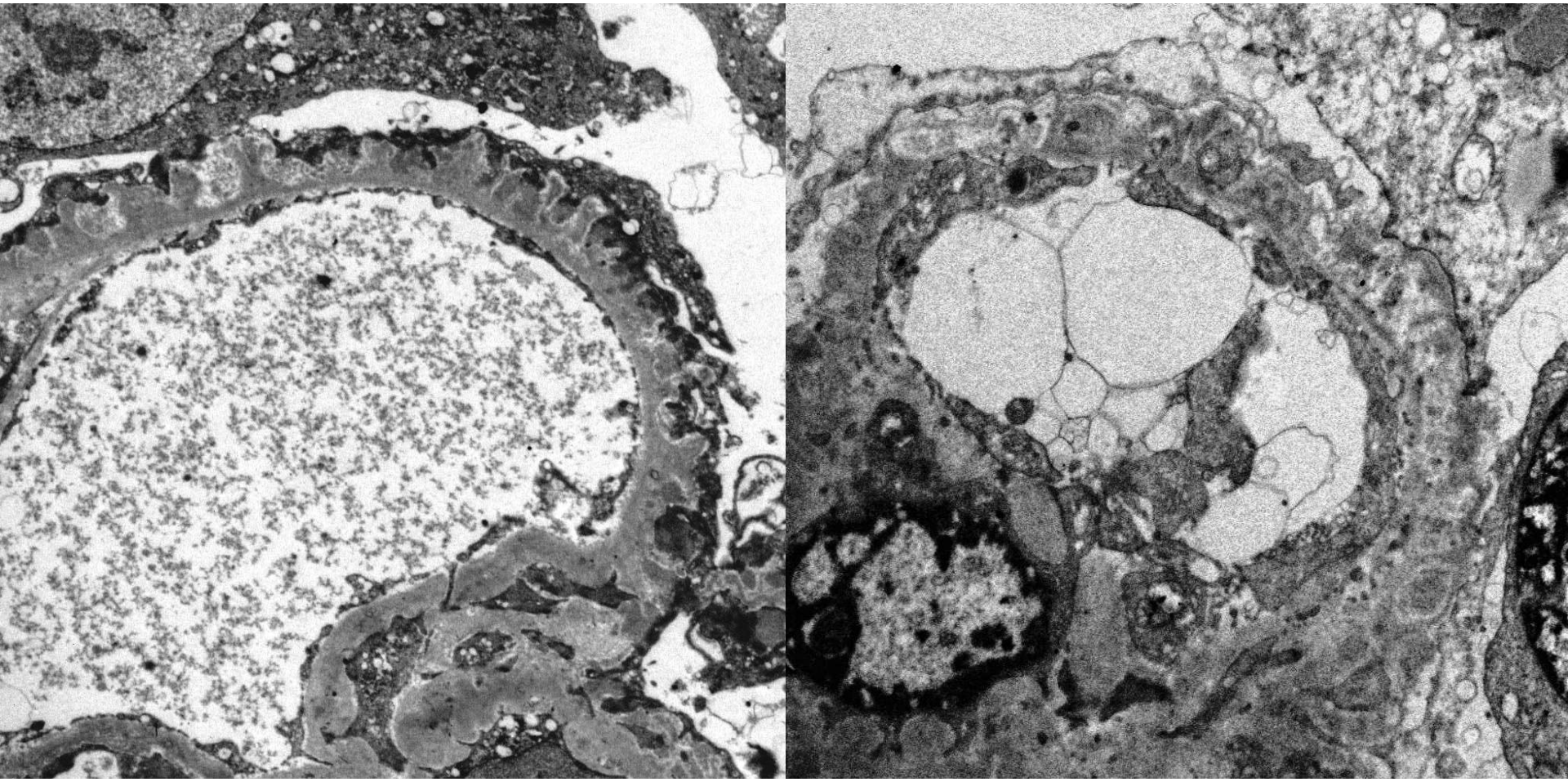




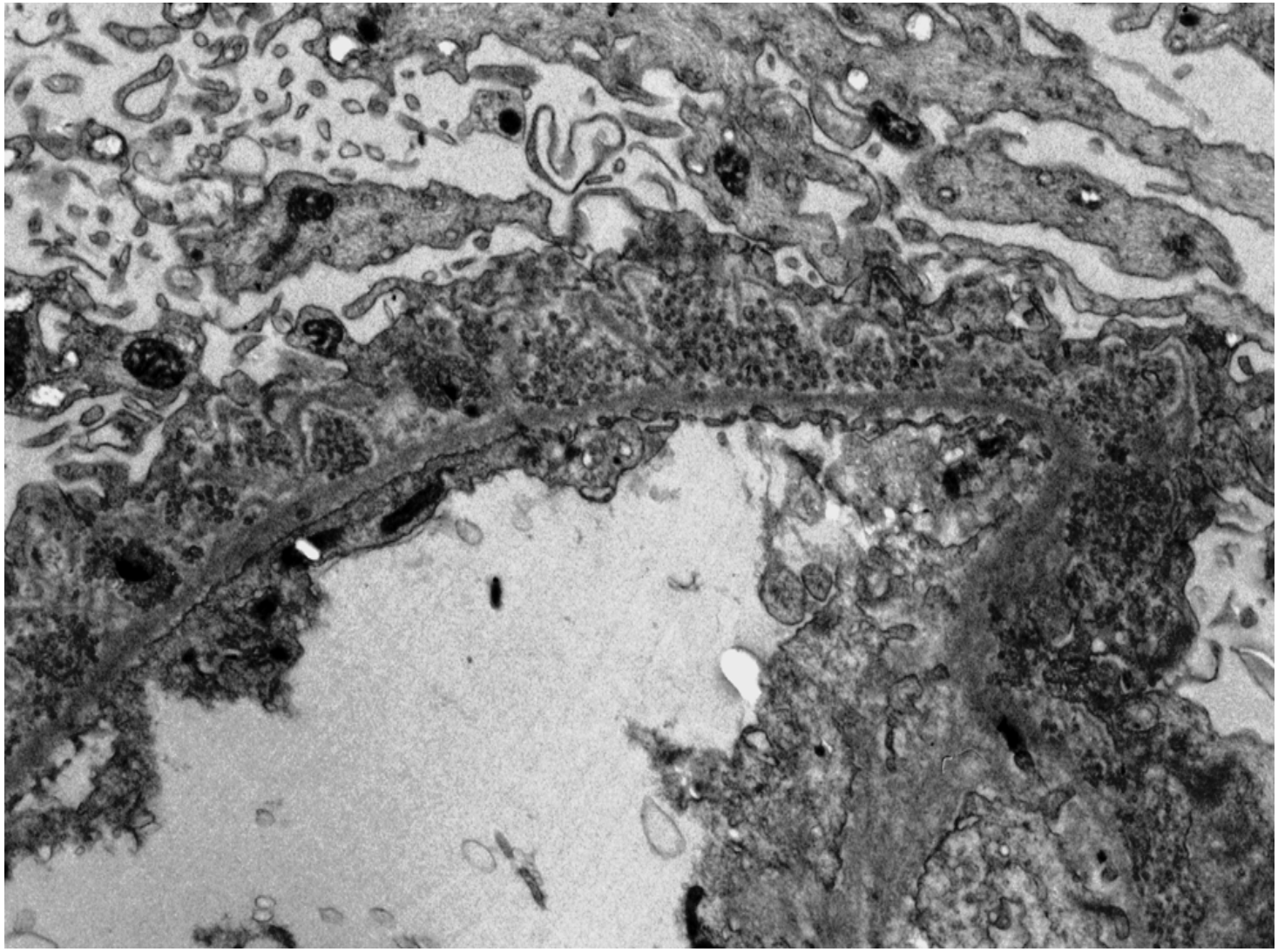
MGN Stage 2



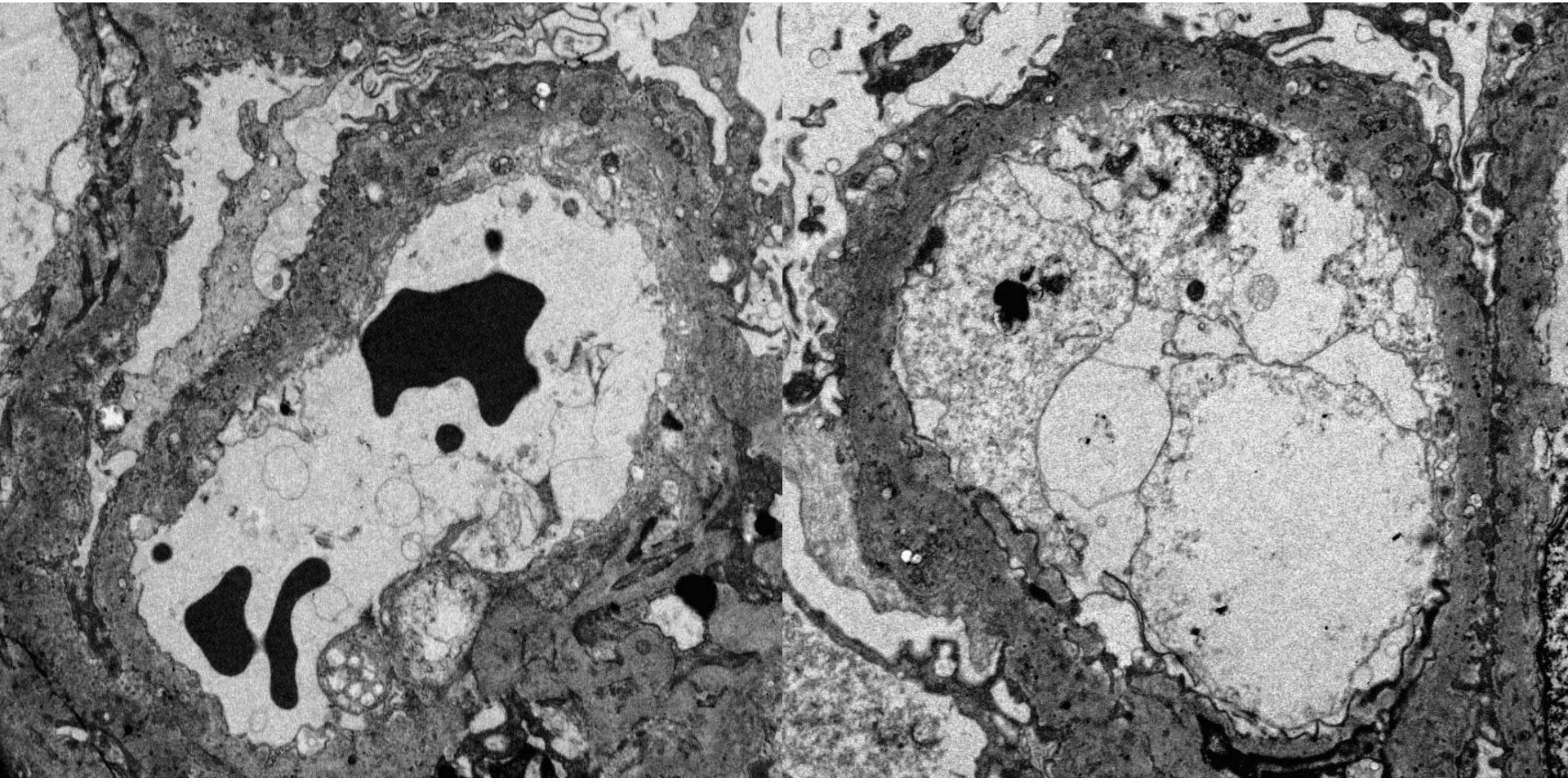
MGN Stage 3



MGN Stage 3



MGN Stage 4



Membranous Glomerulopathy

➢"IDIOPATHIC" (60-80%)

- Anti-PLA2R1 autoantibodies (70%)
- Anti-THSD7A autoantibodies (~10%)
- Others

➢ASSOCIATED WITH / SECONDARY TO:

Autoimmune/collagen vascular disease

Infections

Medications

Neoplasms

Miscellaneous

PLA2R

Granular staining for PLA2R1 along GBMs

PLA2R1 in Membranous Glomerulopathy. 2013 Larsen CP et al

Novel proteins/target antigens in MN

Phospholipase A2 receptor and thrombospondin type-1 domain-containing 7A, exostosin 1/2, neuralepidermal growth-like 1 protein, semaphorin 3B, neural cell adhesion molecule 1, and protocadherin 7. **(Sanjeev Sethi. Clinical Kidney Journal, 2021)**

(Sanjeev Sethi. Clinical Kidney Journal, 2021)

MAYO CLINIC

MAYO CLINIC PROCEEDINGS

CONSENSUS RECOMMENDATIONS

Mayo Clinic Consensus Report on Membranous Nephropathy: Proposal for a Novel Classification

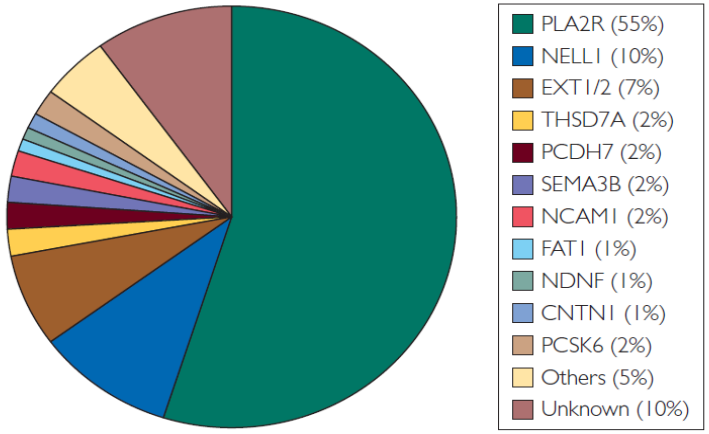
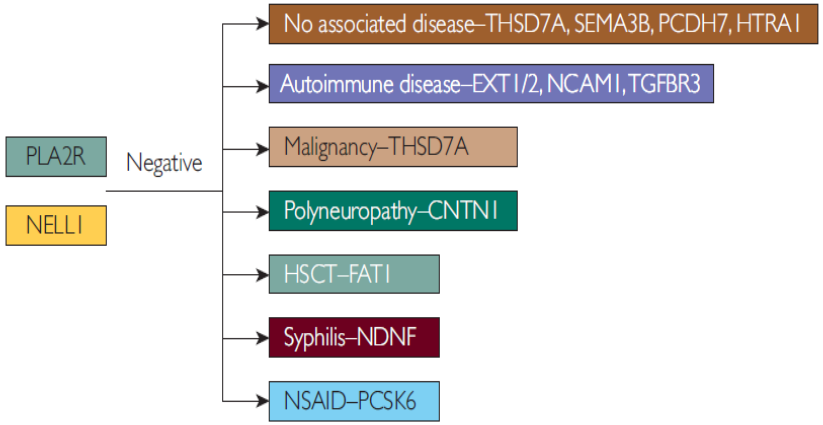


FIGURE 1. **Approximate incidence of membranous nephropathy (MN) antigens.** The target antigen incidence can vary based on demographics, and the incidence (%) shown here is based on cases of M-type phospholipase A2 receptor (PLA2R)—negative MN used for mass spectrometry detection of MN antigens at the Mayo Clinic, Rochester, Minnesota, USA. Others include rare (< 1%) and putative antigens. Neither serine protease HTRA1 nor transforming growth factor beta receptor 3 were detected in any case, on mass spectrometry studies, and hence, they are not shown. CNTN1, contactin 1; EXT, exostosin; FAT1, protocadherin FAT1; NCAM1, neural cell-adhesion molecule 1; NDNF, neuron-derived neurotrophic factor; NELL1, neural epidermal growth factor–like protein 1; PCDH7, protocadherin 7; PCSK6, proprotein convertase subtilisin/kexin type 6; SEMA3B, semaphorin 3B; THSD7A, thrombospondin type-I domain-containing 7A.

1



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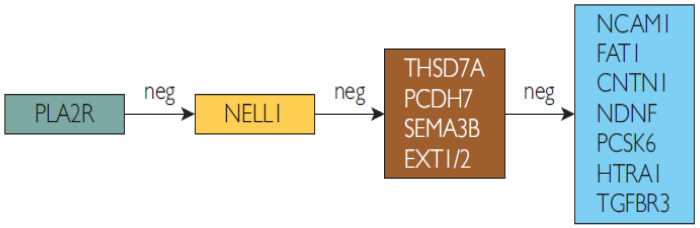


Sanjeev Sethi, et al. Nov. 2023

TABLE 1. Characteristics of (known) MN target antigens

Target antigen	Podocyte expressed? TM vs. secreted	AutoAb detected?	Clinical/disease association	Distinctive histopathologic features
PLA2R	Yes; TM	Yes	None	Global, granular, subepithelial deposits; IgG4 predominant
THSD7A	Yes; TM	Yes	Malignancy	Similar to PLA2R Caveat: there is normal linear basal podocyte staining for THSD7A
NELL1	No[a]; secreted	Yes	Malignancy, drugs, autoimmune	IgG1 predominant, deposits may be segmental or incomplete-loop pattern
SEMA3B	Yes; secreted	Yes	Pediatric	IgG1 predominant, may have additional mesangial deposits; TBM deposits may be present
PCDH7	No; TM	Yes	Older	C3 absent or weak
HTRA1	Yes; secreted	Yes	None	IgG4 predominant, similar to PLA2R
NTNG1	Yes; GPI-linked	Yes	None	IgG4 predominant, similar to PLA2R
EXT1/EXT2	No[a]; TM Golgi protein and secreted	No	Autoimmune disease, lupus	IgG1 predominant, IgA, IgM often present, mesangial deposits, may coexist with class III/IV lupus
NCAM1	No[a]; TM	Yes	Lupus	Similar to EXT1/EXT2
TGFBR3	Yes; TM	No[b]	Lupus	Similar to EXT1/EXT2
CNTN1	No[a]; GPI-linked	Yes	CIDP	IgG4 predominant
FAT1	Yes; TM	Yes	HSCT	TBM deposits can be present
NDNF	Yes; secreted	Yes	Young males, syphilis	Lumpy deposits, superficial hump-like by EM, IgG1
PCSK6	No[a]; secreted	Yes	Prolonged NSAID use	IgG1 and 4

[a]These antigens are not well-expressed by the normal podocyte according to current single-cell transcriptomic data sets, although it is possible that they are upregulated in disease.
[b]Antigen was identified by tissue immunostaining (bound to IgG).

AB, antibodies; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNTN1, contactin 1; EM, electron microscopy; EXT, exostosin; FAT1, protocadherin FAT1; GPI, glycosylphosphatidylinositol (links protein to membrane); HSCT, hematopoietic stem cell transplant; HTRA1, serine protease HTRA1; MN, membranous nephropathy; NCAM1, neural cell-adhesion molecule 1; NDNF, neuron-derived neurotrophic factor; NELL1, neural epidermal growth factor–like protein 1; NSAID, nonsteroidal anti-inflammatory drug; NTNG, netrin G1; PCDH7, protocadherin 7; PCSK6, proprotein convertase subtilisin/kexin type 6; PLA2R, M-type phospholipase A2 receptor; SEMA3B, semaphorin 3B; TBM, tubular basement membrane; TGFBR3, transforming growth factor beta receptor 3; THSD7A, thrombospondin type-1 domain-containing 7A; TM, transmembrane.

THE KIDNEY BIOPSY REPORT

The following should be addressed in the kidney biopsy report when MN is encountered:

(1) Pattern-of-injury: MN. Additional comments on morphologic features suggesting a specific antigen or underlying disease may be included (eg, segmental lesions, mesangial, subendothelial and/or extraglomerular deposits, full-houselg, complement deposition, presence or absence of endothelial tubuloreticular inclusions).

(2) The target antigen detected; if this is not known, the staining studies that were performed and returned with a negative result should be reported.

(3) Clinical association and prognostic implications of the target antigens; if this is not known, suggest evaluation in the comment section, depending on the antigen identified.

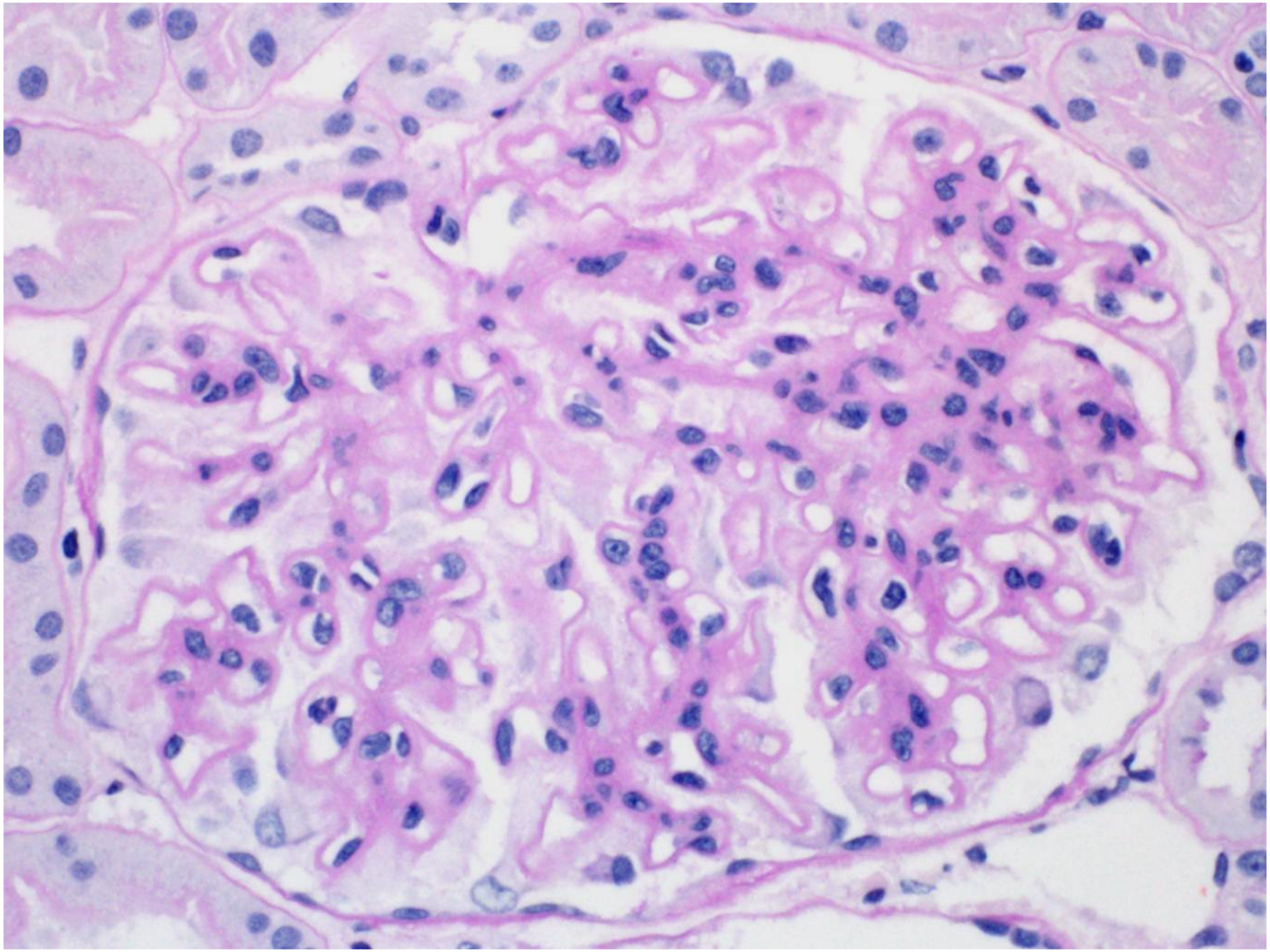
(4) IgG subclass description, if performed. IgG subtype can be an ancillary test in confirming an antigen or can guide testing for certain antigens.

(5) Electron microscopy stage based on Ehrenreich and Churg staging, despite the limitations of the staging system.

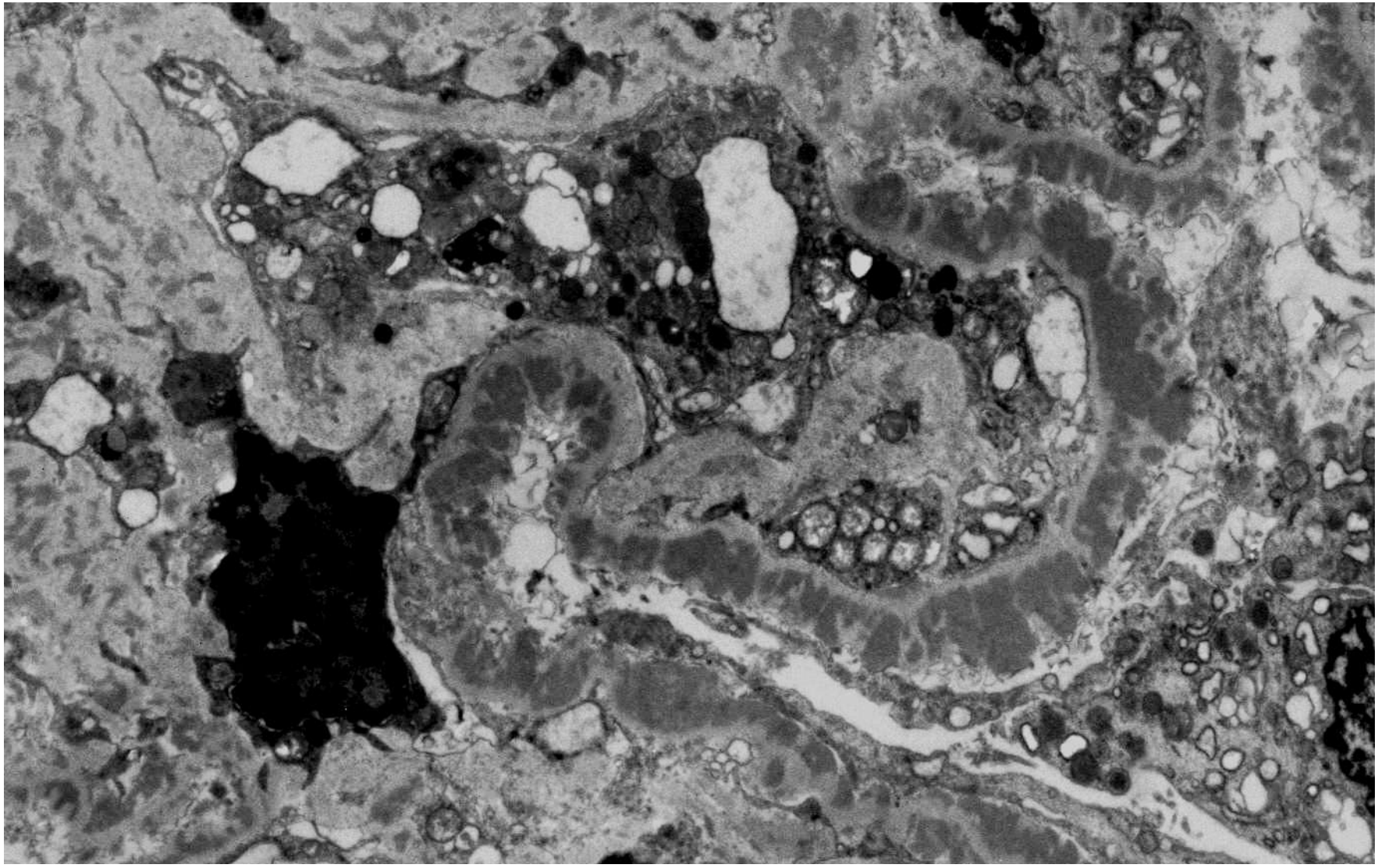
(6) Findings that have prognostic implications, including but not limited to secondary focal segmental glomerular sclerosis, extent of glomerulosclerosis, interstitial fibrosis/tubular atrophy, and vascular disease.

Sanjeev Sethi, et al. Nov. 2023

Secondary Membranous Glomerulopathy



Secondary Membranous Glomerulopathy

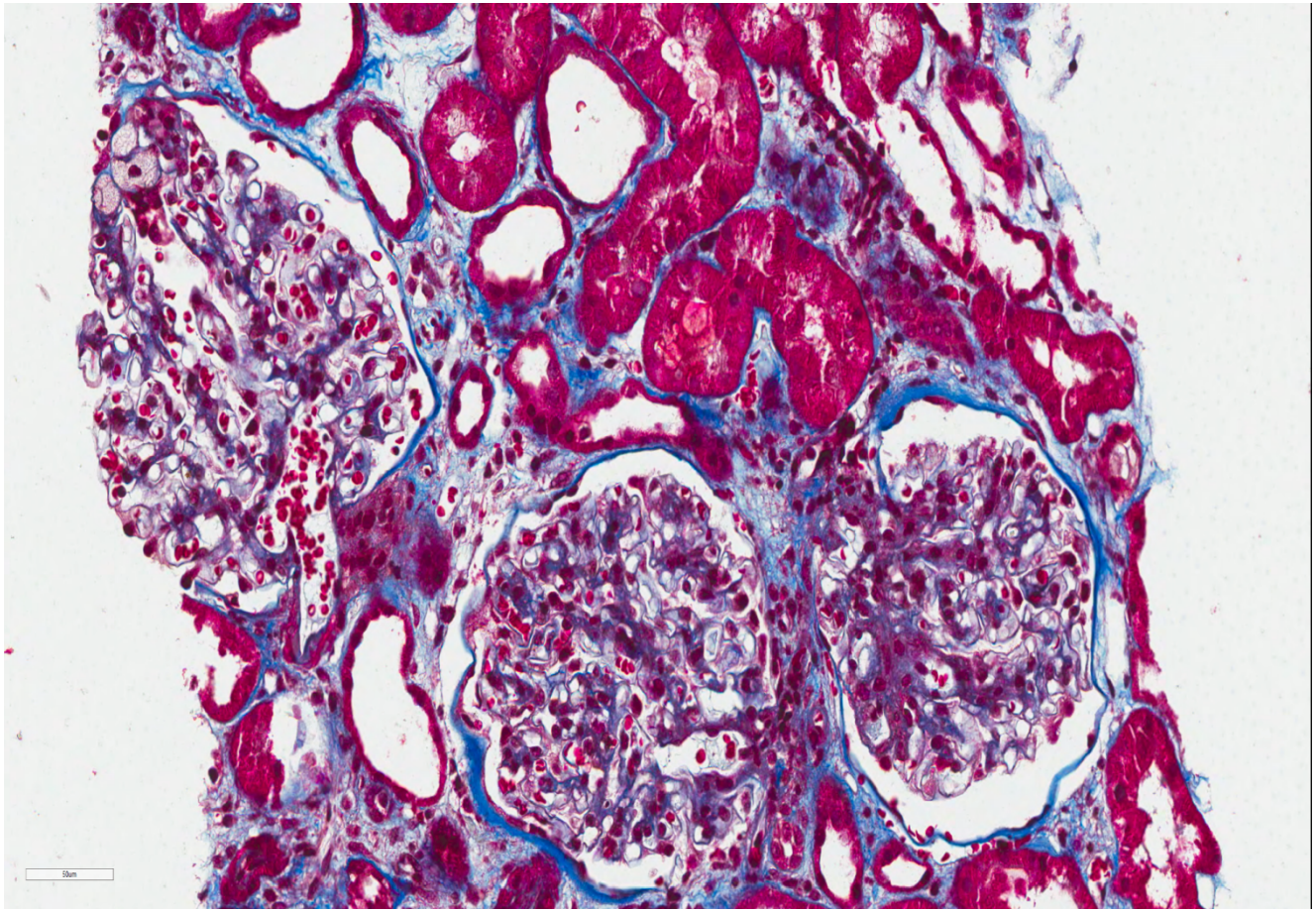



THANK YOU

CASES

CASE 1

- An 18 year-old male presented with nephrotic range proteinuria.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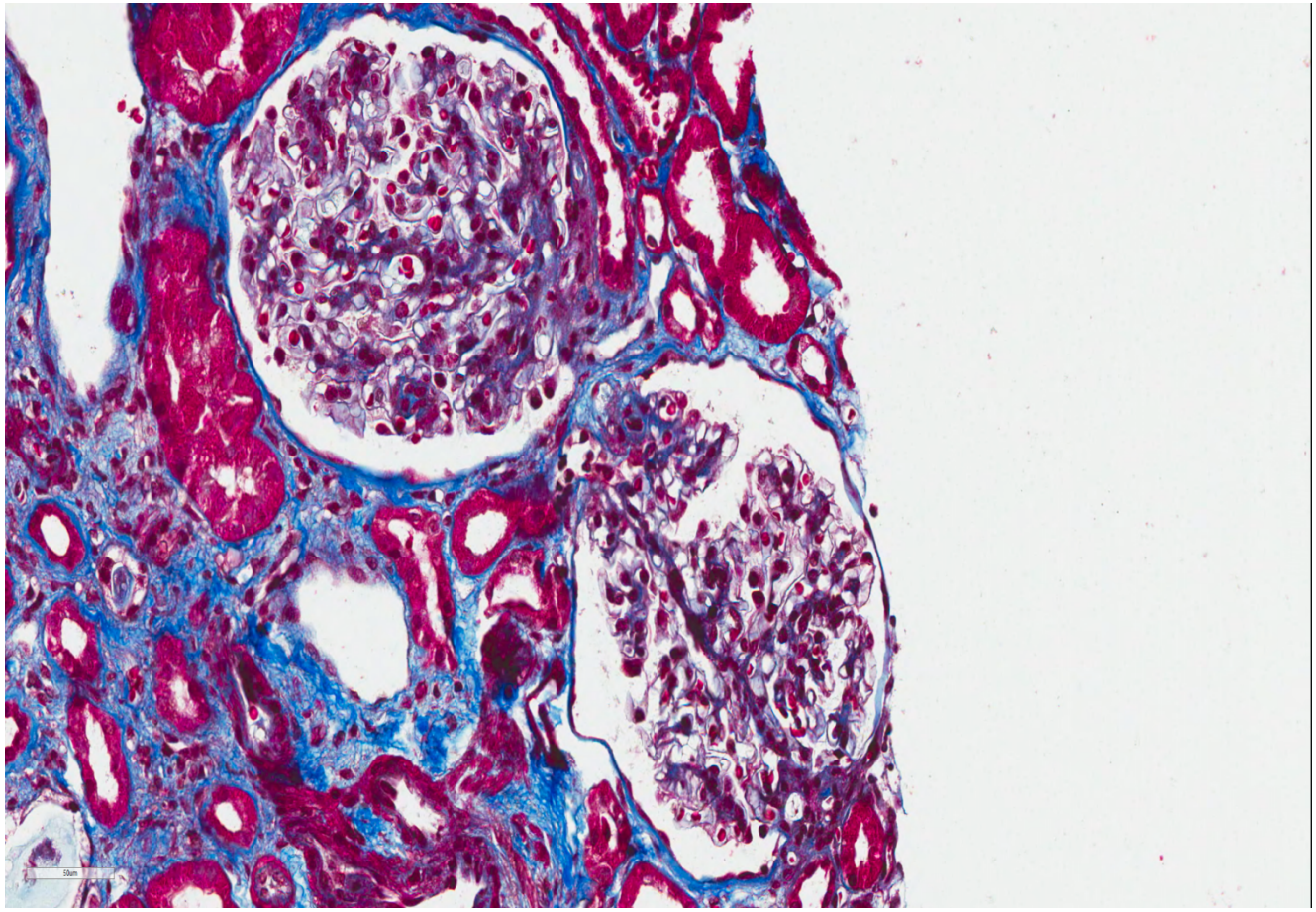
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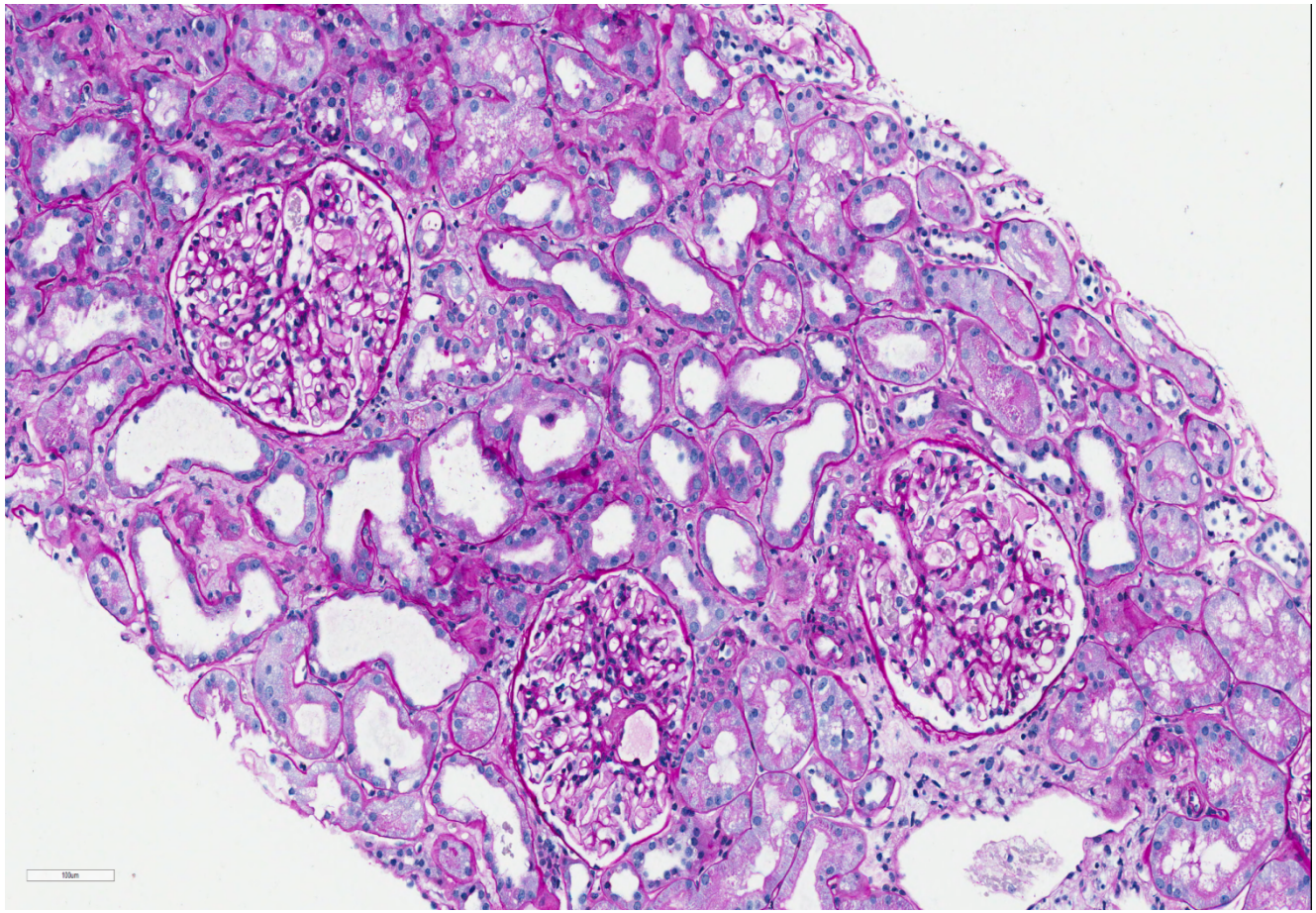
DIF AND EM

DIAGNOSIS

FSGS, TIP VARIANT

CASE 2

- A 65 year-old male presented with high creatinine and nephrotic range proteinuria.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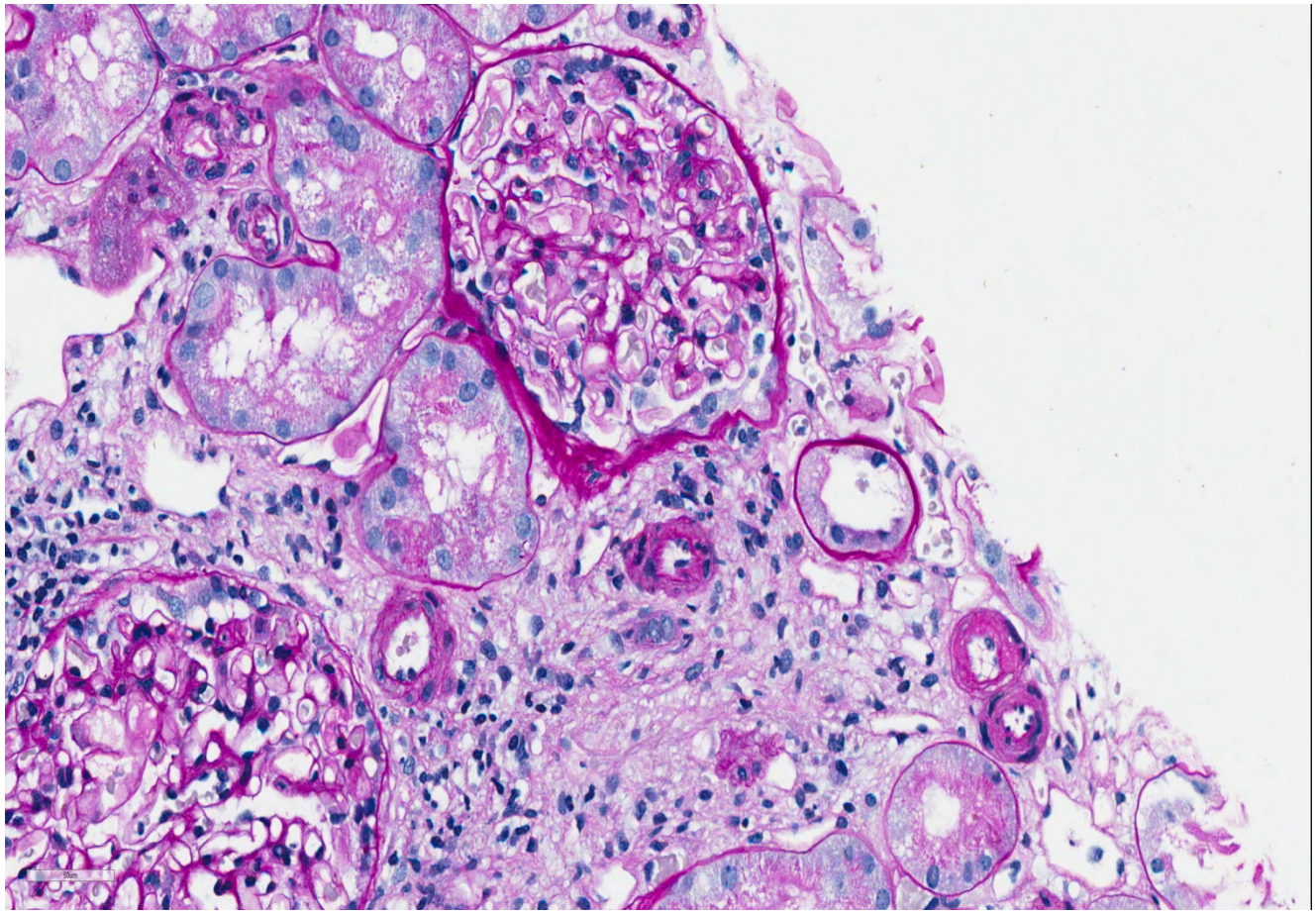

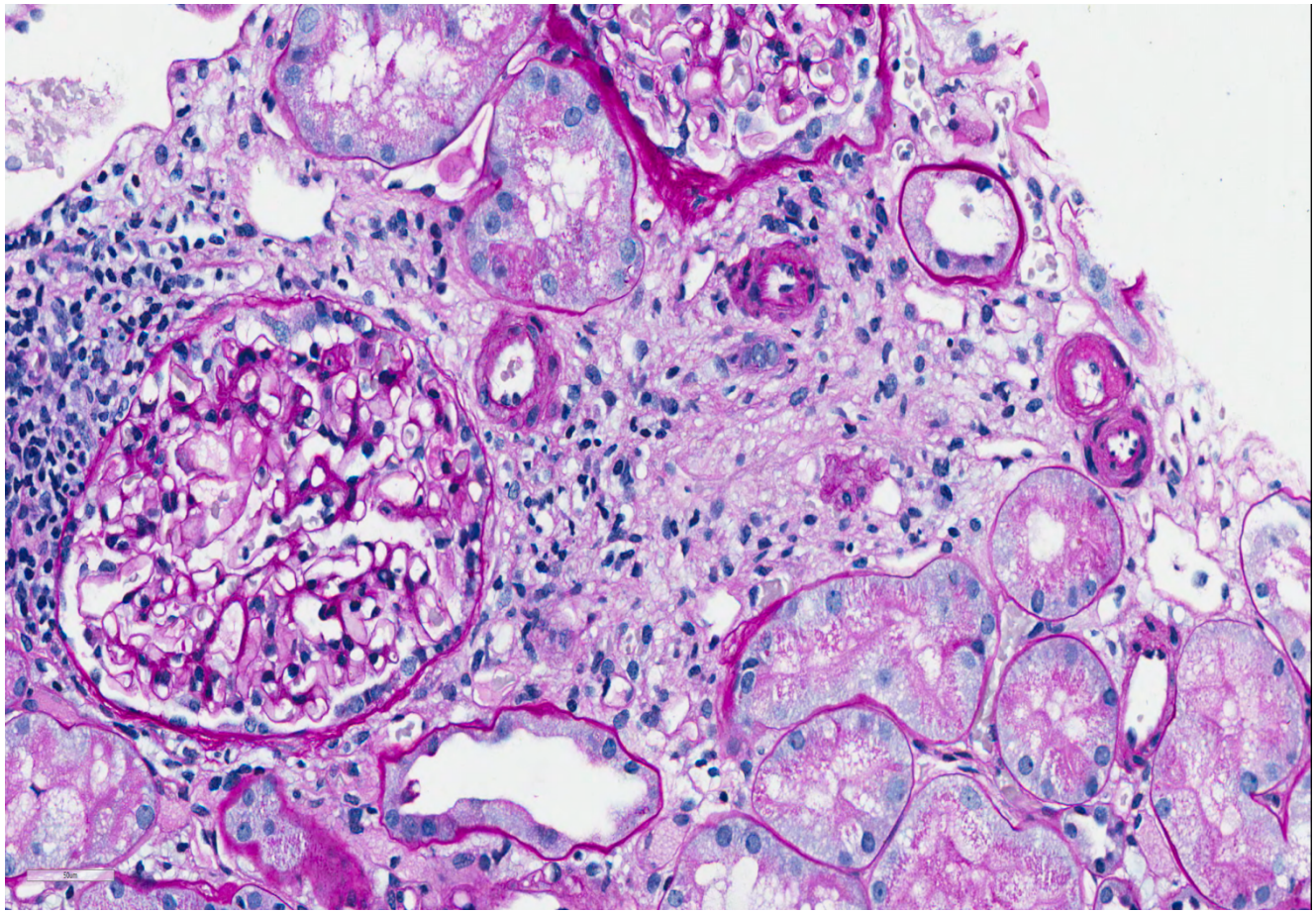

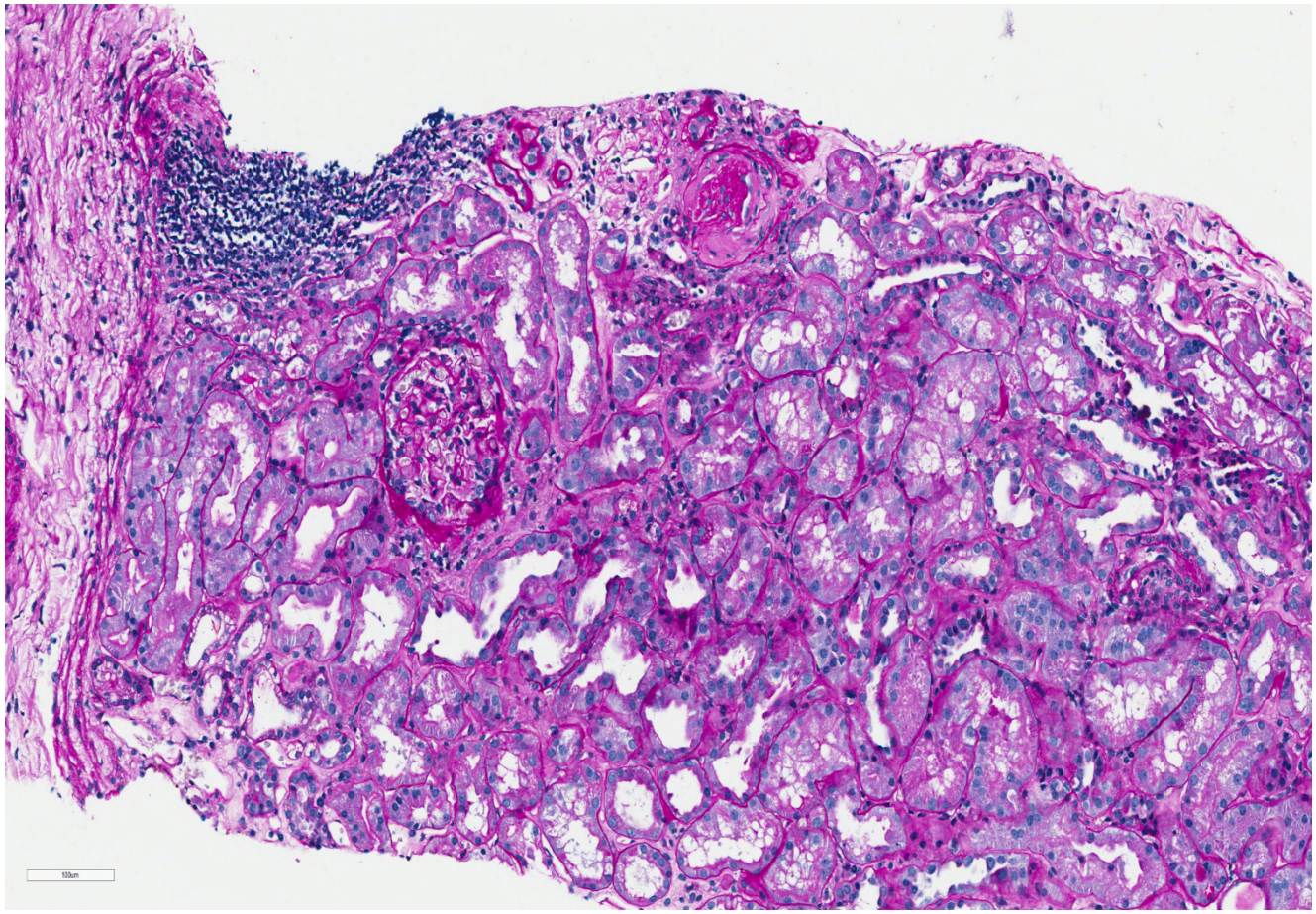
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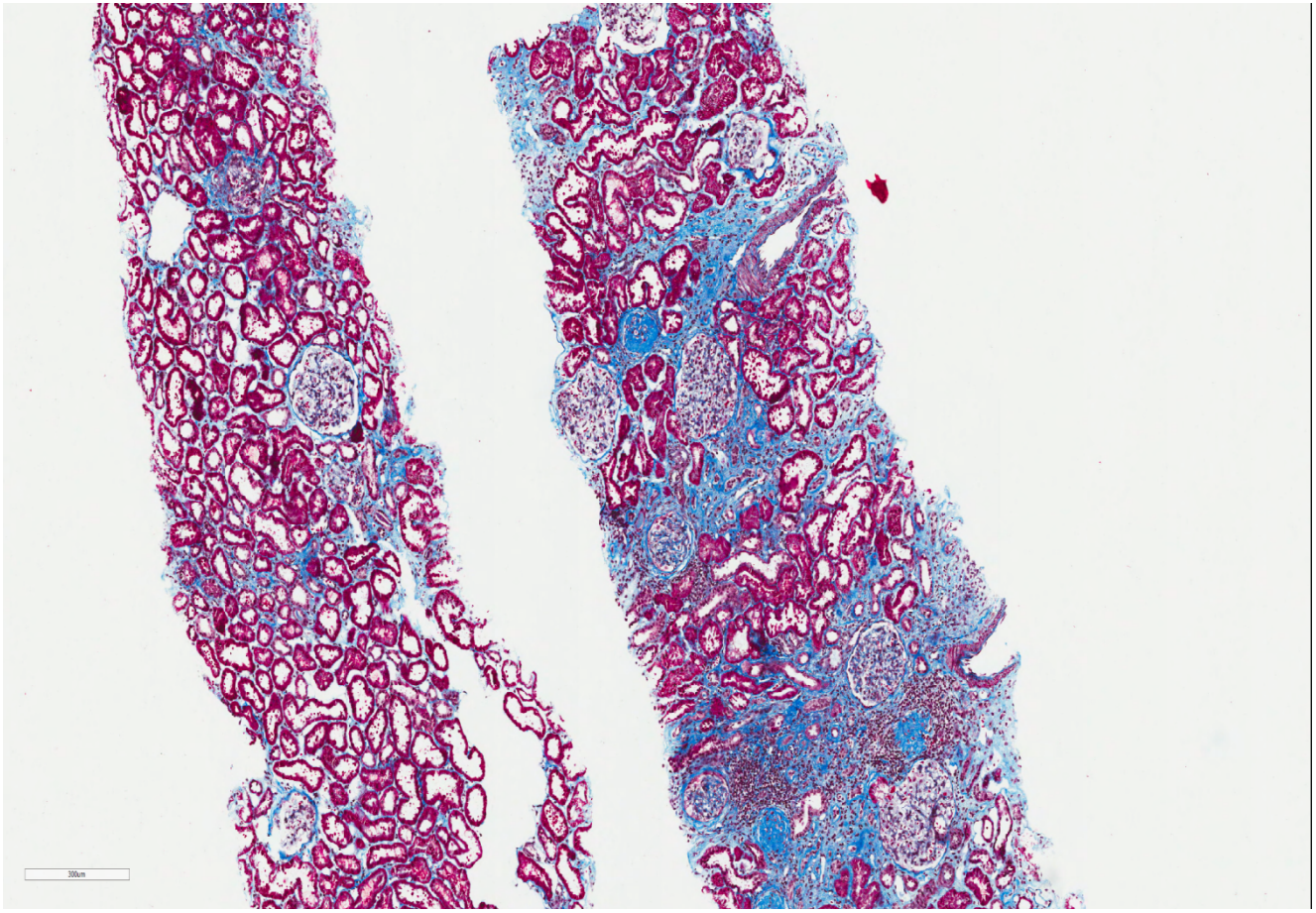
DIF AND EM

DIAGNOSIS

MINIMAL CHANGE DISEASE
ACUTE TUBULAR INJURY

CASE 3

- A 15 year-old female presented with nephrotic range proteinuria.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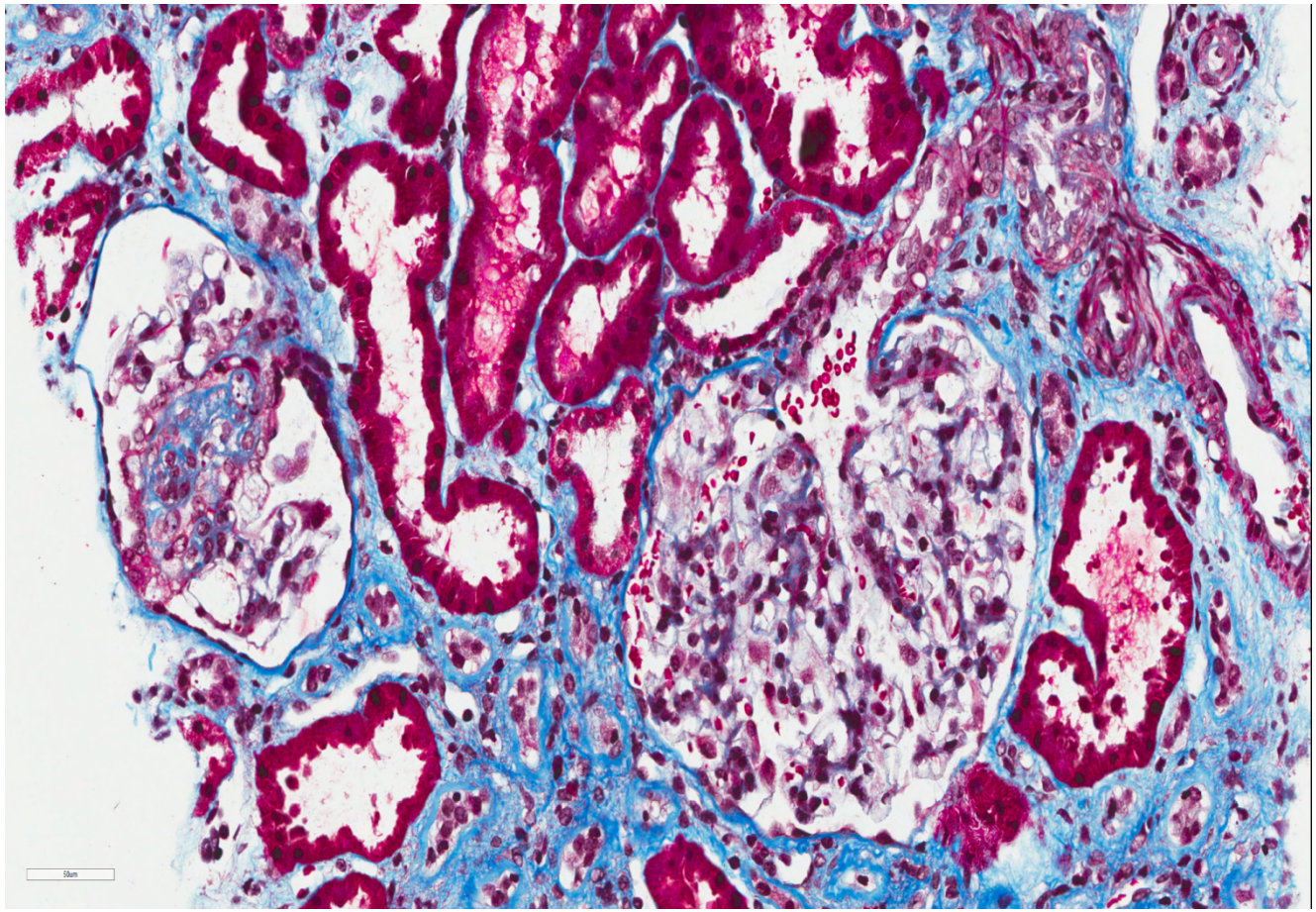
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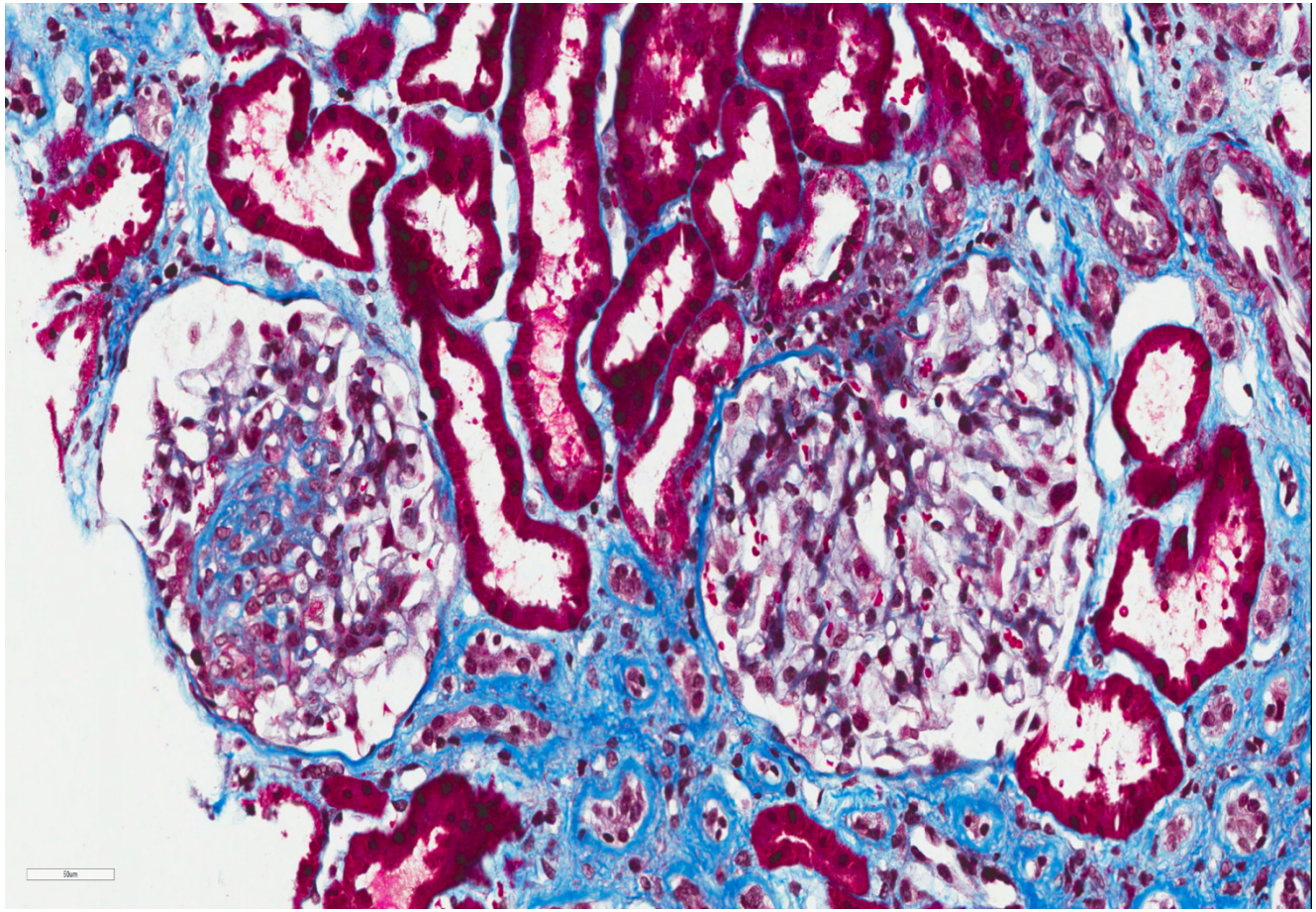
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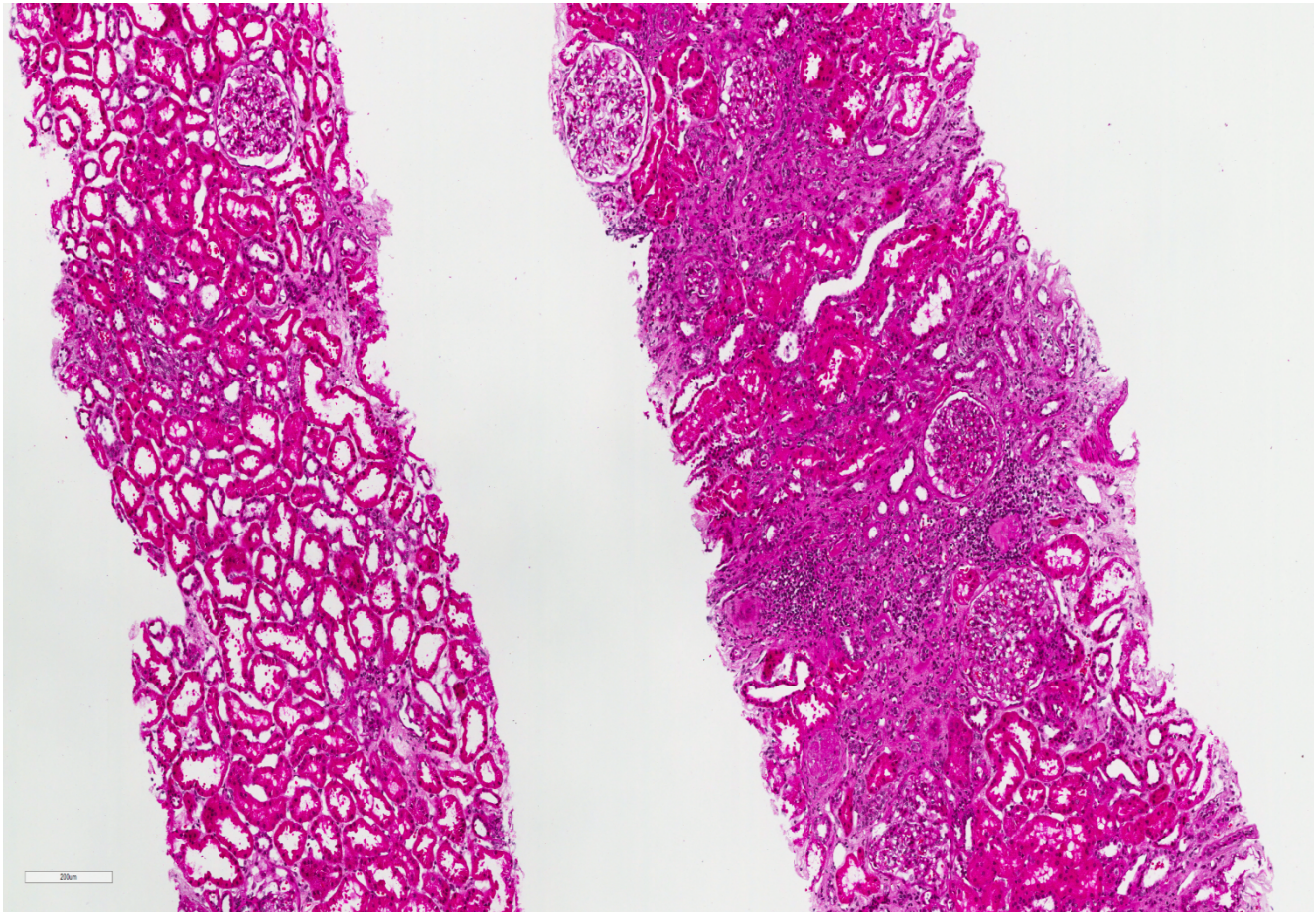
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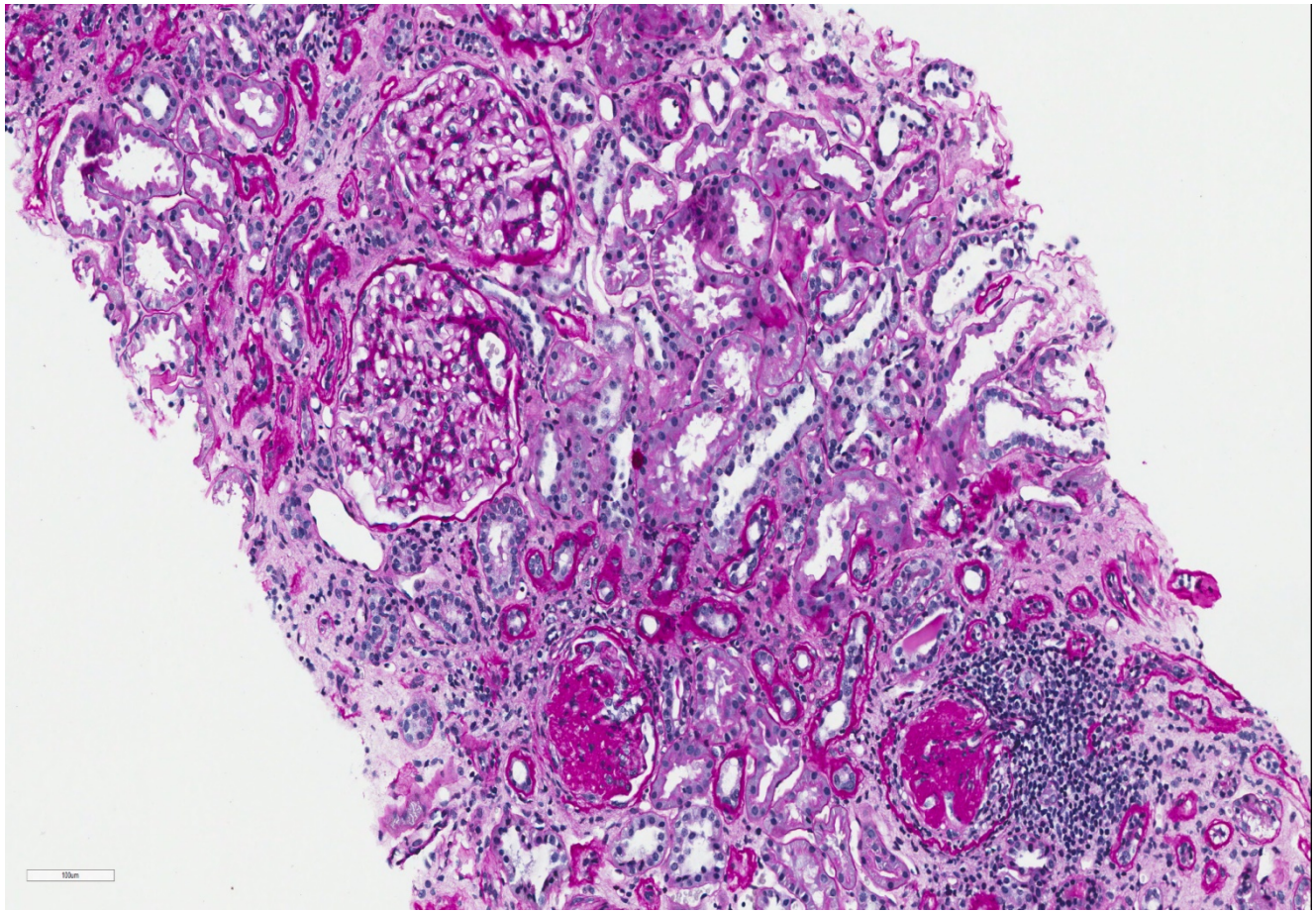
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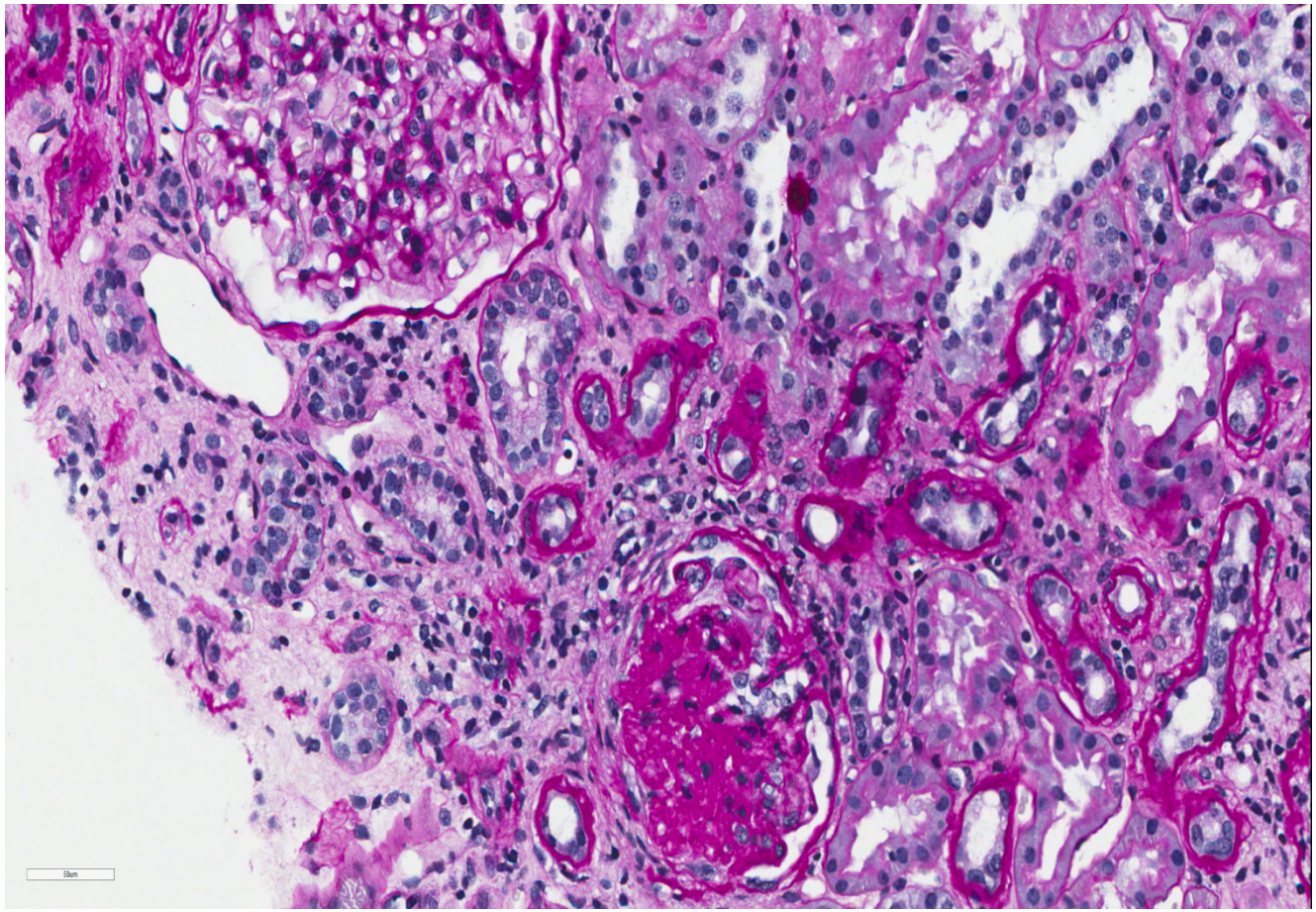
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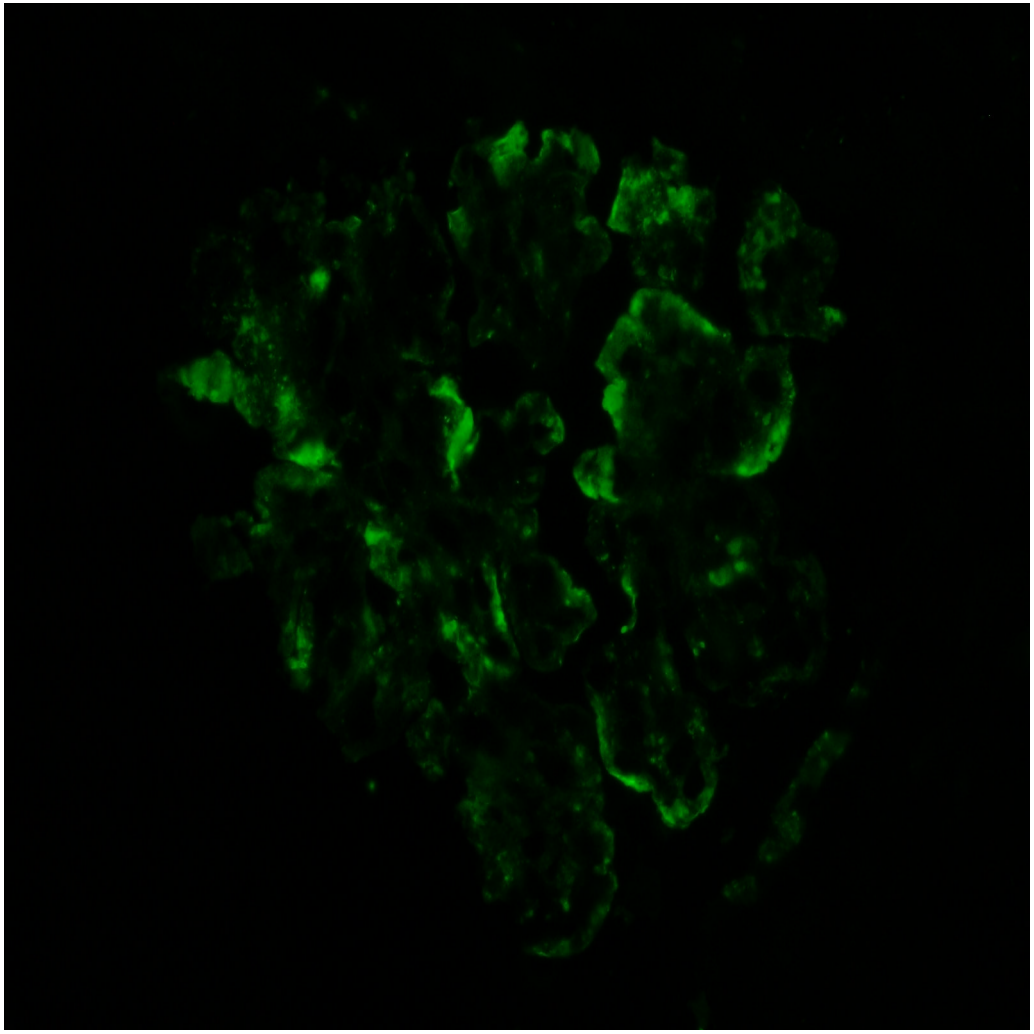
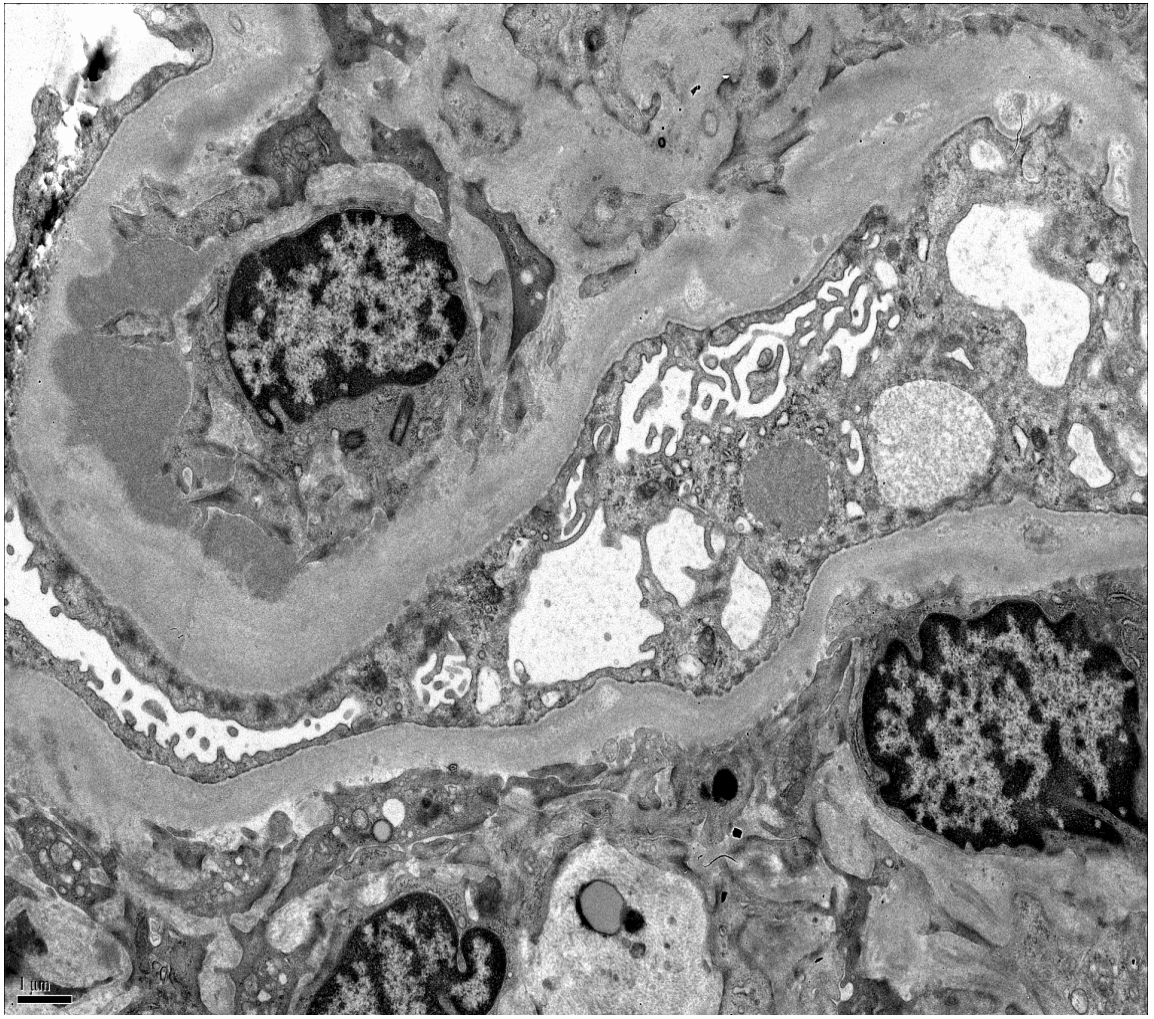
Differential diagnosis?

DIF AND EM (next slides)

C1q

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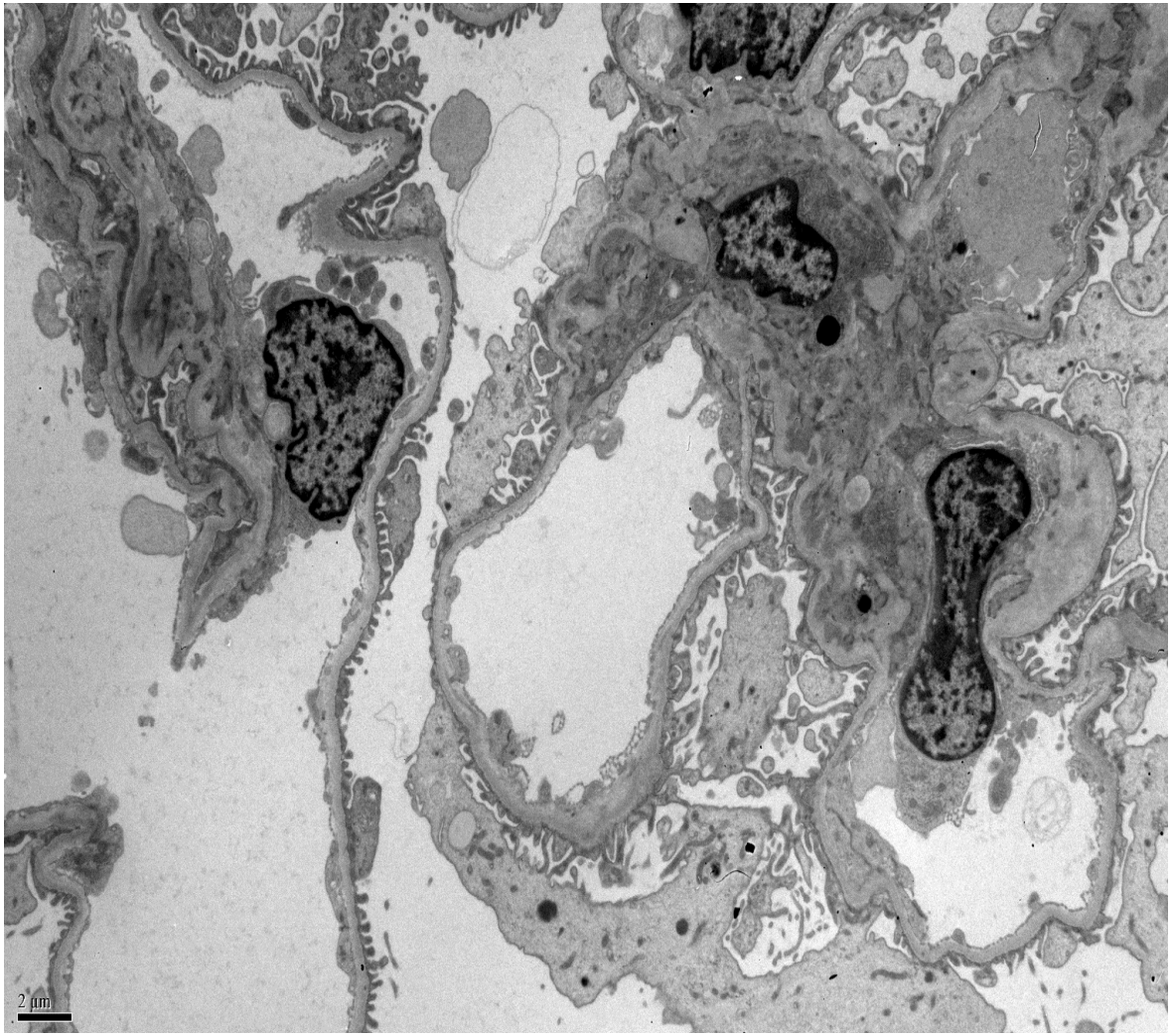
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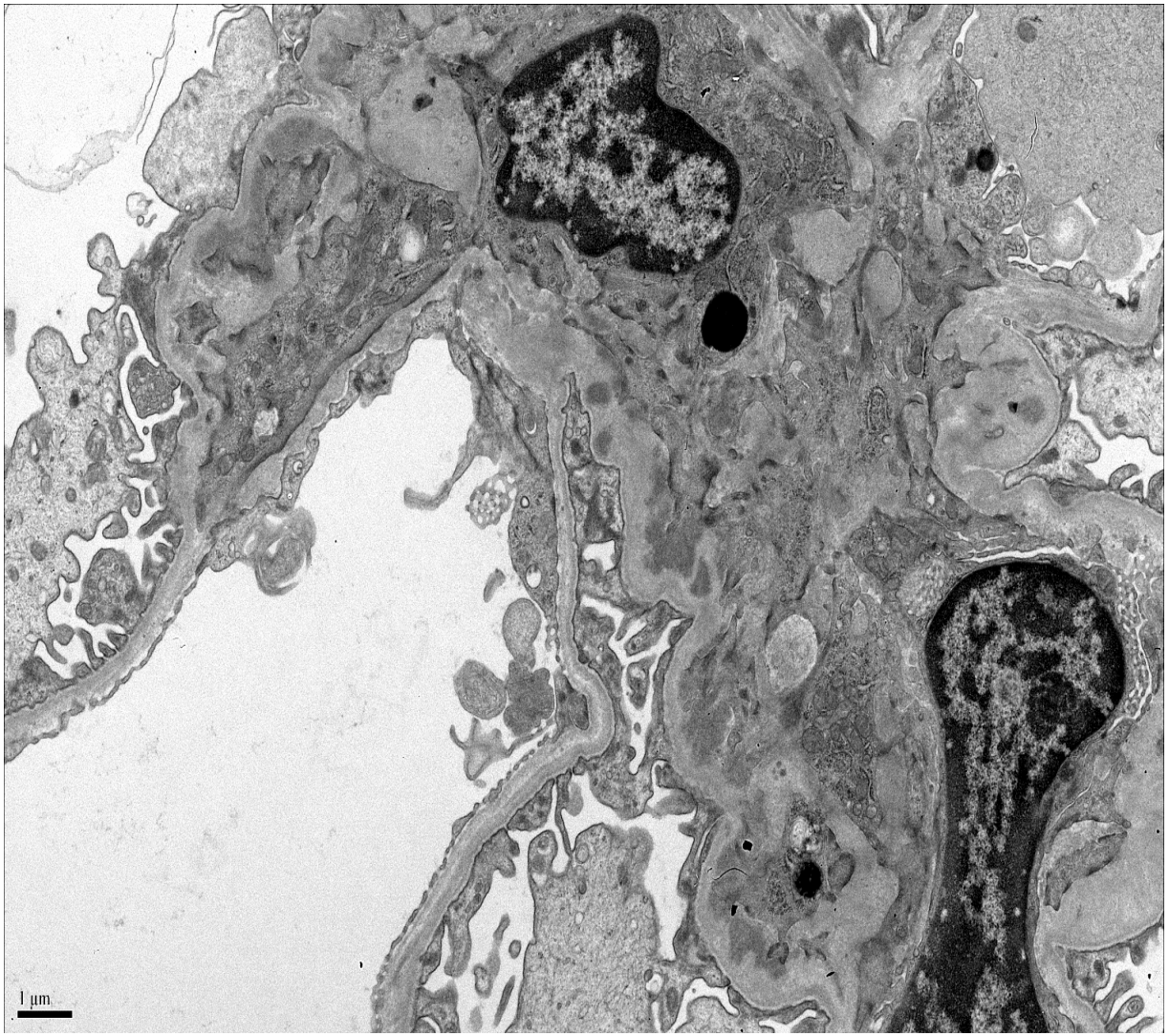
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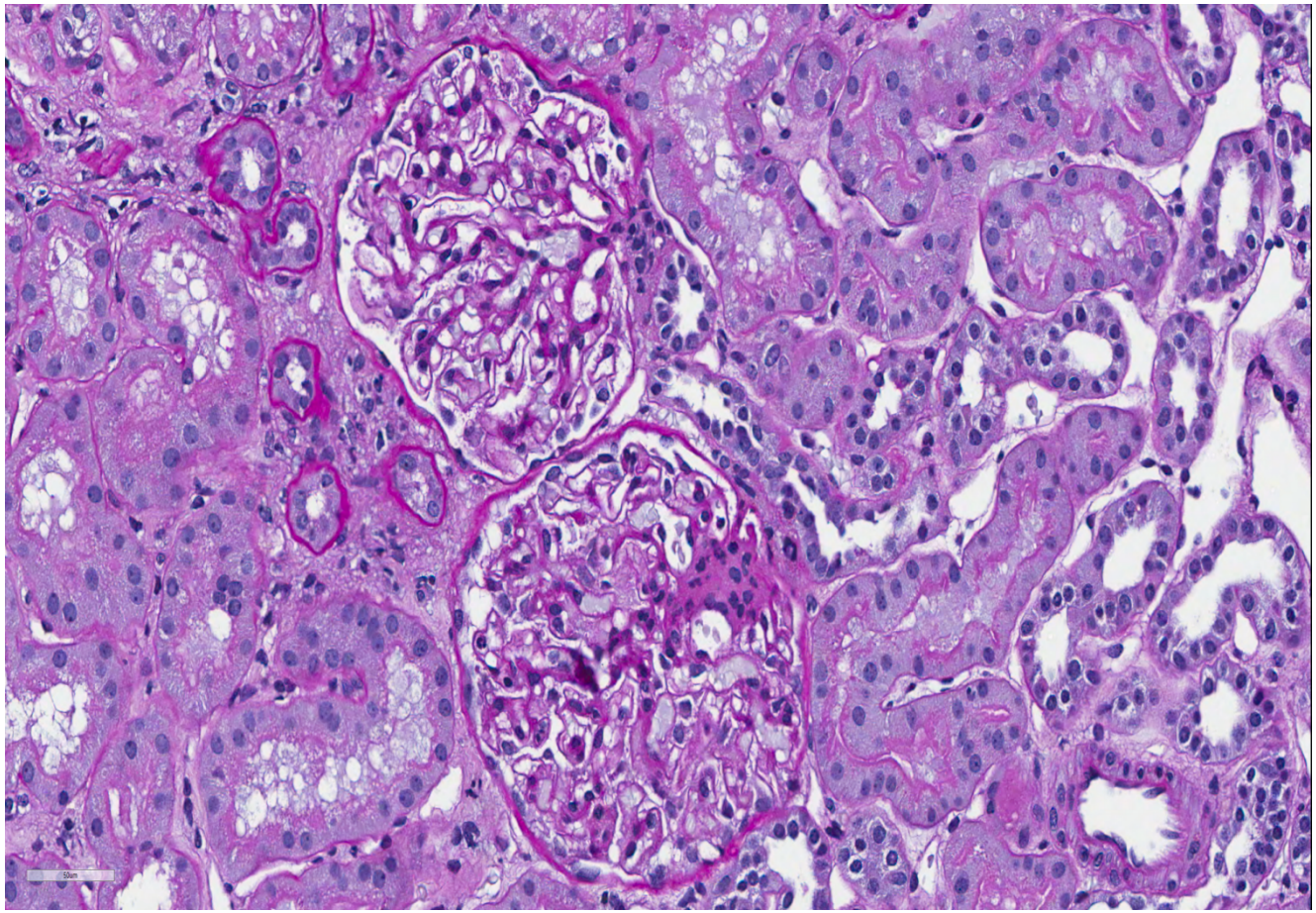
DIAGNOSIS

C1q NEPHROPATHY

CASE 4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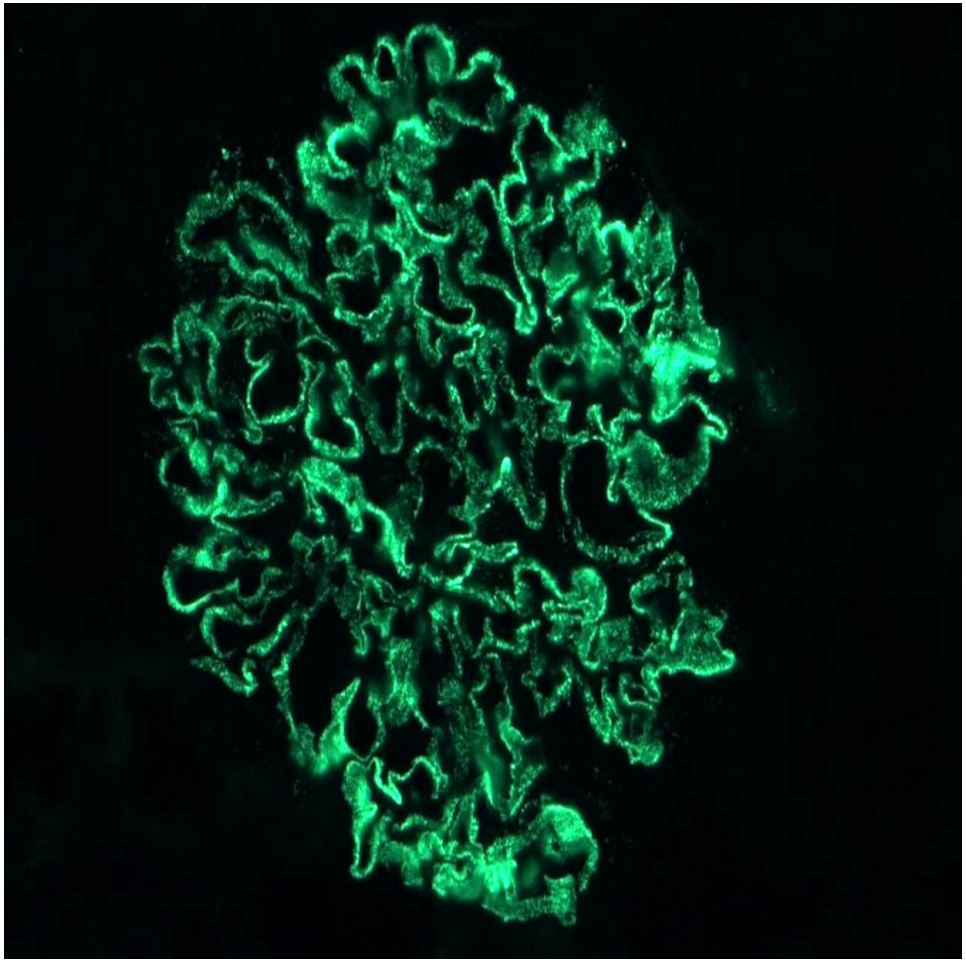
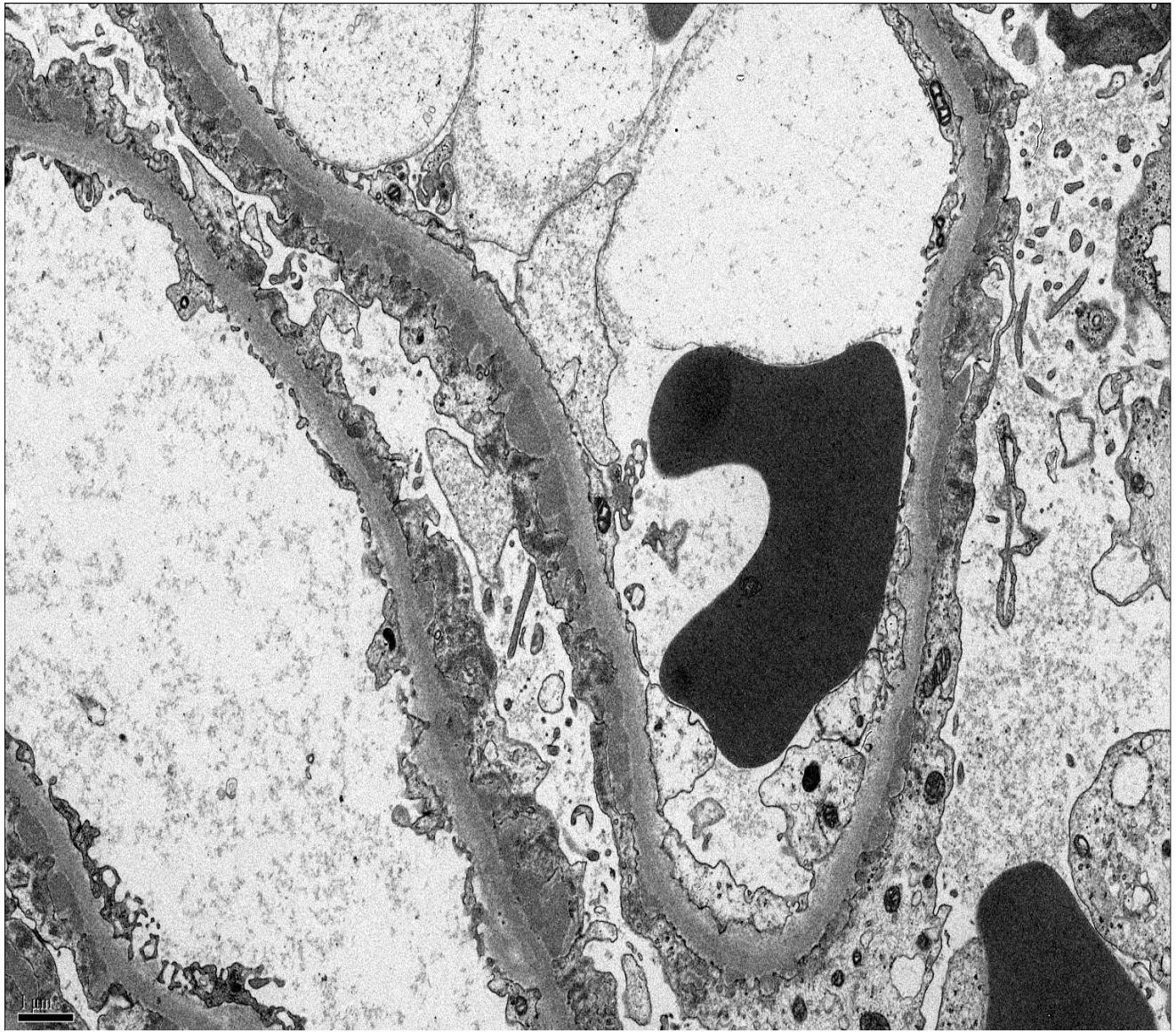
DIF AND EM




1 µm

DIAGNOSIS

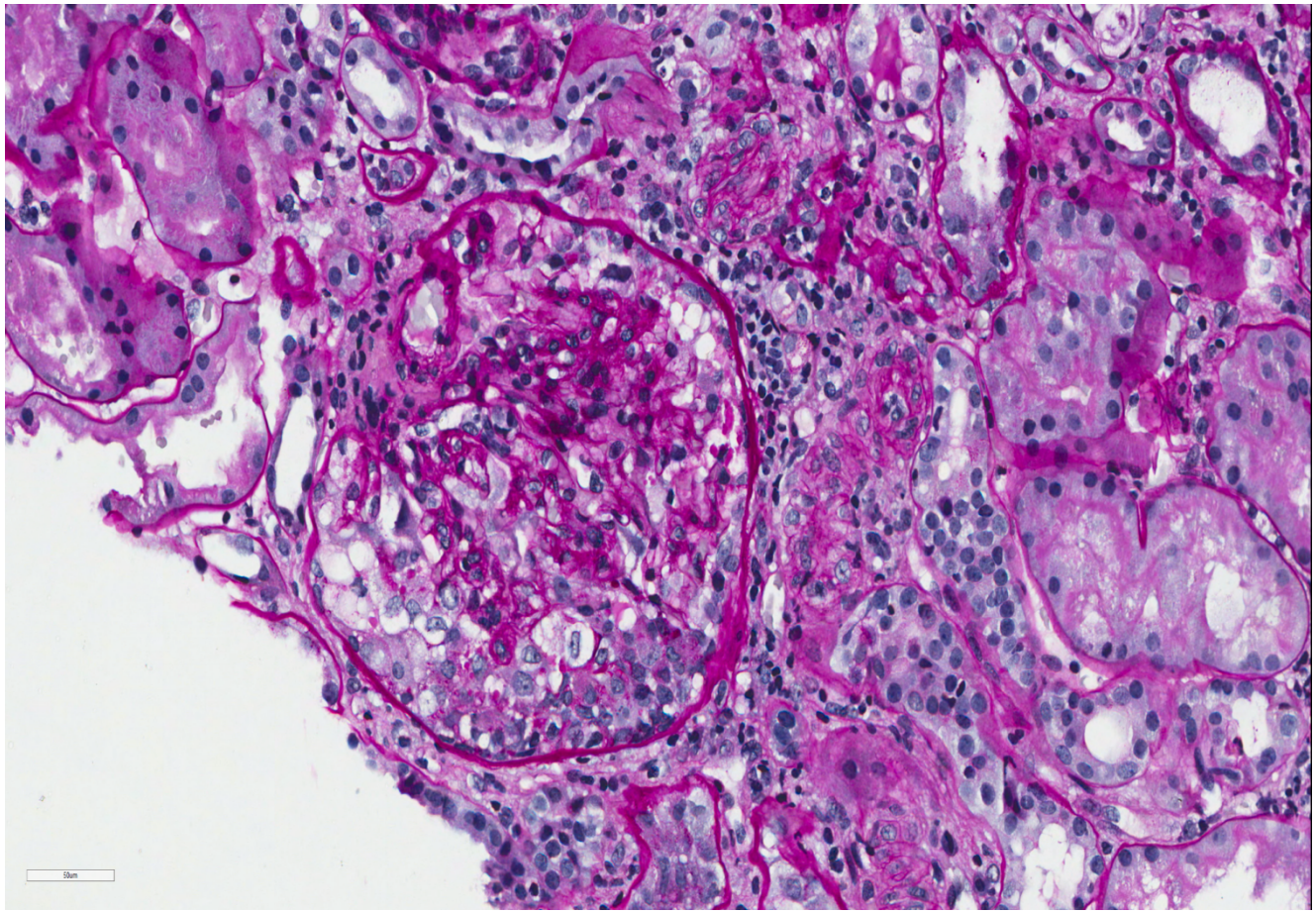
MEMBRANOUS NEPHROPATHY

The following should be addressed in the kidney biopsy report when MN is encountered:

1. Pattern-of-injury
2. The target antigen detected
3. Clinical association and prognostic implications of the target antigens
4. IgG subclass description
5. Electron microscopy stage
6. Findings that have prognostic implications

CASE 5

- A 35 year-old male presented with proteinuria 6gm/24 hour and rapid decrease in kidney function.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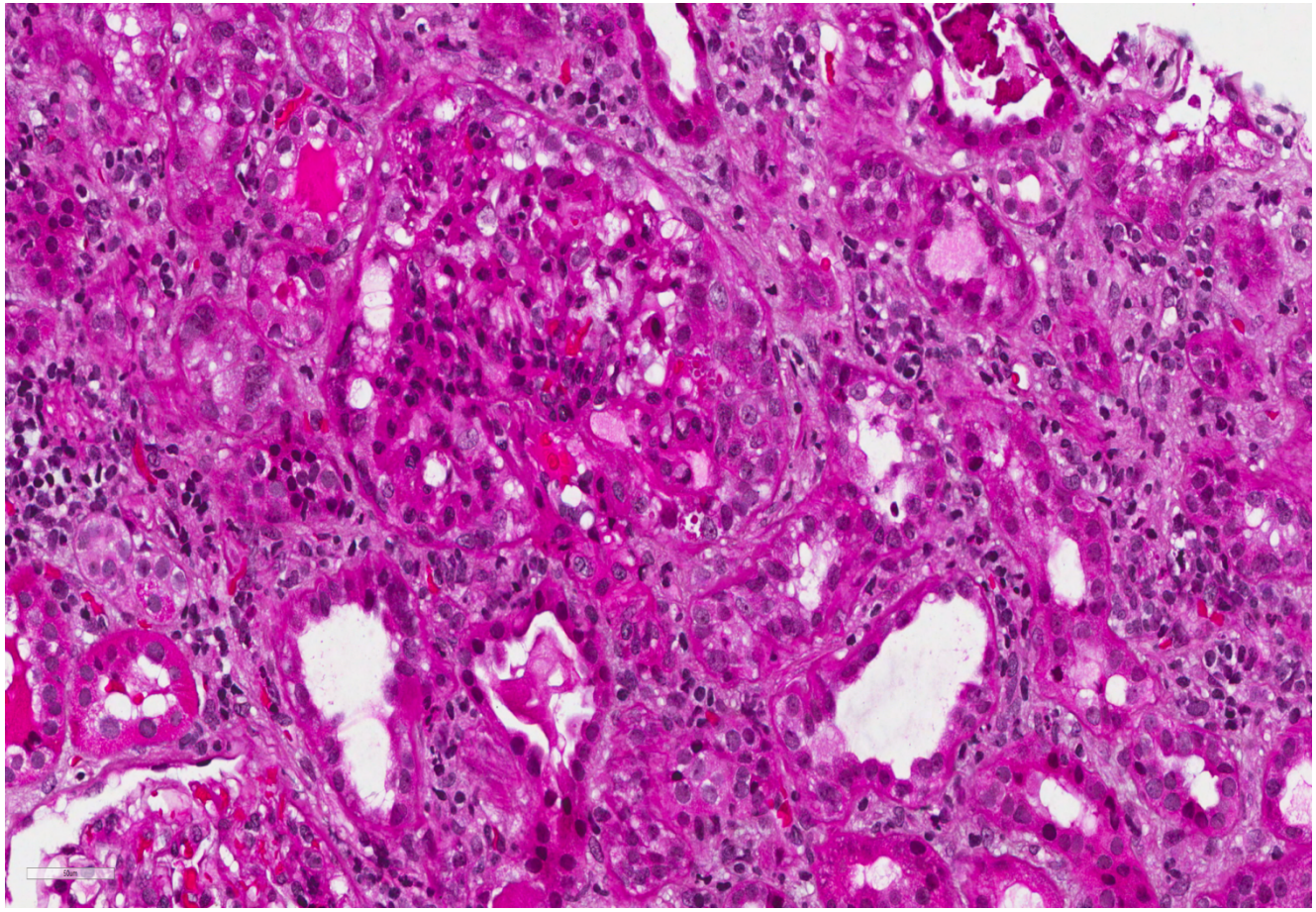

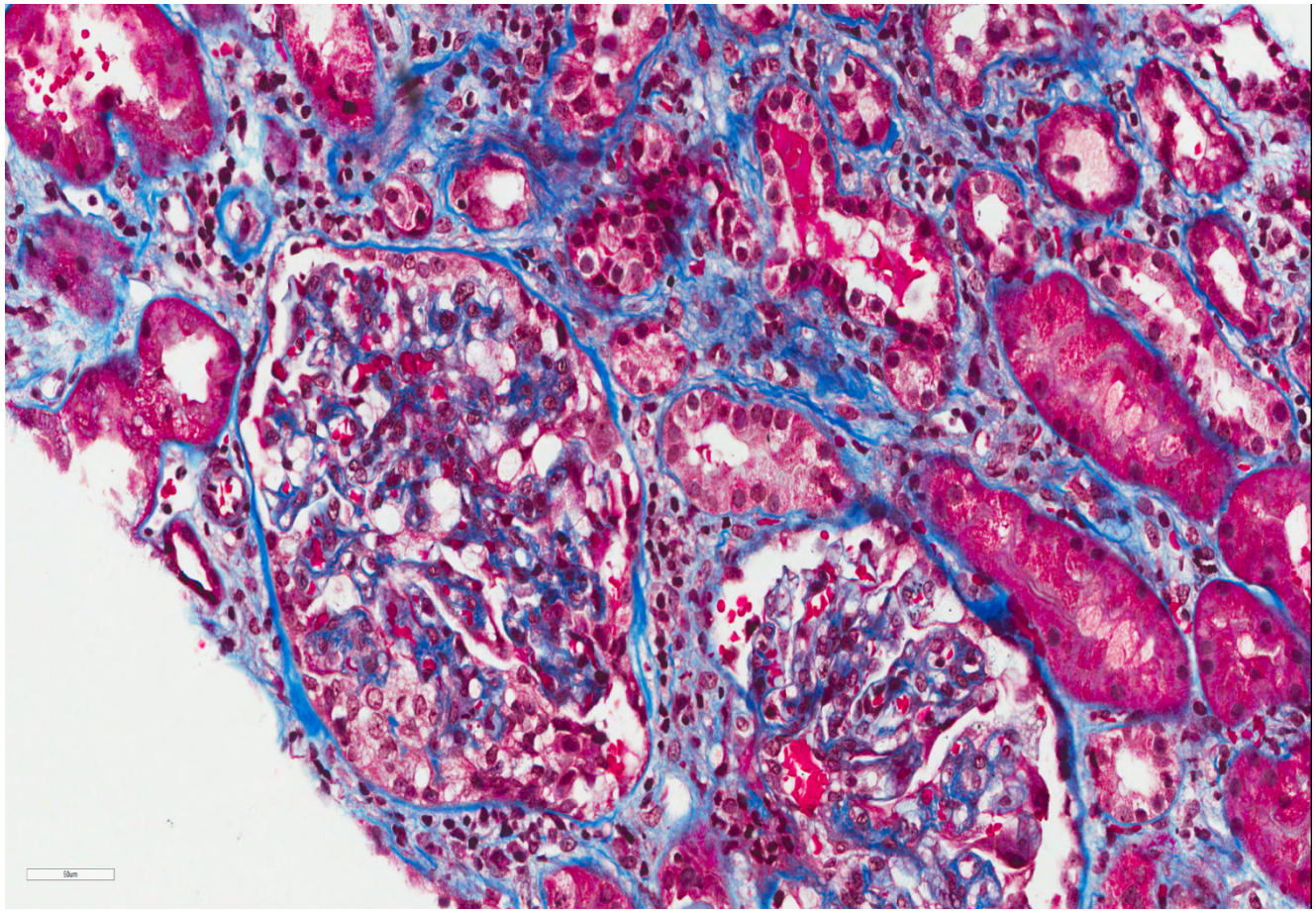
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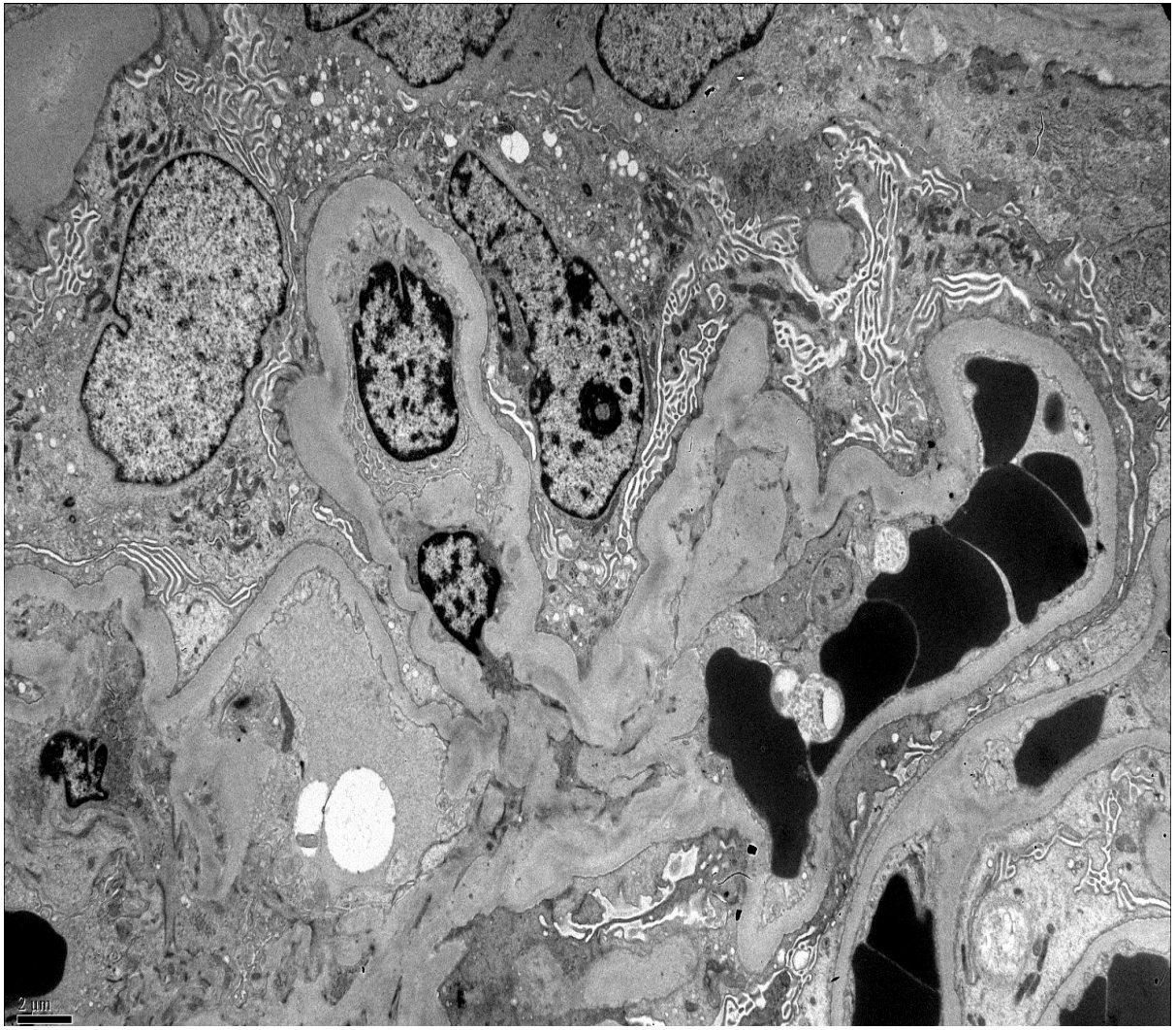
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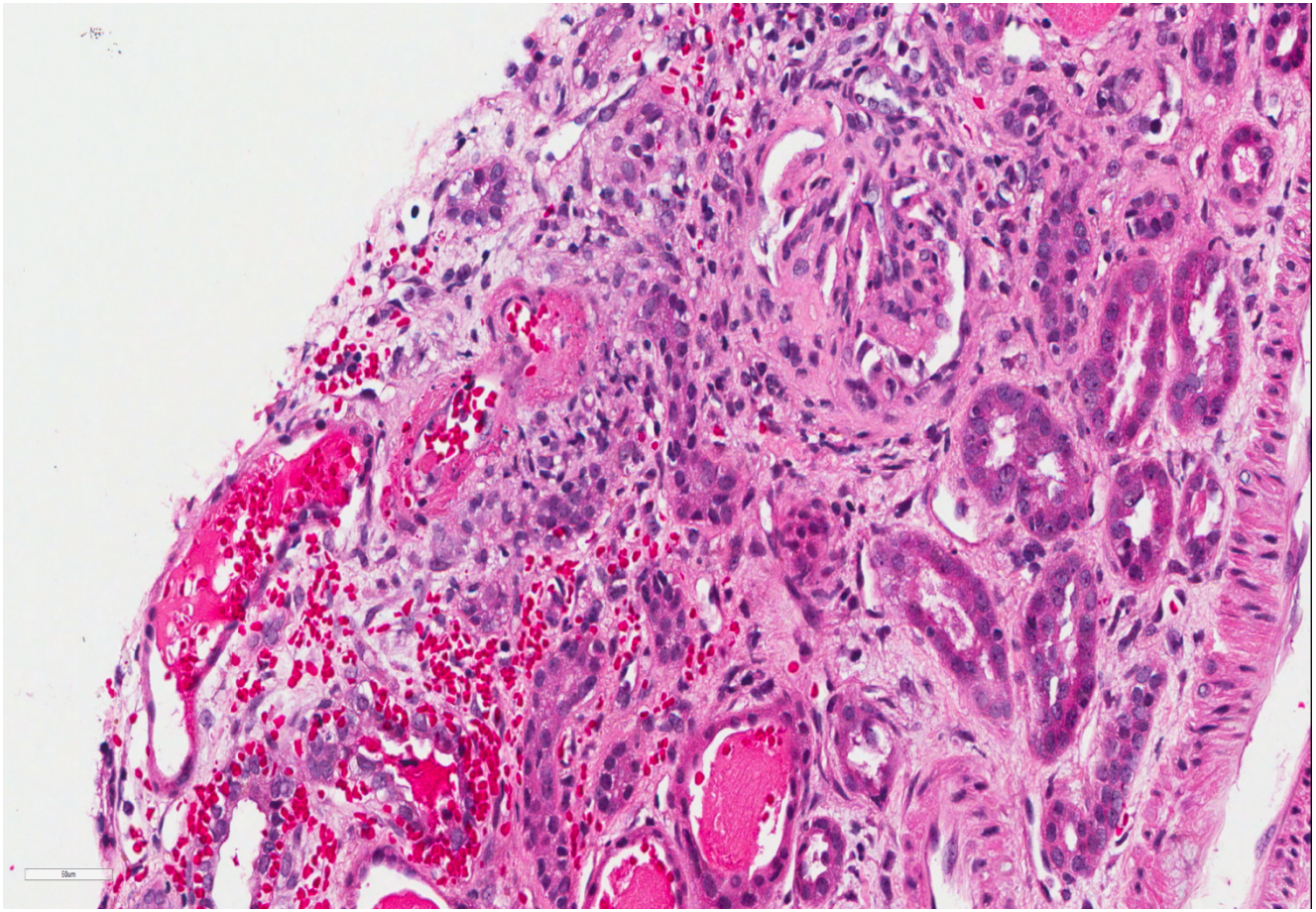
DIAGNOSIS

FSGS, COLLAPSING VARIANT

CASE 6

- A 45 year-old female with history of SLE presented with nephrotic range proteinuria, hematuria, high serum creatinine, and Low C3 level.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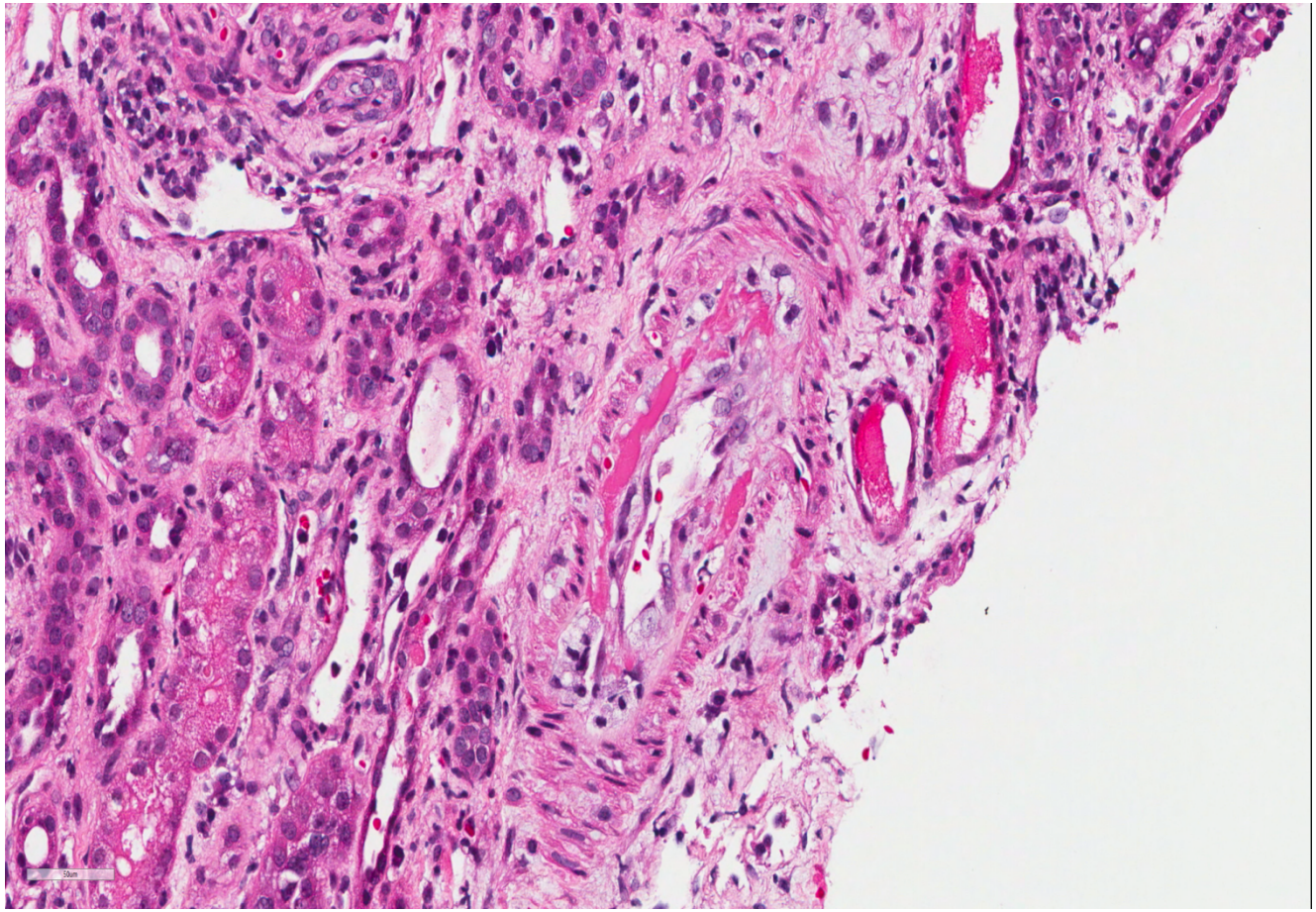
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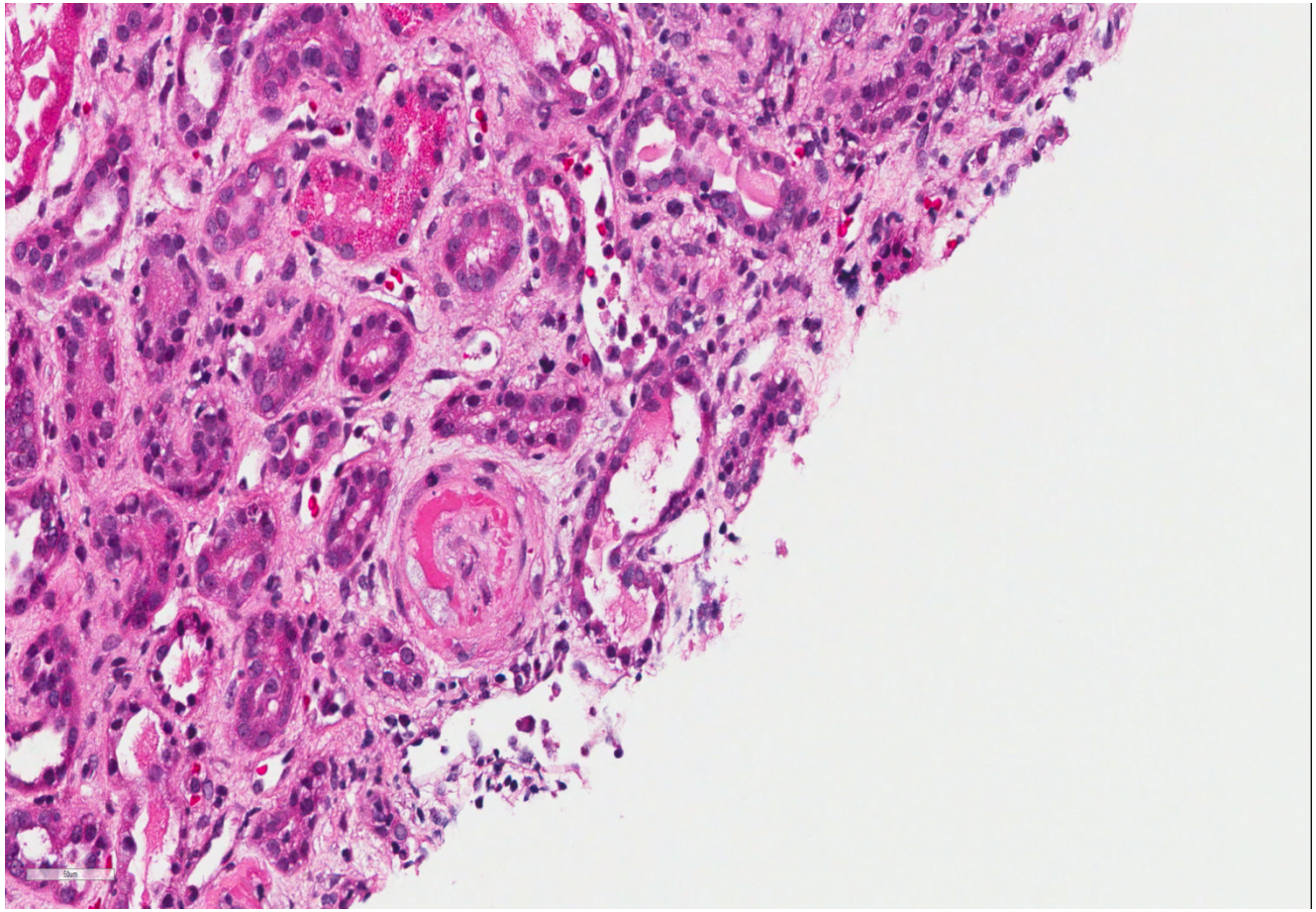
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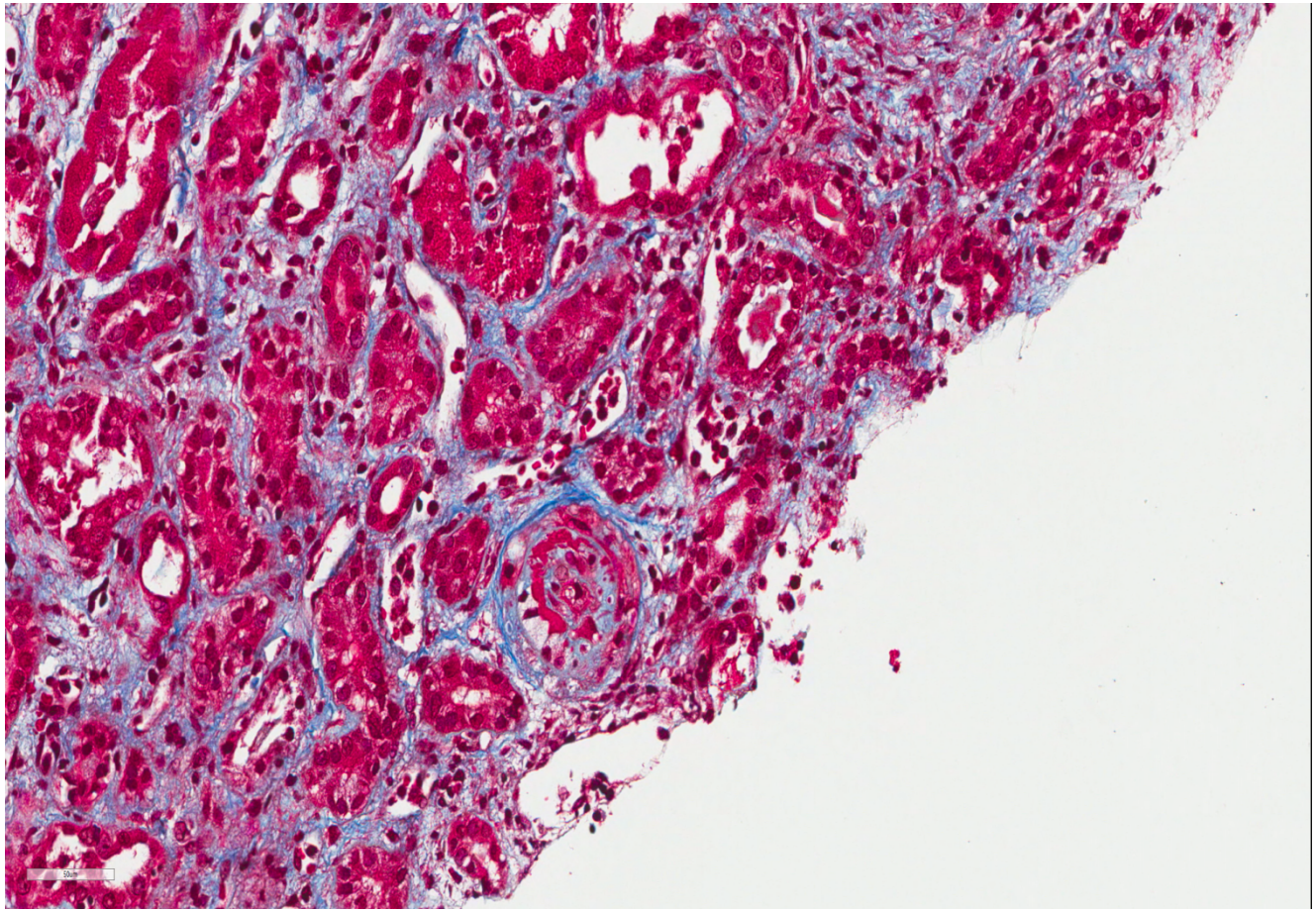

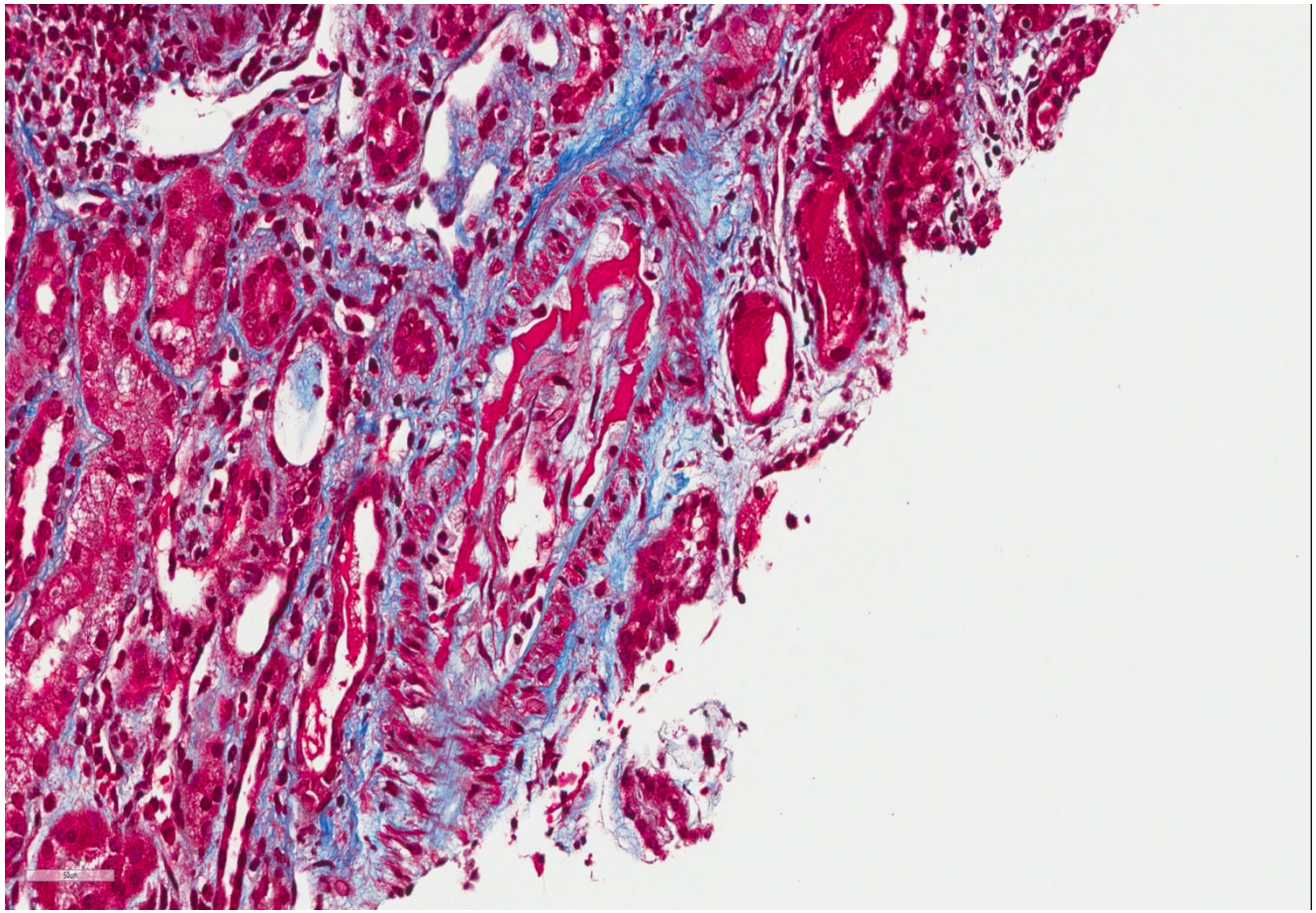

DIF AND EM

DIAGNOSIS

LUPUS VASCULOPATHY