

# Conditions that present commonly with the Nephrotic Syndrome.

Dr C. J. Horsfield

Guy's & St Thomas' NHSFT

Renal biopsy study day February 2021

# Outline of Talk

- Definition of the Nephrotic Syndrome
- Overview of the primary conditions associated with it:
  - Minimal Change Disease
    - Causes of Secondary MCD
  - Focal and Segmental Glomerulosclerosis
    - Classification and Variants
  - Membranous Nephropathy
    - Autoantibodies associated with Primary Membranous Nephropathy
    - Causes of Secondary Membranous Nephropathy
- Systemic disease causing Nephrotic Syndrome including Diabetes and Amyloid

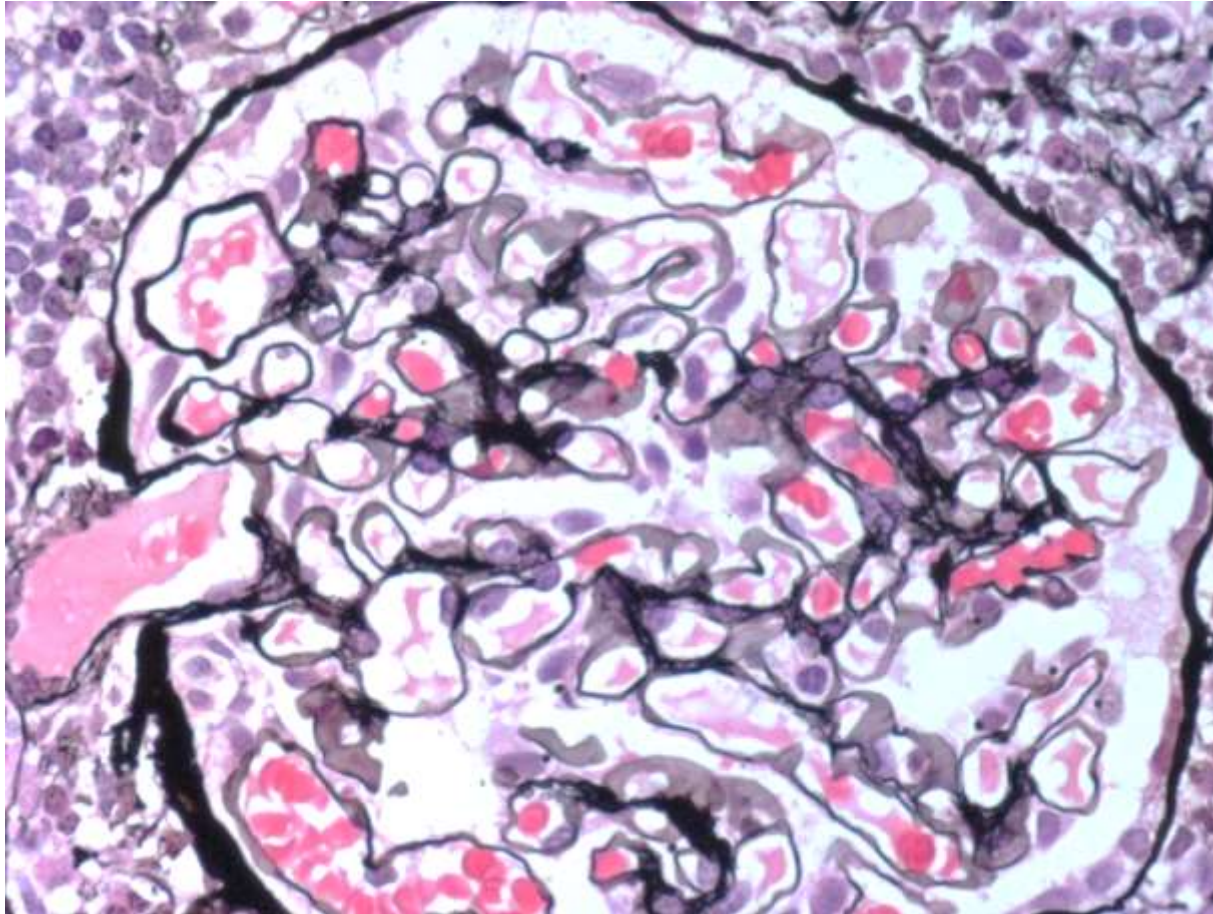
# Definition of the Nephrotic Syndrome

- Abrupt onset heavy proteinuria;
  - Adults:  $>3.5\text{g/day}$
  - Children: protein excretion rate of  $>40\text{mg/m}^2/\text{hr}$  of body surface area in an overnight collection
    - International Study of Kidney Diseases in Children
- Hypoalbuminaemia;
- Oedema;
- Raised serum cholesterol.

# Minimal Change Disease

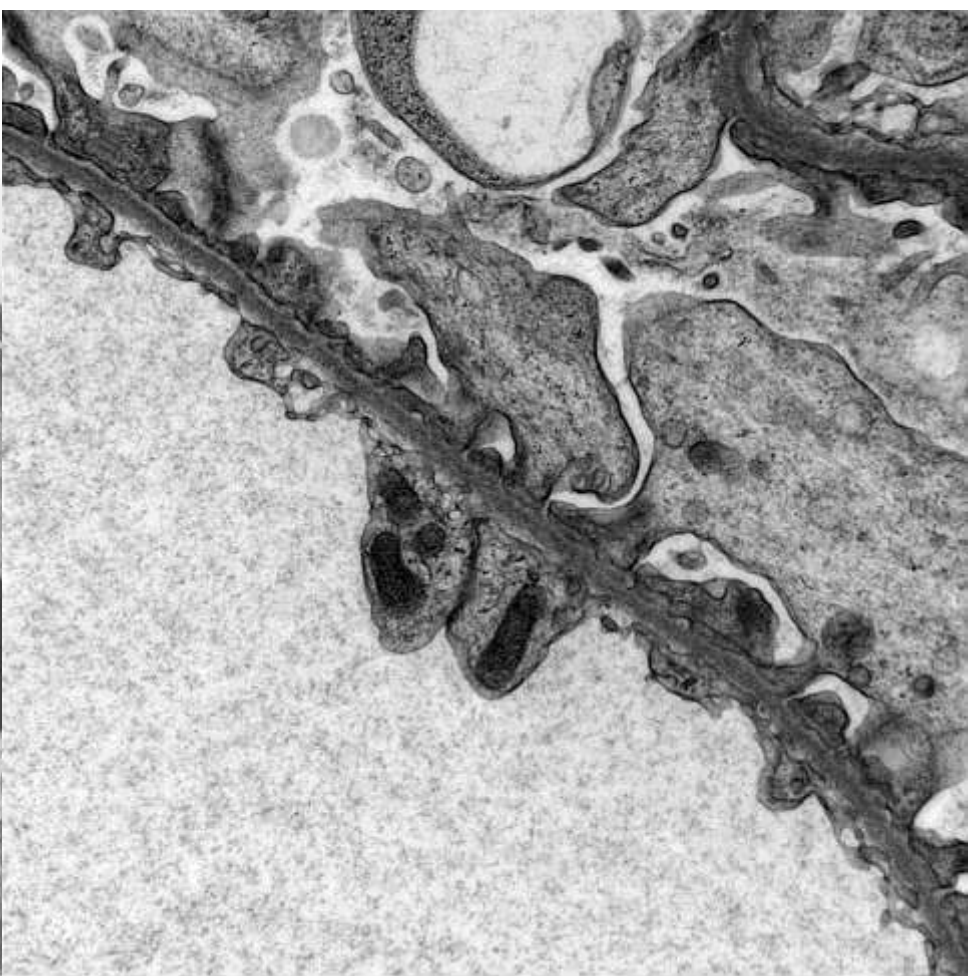
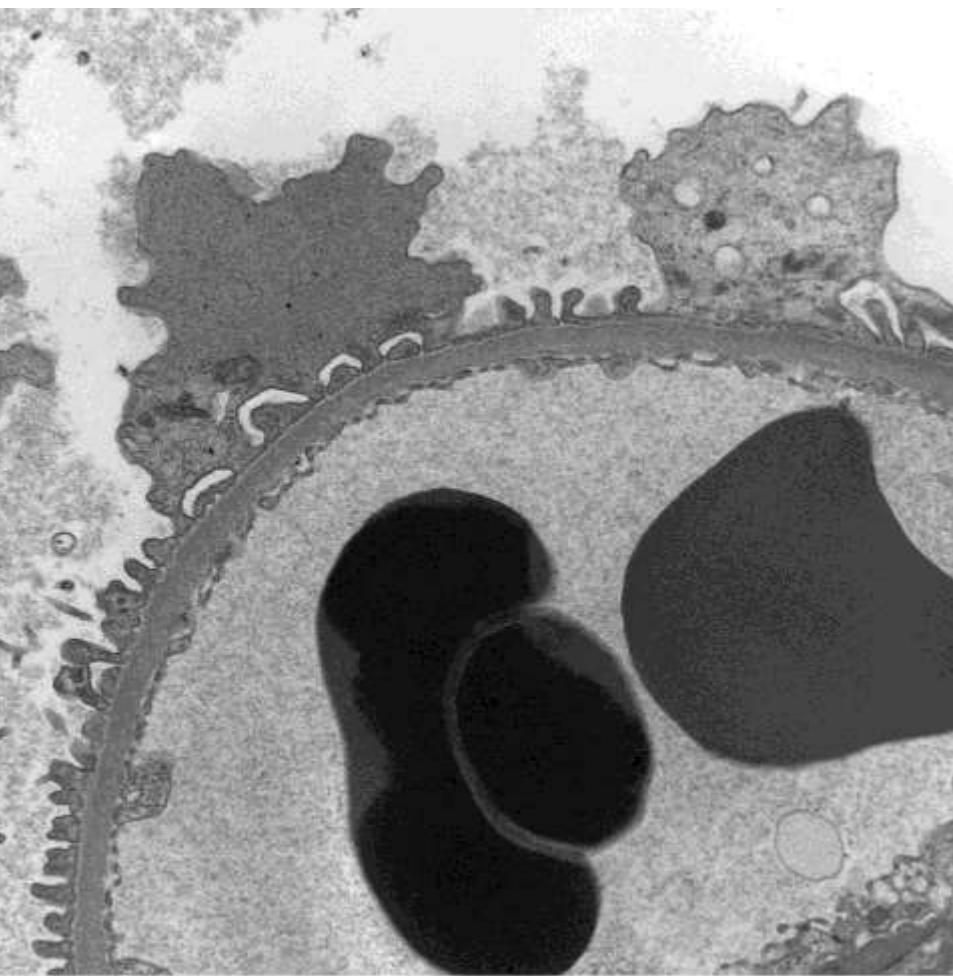
- 'Lipoid Nephrosis'
- 'Nil disease'
- Childhood >> adults
- In adulthood, more common in elderly
- Usually there is no associated renal insufficiency, no hypertension, no haematuria
- However, if hypoalbuminaemia considerable, can cause pre-renal ARF

# Light microscopy - morphology

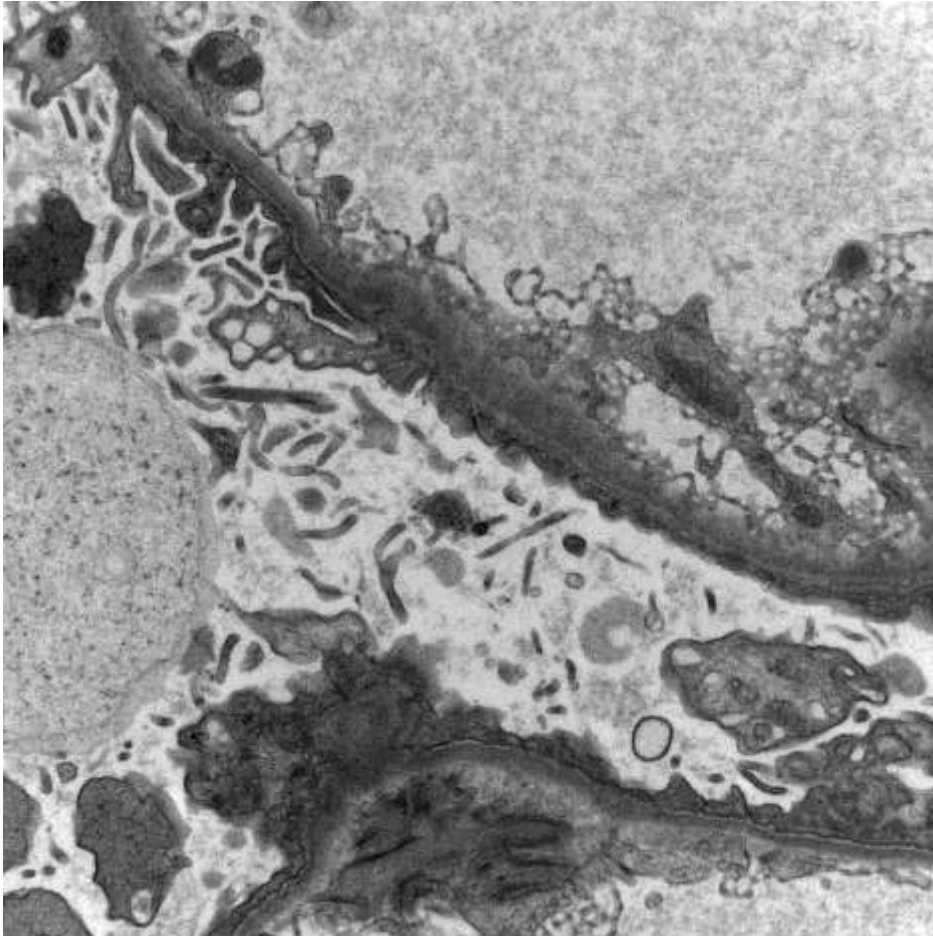


# Morphology - LM

- Expect:
- Well preserved renal parenchyma, without established chronic damage
- Near / normal glomeruli
  - NO closure of capillary loops – foam/sclerosis
    - Focal podocyte prominence allowed, but no hyperplasia or capping, and no true synechiae
    - Slight increase in mesangial cells/matrix allowed
- Possibly tubular protein resorption droplets
- Compact interstitium
- Negative immuno, not more than 1+ C3
  - <5% of cases, weak Ig staining but no electron dense deposits; may have a worse prognosis
  - If co/dominant IgA or C1q consider dual pathology, in which case there will be electron dense deposits



# Electron microscopy - morphology



- **PODOCYTES:**
  - Hypertrophic cell bodies
  - Slender microvillous extensions of cytoplasm [microvillous change] but
  - Diffuse effacement [fusion] of the foot processes of podocytes >75% surface area
  - Condensations in the cytoplasm of the fused foot processes – may mimic electron dense deposits in a subepithelial location
- If the patient has been treated with some clinical response, there will be restoration of the foot processes
- These changes are reversible



# Treatment and Prognosis

- Childhood MCD – excellent prognosis
  - Pre-steroid era saw spontaneous remission in 70%
  - A child presenting with uncomplicated NS is given a trial of steroids for 8/52 given that in 80% of the cases it will be MCD, 95% will enter remission on steroids
- If no response, then biopsy
- Common to relapse [50% of children]
- May see steroid resistant case or frequently relapsing case – requiring biopsy and second line treatments

# Treatment and Prognosis

- Adult MCD:
- Any adult presenting with unexplained Nephrotic Syndrome - BIOPSY
- Adult MCD: there may be a slower response to steroids, often require 16/52 course
- Consider the secondary causes

# Secondary MCD

- Drugs
  - May also see foci of tubulitis – ‘acute interstitial nephritis, often without eosinophils\*’
    - NSAIDs\*; Lithium
- Malignancy
  - Haematological
    - MCD may precede Hodgkin’s Lymphoma, or be simultaneous with it
    - T cell lymphomas; MF
    - Intravascular large cell lymphomas -> check glomeruli!
- Viruses
  - Mononucleosis
  - HIV
- Allergy
- Bee stings
- Following childhood immunisations

## Adult Minimal-Change Disease: Clinical Characteristics, Treatment, and Outcomes

Meryl Waldman,<sup>\*</sup> R. John Crew,<sup>†</sup> Anthony Valeri,<sup>‡</sup> Joshua Busch,<sup>‡</sup> Barry Stokes,<sup>§</sup> Glen Markowitz,<sup>§</sup> Vivette D'Agati,<sup>§</sup> and Gerald Appel<sup>†</sup>

*<sup>\*</sup>National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; Departments of <sup>†</sup>Nephrology and <sup>§</sup>Pathology, Columbia Presbyterian, New York, New York; and <sup>‡</sup>Department of Medicine, University of Washington, Seattle, Washington*

Minimal-change disease (MCD) counts for 10 to 15% of cases of primary nephrotic syndrome in adults. Few series have examined this disease in adults. A retrospective review was performed of 95 adults who had MCD and were seen at a single referral center. Examined were presenting features, response to daily *versus* alternate-day steroids, response to second-line agents, relapse patterns, complications of the disease and therapy, presence of acute renal failure (ARF), and outcome data. Sixty-five patients received daily and 23 received alternate-day steroids initially. There were no differences in remissions, time to remission, relapse rate, or time to relapse between daily- and alternate-day-treated patients. More than one quarter of patients were steroid resistant. At least one relapse occurred in 73% of patients; 28% were frequently relapsing. A significant proportion of frequently relapsing patients became steroid dependent. Second-line agents were used for steroid dependence, steroid resistance, or frequent relapses. No single agent proved superior. There were more remissions with second-line agents in steroid-dependent patients compared with steroid-resistant patients, and remissions were more likely to be complete in steroid-dependent patients. ARF occurred in 24 patients; they tended to be older and hypertensive with lower serum albumin and more proteinuria than those without ARF. At follow up, patients with an episode of ARF had higher serum creatinine than those without ARF. Four patients progressed to ESRD. These patients were less likely to have responded to steroids and more likely to have FSGS on repeat renal biopsy. In this referral MCD population, response to daily and alternate-day steroids is similar. Second-line agents give greater response in patients who are steroid dependent. ARF occurs in a significant number of adult MCD patients and may leave residual renal dysfunction. Few patients progress to ESRD.

*Clin J Am Soc Nephrol* 2: 445-453, 2007. doi: 10.2215/CJN.03531006

Clinics and Practice 2018; volume 8:1046

## Nephrotic syndrome in very elderly: Should we treat aggressively?

Abhilash Koratala, Jogiraju Tantravahi  
Division of Nephrology, Hypertension  
and Renal Transplantation, University  
of Florida, Gainesville, FL, USA



# Focal and Segmental Glomerulosclerosis (FSGS)

The Nephrotic Syndrome in the presence of focal and segmental sclerosing glomerular lesions

Initially the lesions are focal, but these become more widespread as the disease progresses, eventually diffuse and global in distribution

Sampling problem that makes this diagnosis difficult at times – yet far more aggressive disease than MCD

# Aetiological classification of FSGS

## Primary (idiopathic) FSGS

## Secondary FSGS

### 1. Familial/genetic

- A. Mutations in  $\alpha$ -actinin 4
- B. Mutations in podocin
- C. Mutations in WT-1
- D. Mutations in  $\beta$  integrin

### 2. Virus-associated

- A. HIV-1 (HIV-associated nephropathy)
- B. Parvovirus B19

### 3. Drug-induced

- A. Heroin (heroin nephropathy)
- B. Interferon- $\alpha$
- C. Lithium
- D. Pamidronate

### 4. Mediated by adaptive structural-functional responses

#### A. Reduced renal mass

- Oligomeganephronia
- Unilateral renal agenesis
- Renal dysplasia
- Reflux nephropathy
- Sequela to cortical necrosis
- Surgical renal ablation
- Chronic allograft nephropathy
- Any advanced renal disease with reduction in functioning nephrons

#### B. Initially normal renal mass

- Hypertension
- Atheroemboli or other acute vaso-occlusive processes
- Obesity
- Cyanotic congenital heart disease
- Sickle cell anemia

# Morphological classification of FSGS

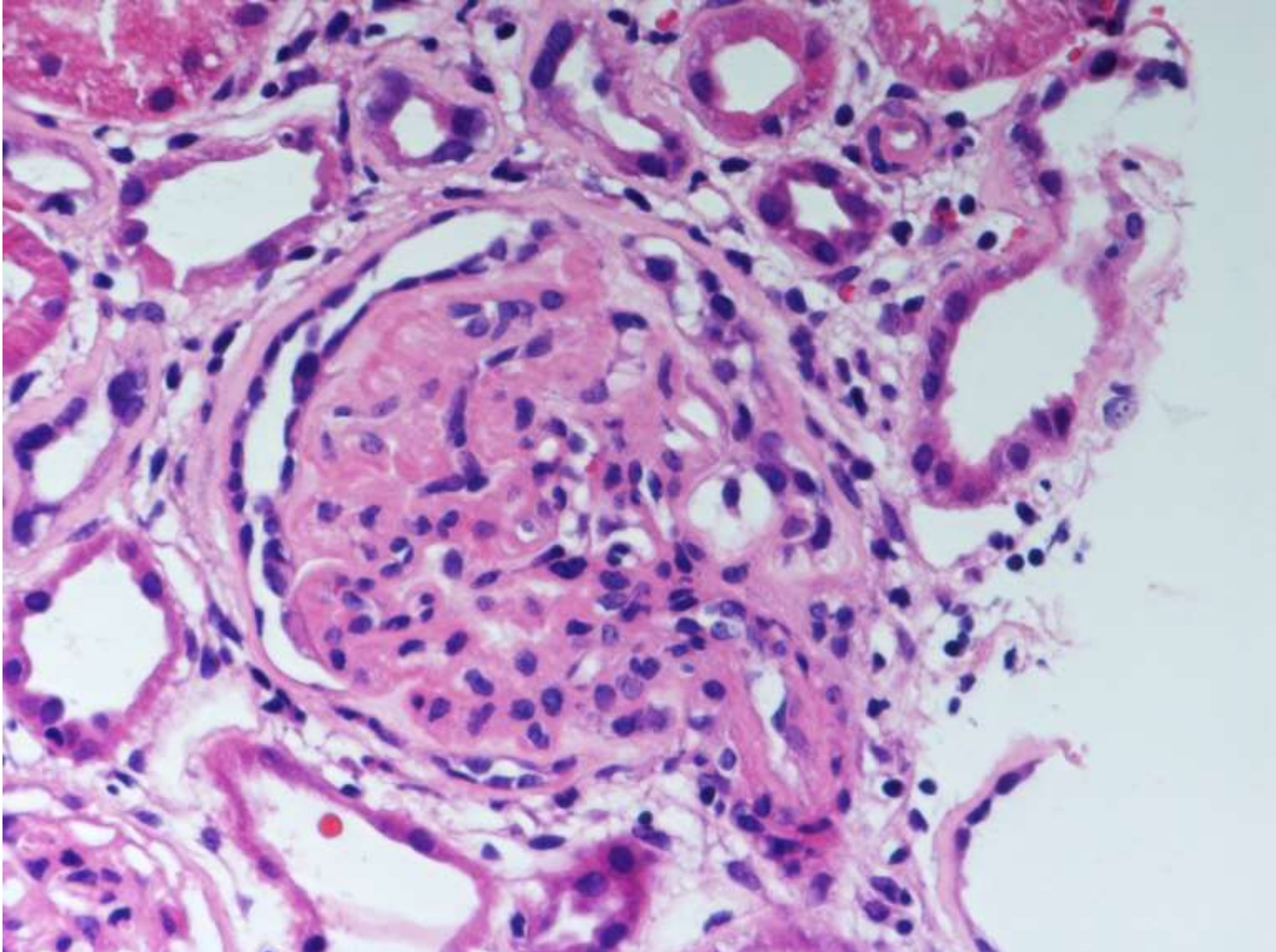
Variant	Inclusion Criteria	Exclusion Criteria
FSGS (NOS)	At least 1 glomerulus with segmental increase in matrix obliterating the capillary lumina There may be segmental glomerular capillary wall collapse without overlying podocyte hyperplasia	Exclude perihilar, cellular, tip, and collapsing variants
Perihilar variant	At least 1 glomerulus with perihilar hyalinosis, with or without sclerosis >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis	Exclude cellular, tip, and collapsing variants
Cellular variant	At least 1 glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variants
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
Collapsing variant	At least 1 glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia	None

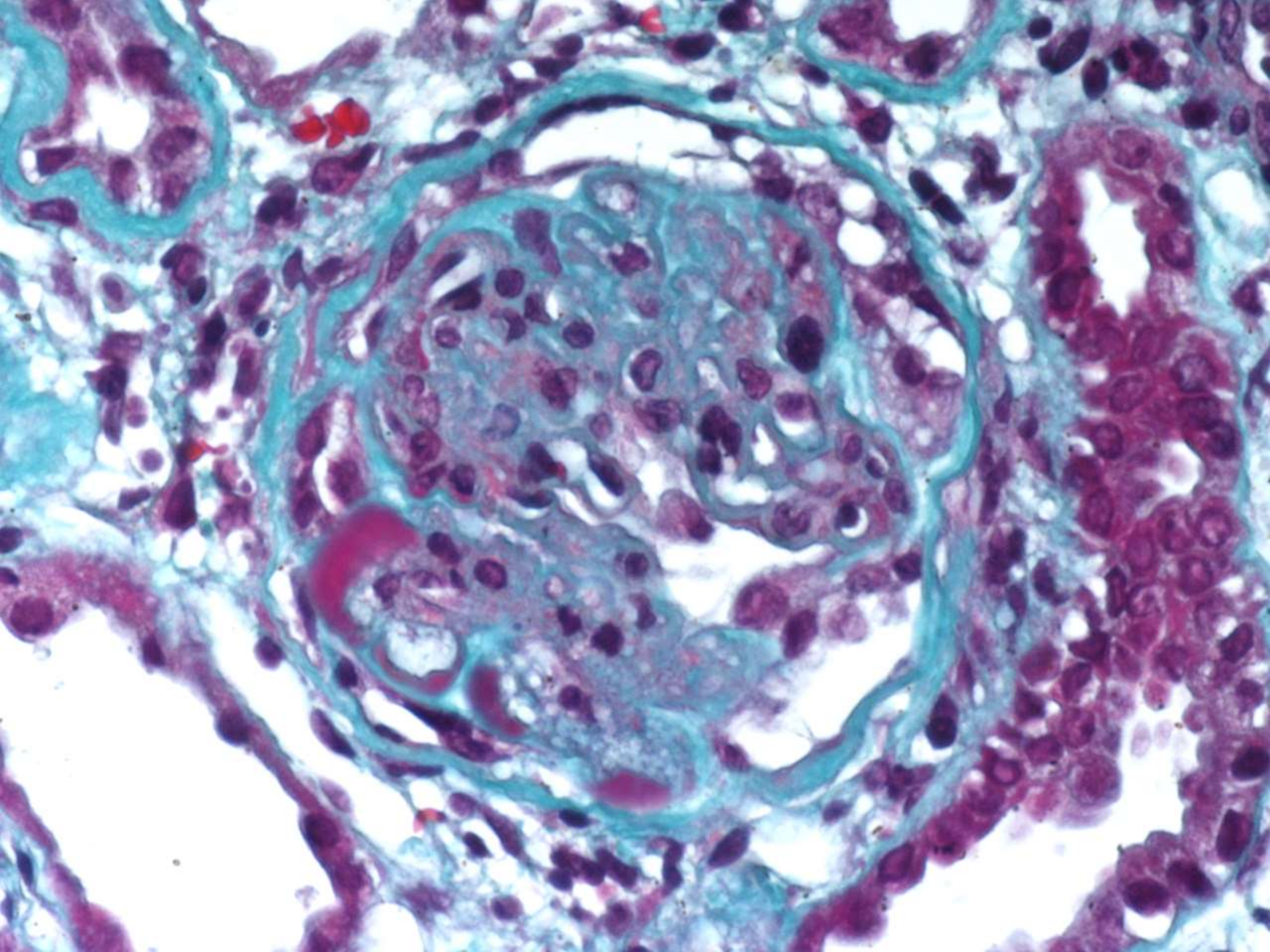
Morphological Classification of FSGS

# Classification of Primary FSGS

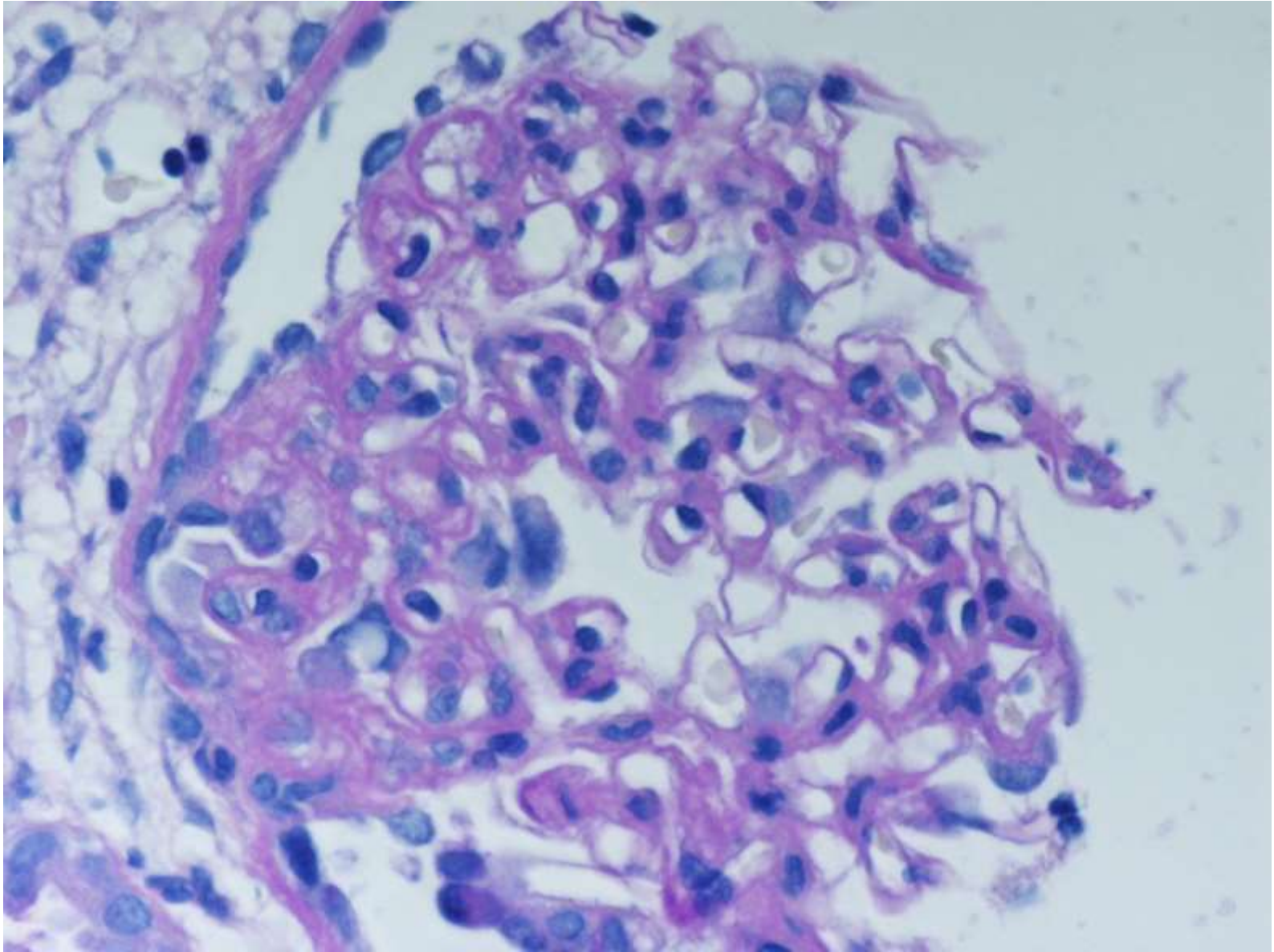
- Collapsing FSGS;
- Cellular FSGS;
- Glomerular Tip Variant;
- Perihilar FSGS;
- FSGS, NOS (not otherwise specified).

## Morphology of Classic FSGS (NOS)





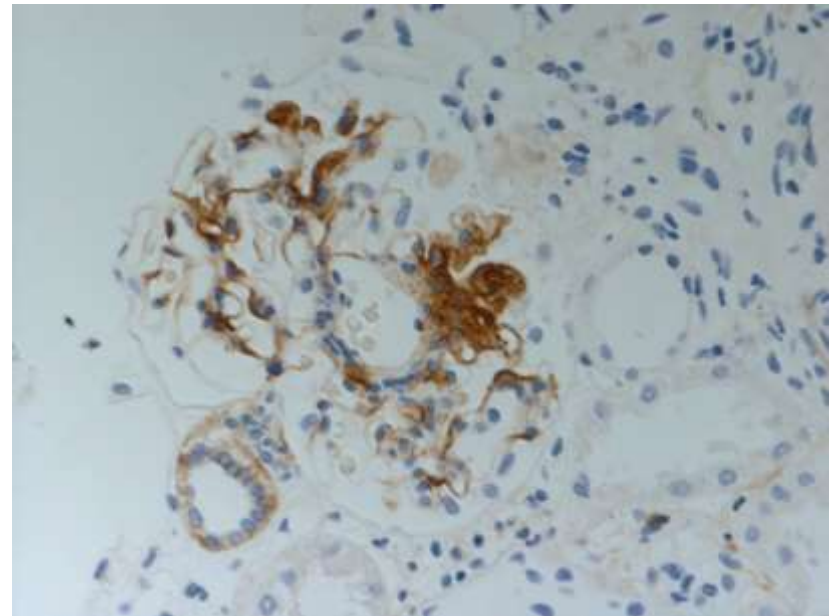
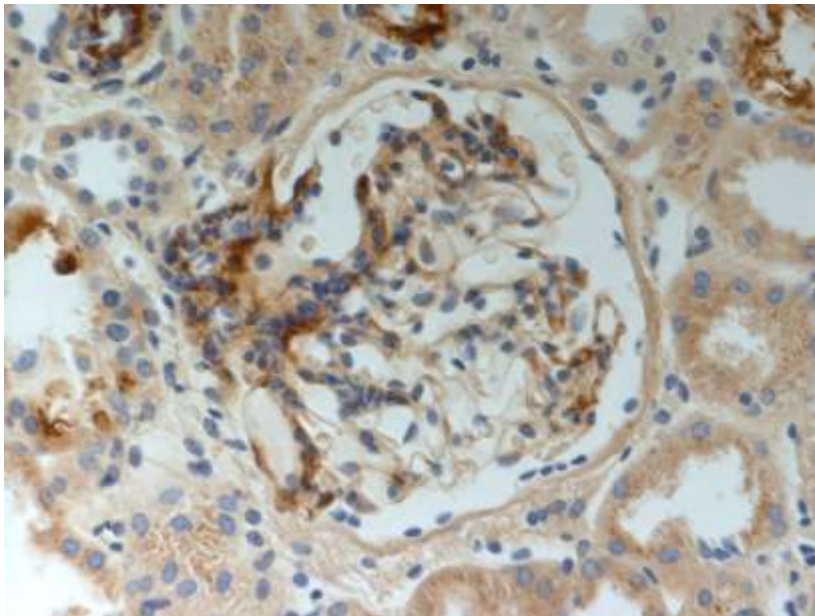
# Morphology of Classic FSGS

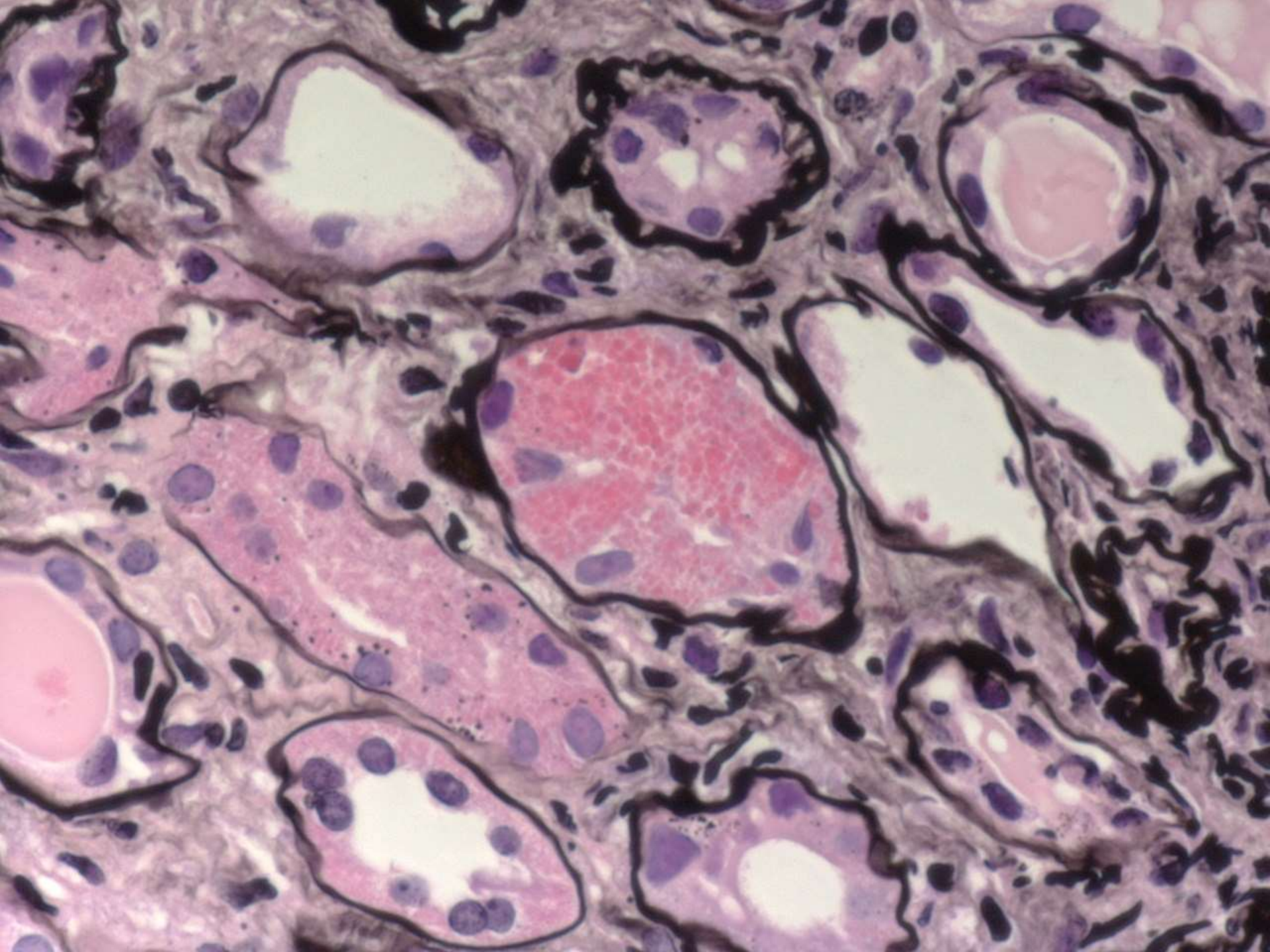


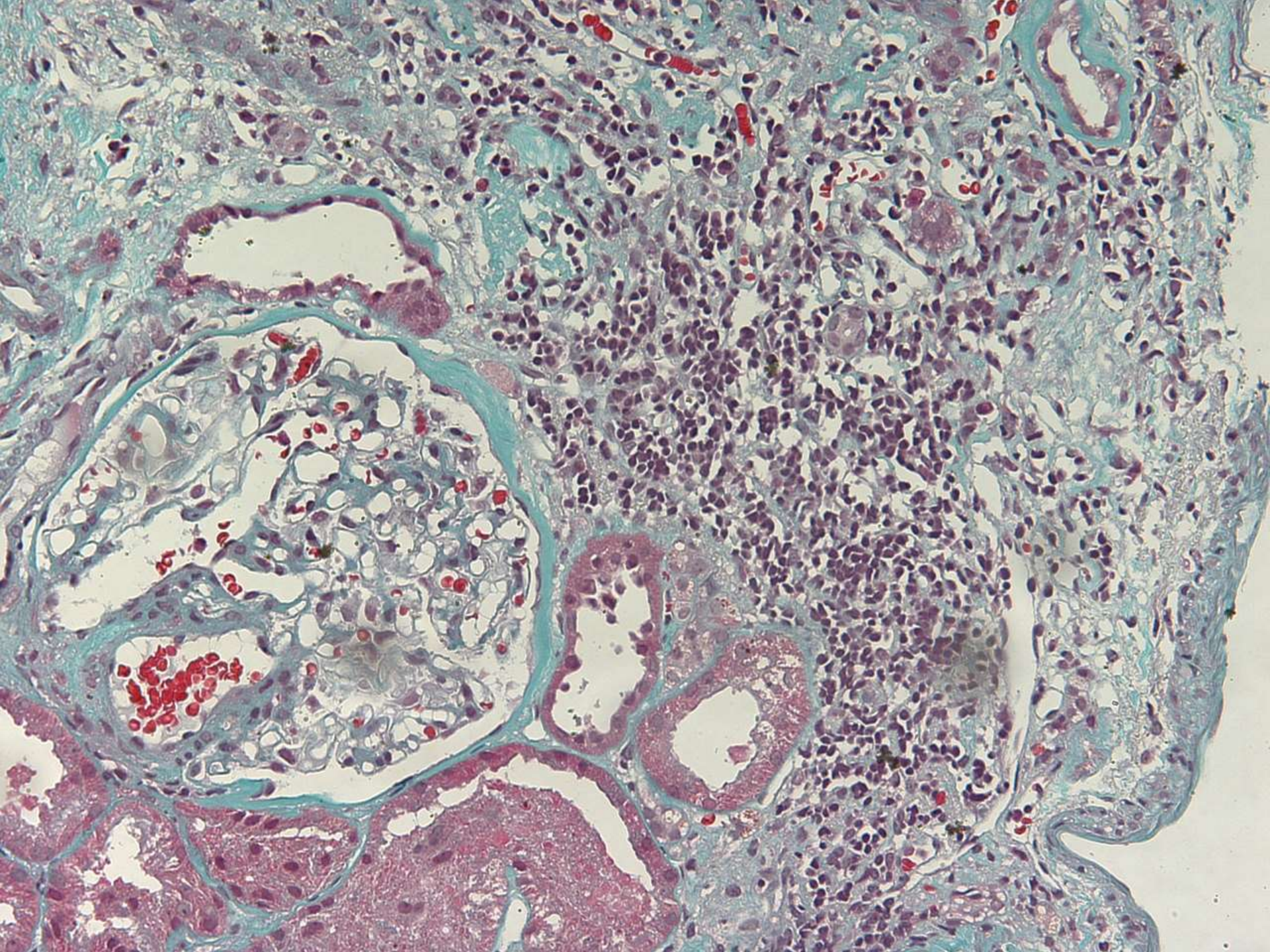
# Morphology

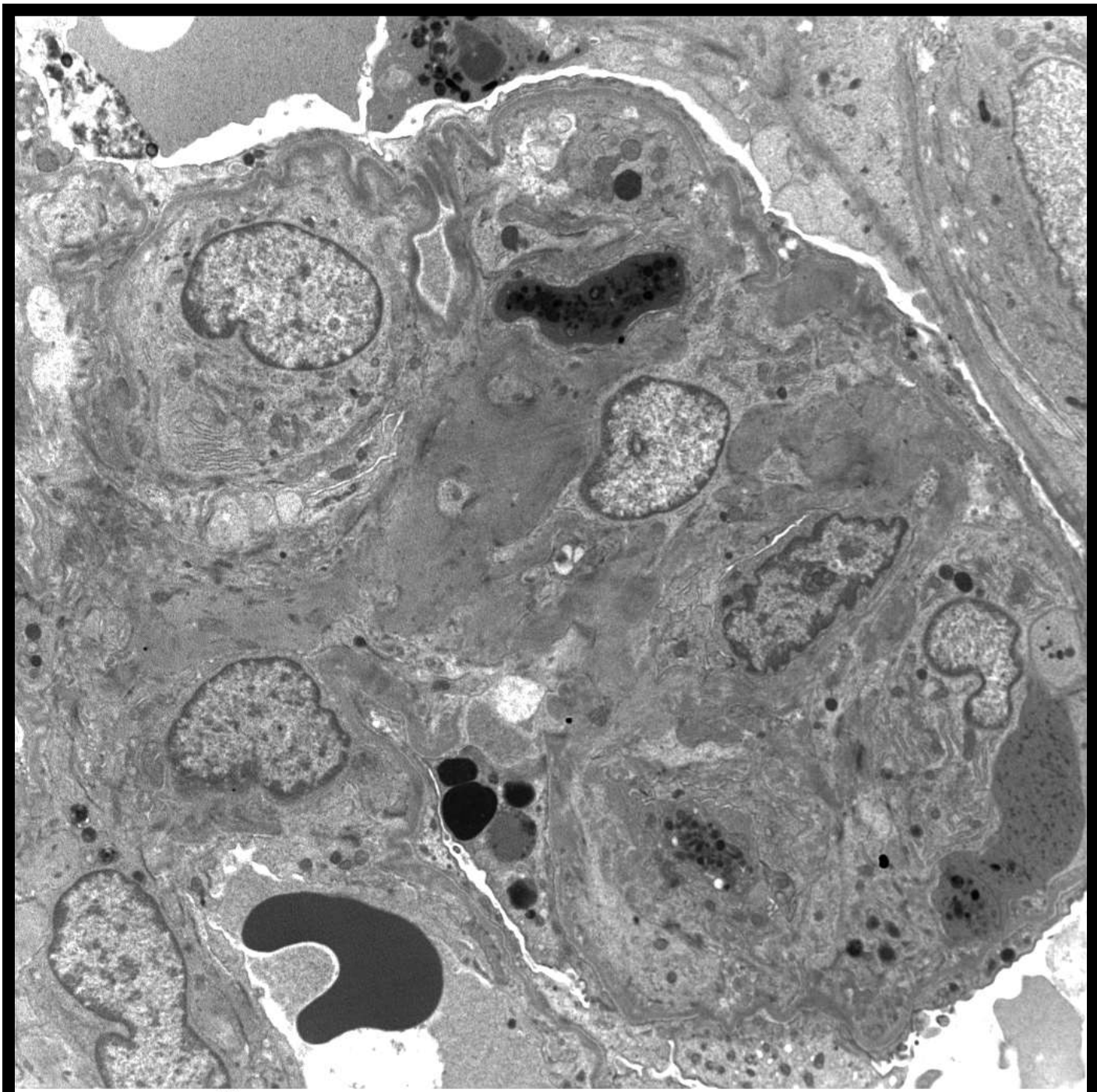
- Focal and segmental consolidation or closure of capillary loops and glomerular segments
  - Due to increased matrix;
  - Vacuolation of the matrix;
  - Podocyte enlargement over the top of the segmental lesion - 'podocyte cap';
  - Often with some wrinkling of the involved length of the glomerular capillary wall and adhesion to overlying Bowman's capsule.
- Earliest stage of the disease – more frequently found at corticomedullary junction (AR Rich, 1957)
  - Search will include additional serial sections and rapid examination of the resin-embedded semi-thin sections of the tissue taken for EM

IgM, C3, C1q trapping often seen









# Treatment & Prognosis

- 20 - 30% of patients renal insufficiency at presentation when FSGS
- 30 – 45% have hypertension
- 55% children, 45% adults also have microscopic haematuria
  
- Rx: prolonged steroids 3-9/12
- Cyclophosphamide/cyclosporin [nephrotoxic]
- ACE inhibitors; angiotensin II receptor antagonists adjunct to reduce the tubulo-toxic proteinuria

# Prognosis

- Related to serum creatinine at presentation; level of proteinuria;
  - <3 years to end-stage if >10g/day
- Much better prognosis if undergo remission with treatment
- Histologically = extent of fibrosis
- 30-40% recurrence in transplants
  - Treated at that point with plasmapheresis

# Pathogenesis?

- Direct podocyte damage
- Dysregulated podocyte phenotype
- Circulating factors
- In familial forms, genetic mutations affecting abnormal cytoskeletal proteins in podocyte

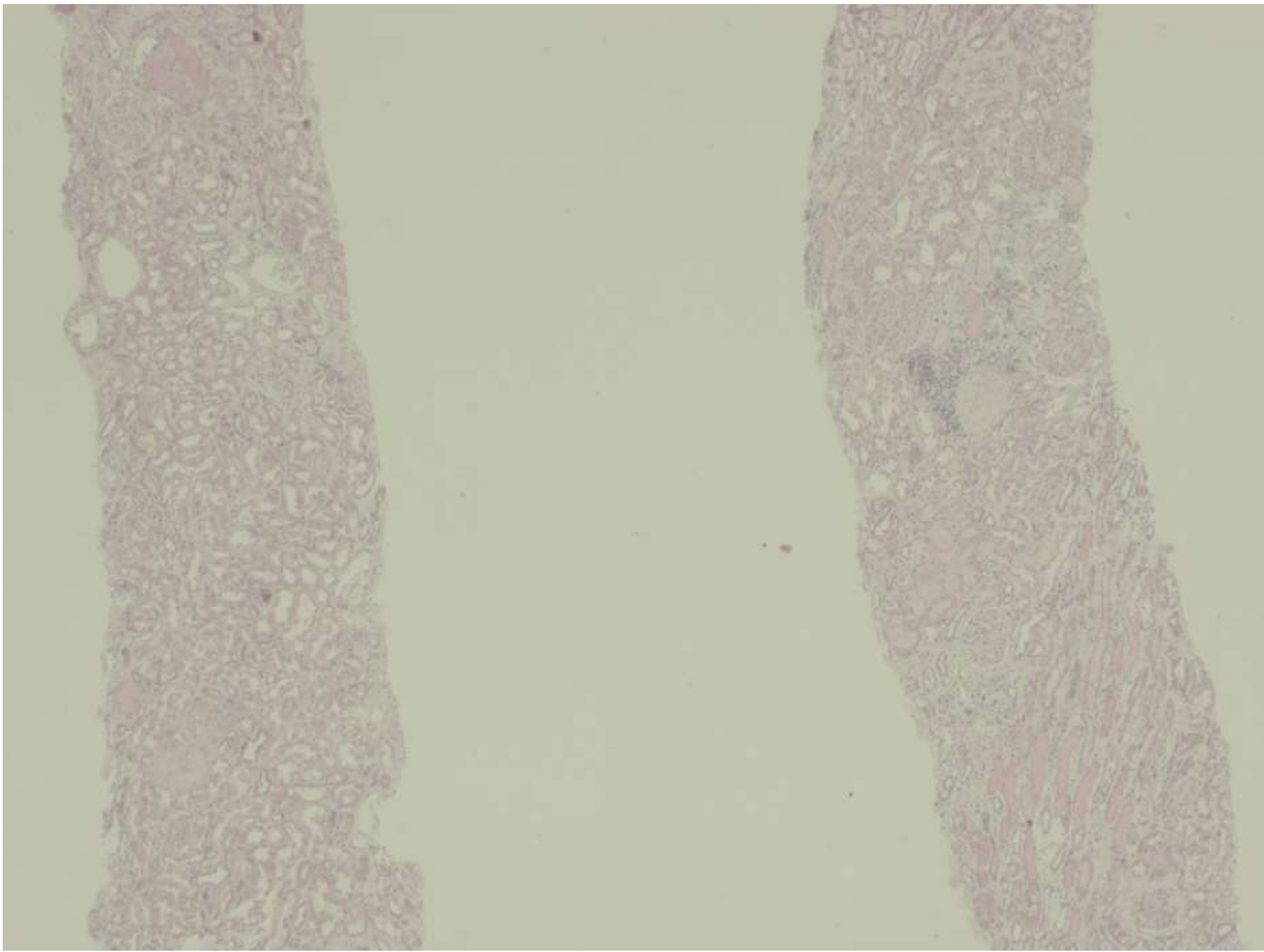
# FSGS, Collapsing Variant

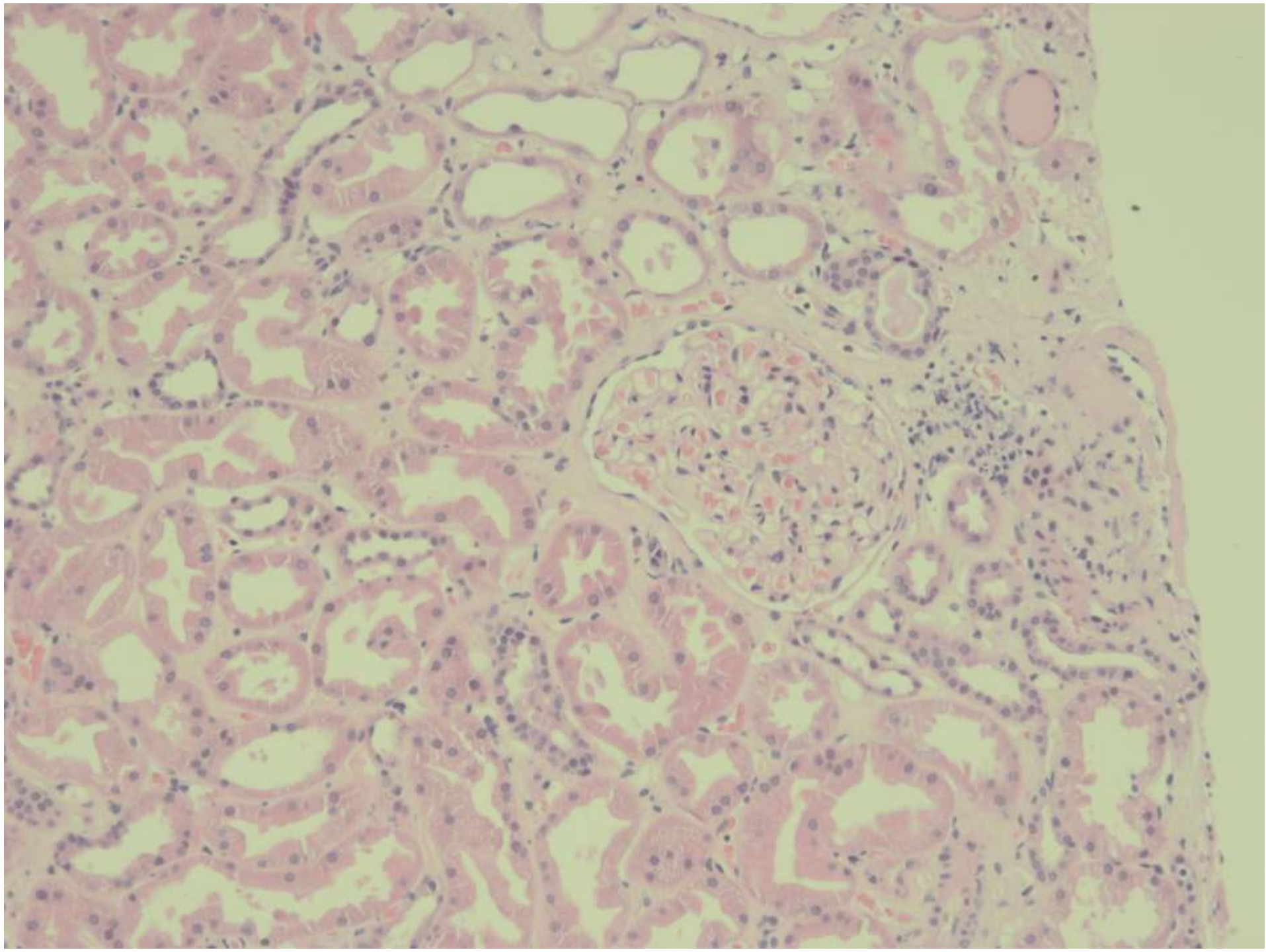
- Striking morphology:
- In which glomerular capillary lumina show segmental or [usually] global obliteration by wrinkling and collapse of GBM, with hypertrophy of the overlying podocytes; endothelial cells inconspicuous
- = implosion of the glomerular tuft
- = relative expansion of Bowman's space
- Weiss et al, 1986
- 6 black patients, presented with severe NS
- 2 required dialysis within 10 weeks of presentation
- 5 had ill-defined febrile illness
- One subsequently died of HIV/AIDS.
- Incidence increasing
- 'Malignant phenotype'

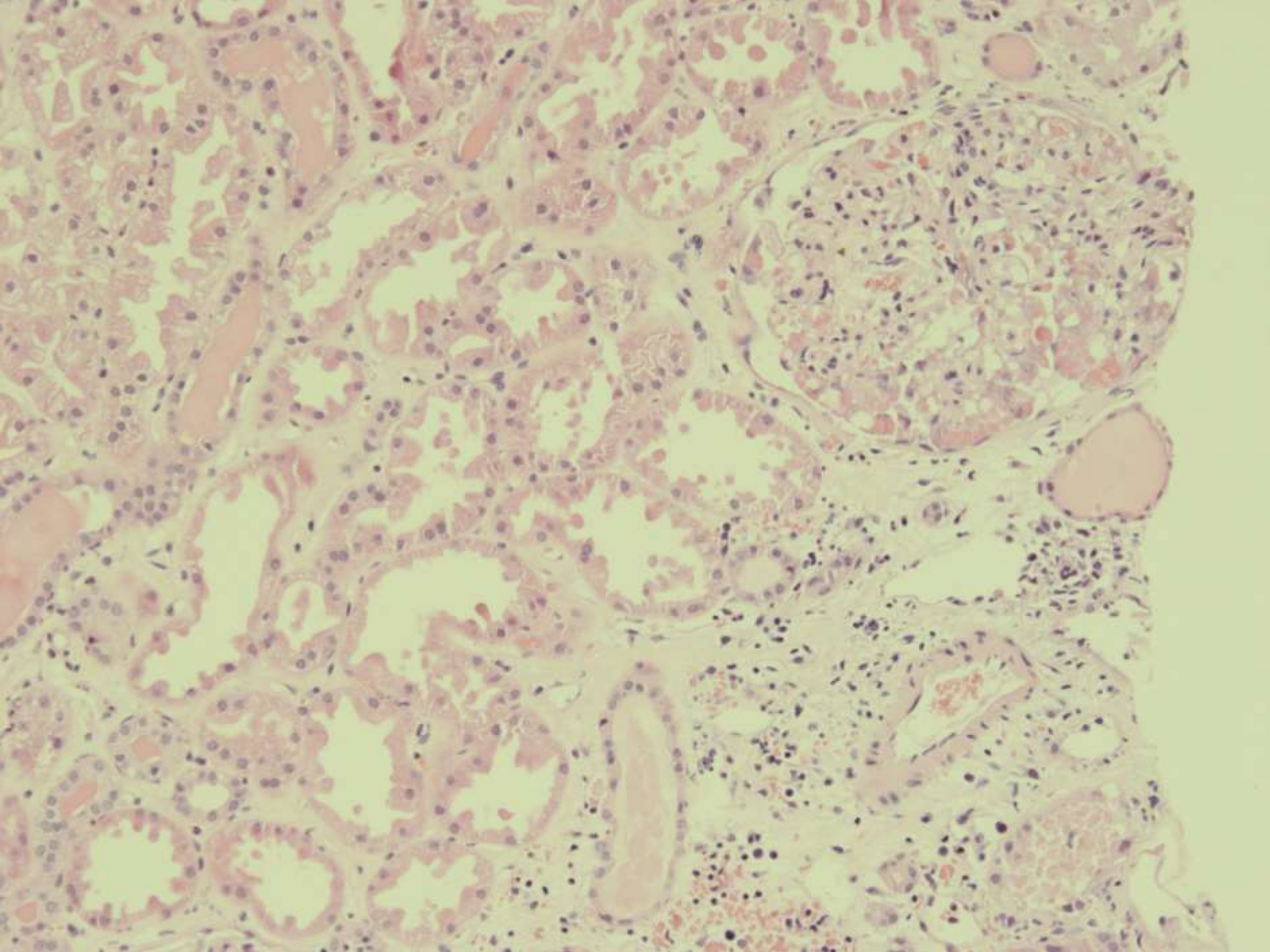
# Demonstrate cFSGS with a case from April 2020:

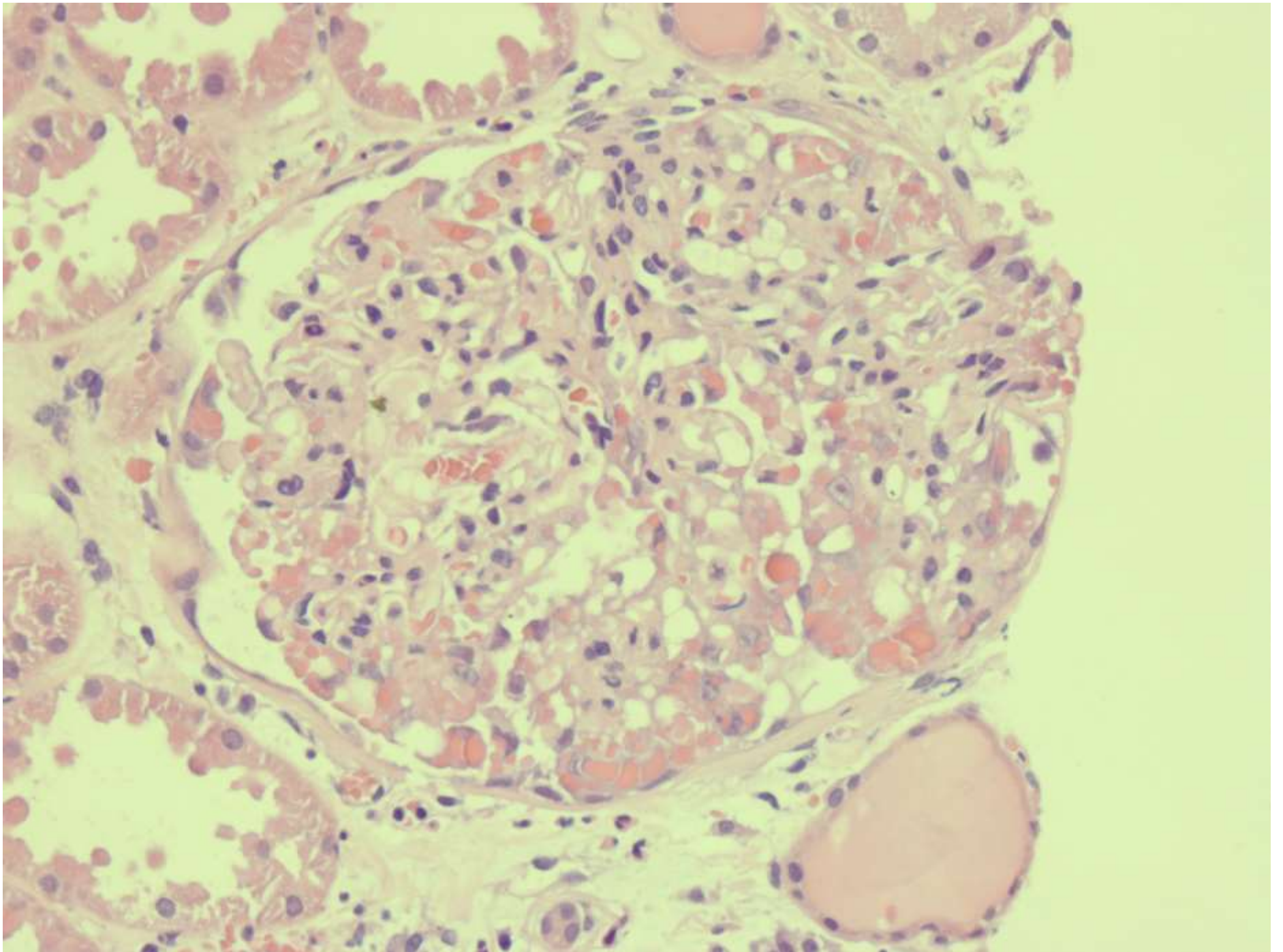
## Clinical history at time of biopsy:

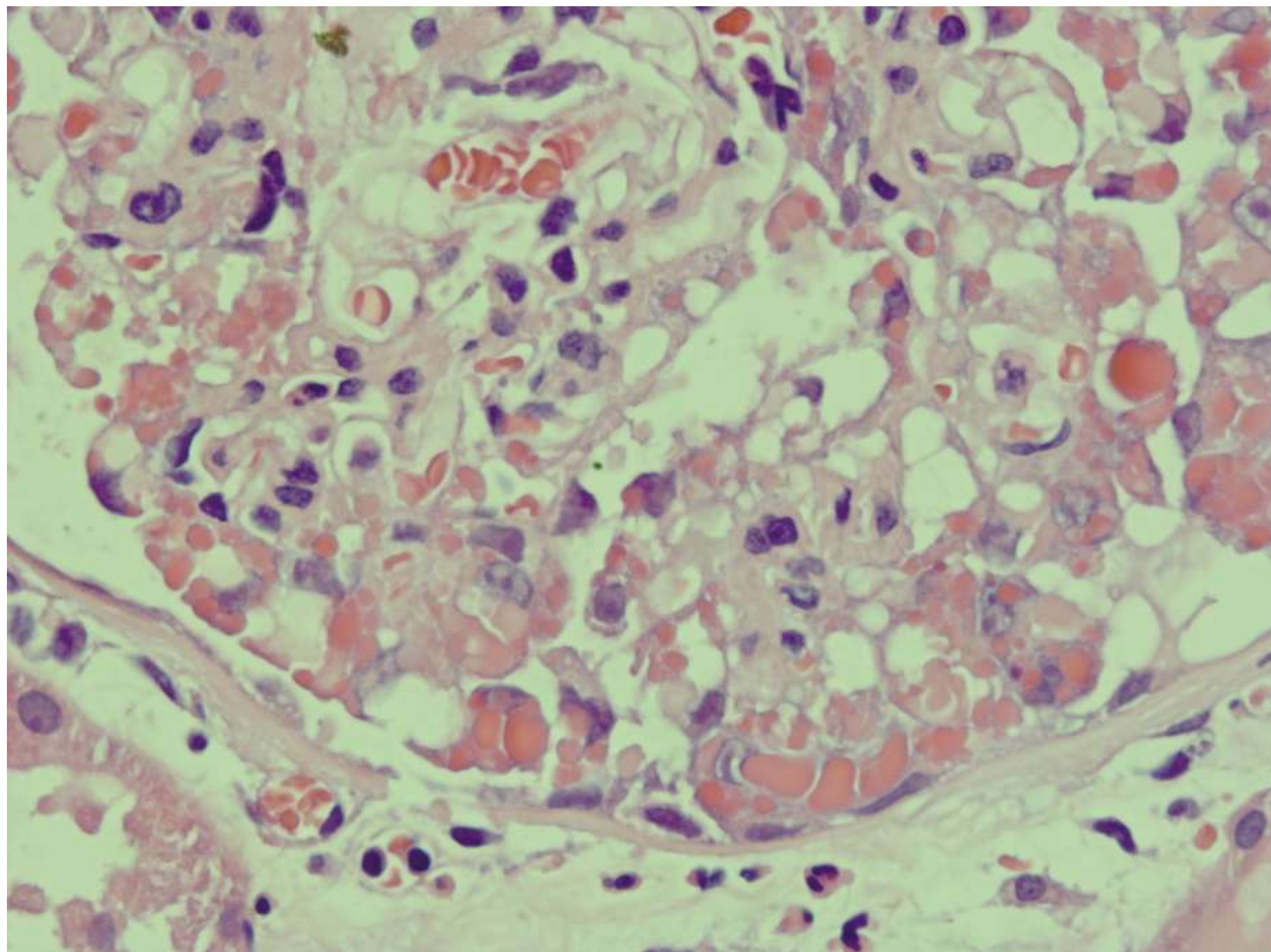
- 54 Nigerian male referred to Guy's;
- 10 day history malaise, fatigue and anorexia;
- PMHx:
  - Well controlled hypertension (Bendroflumethiazide and amlodipine);
  - EtOH misuse (20 units/day); herbal remedies;
- Clinical examination at Guy's unremarkable other than BP 145/86;
- Creatinine 525umol/L from baseline (December 2019) 97;
- UPCR 59; albumin low normal;
- CK – 270 (0-229 IU/L normal range).

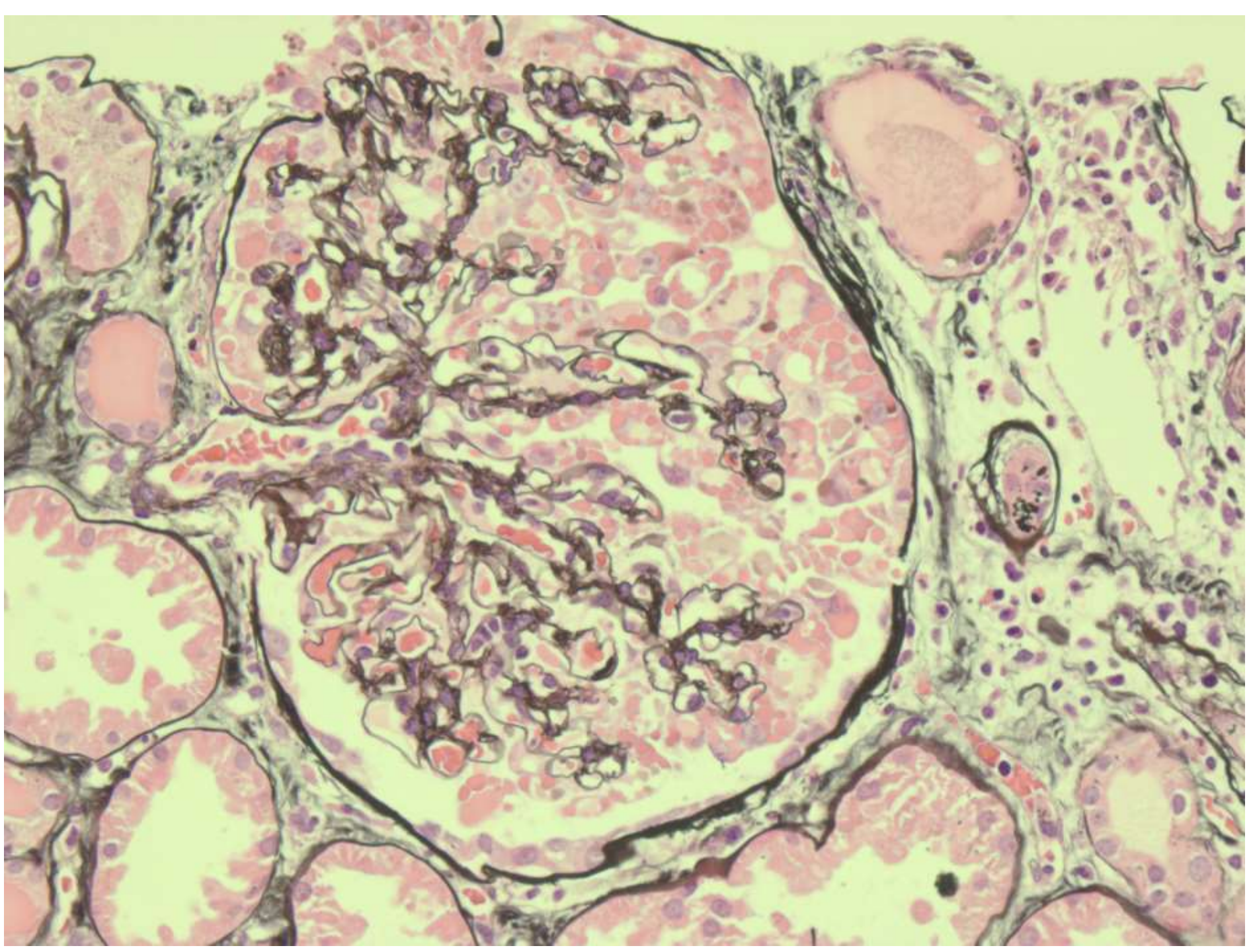


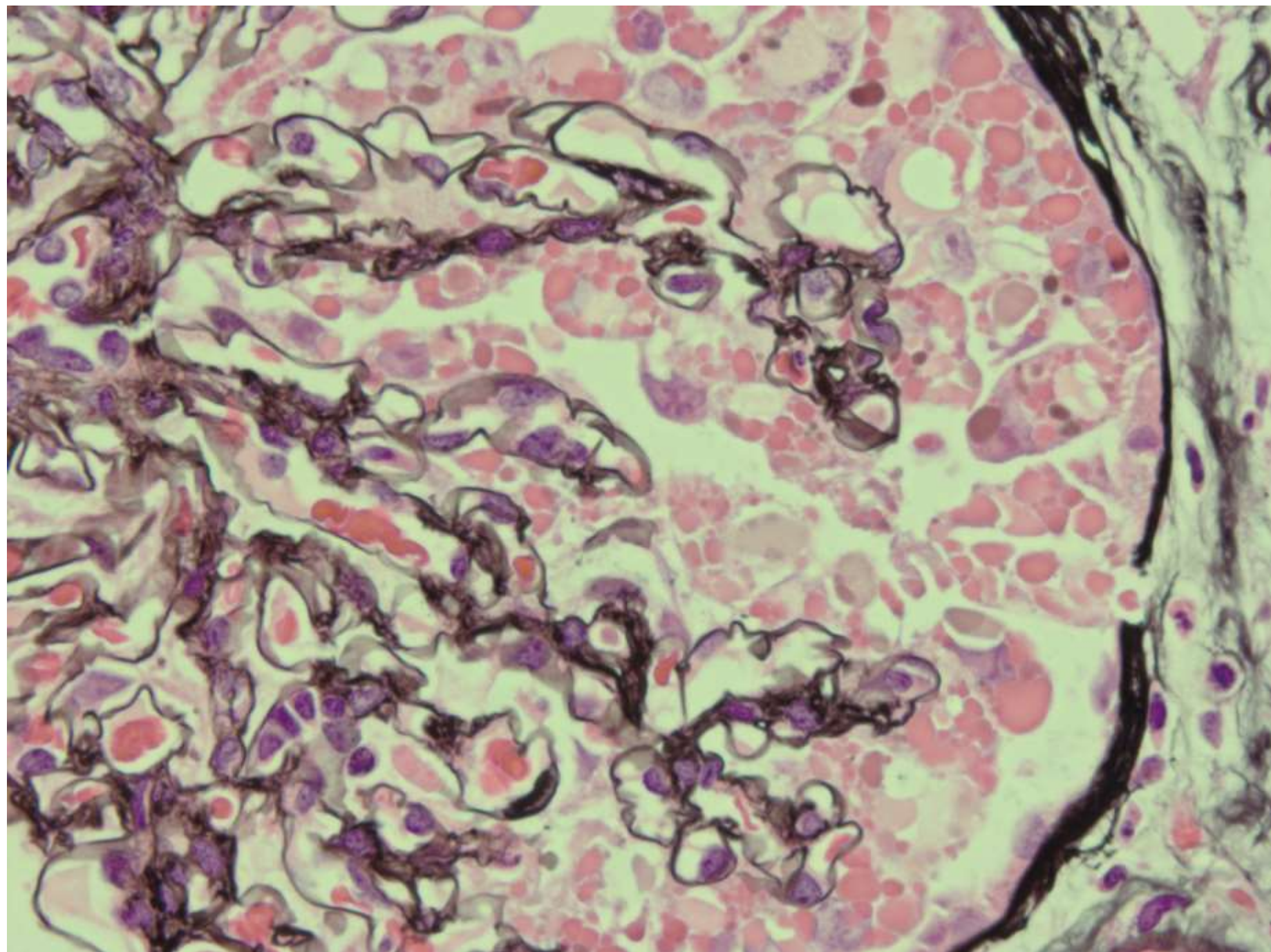


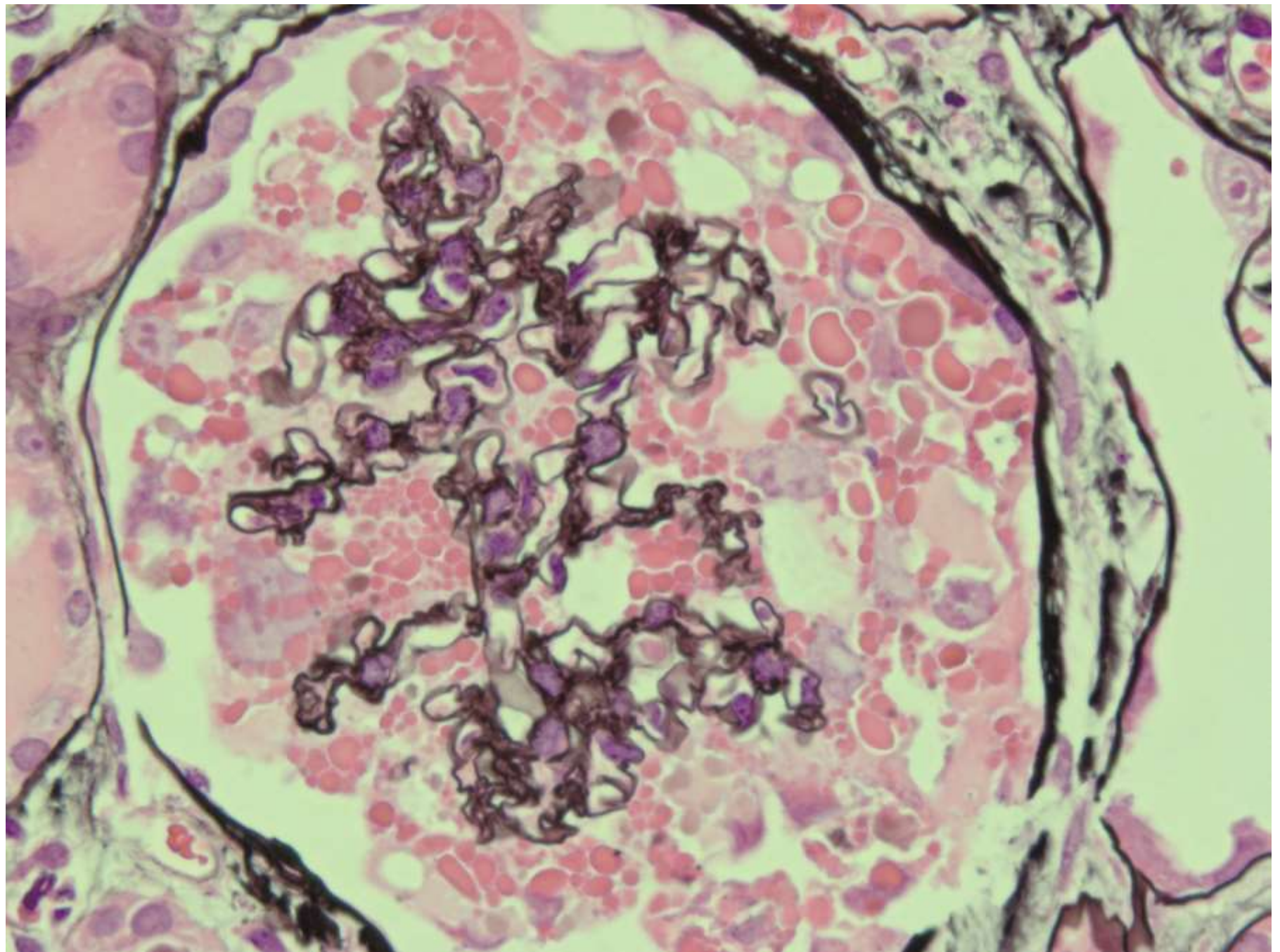


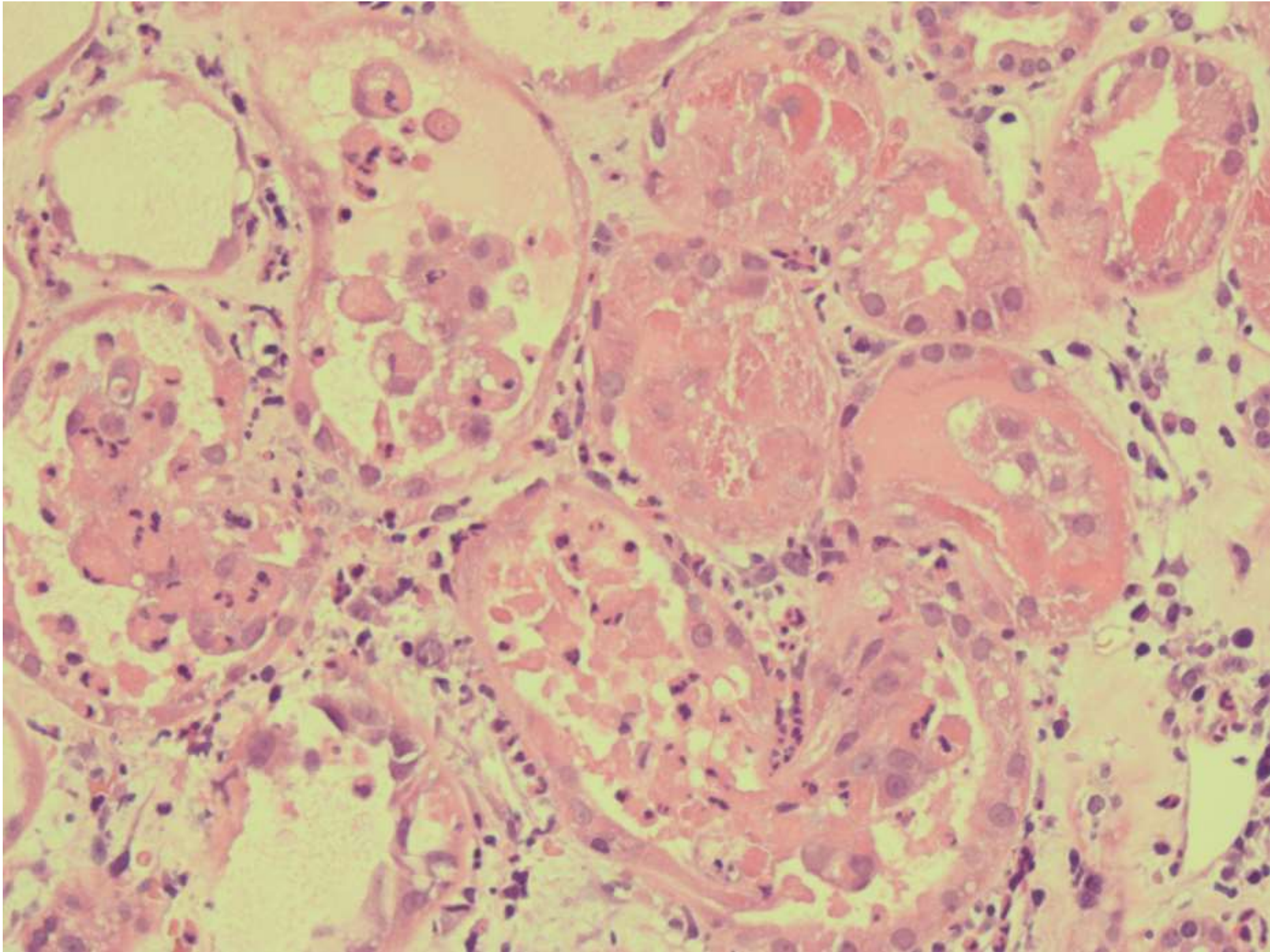


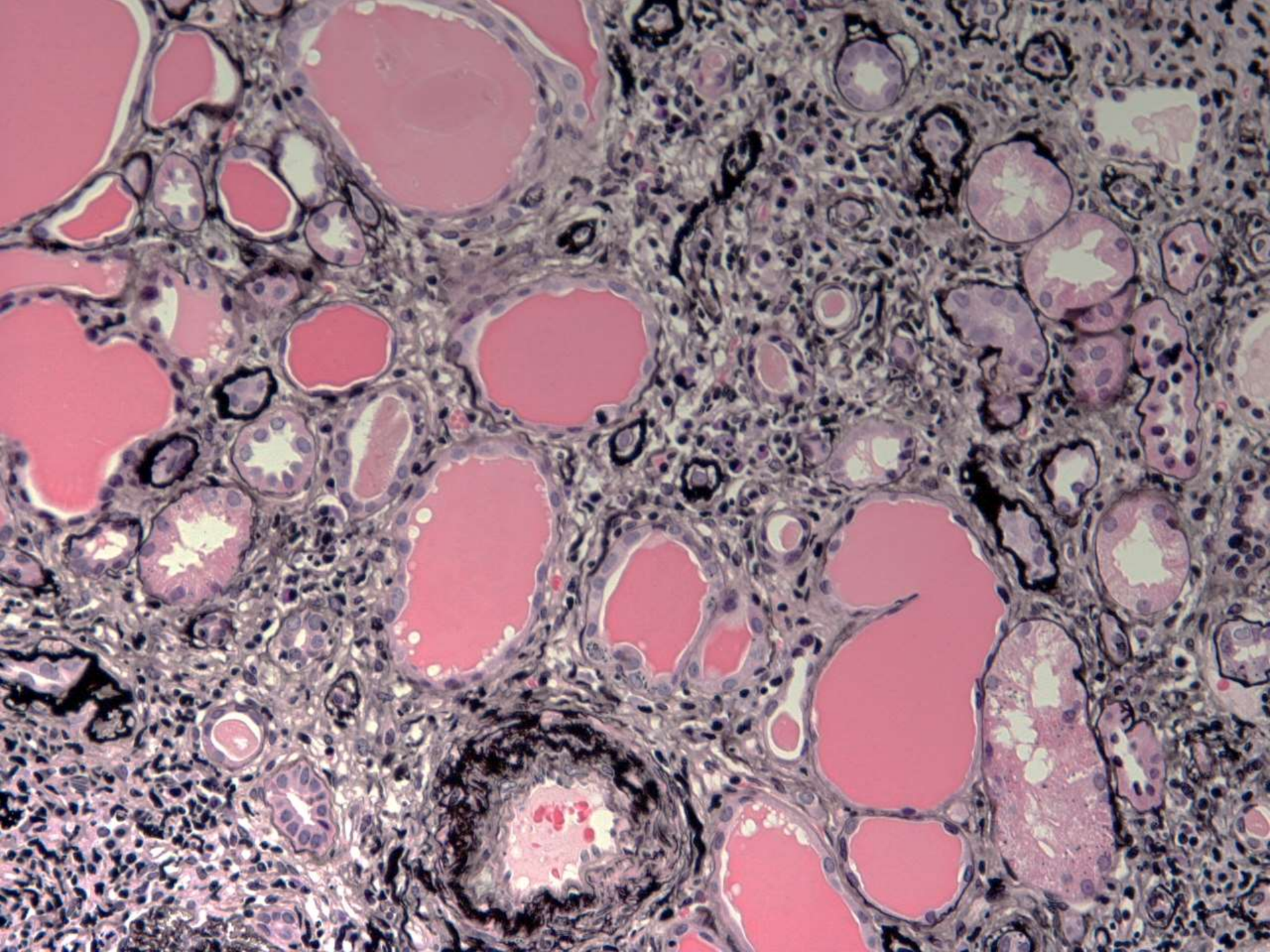












10 days previously at referring centre:

- UPCR - 250;
  - Albumin - 26;
  - Covid19 nasopharyngeal swab PCR positive.
- 
- HIV negative;
  - Parvovirus negative;
  - No recent foreign travel.

- Diagnosis:
- Covid-19 Associated Collapsing FSGS

## COVID-19–Associated Collapsing Glomerulopathy: An Emerging Entity



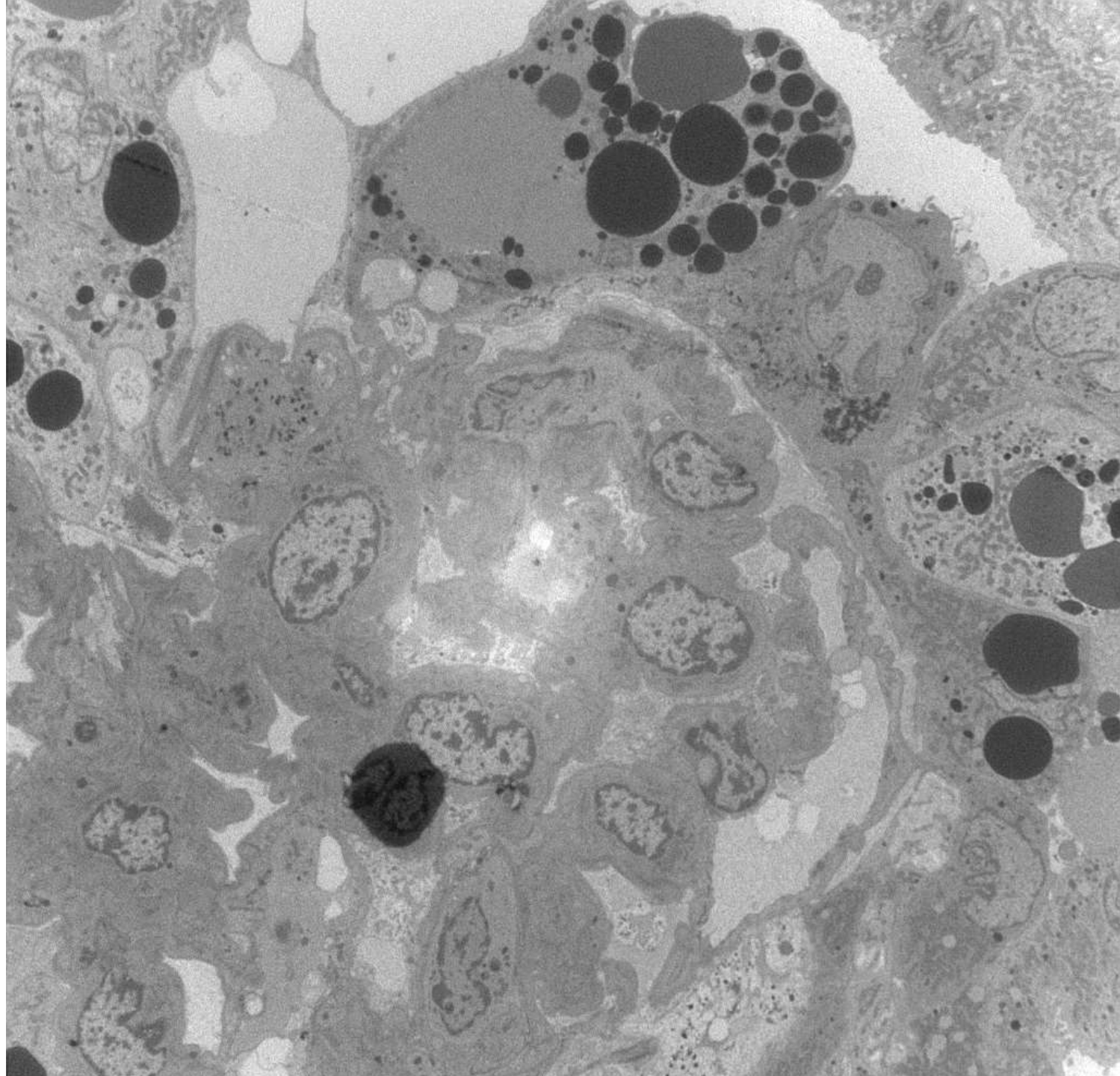
Samih H. Nasr<sup>1</sup> and Jeffrey B. Kopp<sup>2</sup>

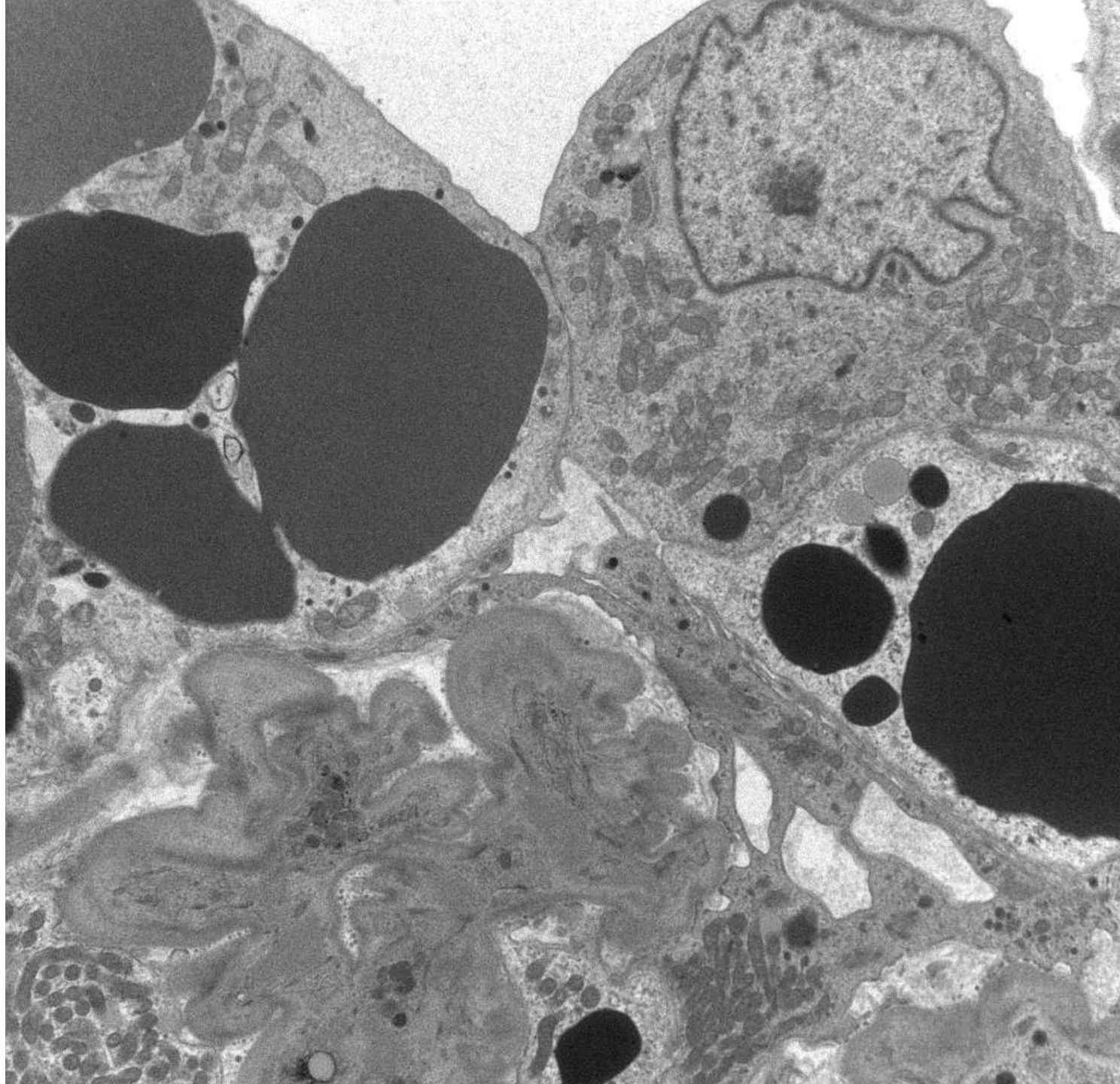
<sup>1</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; and <sup>2</sup>Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

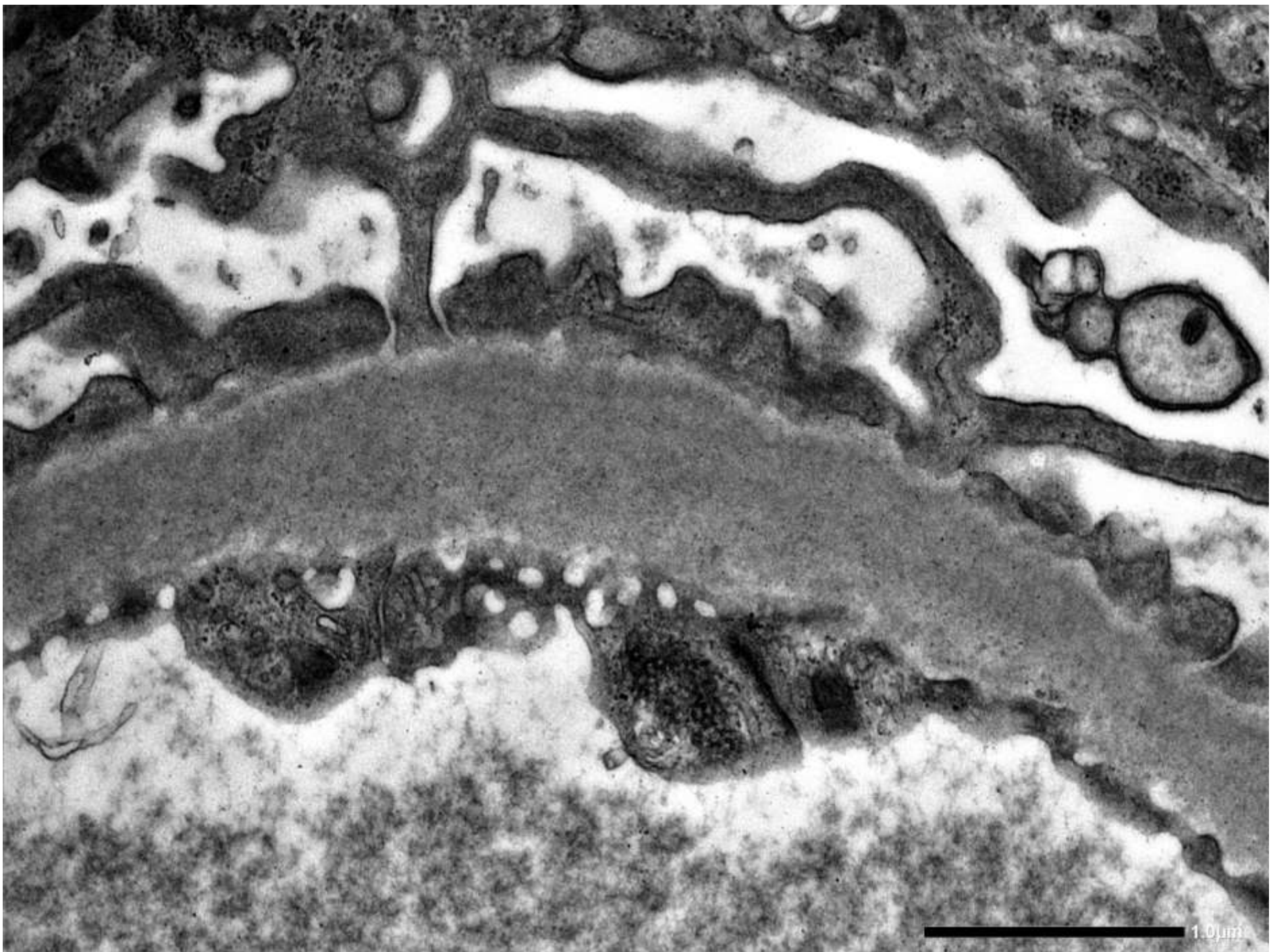
*Kidney Int Rep* (2020) **5**, 759–761; <https://doi.org/10.1016/j.ekir.2020.04.030>

© 2020 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

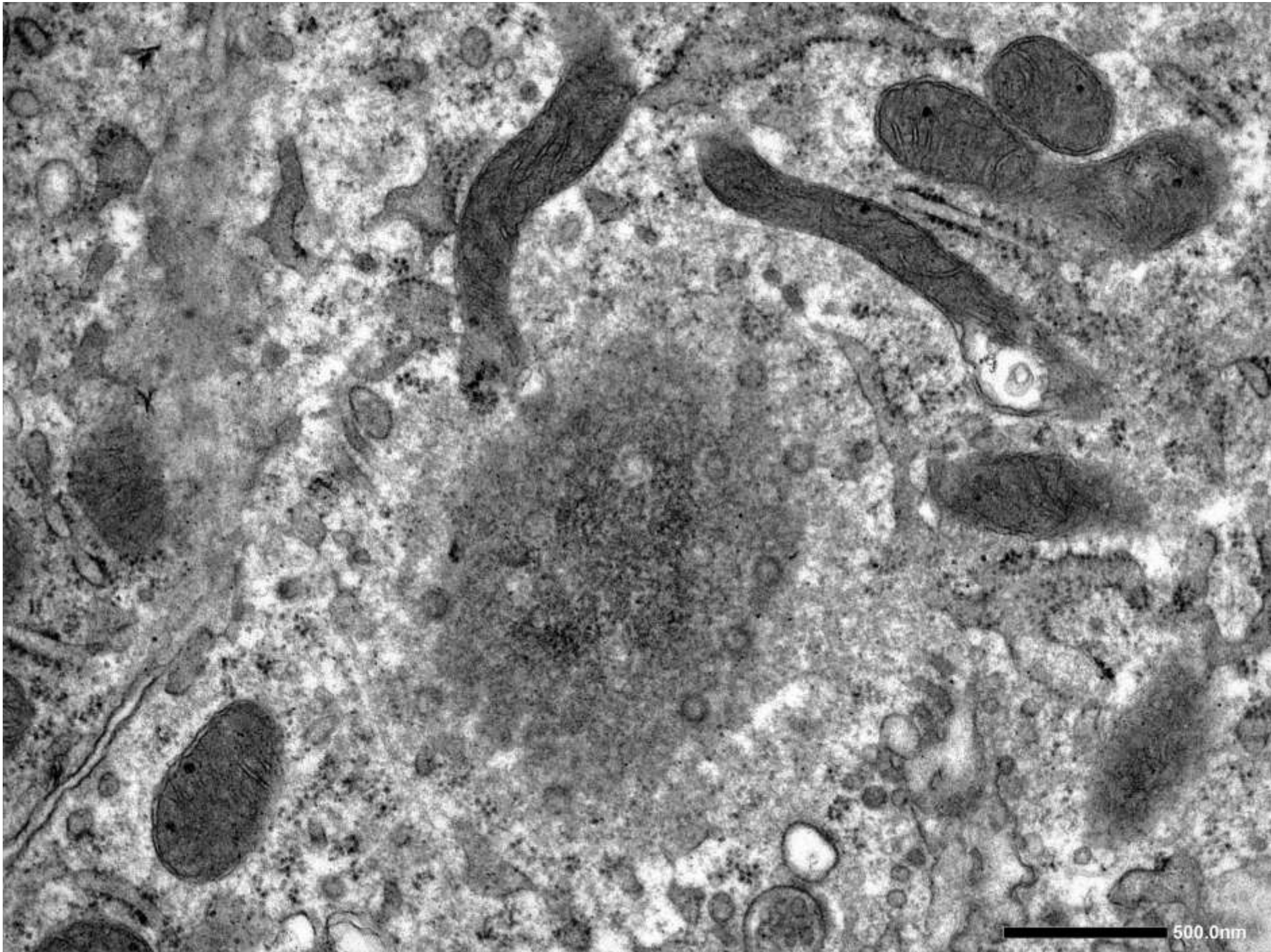
**See Nephrology Rounds on Page 940**







1.0 μm



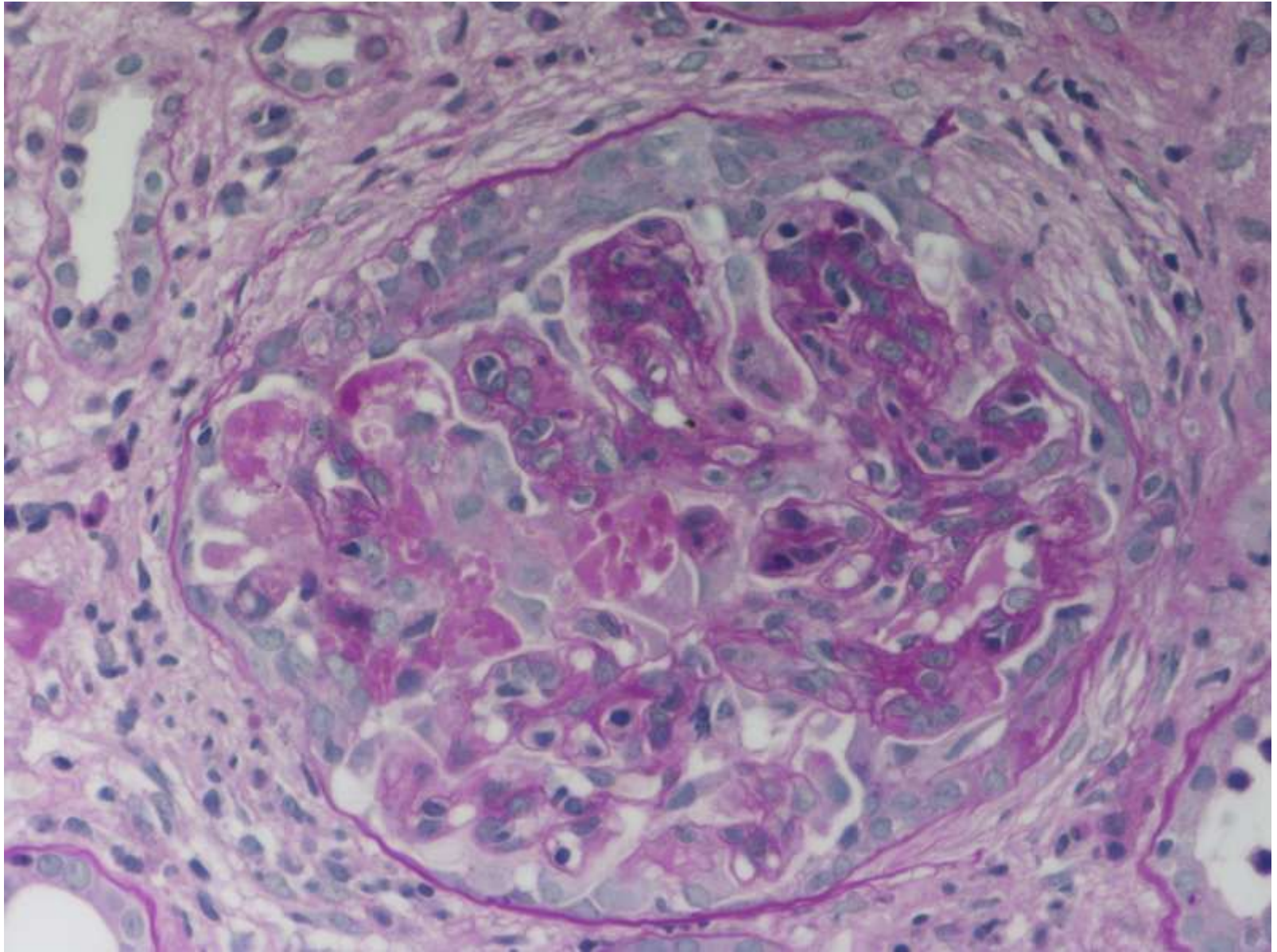
# Clinical progression

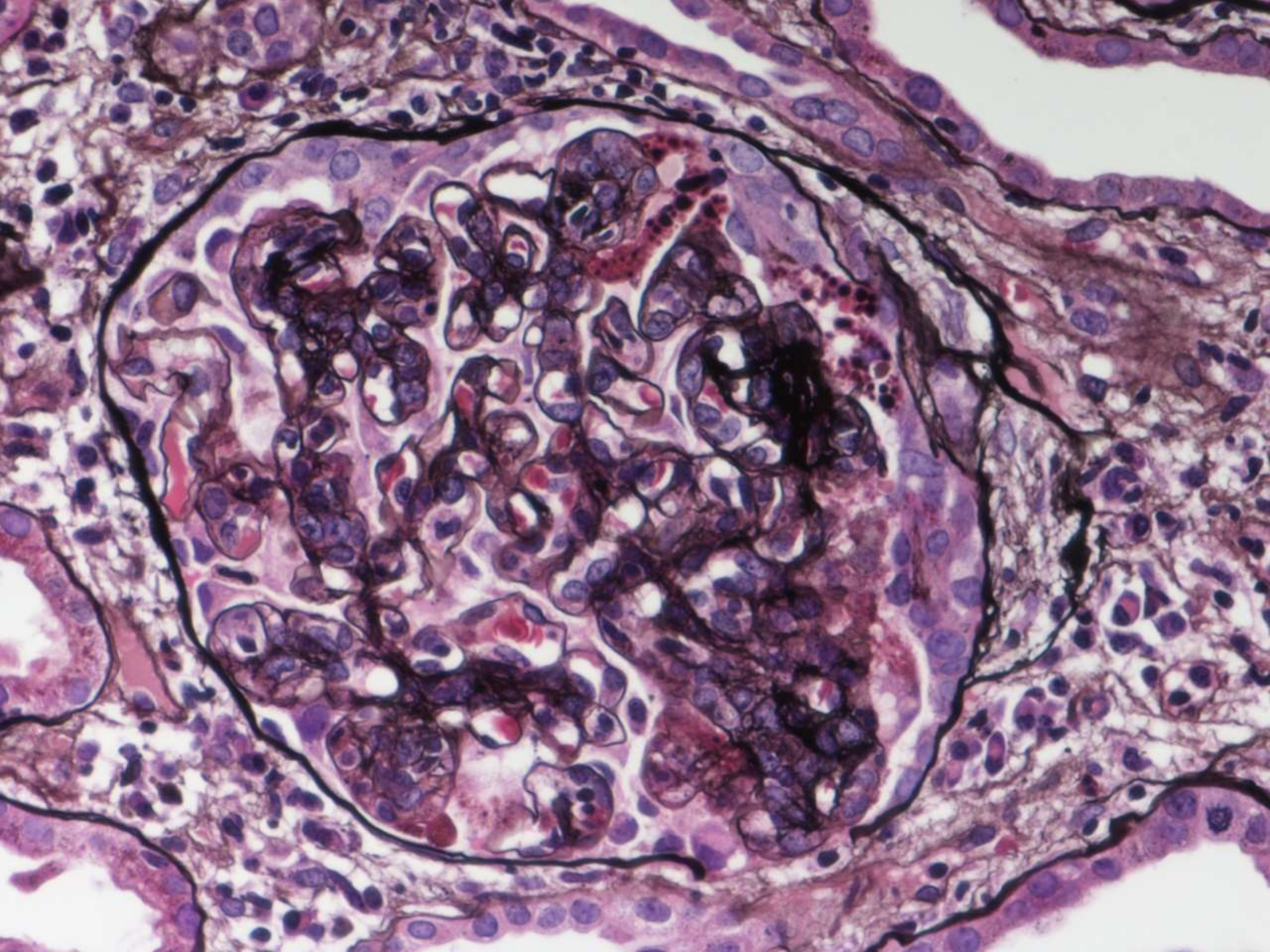
- Largely supportive;
  - He did not require renal replacement therapy;
  - Steroids were not given.
- 
- Creatinine fell spontaneously to 389 after 3 days, and 205 after 12 days.
  - ApoL1 genetic variant demonstrated.

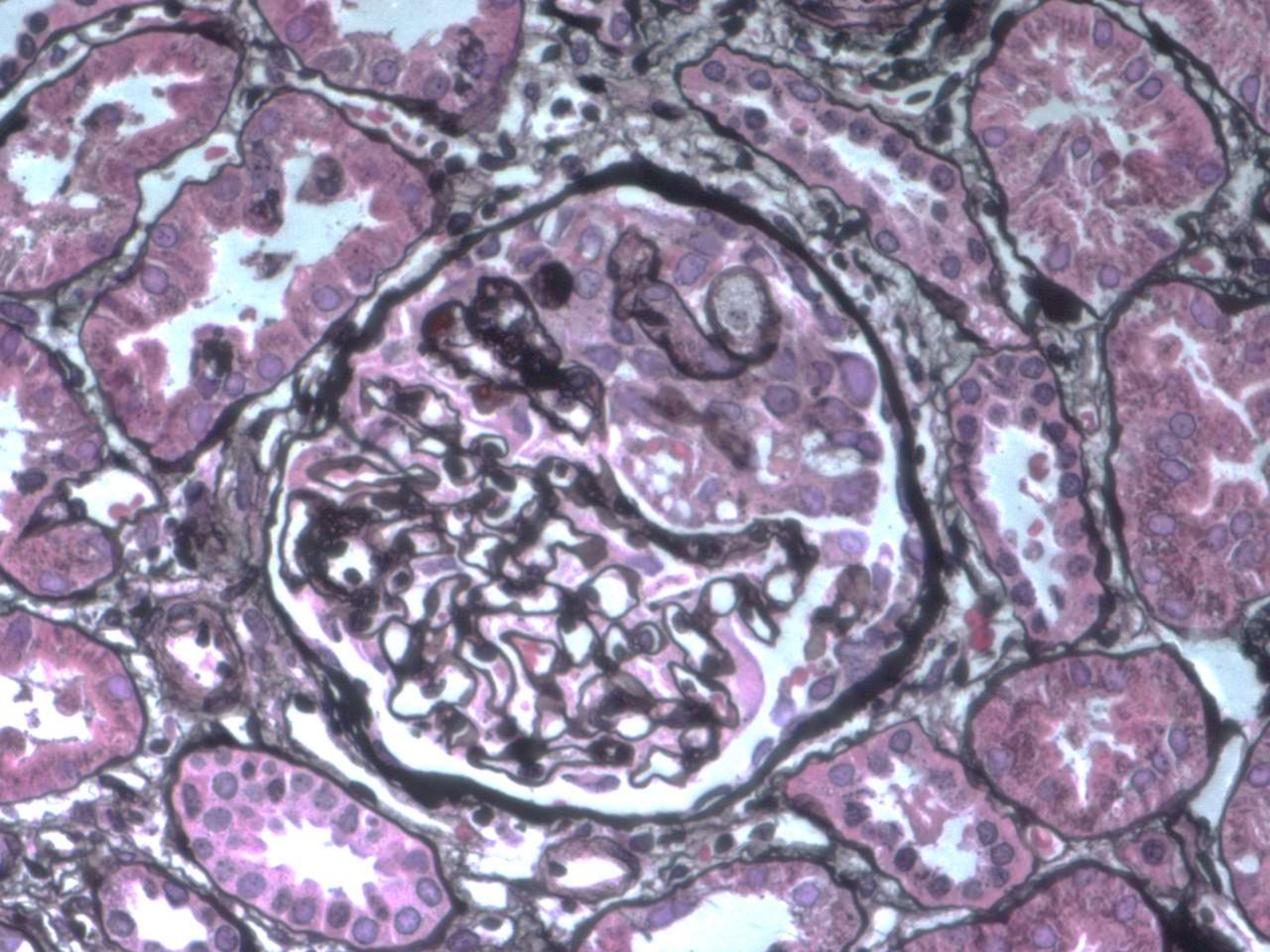
# Collapsing phenotype

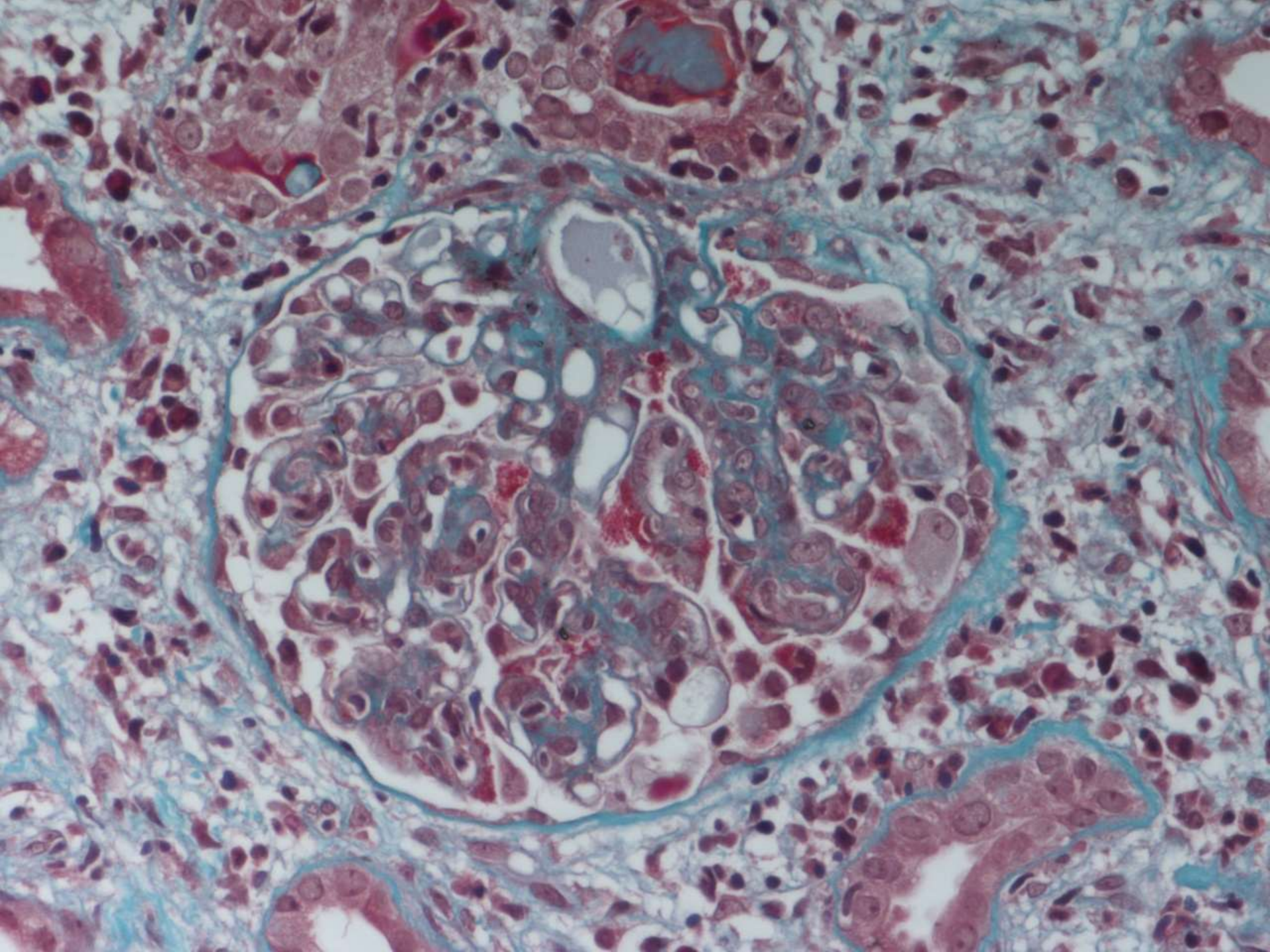
- As a subtype of idiopathic FSGS
- Also in forms of Secondary FSGS
  - Associated with drugs, lithium, pamidronate
  - Associated with viruses
    - Parvovirus
    - HIV

## FSGS, Cellular Variant







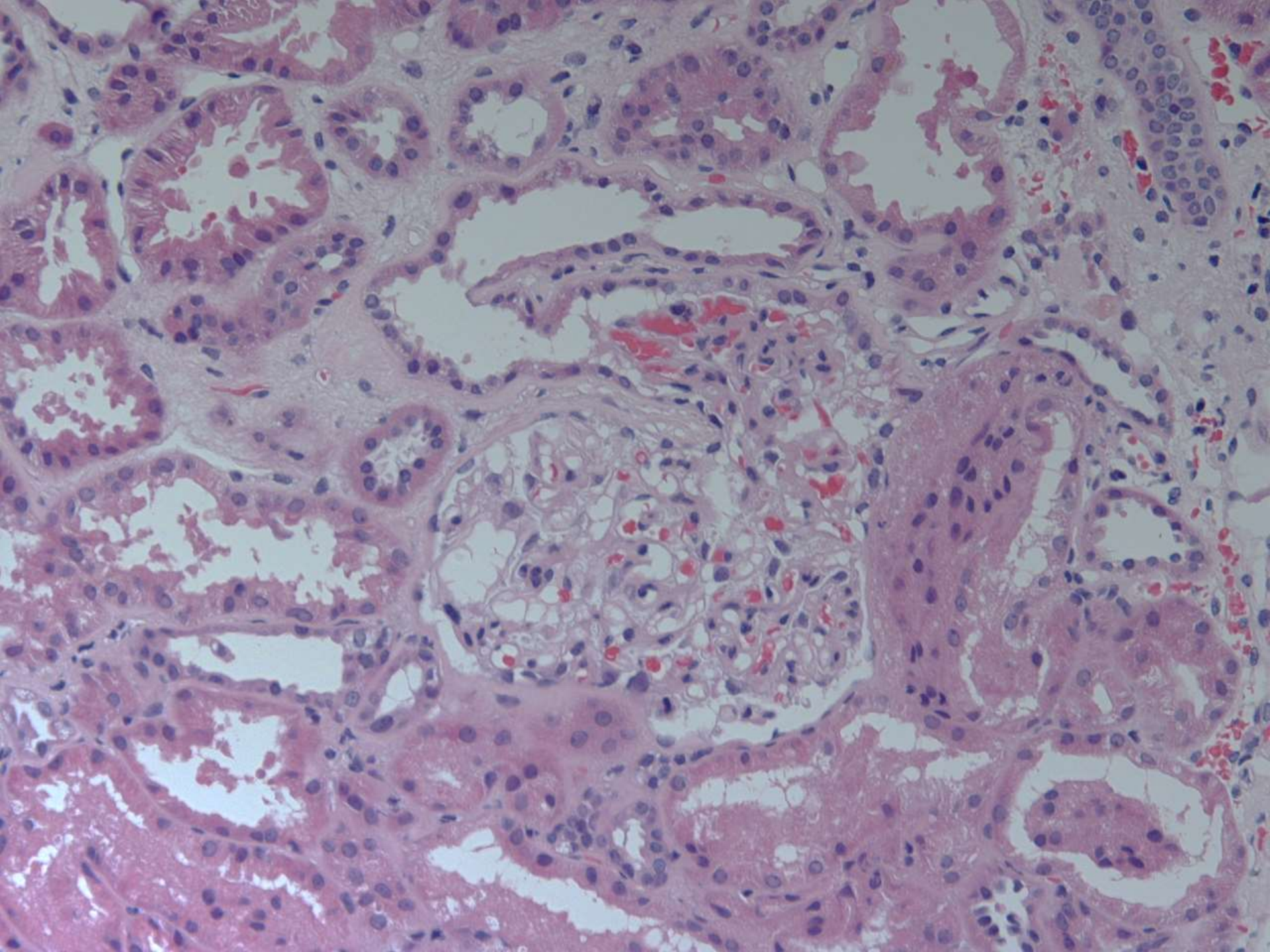


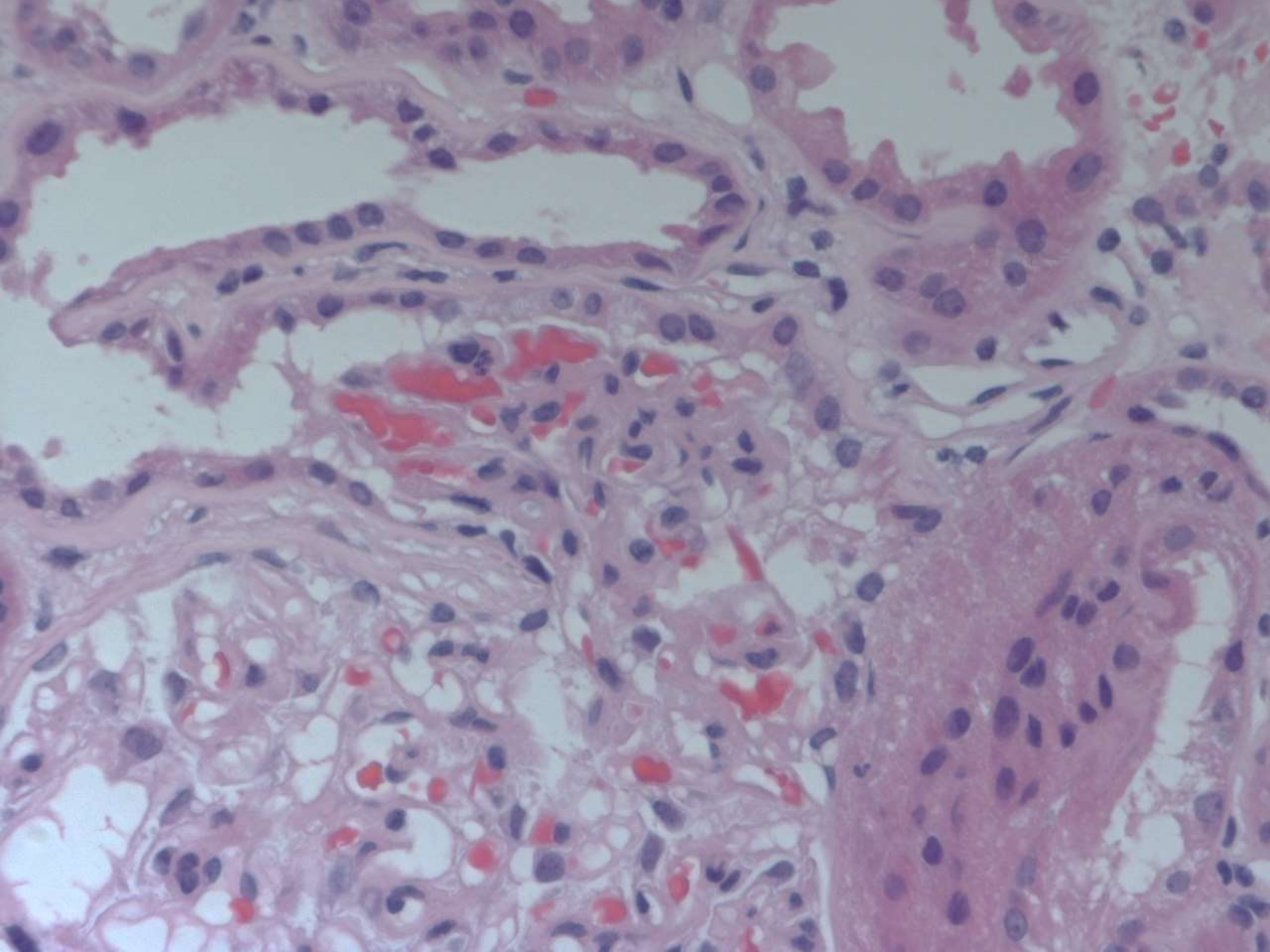
# Schwartz and Lewis, 1985

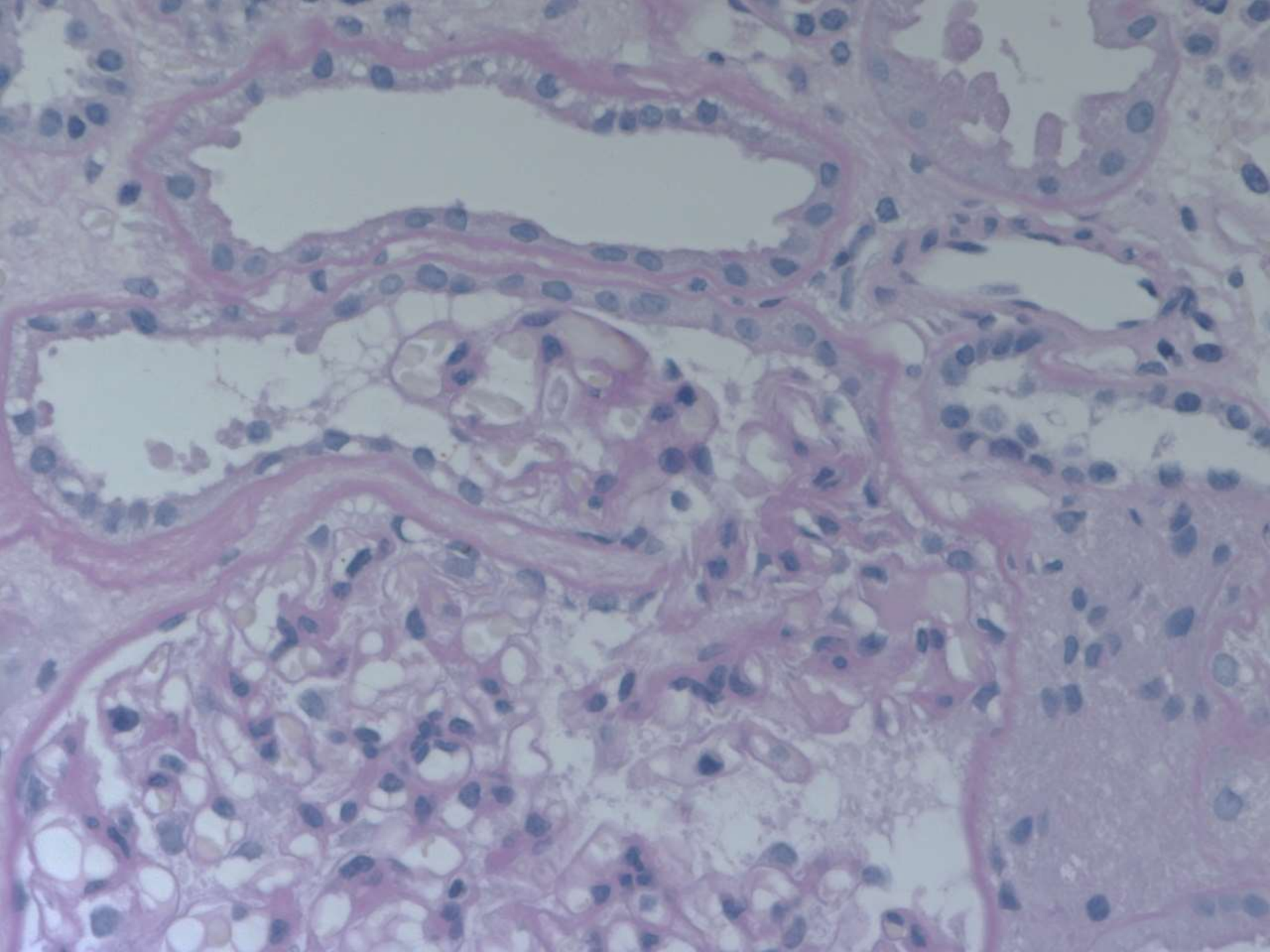
- Glomerular segments closed due to endocapillary hypercellularity, foam cells, +/- karyorrhexis, podocyte hypertrophy
- Resembles early proliferative GN, with pseudocrescents, however the exuberant visceral epithelial cells in Bowman's space are plump, round, discohesive, often with intracytoplasmic PRD
- Examine serial sections of these pseudocrescents and immunoprofile in order to differentiate Cellular Variant from a proliferative GN
- Cellular Variant of FSGS may represent an early stage of the disease, subsequent biopsies often show Classic FSGS appearances

# Glomerular Tip Lesion

- Pathologic classification of focal segmental glomerulosclerosis: a working proposal [2004]
- The glomerular tip lesion: a previously undescribed type of segmental glomerular abnormality [1984]
  - Howie and Brewer



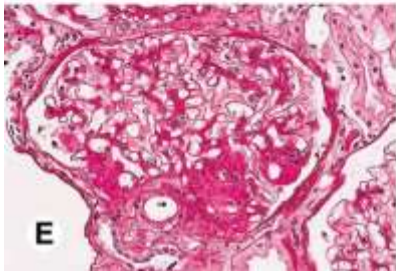
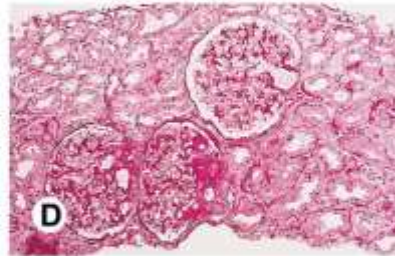
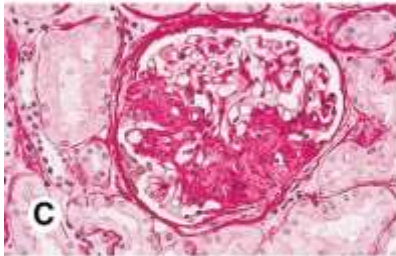
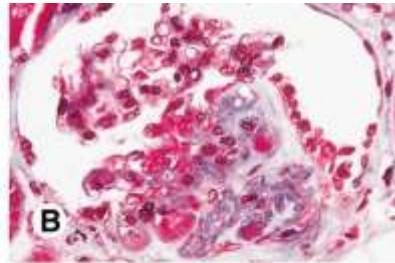
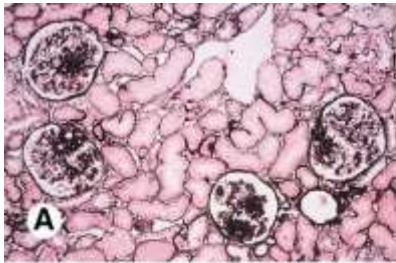




## Tip variant of FSGS

- Segmental lesions at the origin of the proximal tubule
- May see endocapillary hypercellularity at that site
- Adhesion
- Alteration of the epithelial cell morphology of the tubules
- Prolapse of the glomerular tuft
- Favourable prognosis, may behave more like MCD
- The morphological lesion is seen in other settings
  - Membranous nephropathy
  - IgA Nephropathy
  - Diabetes

# Perihilar variant of FSGS

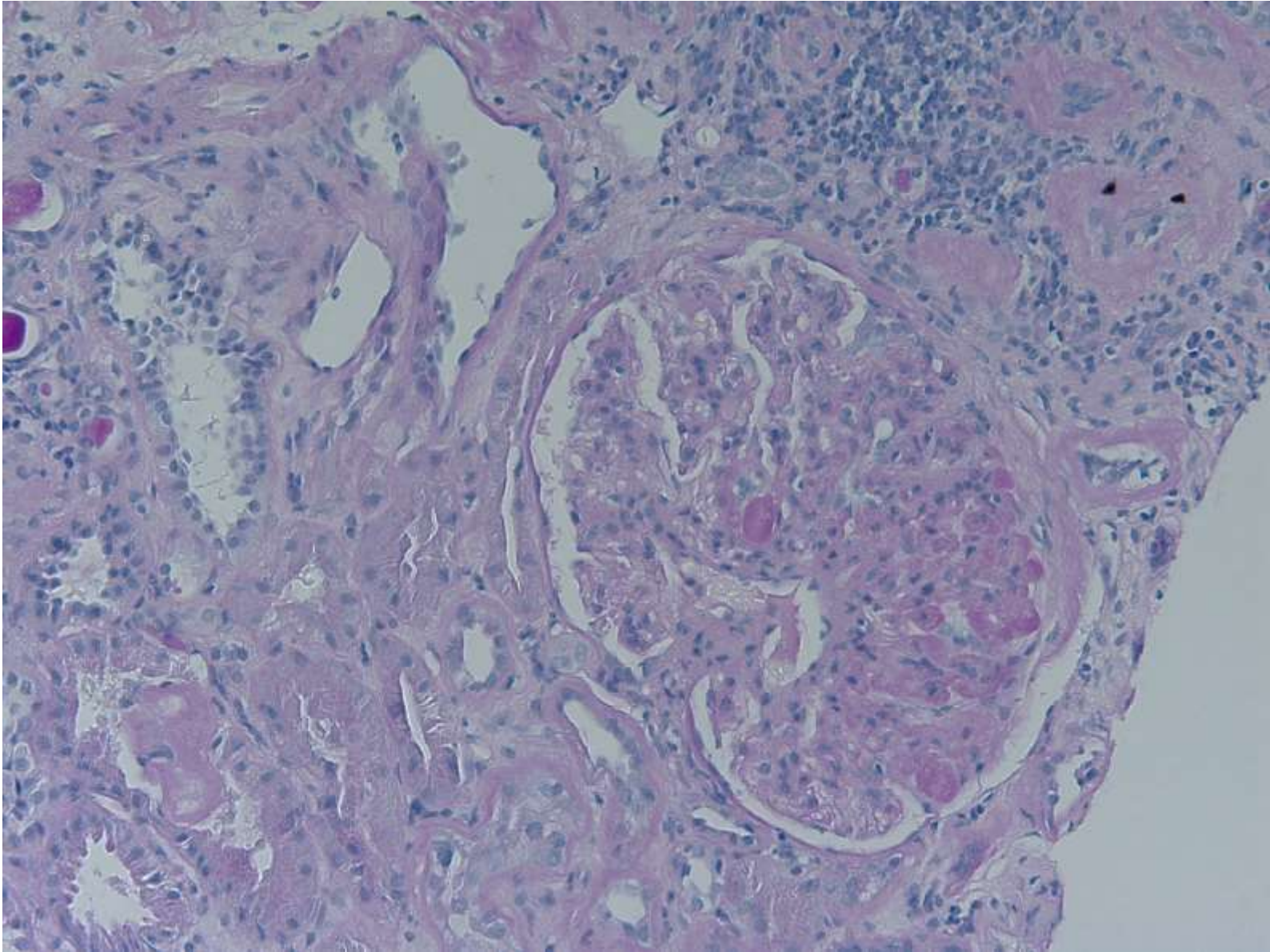


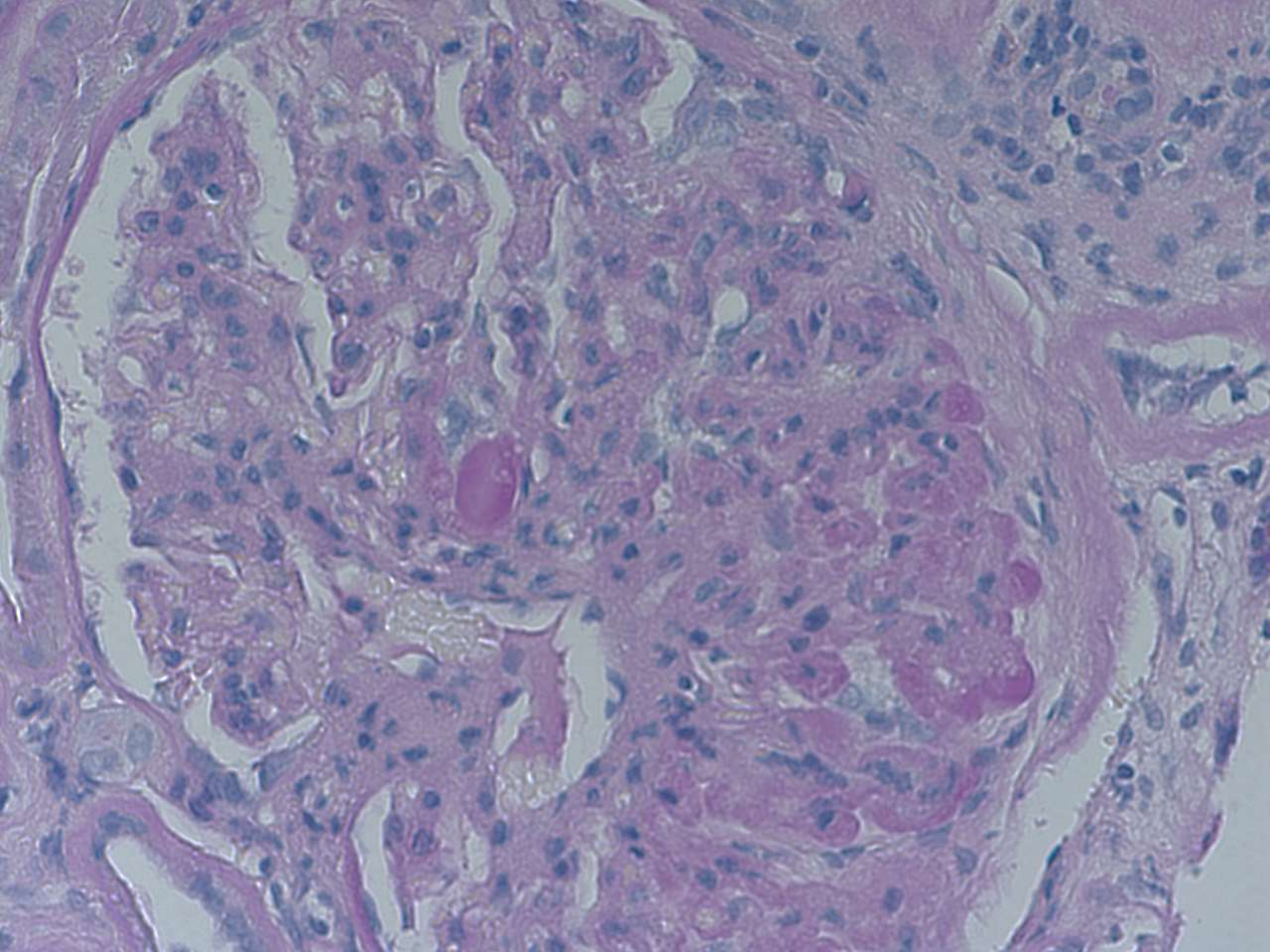
- At least 1 glomerulus with perihilar hyalinosis, with or without hyalinosis
- >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis

# Secondary FSGS mediated by adaptive structural/functional responses

- Obesity
- Solitary kidney
- Hypertensive Nephrosclerosis
- Sickle cell disease
- Reflux nephropathy
- Advanced renal disease

# Reduced functioning nephrons





# FSGS: Summary

- Primary FSGS diagnosed in the setting of the Nephrotic Syndrome;
- 5 morphological variants can be described by histological criteria based on light microscopical alterations;
- FSGS (NOS) is the generic most common lesions of FSGS, synonyms classic FSGS or FSGS of usual type; and this requires the other morphological categories have been excluded (perihilar, cellular, tip and collapsing variants);
- The other variants may evolve into FSGS (NOS).

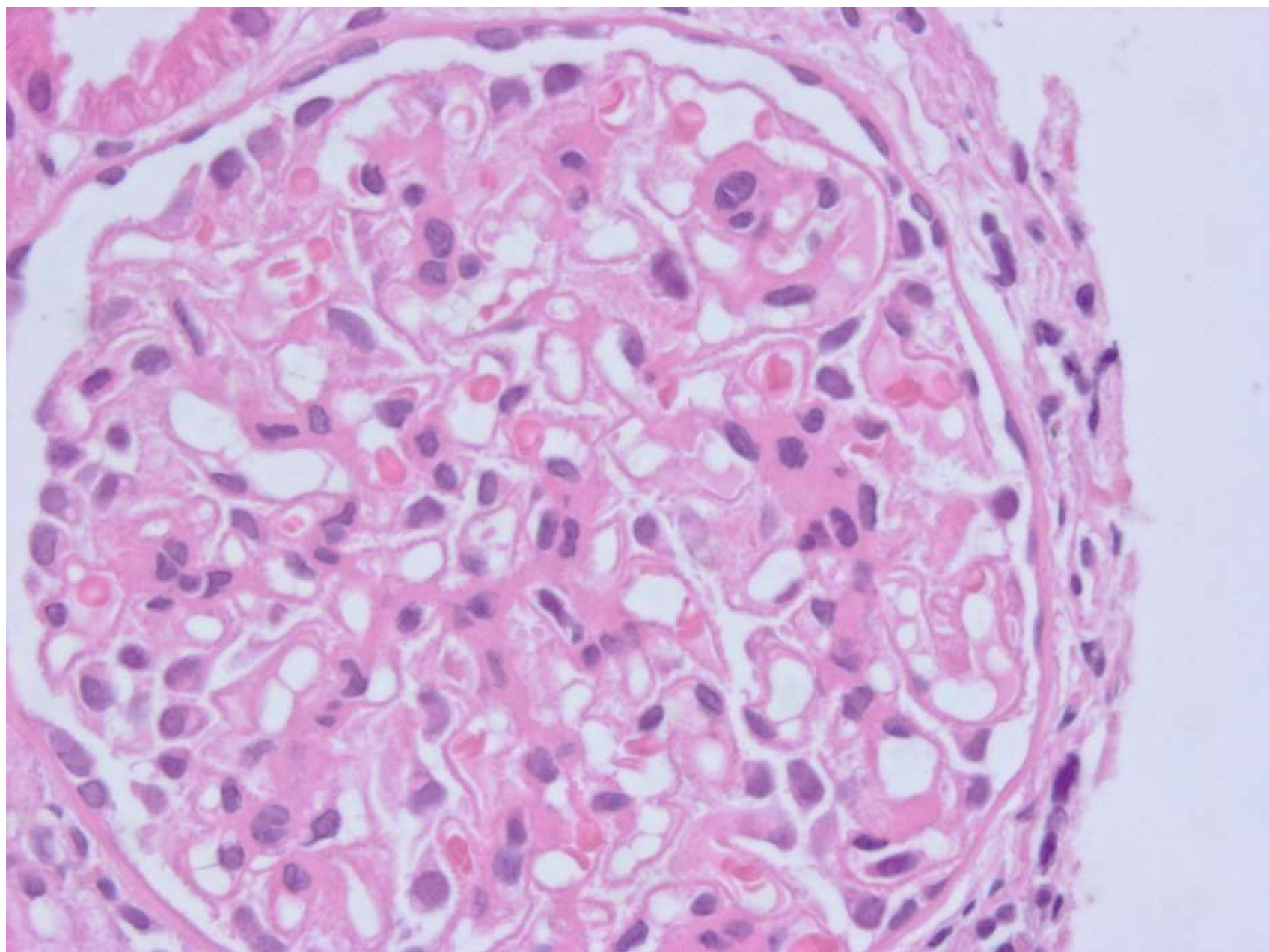


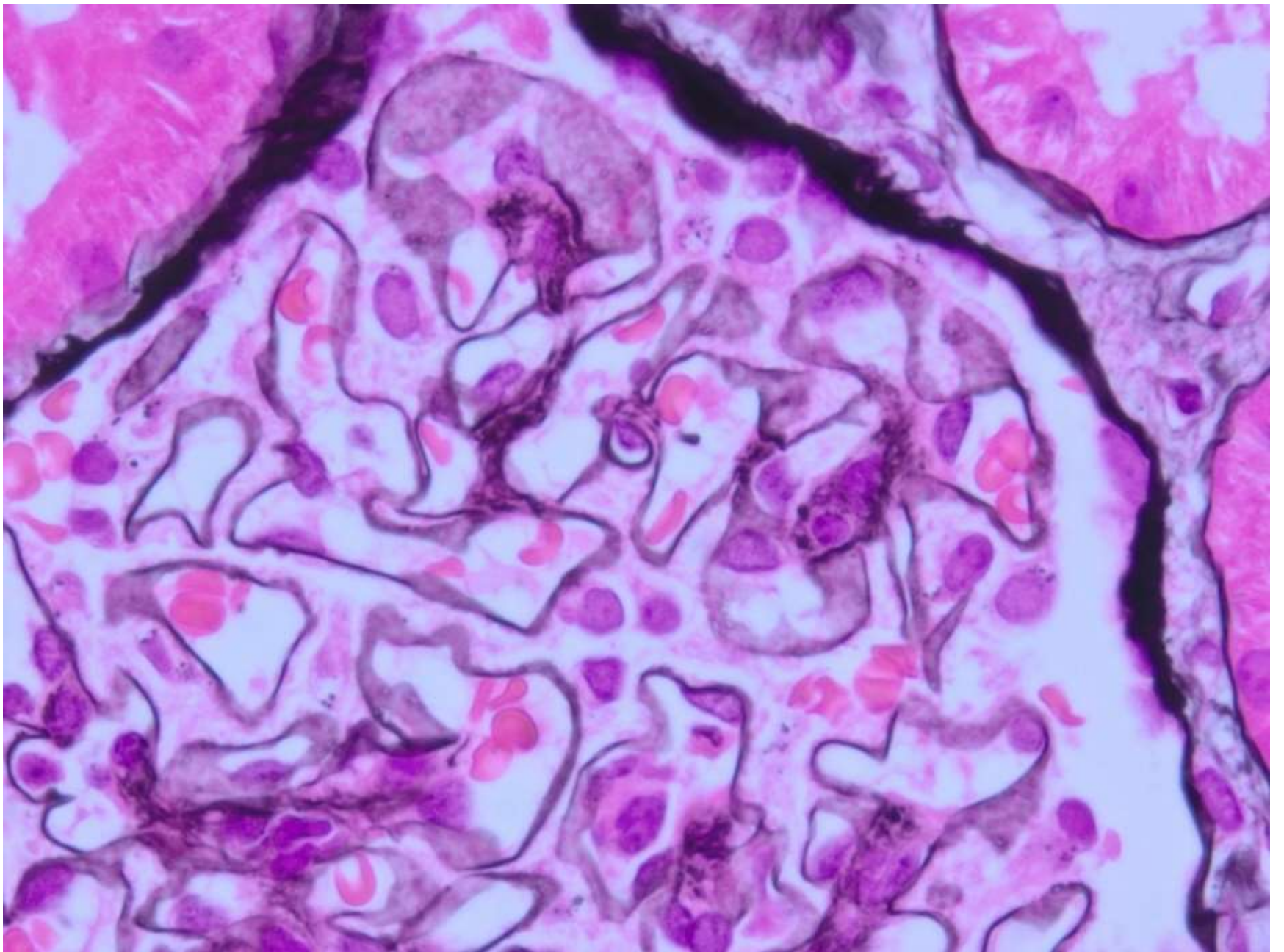
# Membranous Nephropathy

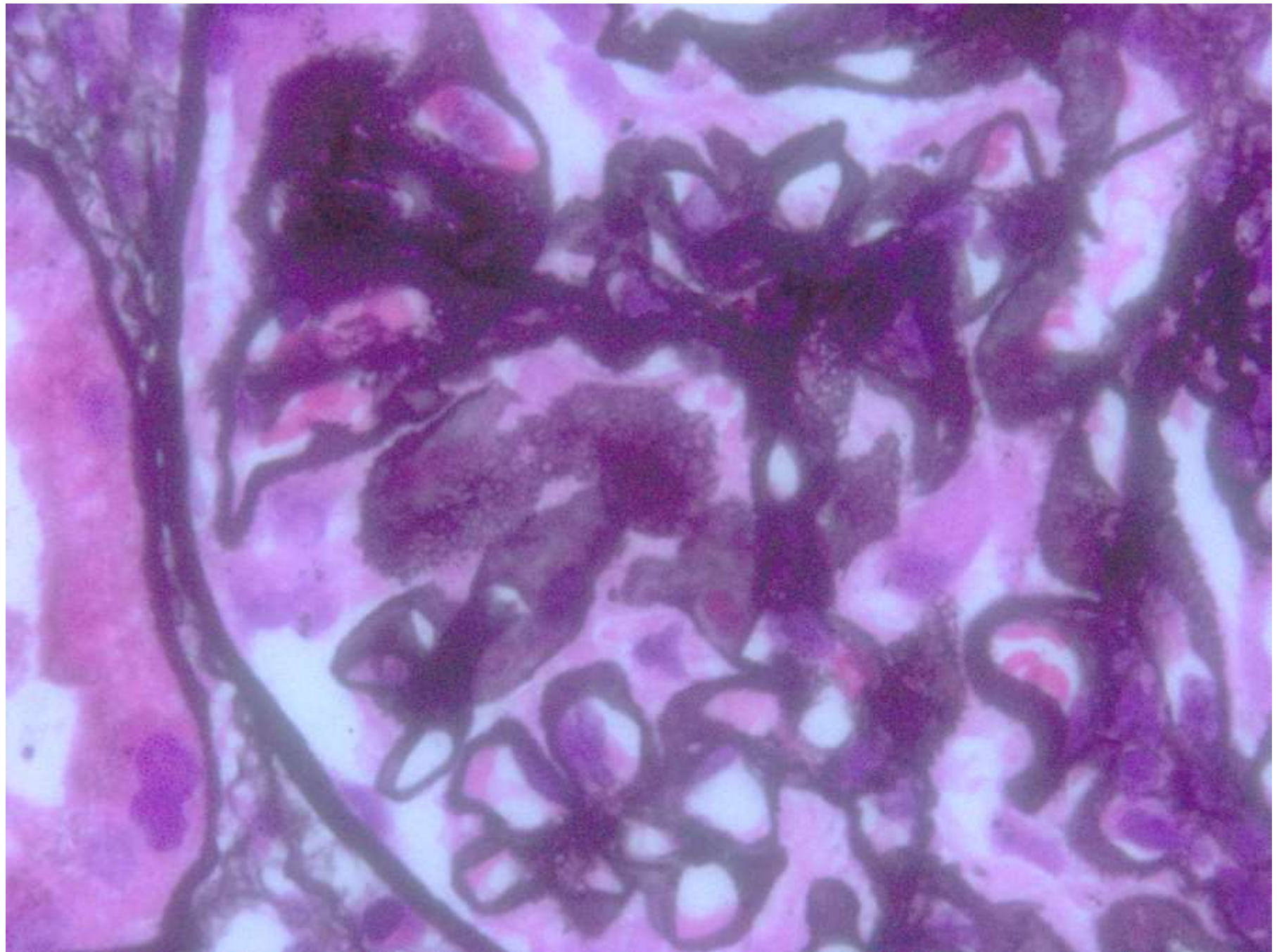
- Commonest cause of Nephrotic Syndrome in adults in the UK;
  - Although the incidence of FSGS is increasing rapidly in some groups of patients
- Proteinuria may be <nephrotic range at presentation [50% also have haematuria]

Results from subepithelial antigen-antibody complex deposition along the glomerular basement membrane.

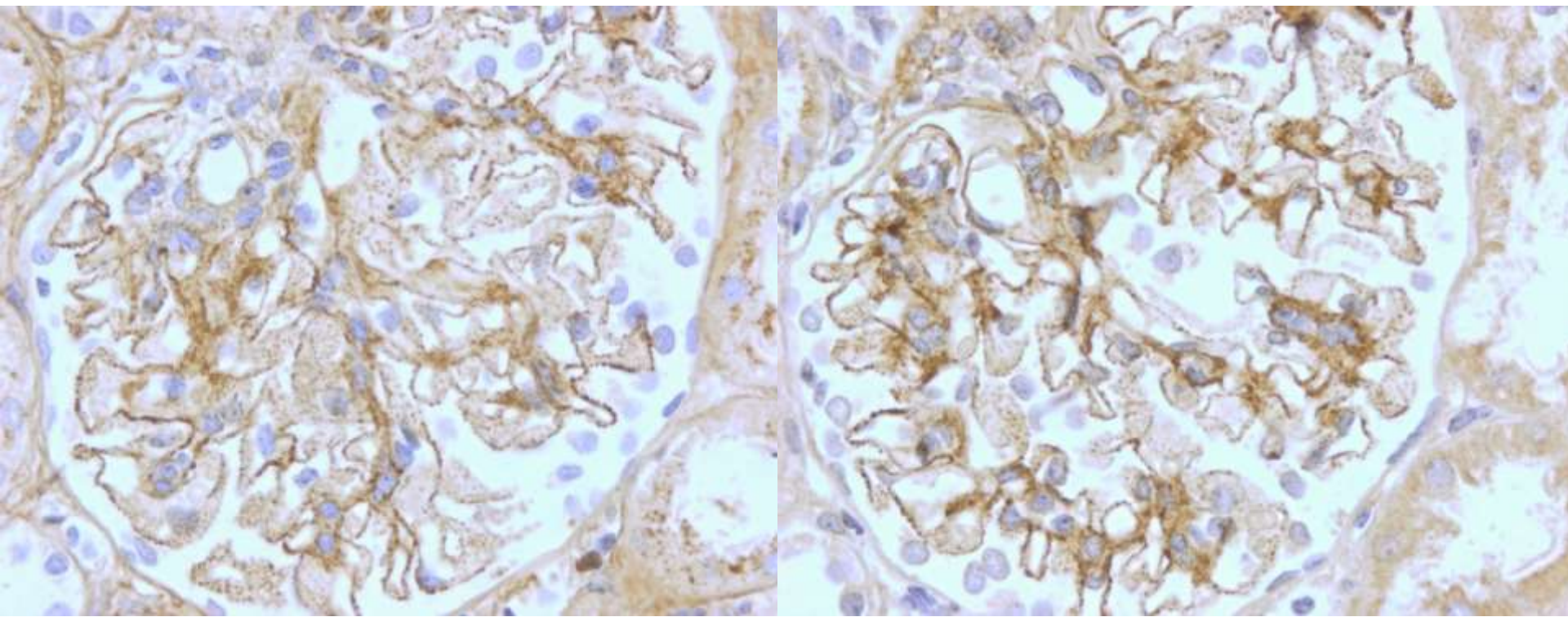
Primary and Secondary membranous nephropathy.

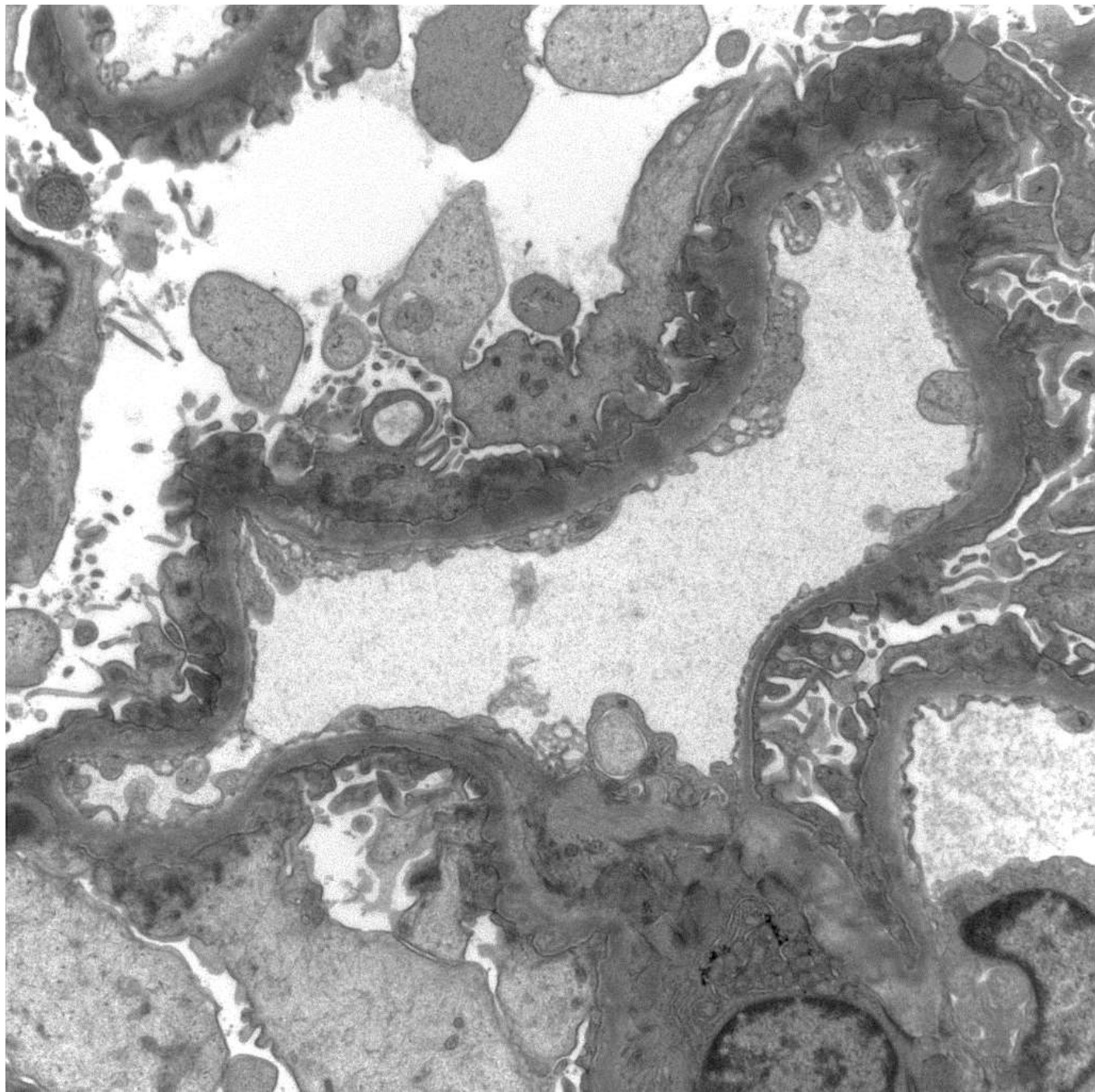


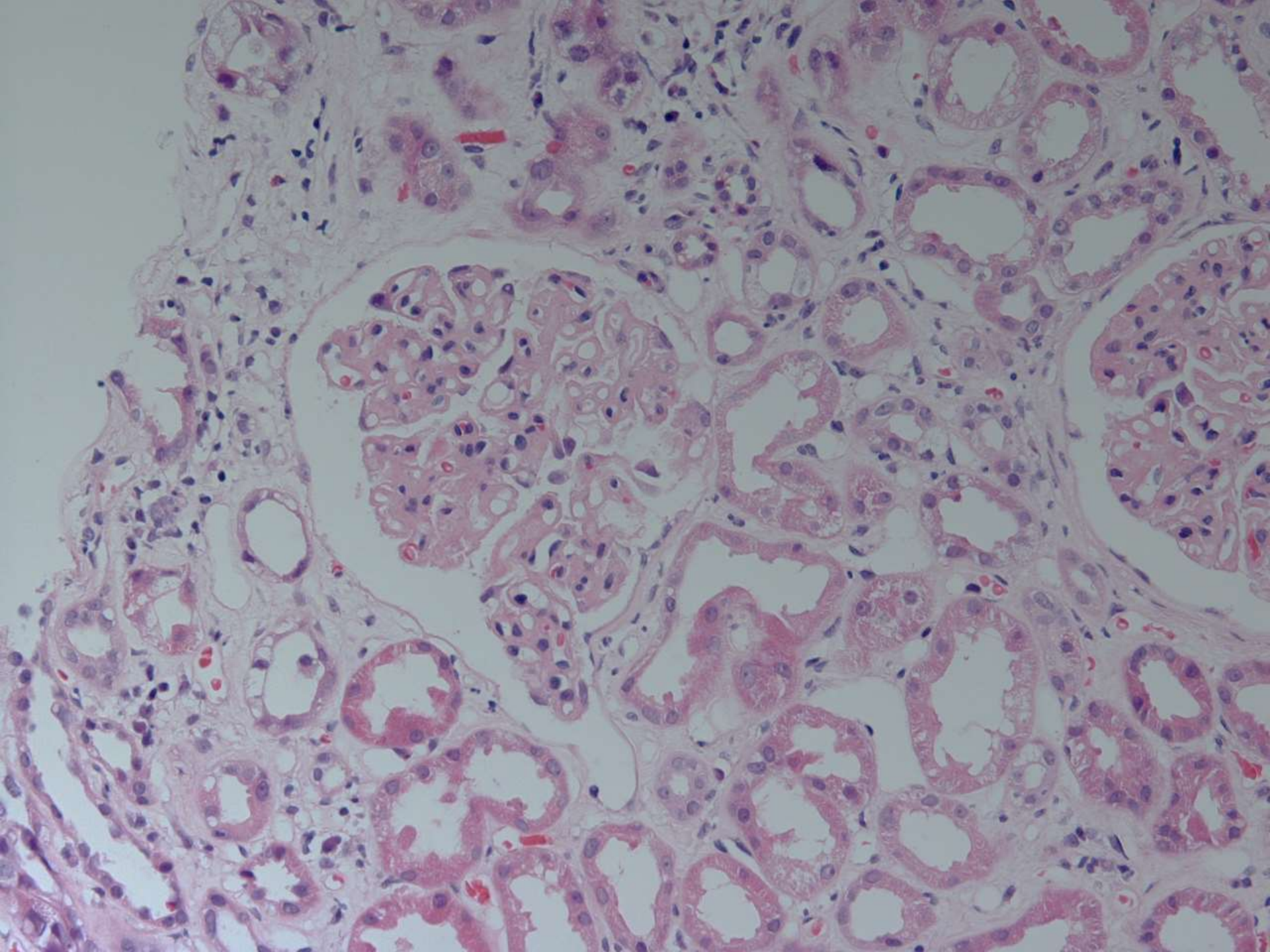


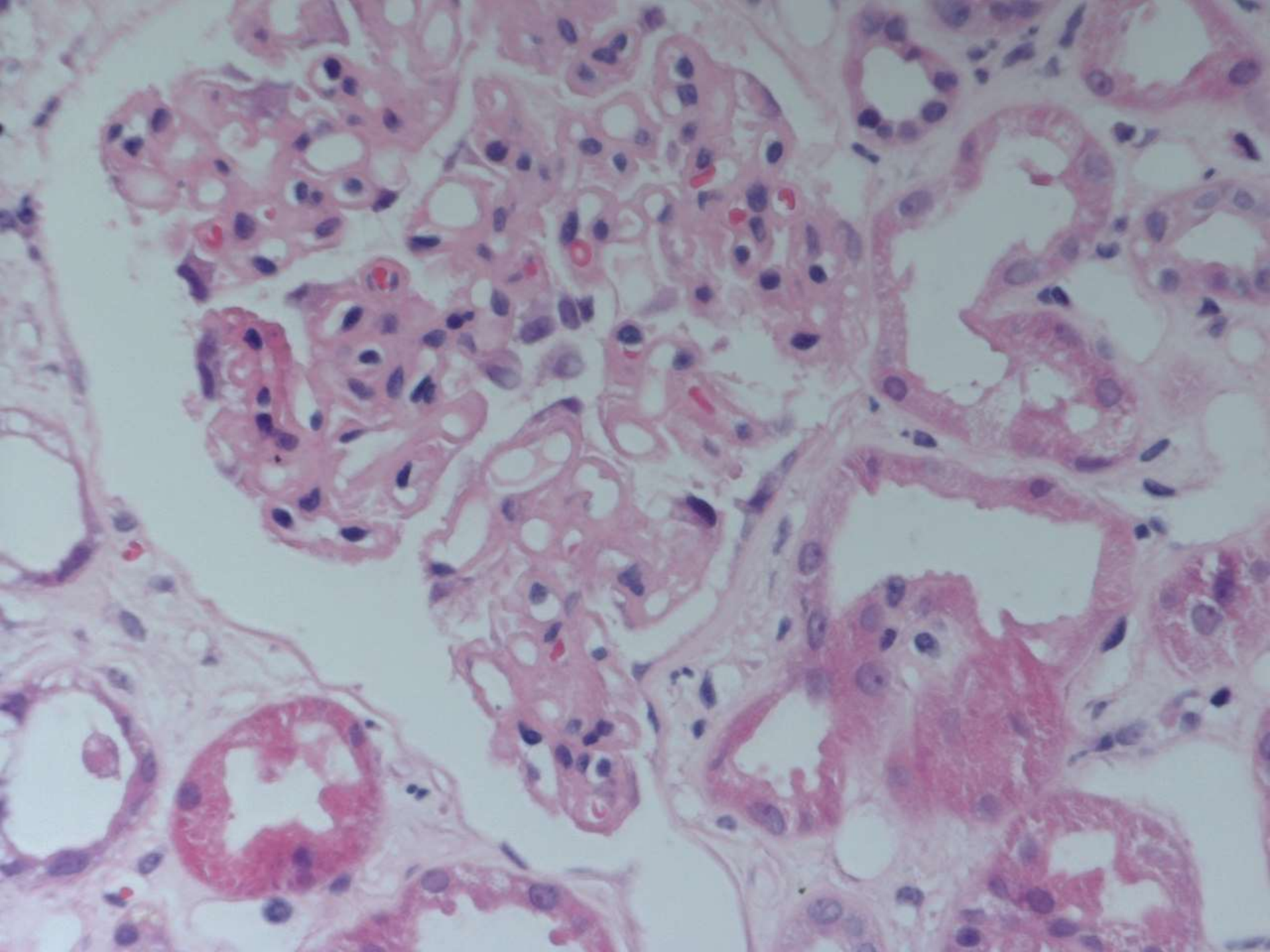


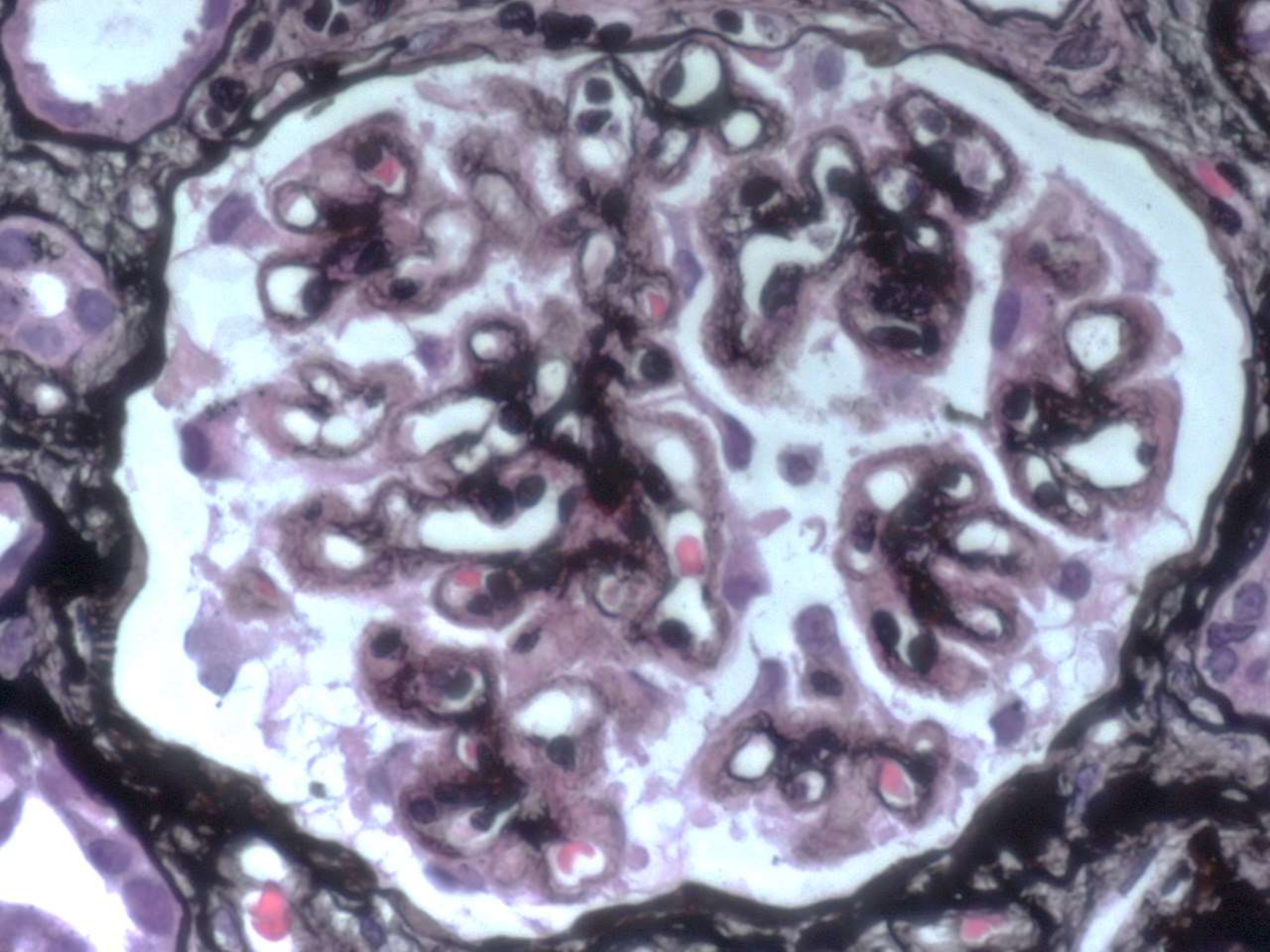
IgG : C3

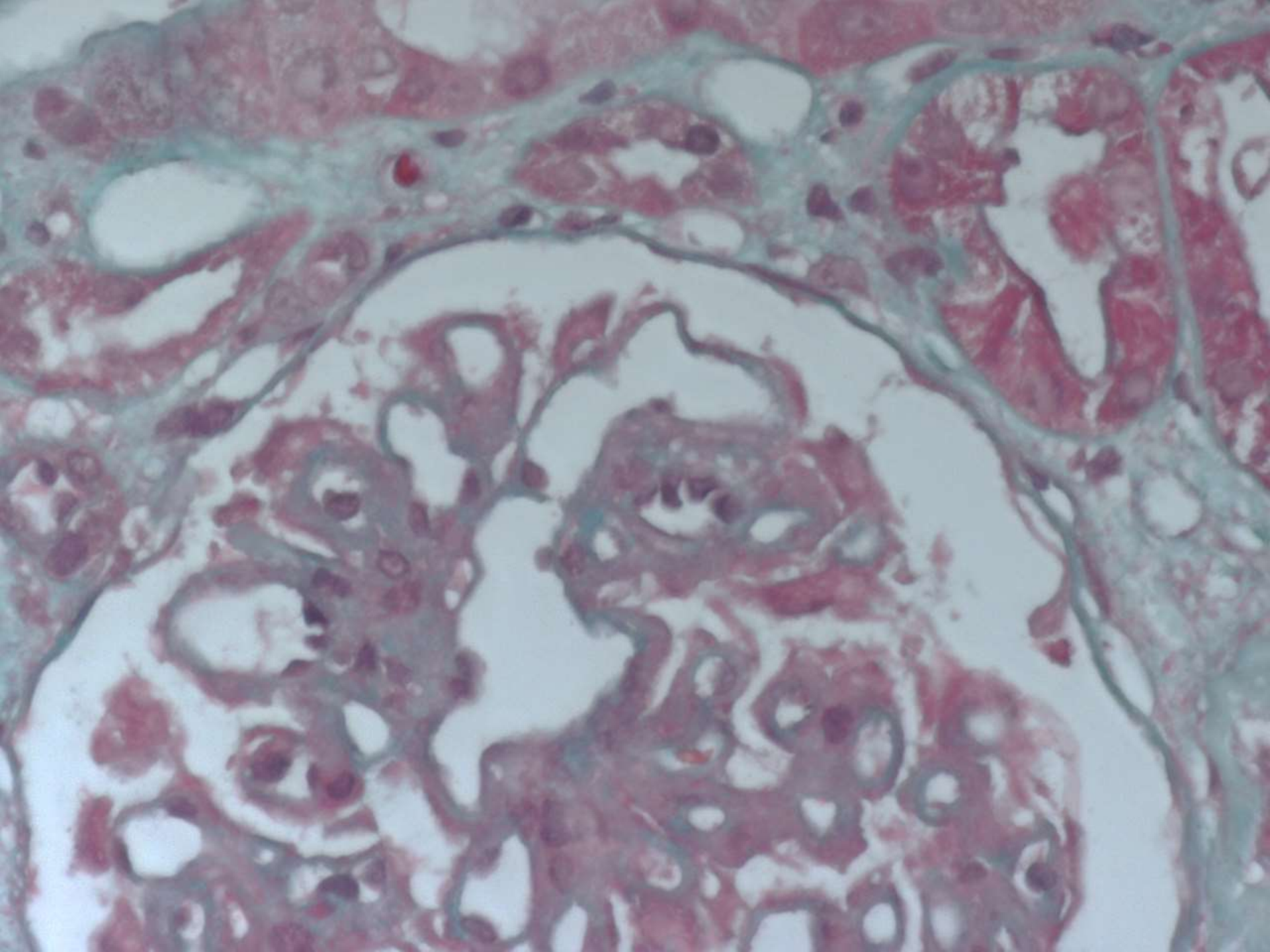




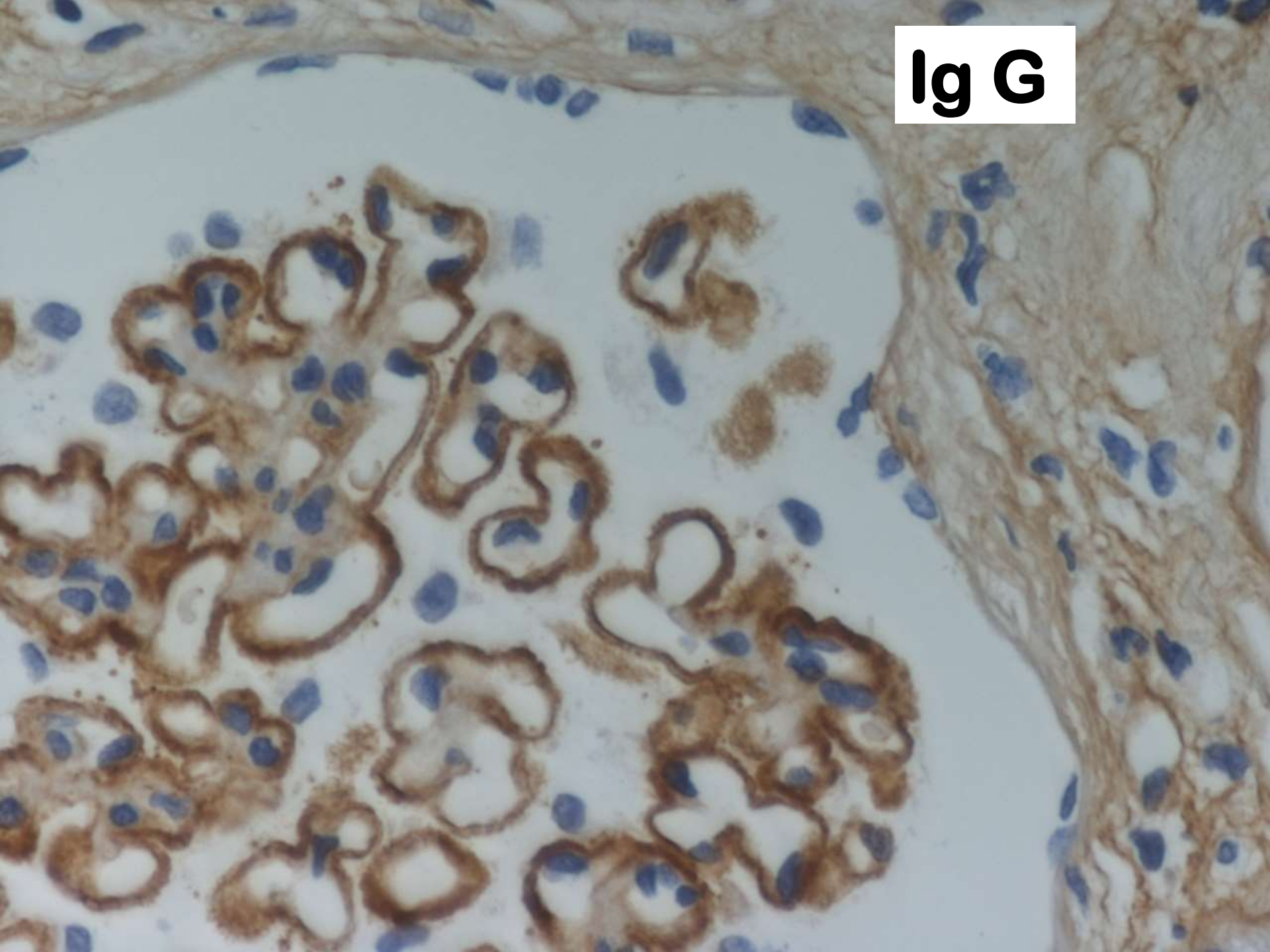




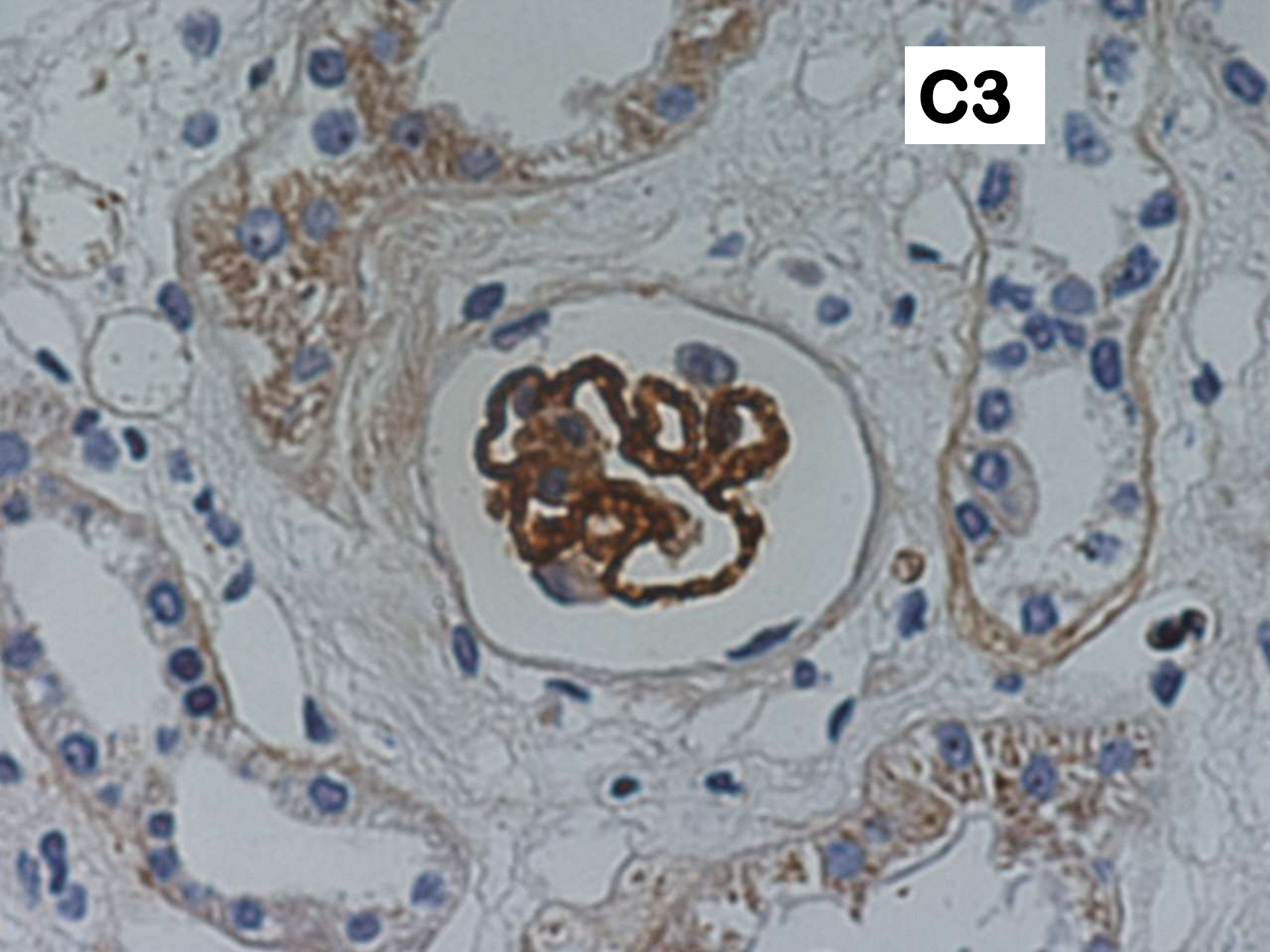


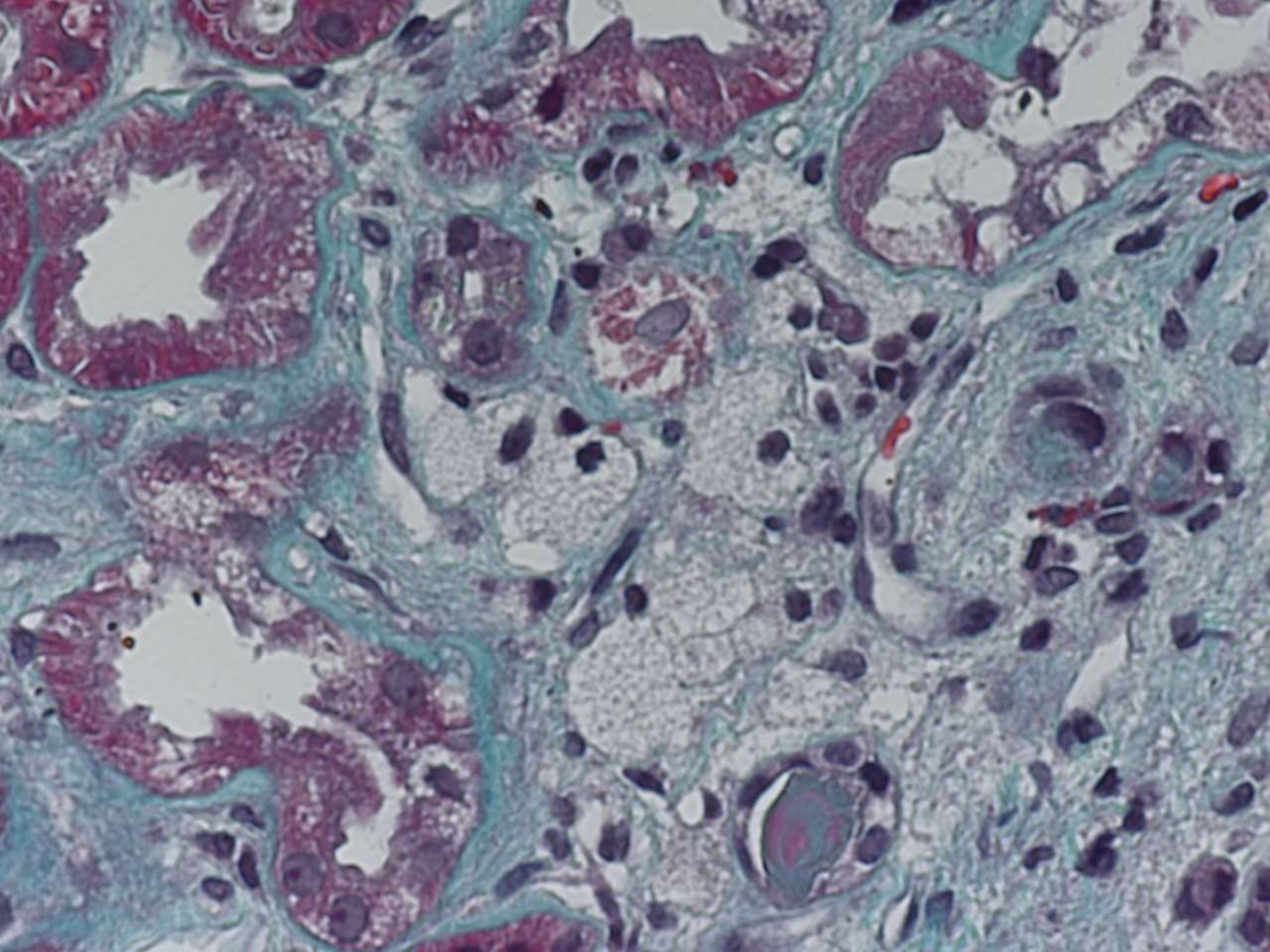


**Ig G**



**C3**





- Glomerular capillary wall abnormalities due to deposition of immune complex deposits along and within the GBM – thickened walls
- 60-80% in adults Primary MN, 65 - 70% patients have raised serological levels of Anti-PLA2R
- Thrombospondin type I domain-containing 7A (THSD7A) in 10% of (PLA2R)-negative MN

# Primary Membranous Nephropathy

- Target antigen in primary MN:
  - M-type phospholipase A2 receptor (PLA2R);
  - Thrombospondin type-1 domain-containing 7A (THSD7A for short);
  - Neural epidermal growth factor like-1 protein (NELL-1);
    - Exostosin 1 / exostosin 2 (EXT1/EXT2) putative antigens in secondary autoimmune cases.
      - Protocadherin 7 (associated with Sjogren's/lupus, sarcoid, ca).
      - High Temperature Recombinant protein A1.

www.kidney-international.org

clinical investigation

## Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients

 Check for updates

see commentary on page 1081  
OPEN

Sanjeev Sethi<sup>1</sup>, Hanna Debiec<sup>2,11</sup>, Benjamin Madden<sup>3,11</sup>, Marina Vivarelli<sup>4</sup>, M. Cristine Charlesworth<sup>3</sup>, Aishwarya Ravindran<sup>1</sup>, LouAnn Gross<sup>1</sup>, Tim Ullinski<sup>5</sup>, David Buob<sup>2,6</sup>, Cheryl L. Tran<sup>7</sup>, Francesco Emma<sup>4</sup>, Francesca Diomedei-Camassei<sup>8</sup>, Fernando C. Fervenza<sup>9,12</sup> and Pierre Ronco<sup>2,10,12</sup>

<sup>1</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; <sup>2</sup>Sorbonne Université, Université Pierre et Marie Curie Paris 06, and Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche S 1155, Paris, France; <sup>3</sup>Medical Genome Facility, Proteomics Core, Mayo Clinic, Rochester, Minnesota, USA; <sup>4</sup>Department of Pediatric Subspecialties, Division of Nephrology and Dialysis, Bambino Gesù Pediatric Hospital and IRCCS, Rome, Italy; <sup>5</sup>Pediatric Nephrology Unit, Armand Trousseau Hospital, Paris, France; <sup>6</sup>Department of Pathology, Tenon Hospital, Paris, France, France; <sup>7</sup>Division of Pediatric Nephrology, Mayo Clinic, Rochester, Minnesota, USA; <sup>8</sup>Pathology Unit, Department of Laboratories, Bambino Gesù Pediatric Hospital and IRCCS, Rome, Italy; <sup>9</sup>Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; and <sup>10</sup>Department of Nephrology, Day Hospital, Tenon Hospital, AP-HP 6, Paris, France

# AntiPLA2R

Anti-phospholipase A2 receptor antibody in MN

- Circulating autoantibodies against M-type phospholipase A2 receptor (PLA2R)
- Autoantibodies usually IgG4 subclass
- The dominant autoantigen is expressed on the surface of native glomerular podocytes
- Demonstrated in ~ 70% of patients with idiopathic / Primary Membranous Nephropathy
- Predict long-term outcome and in some cases, predict response to treatment

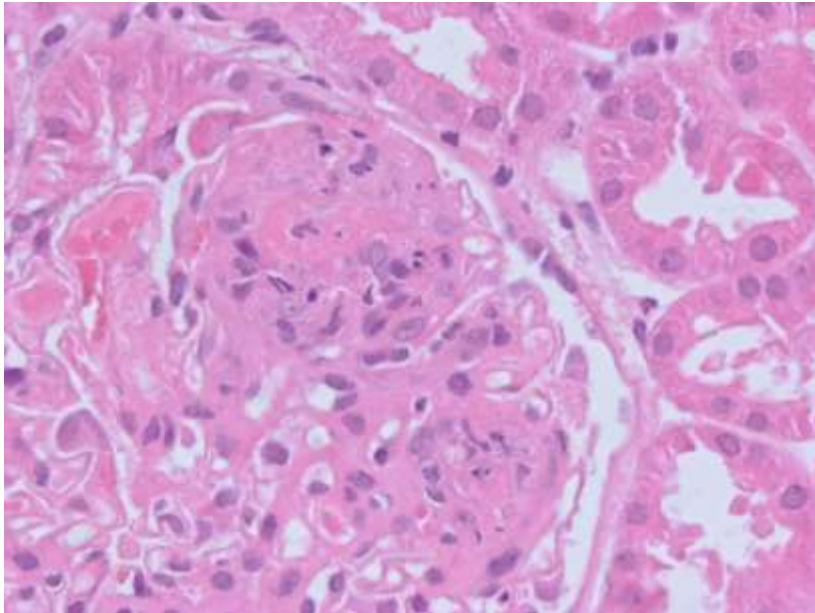
# THSD7A

- Described as a second antigenic target in primary MN.
- Initial series 10% of the PLA2R-negative patients had circulating THSD7A autoantibodies instead.
- Initially thought to be mutually exclusive;
- Occasional cases dual PLA2R and THSD7A autoantibodies.

# Treatment and Prognosis

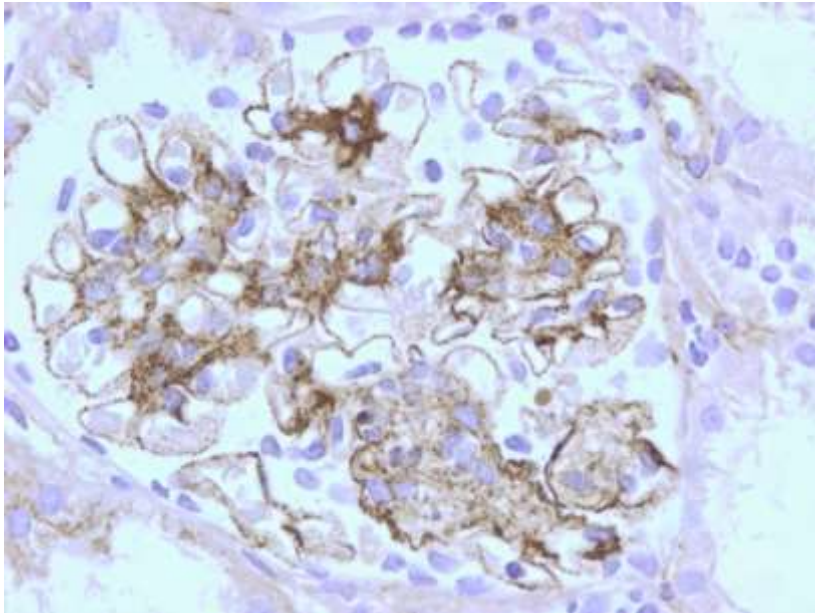
- If untreated variable course of thirds:
  - Spontaneous remission
  - Persistent proteinuria without renal failure
  - ESRD progression over 5-10 years
- Fibrosis offers prognostic relevance;
  - Worse course if crescents present [seen in three settings]
    - Development of anti-GBM antibodies
    - Superimposed ANCA+
    - Neither of the above ie. no identifiable superimposed disease
- Worse prognosis if raised serum creatinine; older; HT; Nephrotic range proteinuria
- If worse prognosis group, may treat with steroids +/- alternating alkylating/cytotoxics
- Rituximab

- How do we differentiate Primary Membranous Nephropathy from Secondary Membranous?
- Serology?
- Histopathological features?



- Morphological findings that suggest a secondary Membranous
  - May see mesangial proliferation and increased matrix;
  - May see superimposed lesions such as endocapillary hypercellularity and crescents.

# C1q



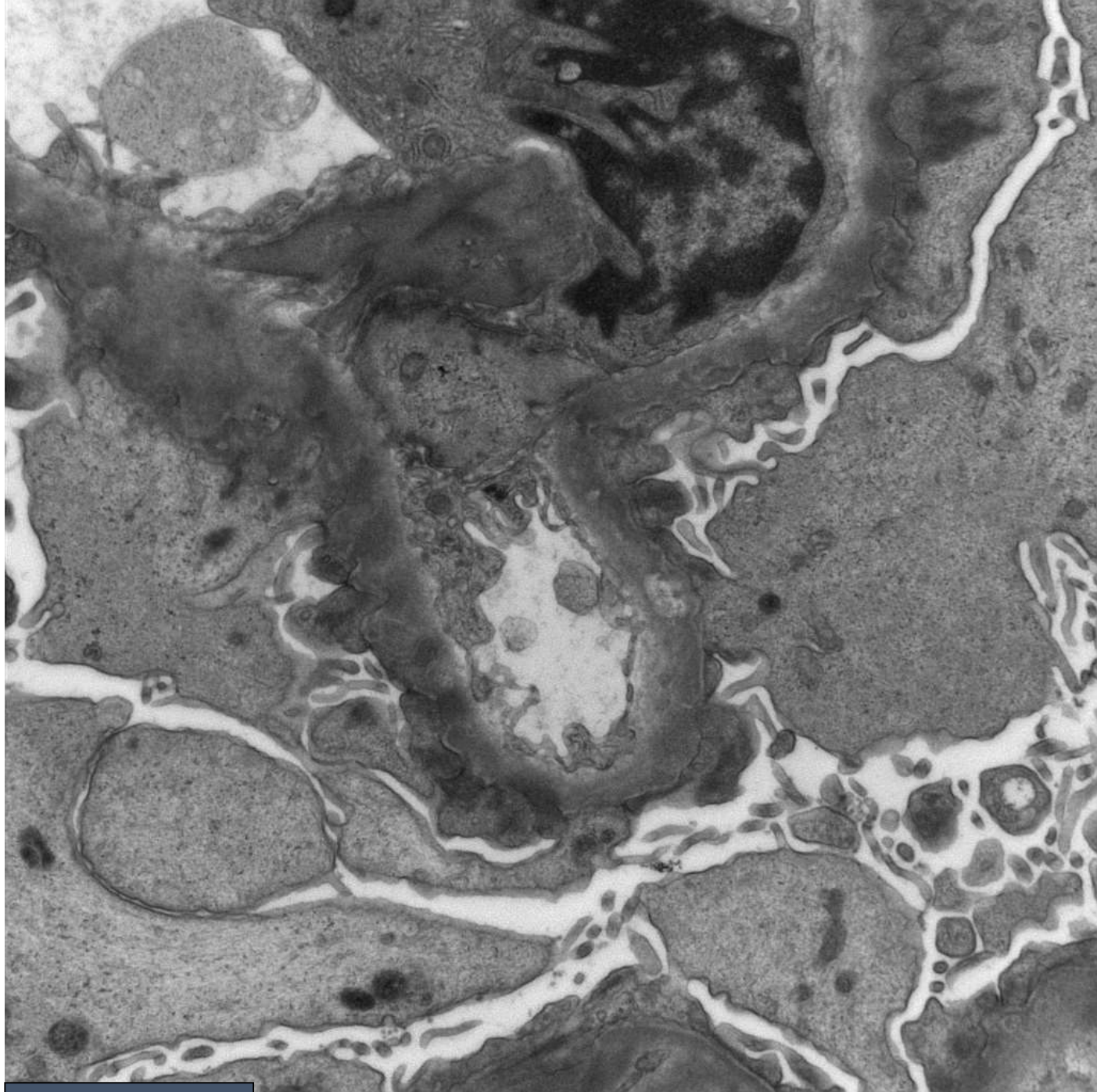
- Immunohistochemistry findings that suggest a secondary Membranous
- Range of what is positive
  - 'Full house'
- Where the positive staining is
  - Not just along the capillary walls, also in the mesangial matrix

# Secondary MN

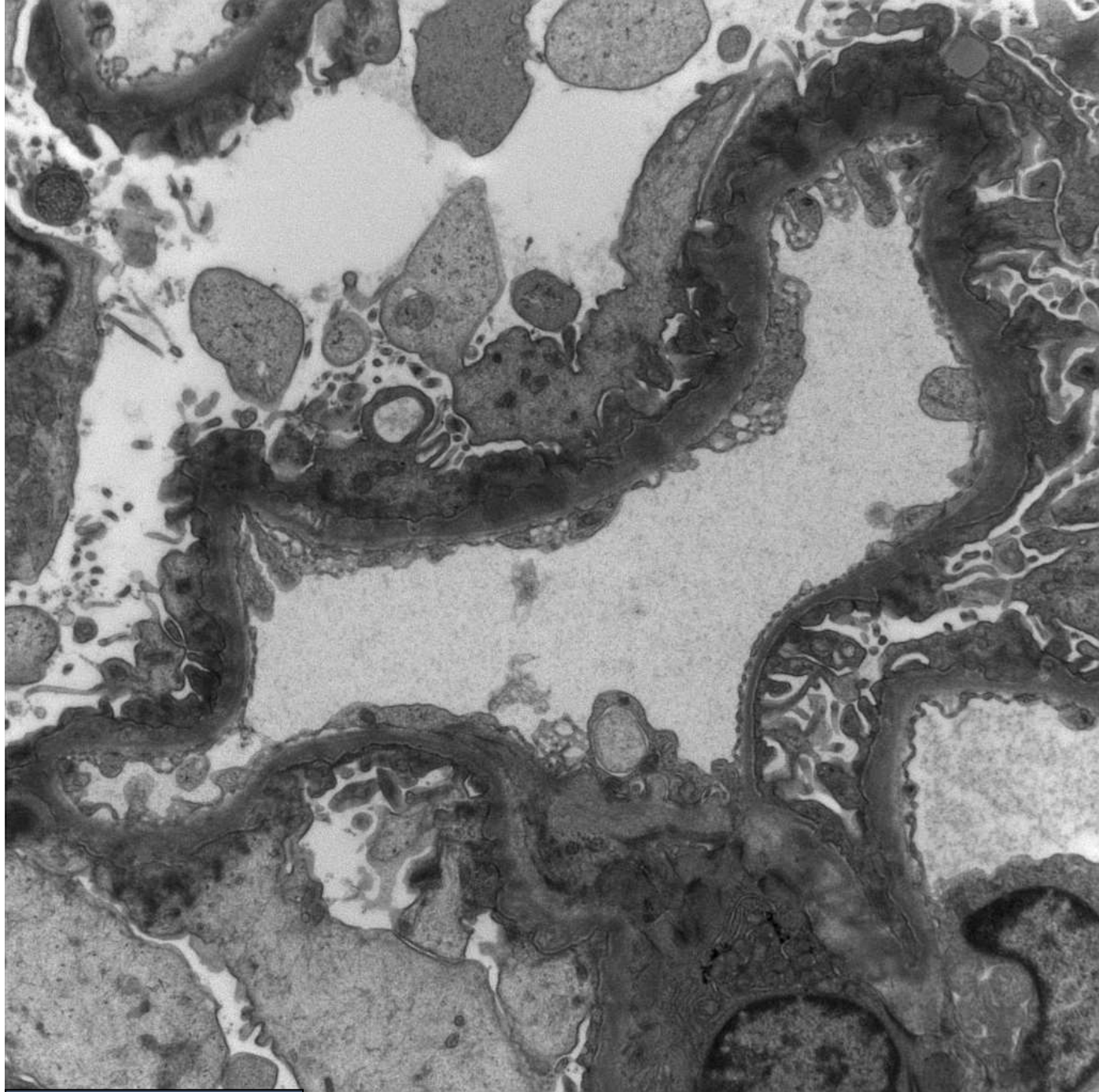
- Expect if <16yrs or >60yrs
- Search for unusual features that may indicate a secondary form:-
- Auto-immune, including SLE:
  - Mesangial, subendothelial, vessel wall deposits; full house immunostaining; endothelial tubuloreticular inclusions, all of which can also be seen with HBV\*
- Infections, HBV\*>HCV, syphilis
- 6-10% of adults with MN have underlying malignancy [breast; lung; GU;GI]
- Drugs: gold, penicillamine; mercury; COX-2 inhibitor
  - More associations:
    - Sickle cell disease, sarcoidosis

# Ehrenreich & Churg [1968]

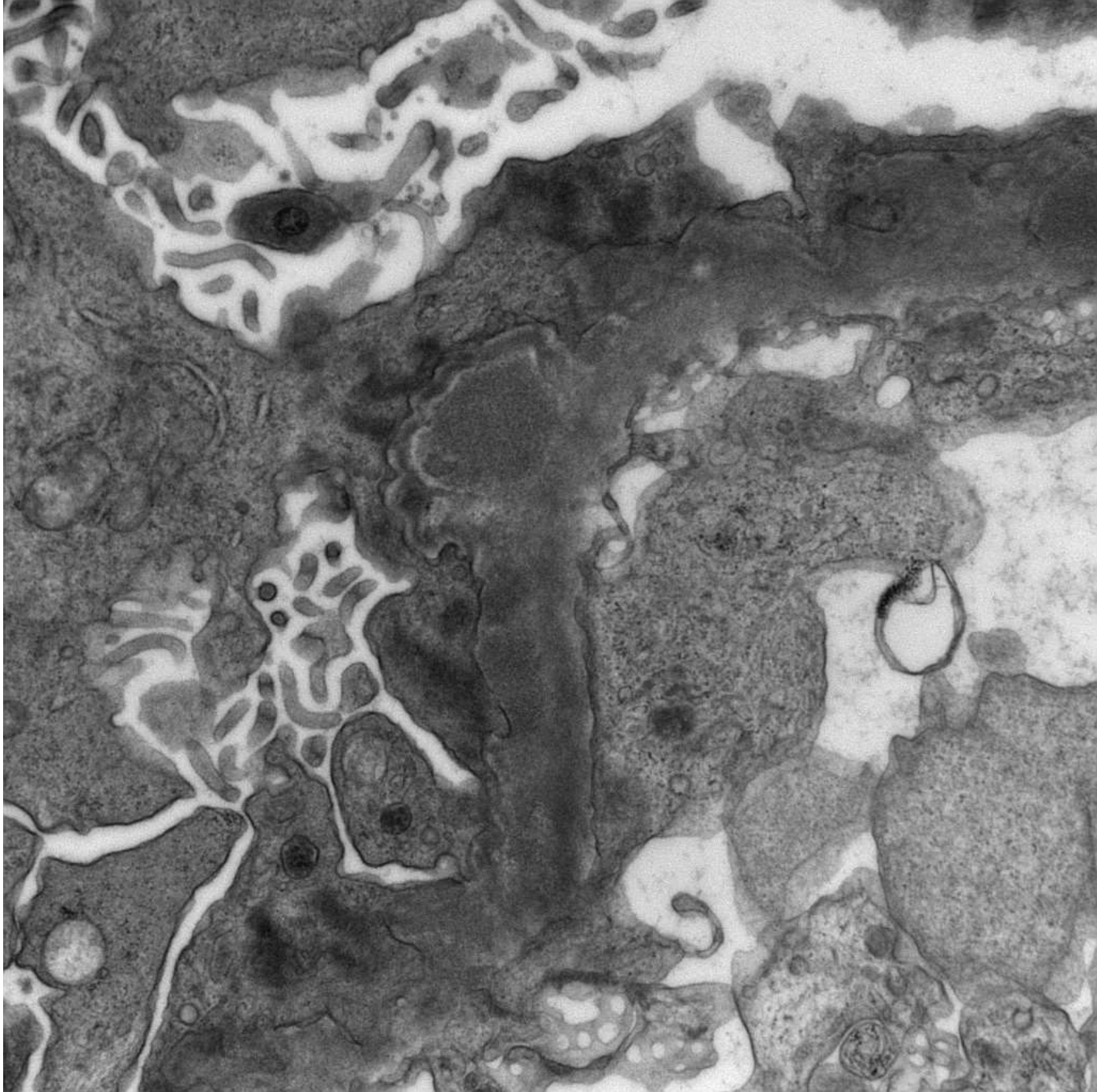
- Stage I –
  - GBM normal/slightly thickened, vacuoles corresponding to small focal subepithelial electron dense deposits. Focal foot process effacement
- Stage II –
  - GBM moderately thickened; spikes and vacuolation corresponding to diffuse subepithelial deposits. Diffuse foot process effacement
- Stage III –
  - GBM markedly thickened; chain-like, with residual spikes and vacuoles – intramembranous deposits, resorbed with lacunae and neomembrane. Diffuse foot process effacement
- Stage IV –
  - Very thick walled, few spikes, vacuoles, sclerotic glomeruli – few deposits, lacunae. Some restoration of foot processes

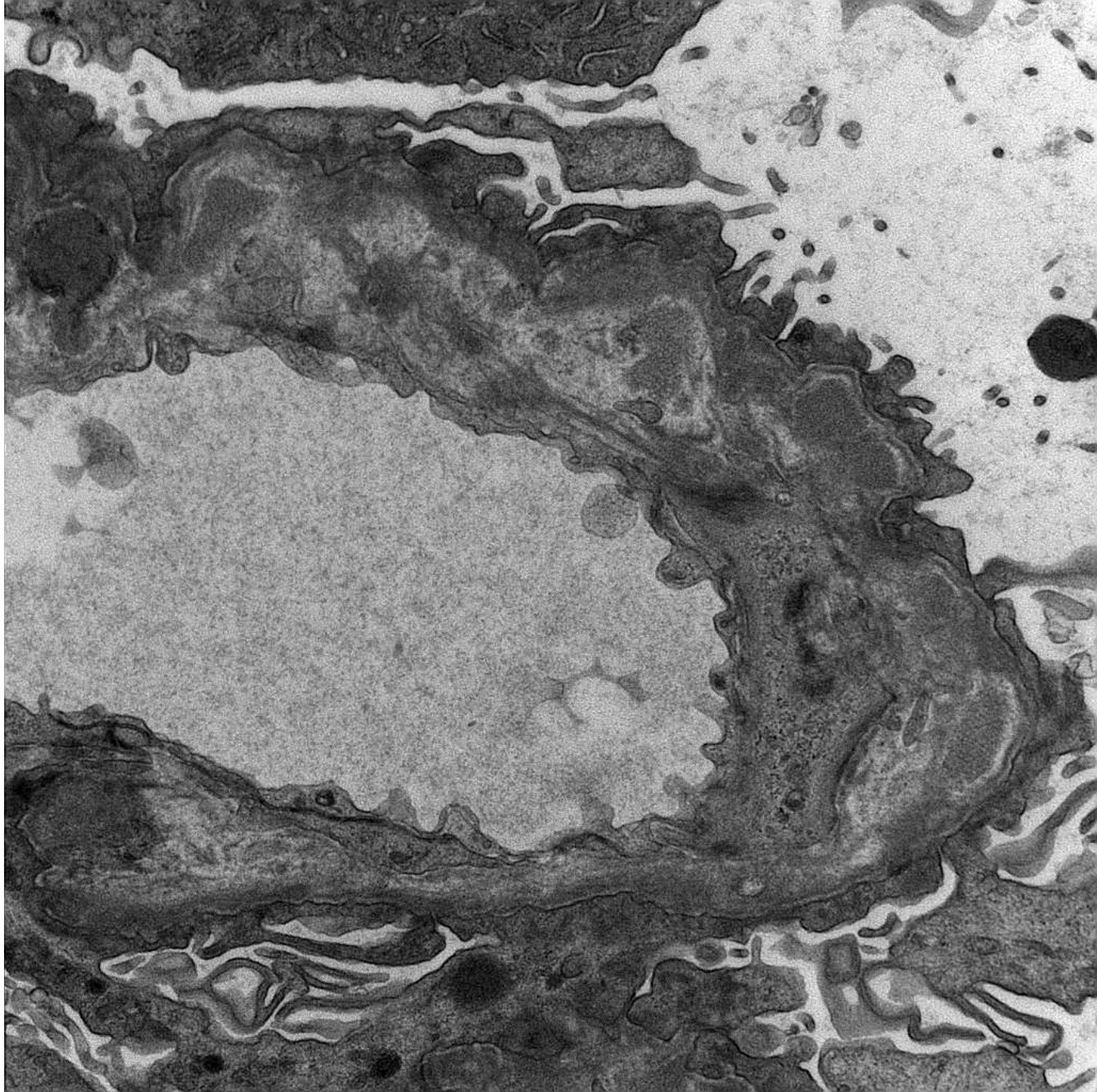


2 microns



2 microns





2 microns

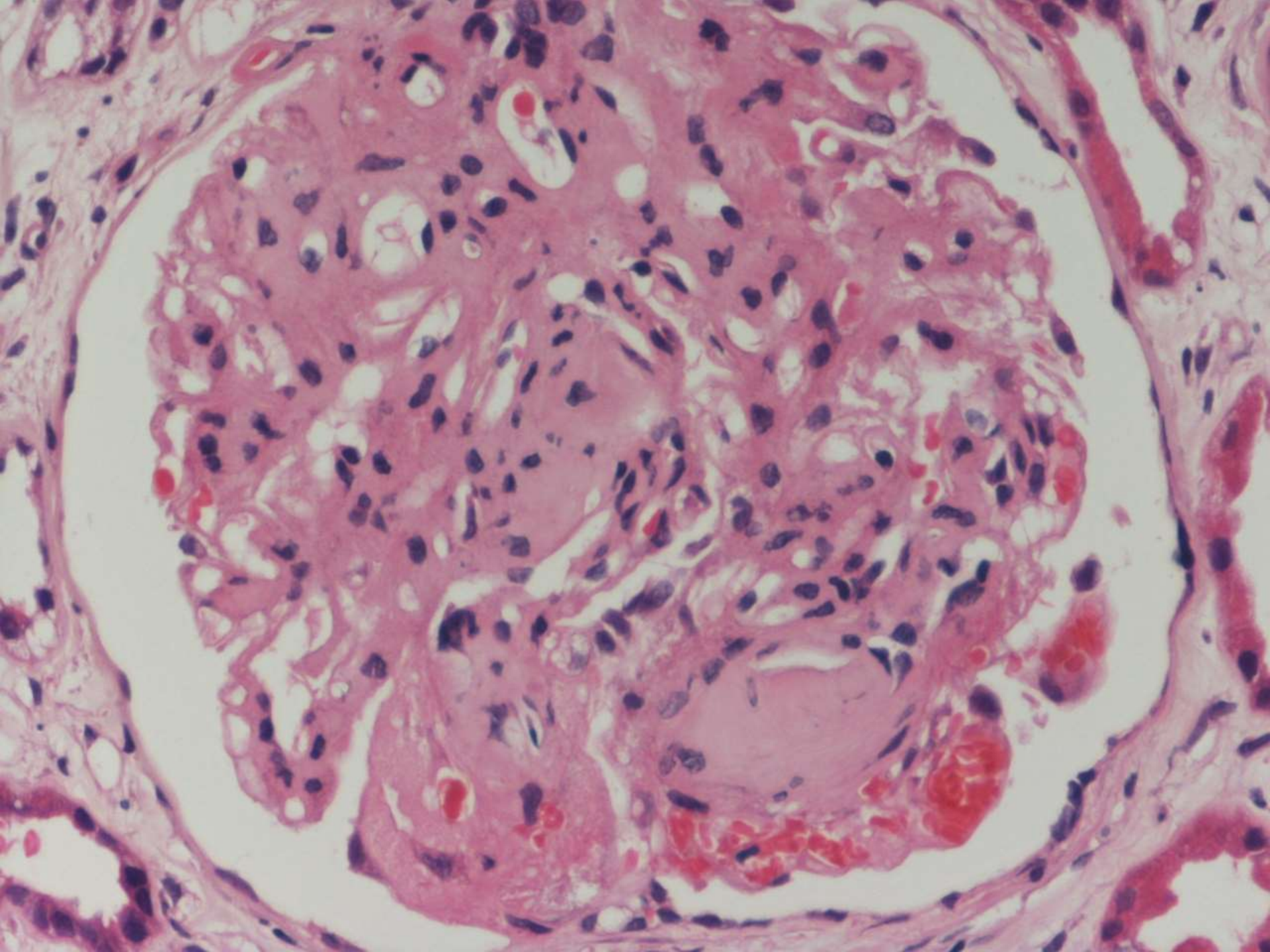
# Interesting encounters

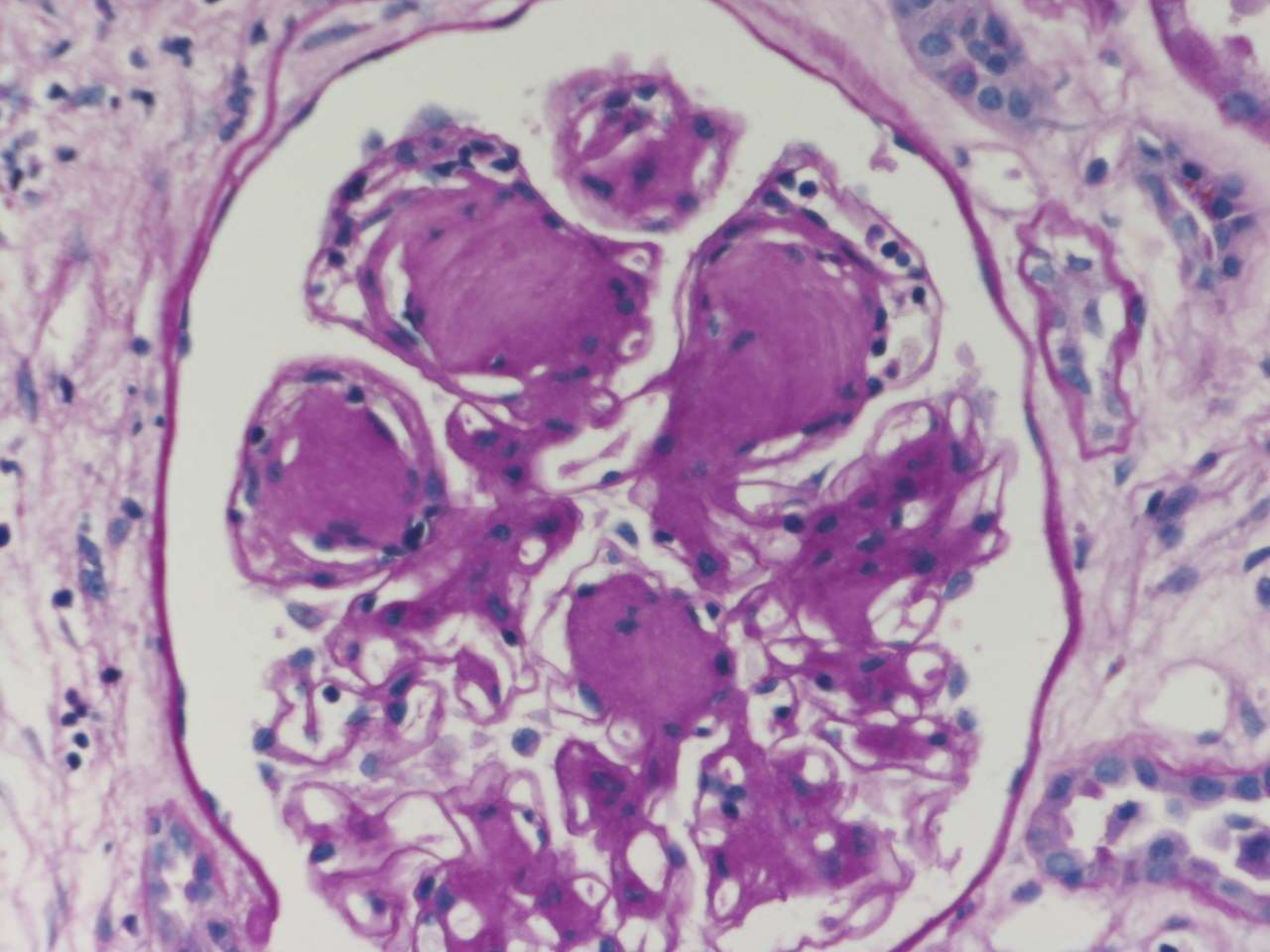
- MN with crescents
- Segmental MN
- MN with FSGS
- MN with IgA:
  - haematuria and proteinuria presentation;
  - often in setting of HBV or in renal transplant with de novo MN and recurrent IgA
- MN in renal graft:
  - 75% of this is de novo, at about 2 yrs.
  - When recurrent it recurs earlier
- MN in diabetes
- MN with renal vein thrombosis : [alb]<2g/dL
- MN in pregnancy:
  - Usually excellent fetal and maternal outcome unless nephrotic range during first trimester

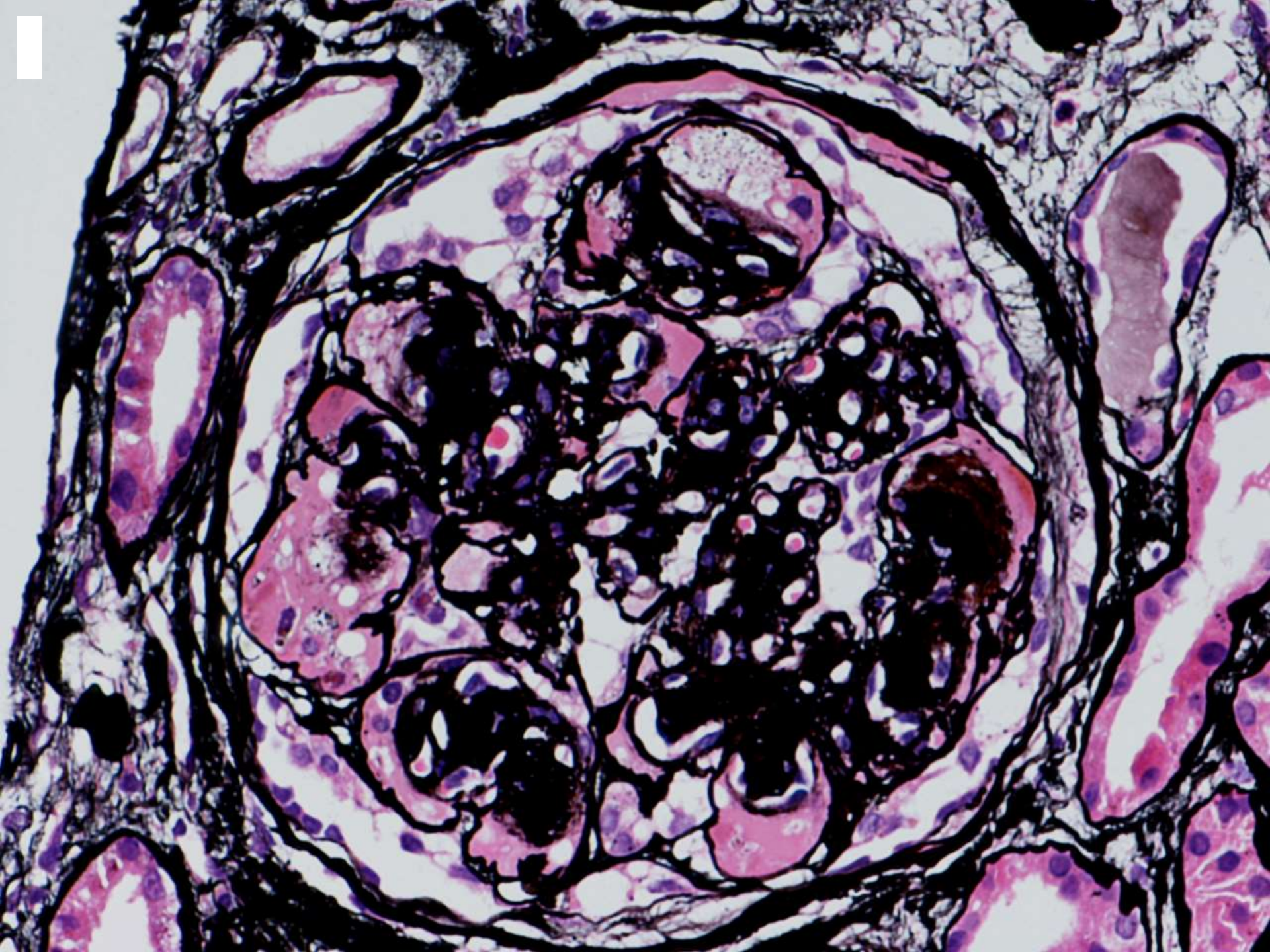


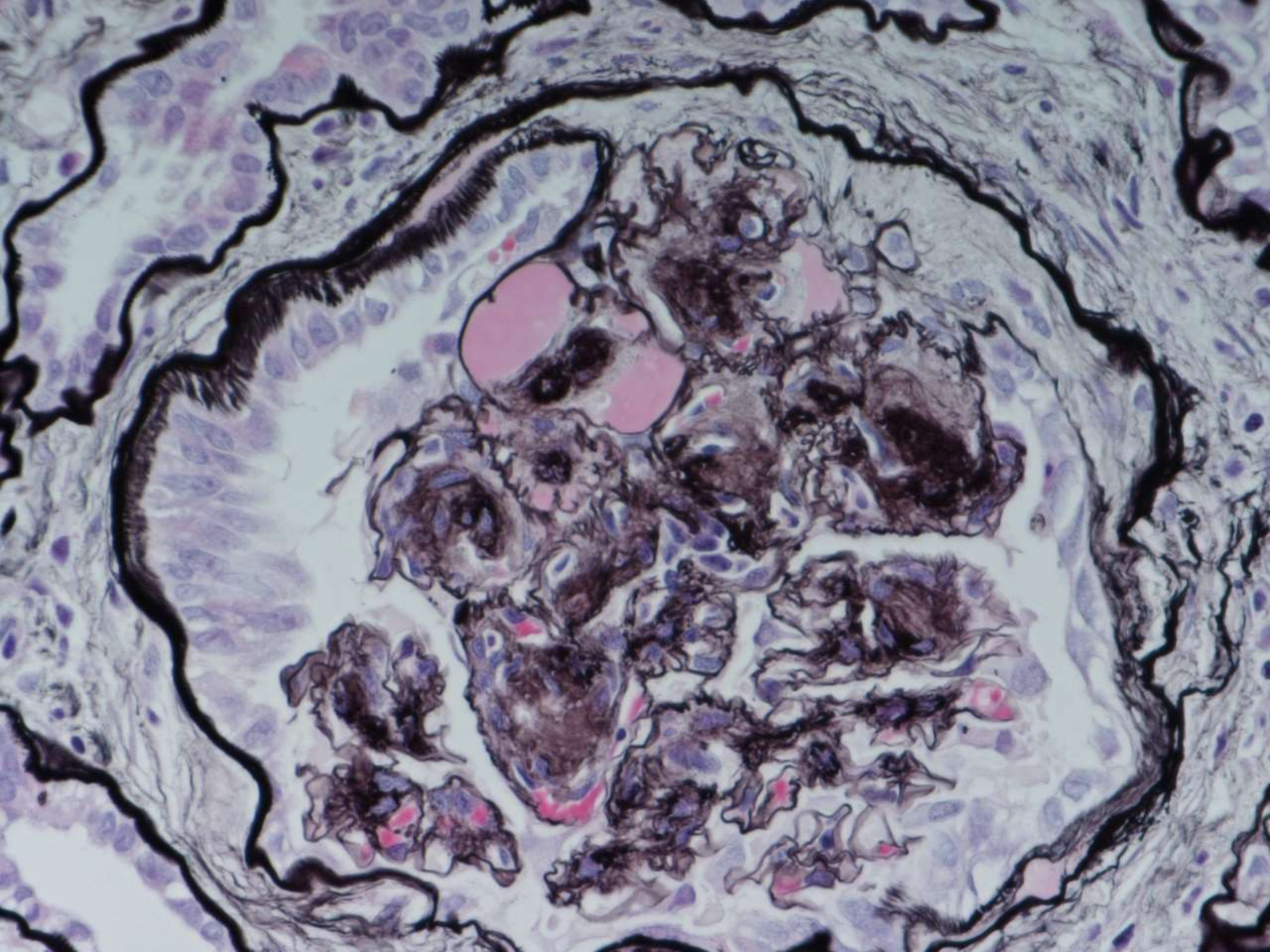
# Systemic diseases causing N/S

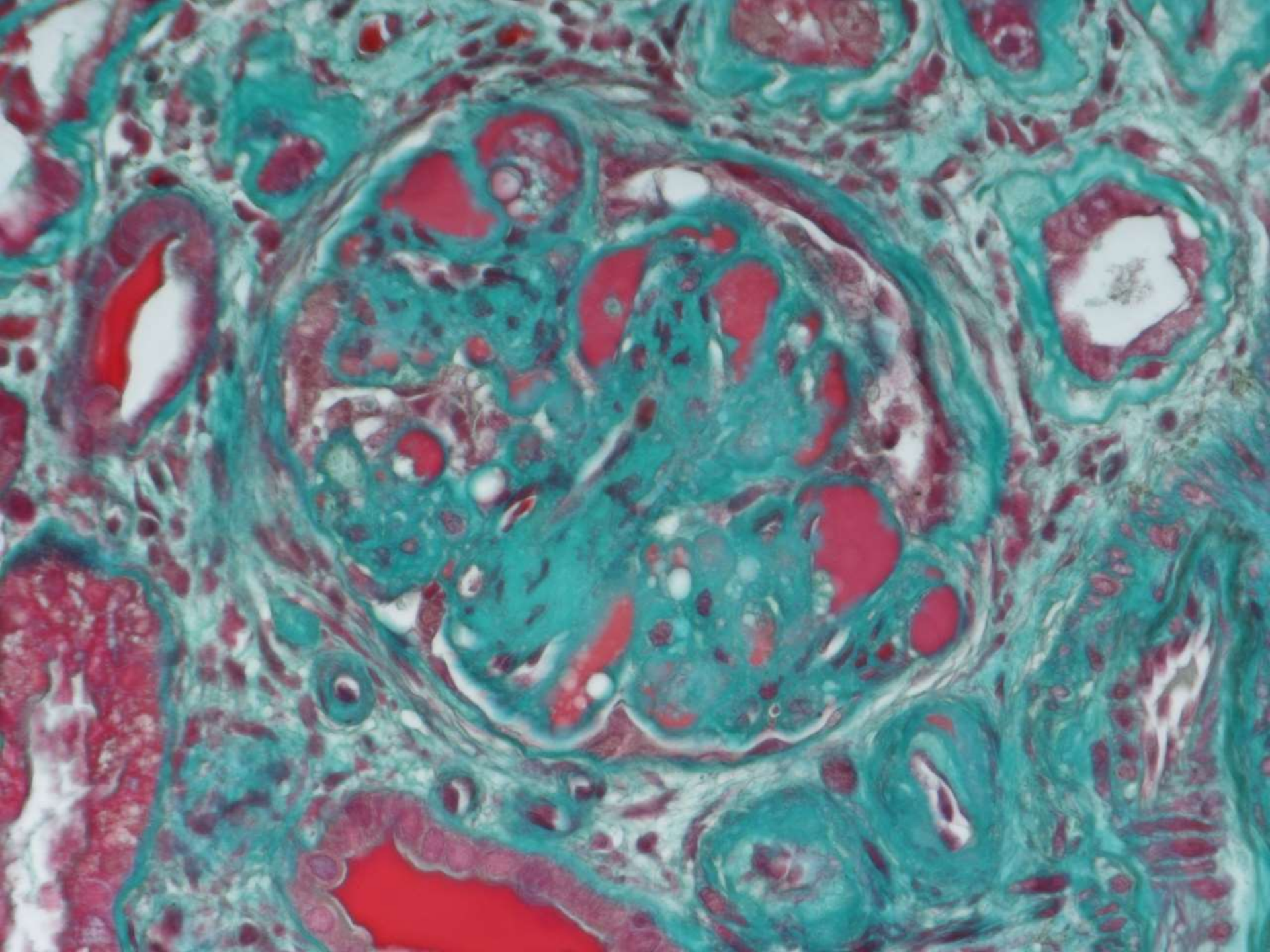
- Diabetes Mellitus
- Amyloid
- Non-amyloid organised deposits

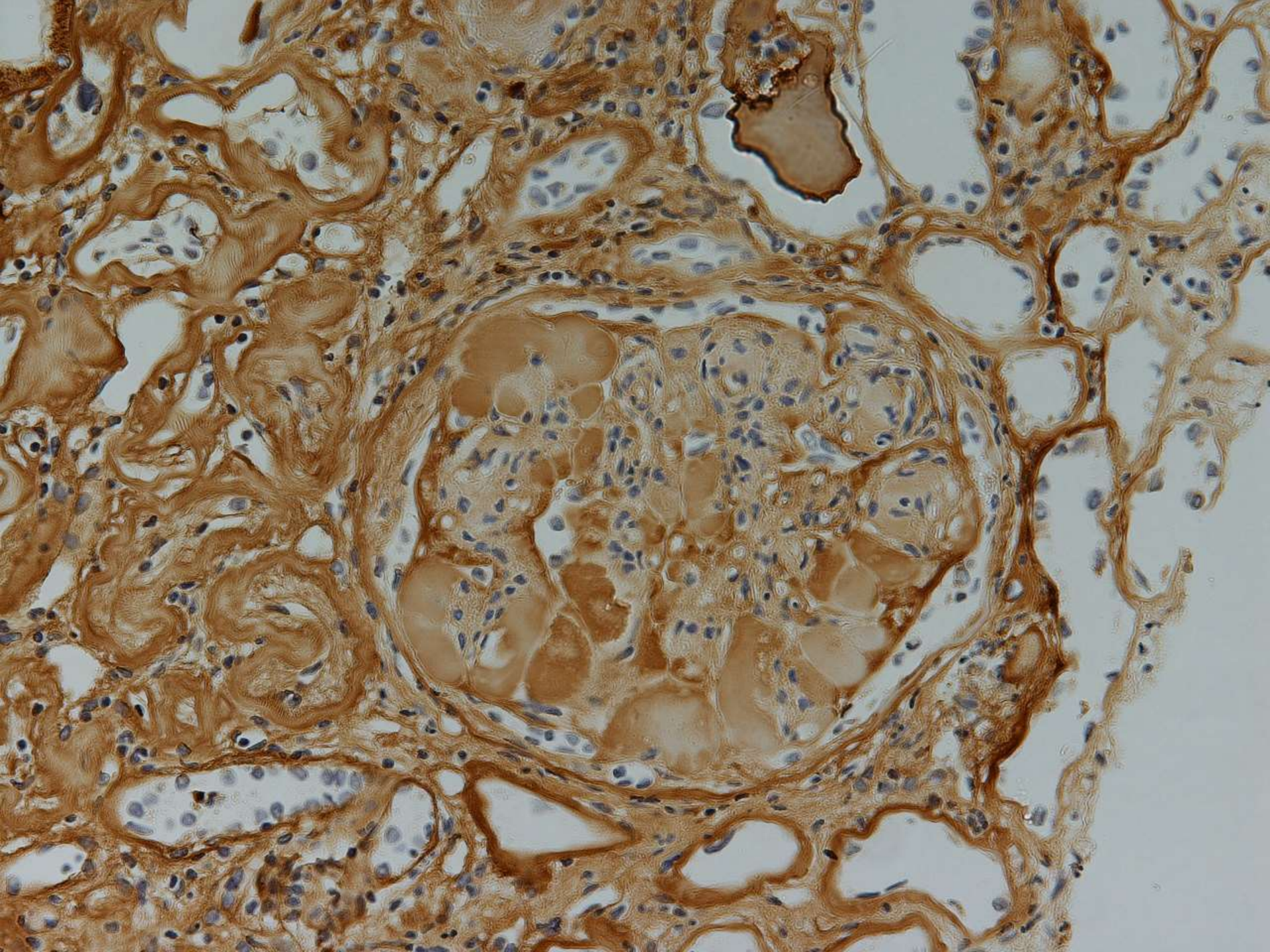


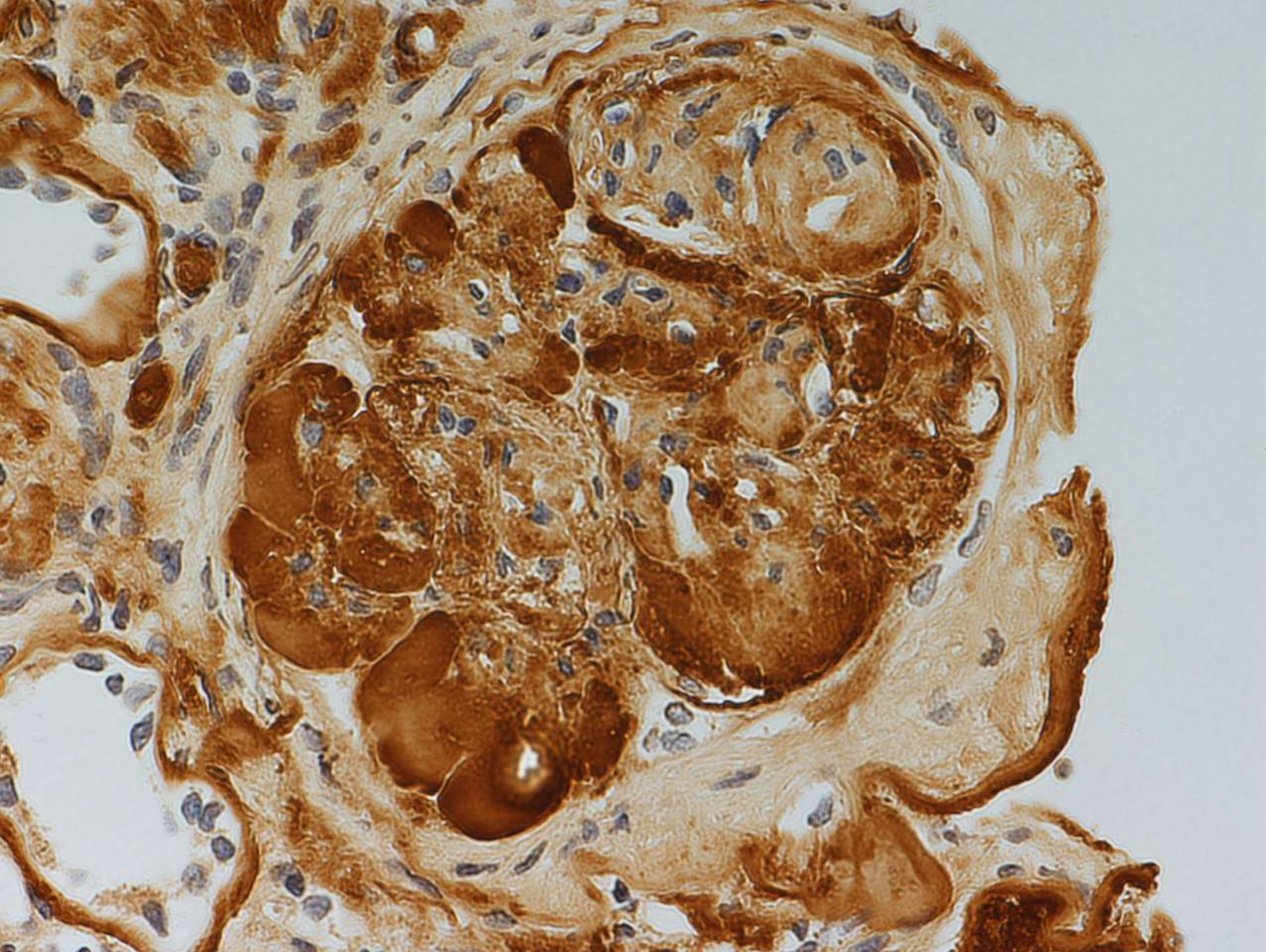


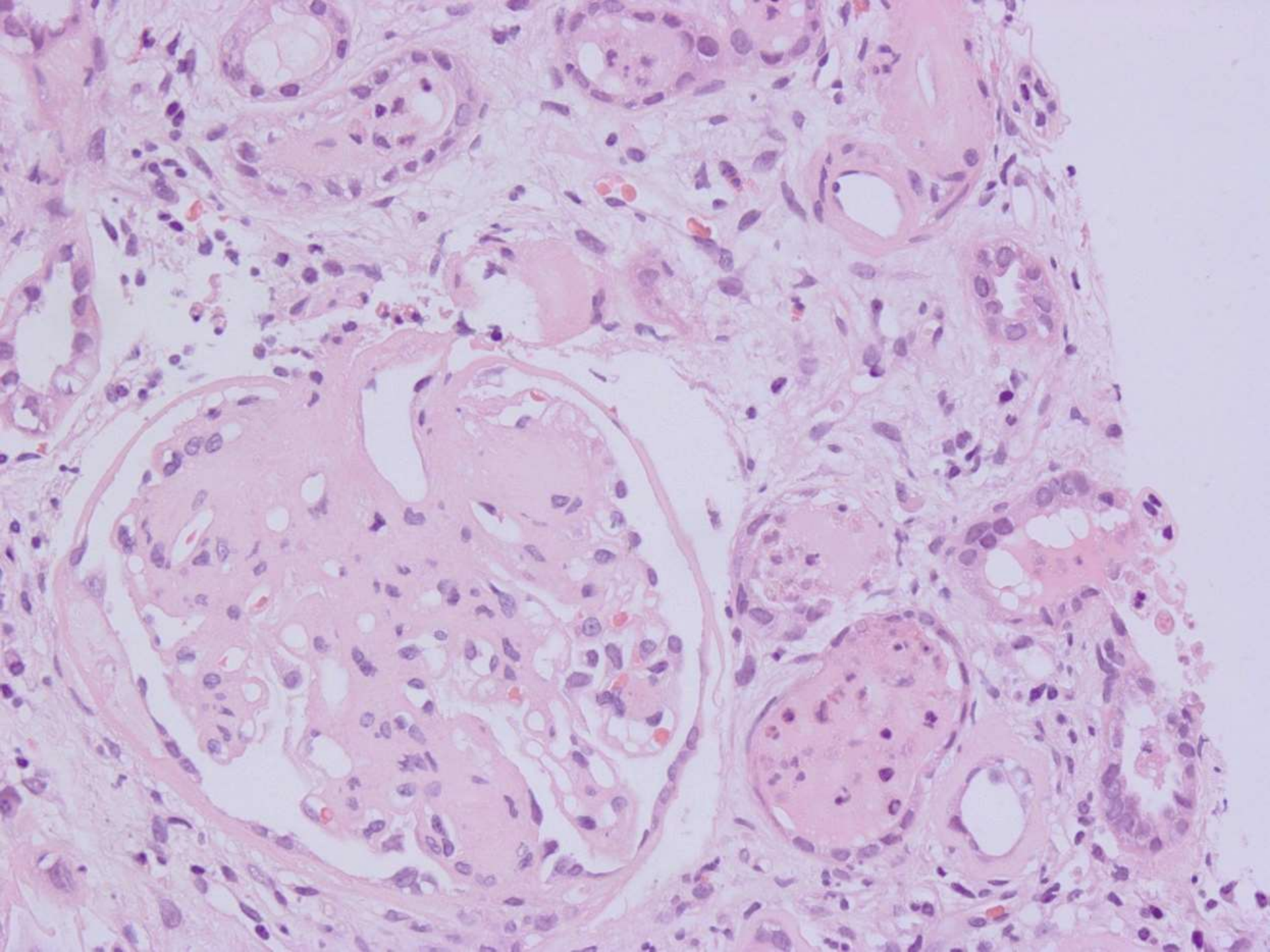












# Diabetic Nephropathy

- Affects all four compartments
- Glomeruli:–
  - early, glomerulomegaly;
  - diffuse diabetic glomerulosclerosis – diffuse thickening of basement membranes and diffuse increase in matrix – even in non-nephrotic cases
  - Nodular diabetic glomerulosclerosis – Kimmelstiel-Wilson nodules
    - Glomerular capillary wall aneurysms, mesangiolysis

www.jasn.org SPECIAL ARTICLE

**Table 1.** Glomerular classification of DN

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM > 395 nm in female and >430 nm in male individuals 9 years of age and older*
IIa	Mild mesangial expansion	Biopsy does not meet criteria for class III or IV Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel-Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel-Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli Lesions from classes I through III

LM, light microscopy.

\*On the basis of direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used.

- Exudative/insudative lesions [3]
- Fibrin cap lesions; capsular drop lesions; hyaline arteriolosclerosis
- May see conditions superimposed on DM
  - Tubulointerstitial Nephritis
  - Membranous Nephropathy
  - IgA Nephropathy

*J. clin. Path.* (1965), **18**, 47

## Exudative lesions in diabetes mellitus

G. I. HORSFIELD<sup>1</sup> AND R. LANNIGAN

*From the Department of Pathology, University of Birmingham*

**SYNOPSIS** Exudative lesions and capsular drops have been examined in a renal biopsy series of 25 diabetics and a post-mortem series of 100 consecutive diabetics. Electron microscopy of a capsular drop and an exudative lesion is described. Exudative lesions were found in 48% of the biopsies and 47% of the necropsy material. Capsular drops were found in 60% of the biopsies and 29% of the necropsy material. No correlation with age, proteinuria, hypertension, or uraemia was noted. The incidence of both types of lesion increased with the known duration of the diabetes.

- Tubules –
  - hyaline change – hyaline protein resorption droplets and lipid droplets;
  - tubular atrophy with striking thickening of tubular basement membranes
- Interstitium –
  - fibrosis – prognostic value; inflammation.
- Vessels –
  - larger arteries – intimal fibroplasia;
  - hyaline arteriosclerosis [plasmacytic insudation] – afferent and efferent glomerular arterioles affected

# Prognosis

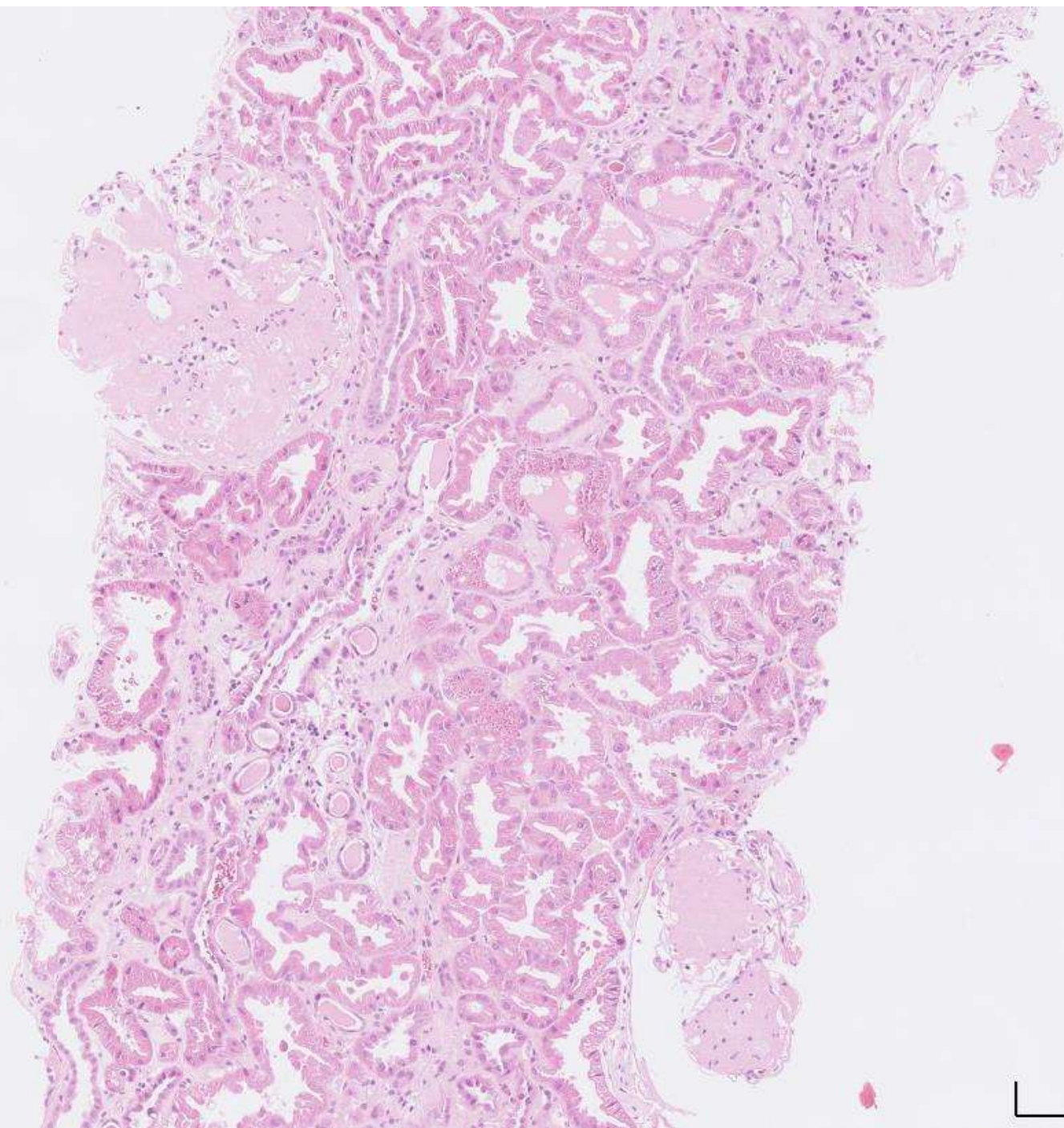
- Diabetes onset to proteinuria usually 10-15 years – possibly depending on glycaemic control
- Then to end stage renal disease averages 5 – 10 years but with great variability between patients
- Once developed, no specific therapy
- Angiotensin converting enzyme inhibitors may reduce proteinuria and slow progression
- Dietary protein restriction may help
- Probably accentuated by hypertension, which should be controlled

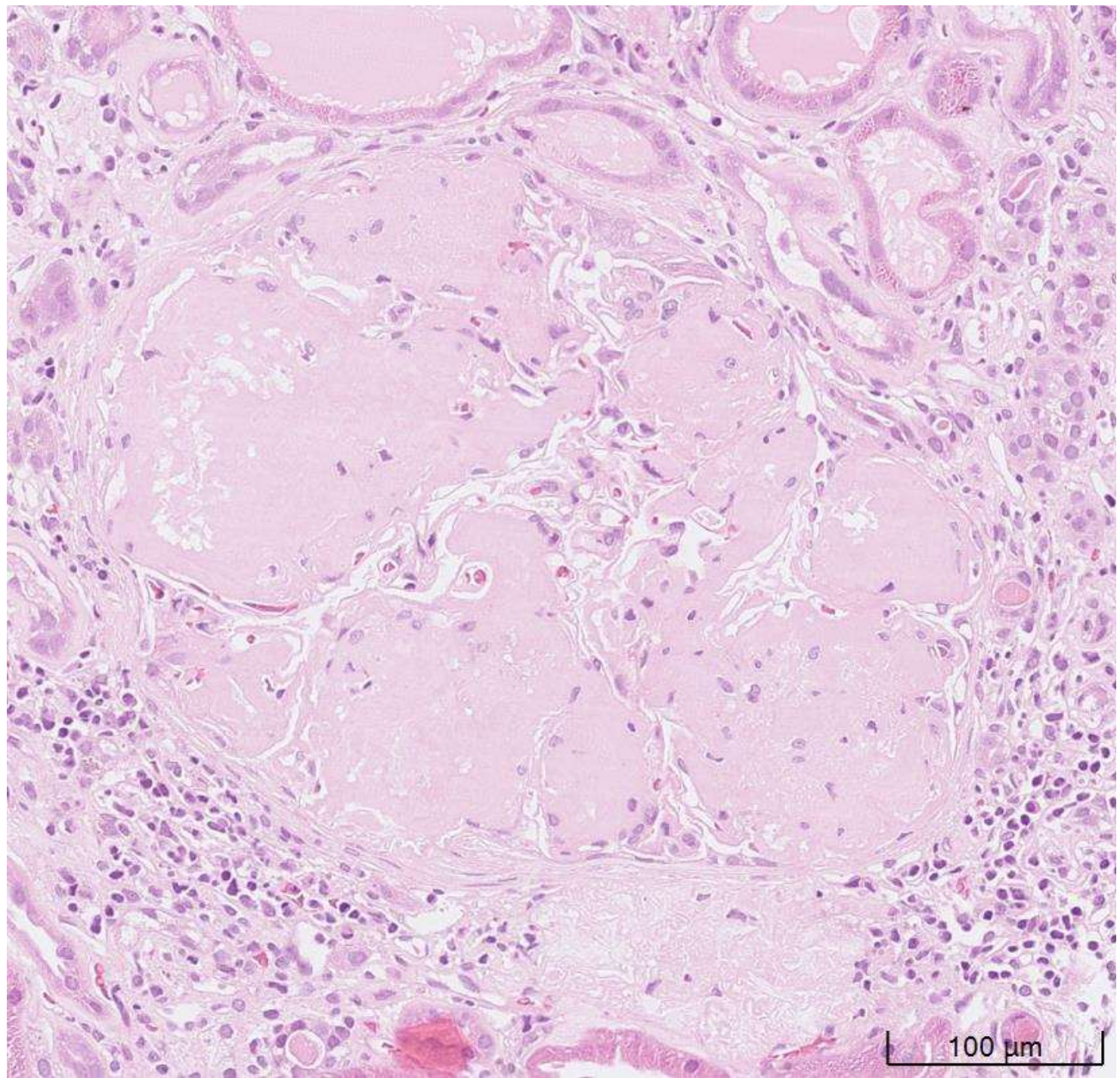
Another systemic condition that can cause Nephrotic Syndrome due to renal involvement. A recent case.

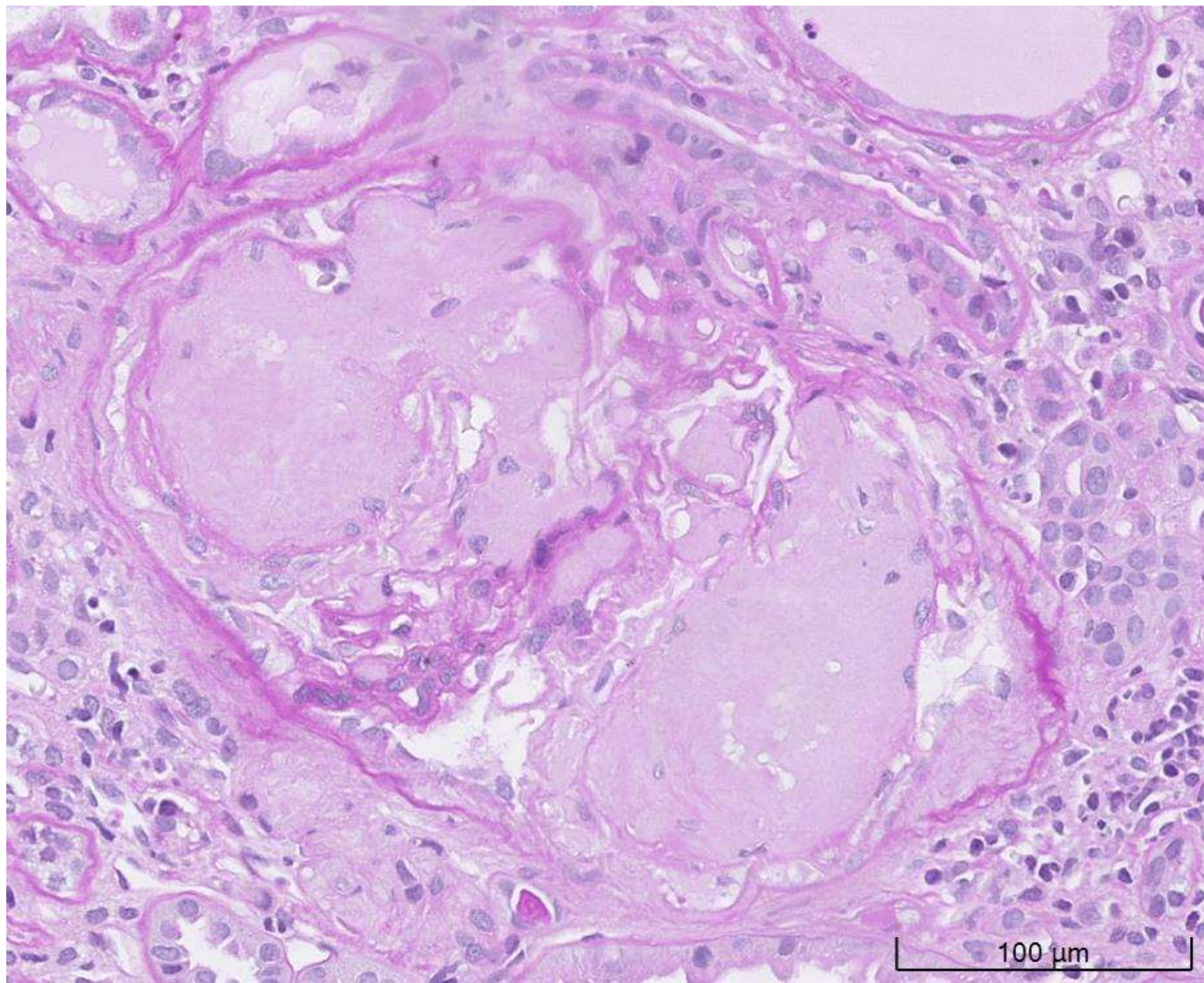
- 60 year old male
- Presents with the Nephrotic Syndrome
  - What are the possibilities even before you look at the slide?

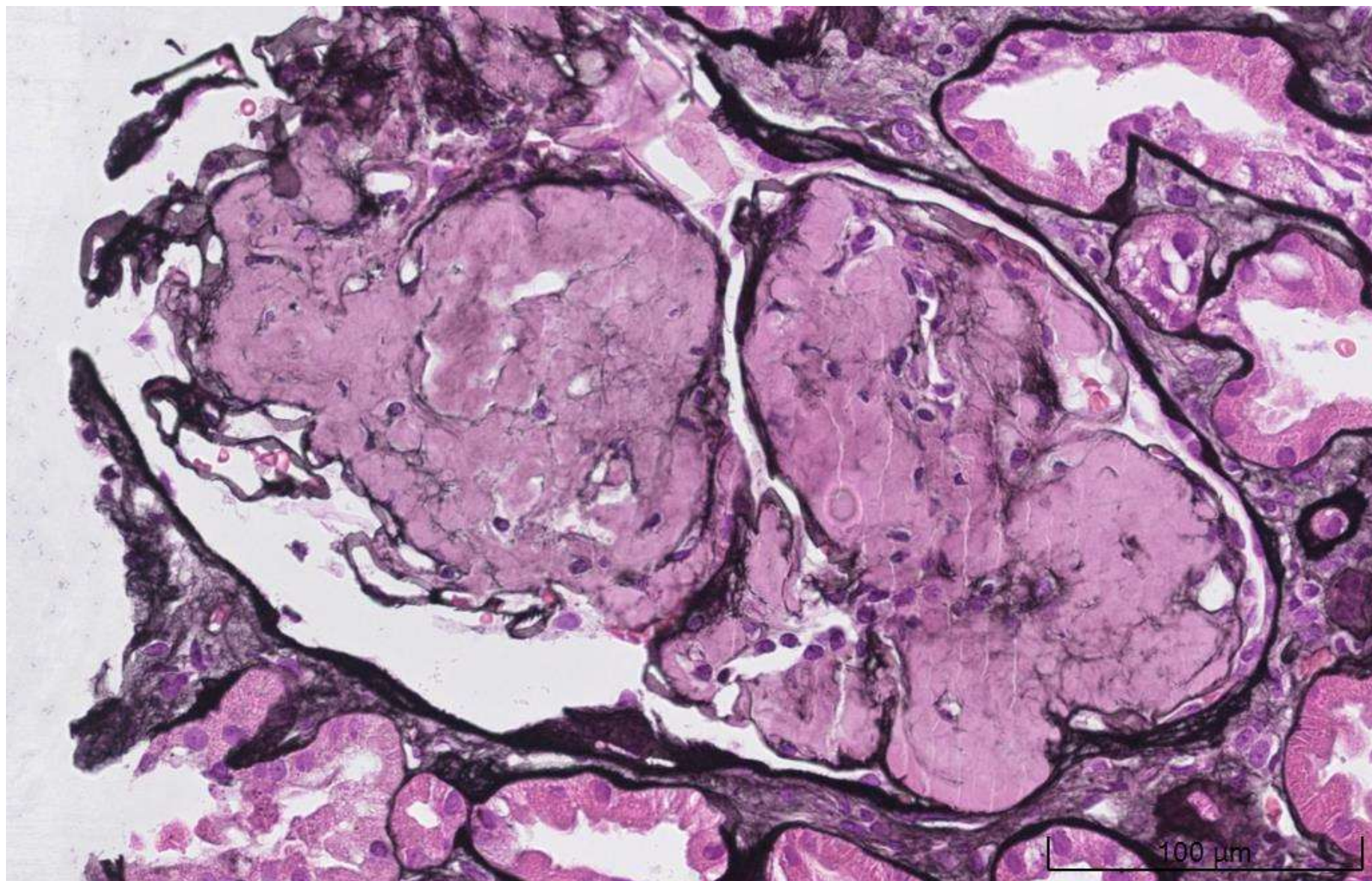


- 2 cores of renal cortex and medulla with 5 glomeruli, one of which is obsolete.
- PAS and PAMS often the easiest sections to make the quickest assessment of glomerular counts.







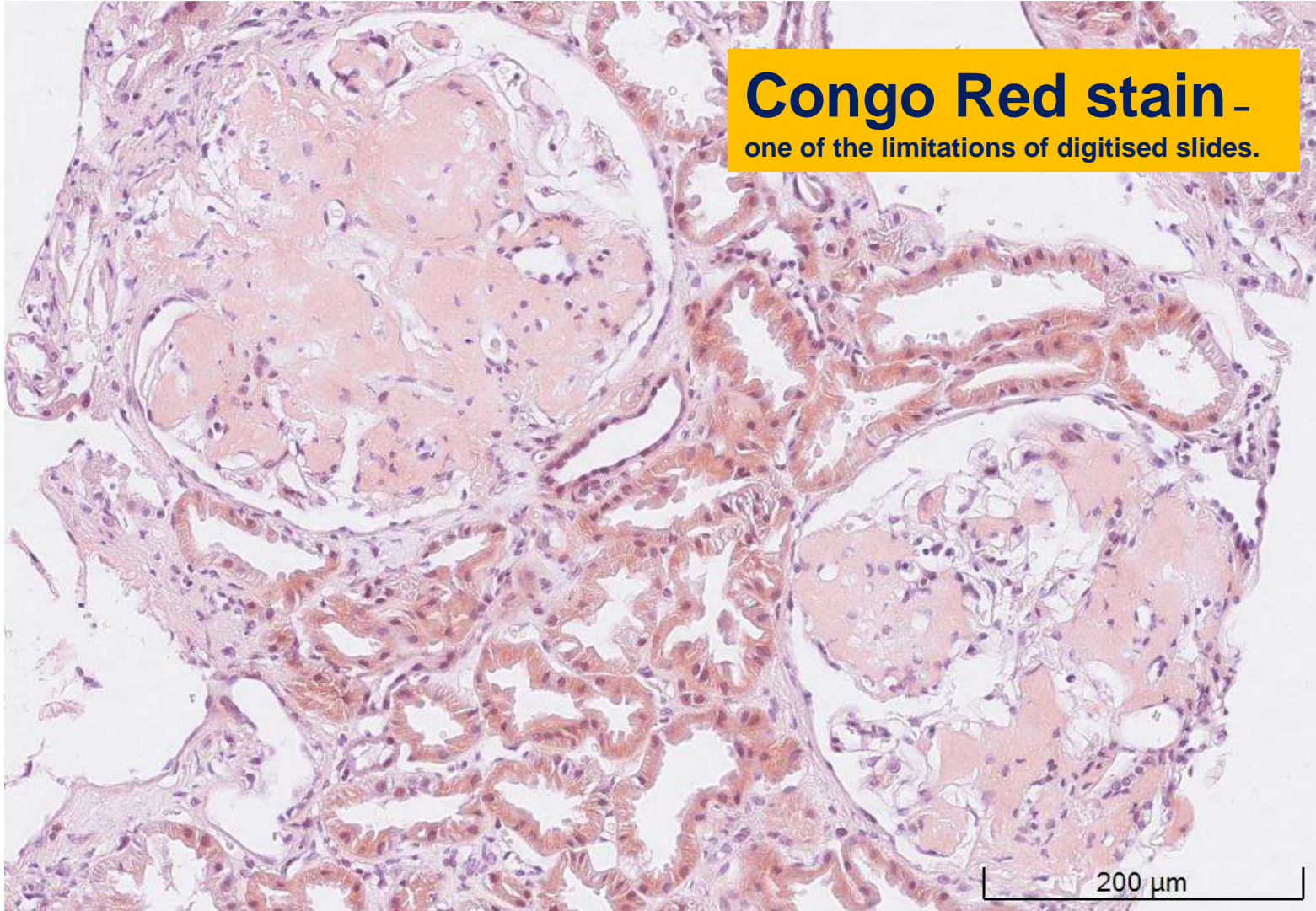


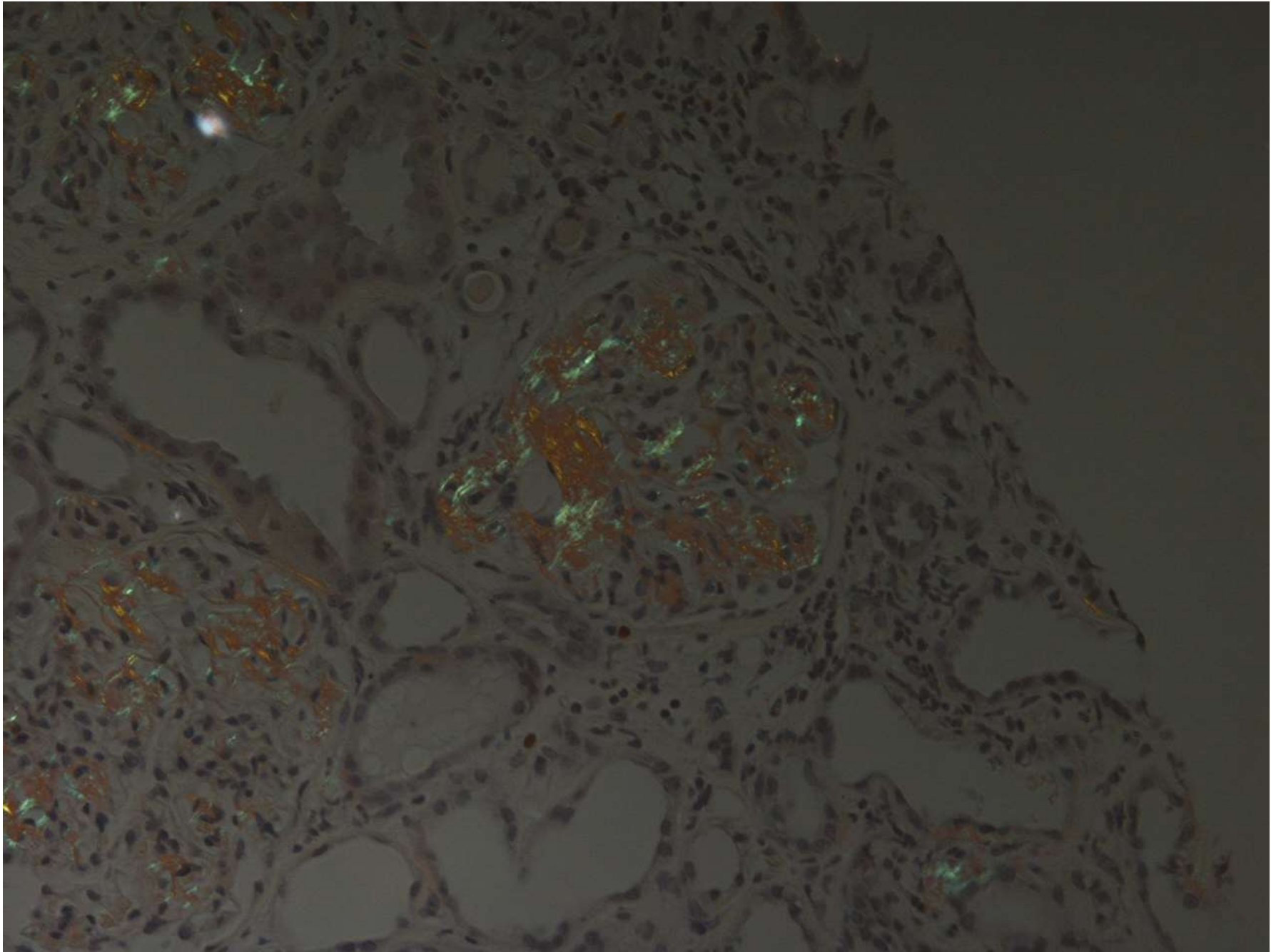
- Massively enlarged glomeruli due to considerable expansion of the region of the mesangial matrix;
- Nodular appearance;
- Staining qualities are not those of mesangial matrix (PAS weak and silver negative).

- Differential diagnosis of nodular glomerulopathy:

- Diabetes;
- Amyloid;
- Light chain deposition disease;
- Non-amyloid organised glomerulopathies;
- Advanced membranoproliferative GNs;
- Heavy smoking;
- Collagenofibrotic nephropathy;
- Very advanced chronic microangiopathy;
- Idiopathic.

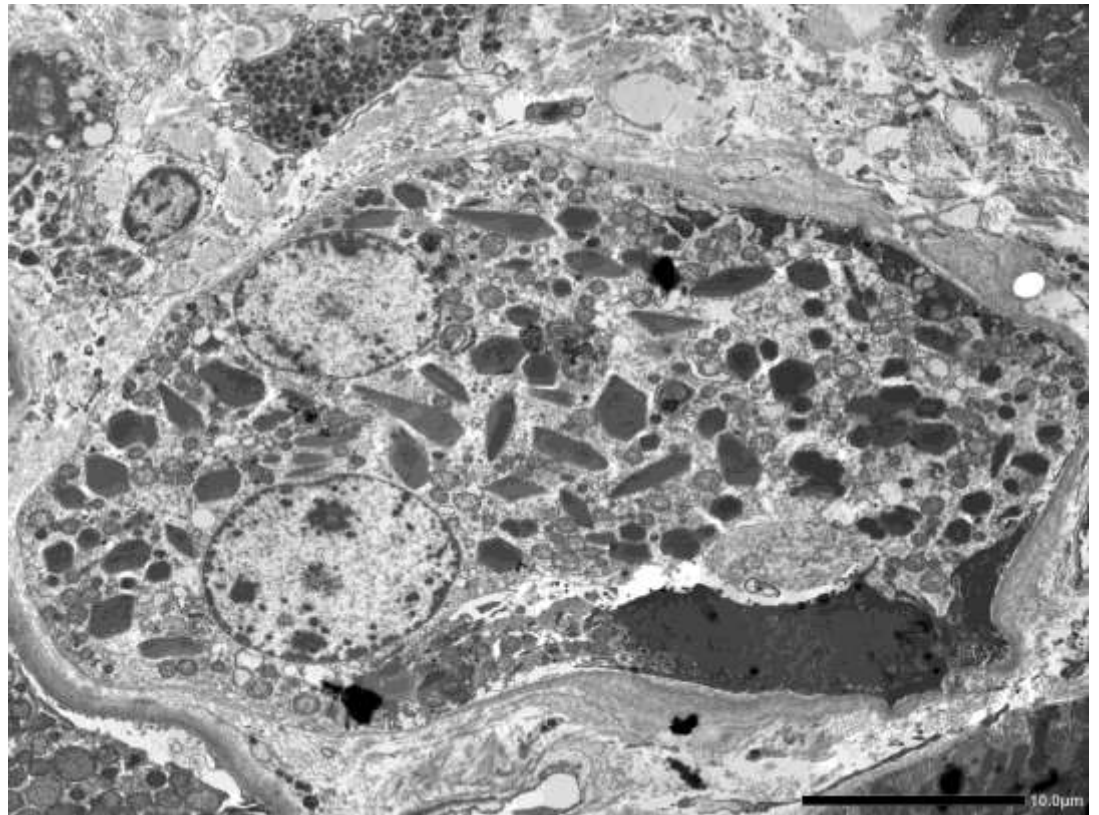
**Congo Red stain -**  
one of the limitations of digitised slides.



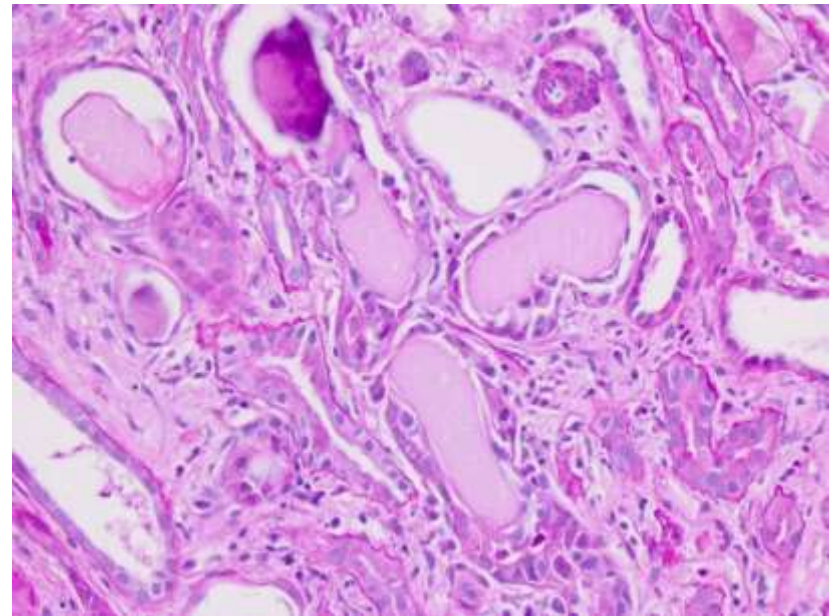
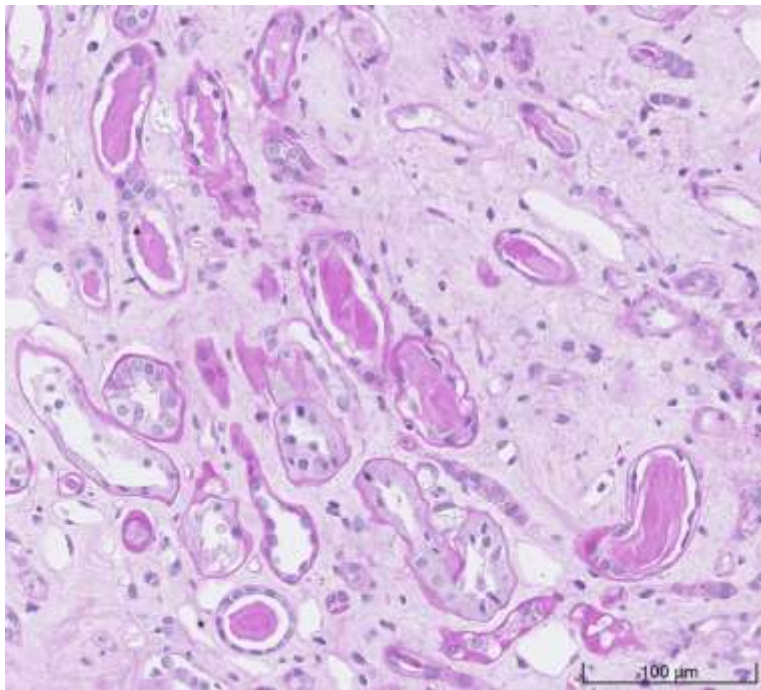


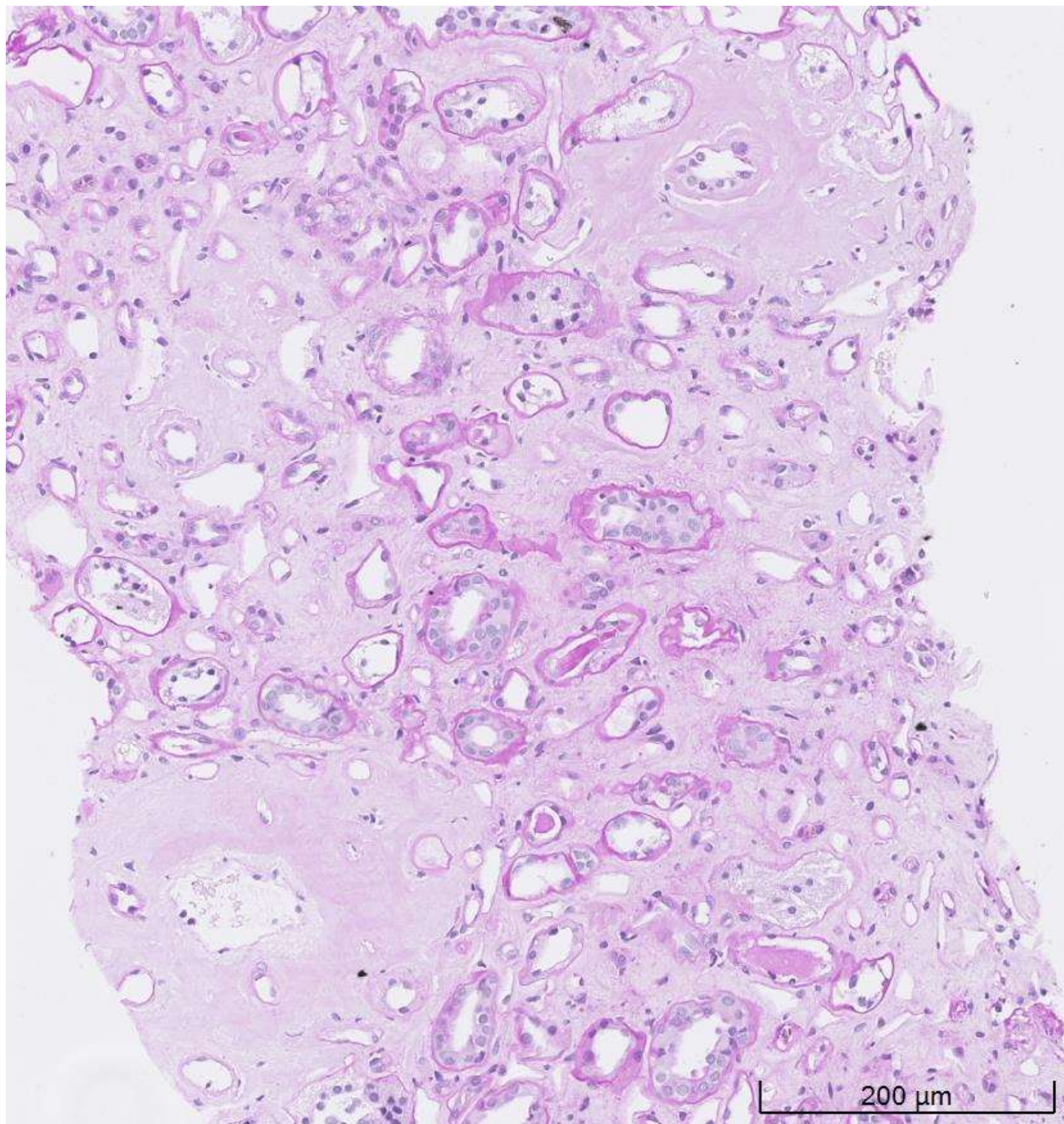


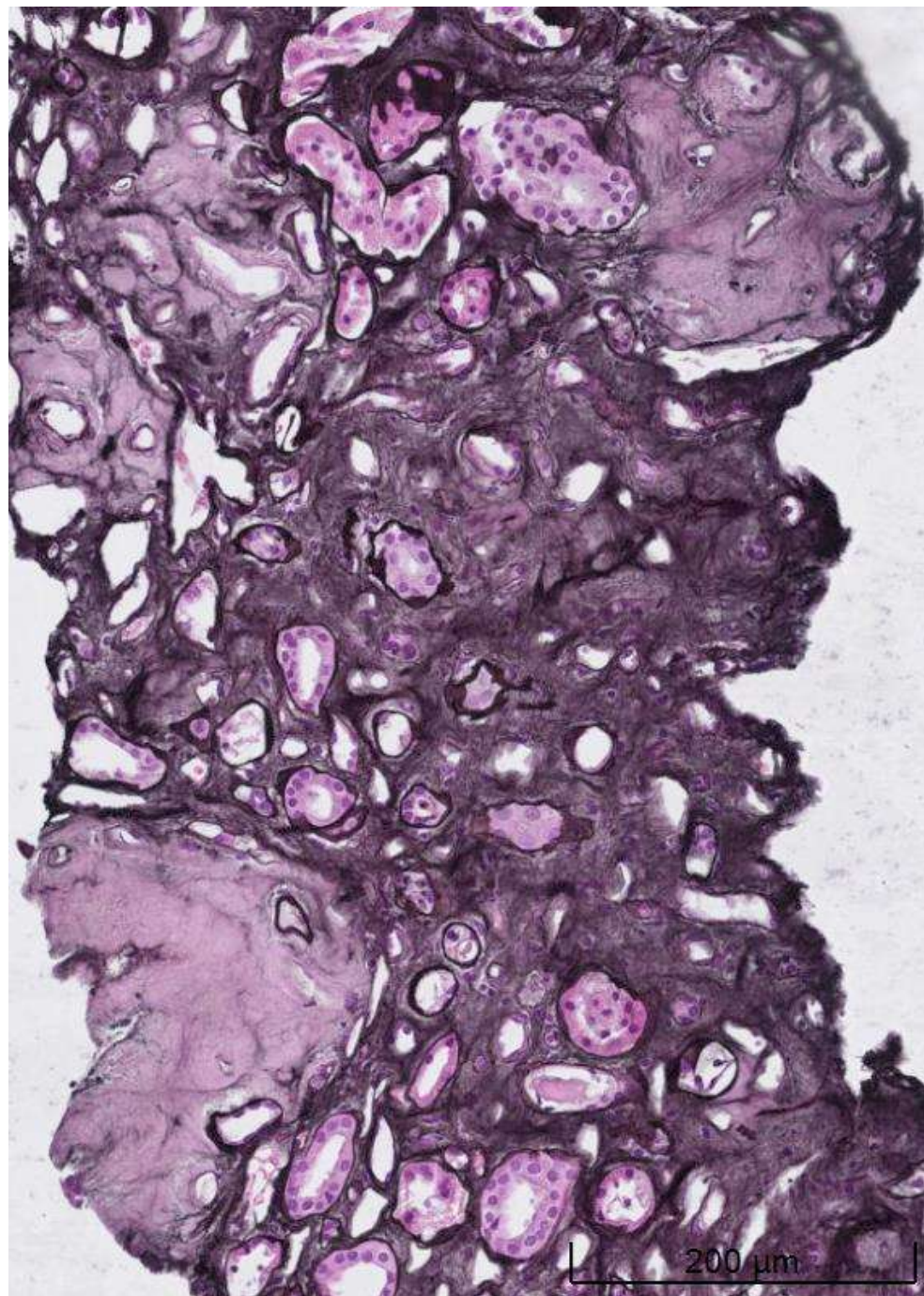
Not in our case, but you would look for..

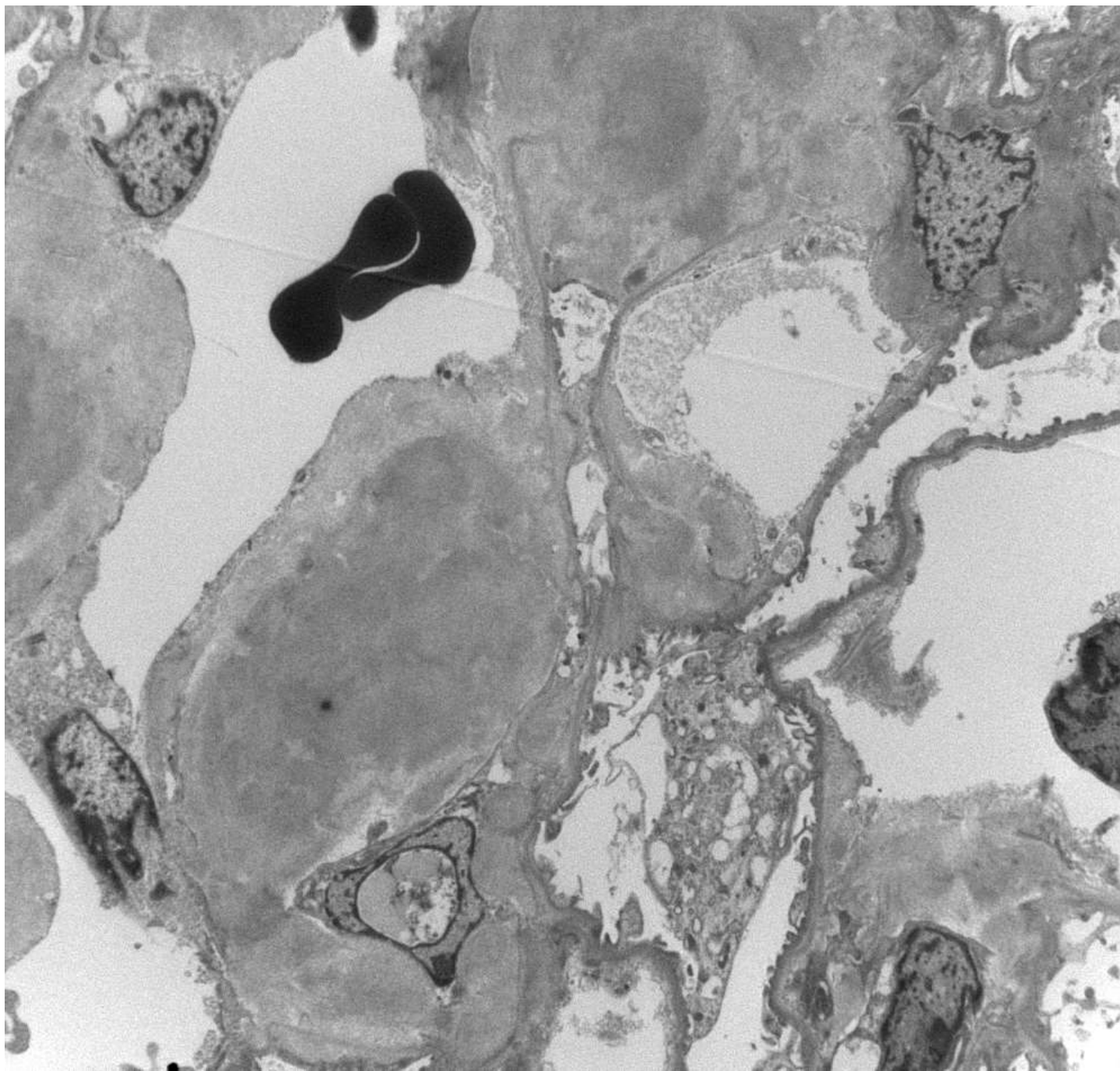


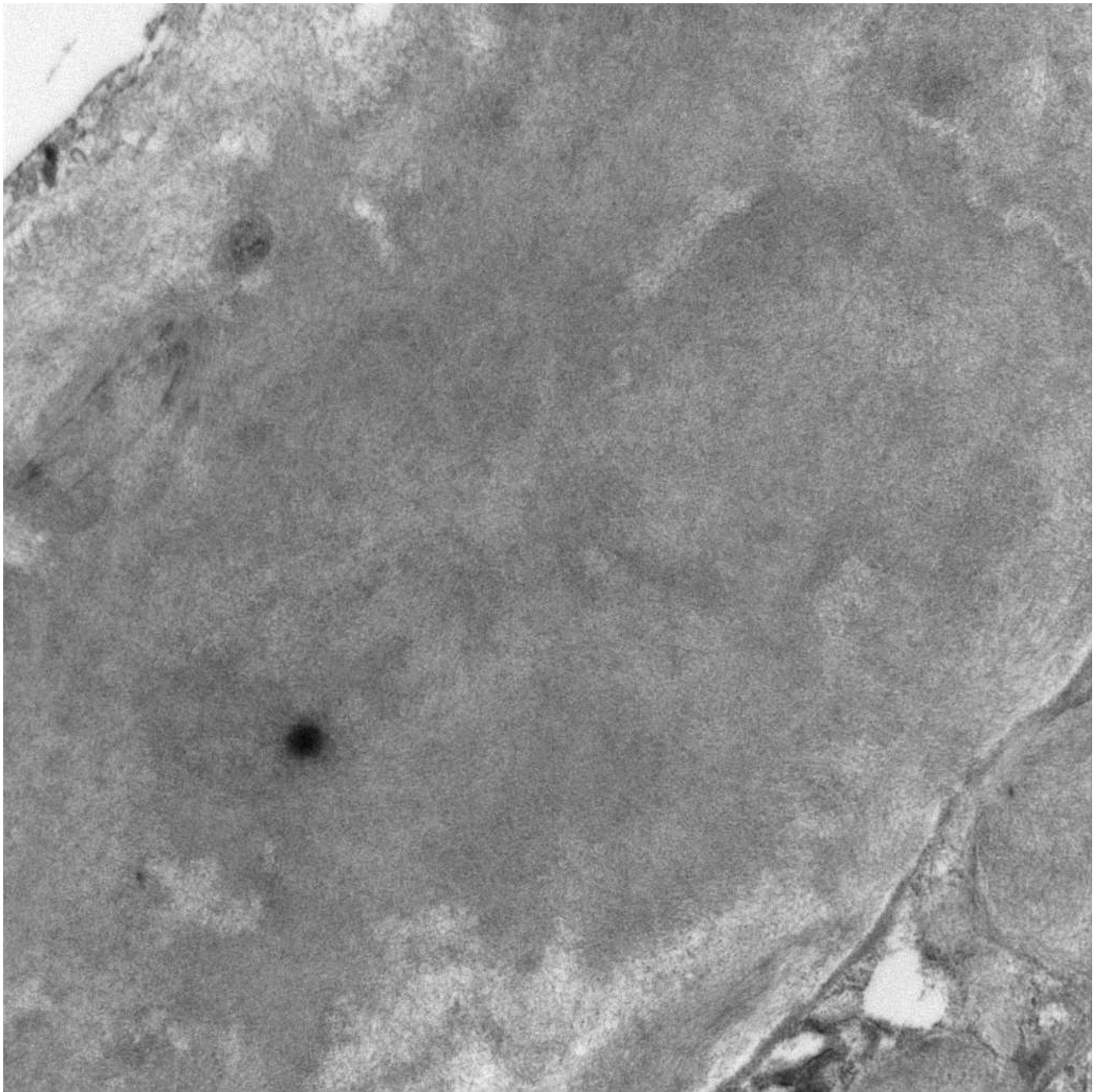
Our case (left) – but would look for (right)











# Electron microscopy

- Fibrillary appearance
  - Diameter of fibrils 8-12nm, mean 10nm
  - Straight, non-branching, randomly arranged
  - Difficult to differentiate individual filaments – ‘cotton wool appearance’
- 
- Starts mesangium – capillary walls
  - Vessels and interstitium

## In this particular case:

- SEP normal; no light chain restriction shown;
- No clinical history to suggest a reason to have secondary amyloidosis due to serum amyloid A;
- Mediterranean ethnicity, and on further questioning a family history of renal disease: Familial Mediterranean Fever.
- NAC report: Amyloid of uncertain type.

- Nodular glomerulopathy showing brick red staining with Congo Red stain;
- Apple green birefringence with cross-polarised light;
- Renal amyloidosis.

- Can anything else stain with Congo Red?
- DNAJB9 in distinguishing congophilic fibrillary GN from amyloidosis.

> Am J Kidney Dis. 2018 Sep;72(3):325-336. doi: 10.1053/j.ajkd.2018.03.017. Epub 2018 Jun 14.

## Congophilic Fibrillary Glomerulonephritis: A Case Series

Mariam P Alexander<sup>1</sup>, Surendra Dasari<sup>2</sup>, Julie A Vrana<sup>3</sup>, Julie Riopel<sup>4</sup>, Anthony M Valeri<sup>5</sup>, Glen S Markowitz<sup>6</sup>, Aviv Hever<sup>7</sup>, Vanesa Bijol<sup>8</sup>, Christopher P Larsen<sup>9</sup>, Lynn D Cornell<sup>3</sup>, Mary E Fidler<sup>3</sup>, Samar M Said<sup>3</sup>, Sanjeev Sethi<sup>3</sup>, Loren Paola Herrera Hernandez<sup>3</sup>, Joseph P Grande<sup>3</sup>, Stephen B Erickson<sup>10</sup>, Fernando C Fervenza<sup>10</sup>, Nelson Leung<sup>10</sup>, Paul J Kurtin<sup>3</sup>, Samih H Nasr<sup>3</sup>

Affiliations + expand

PMID: 29866458 DOI: 10.1053/j.ajkd.2018.03.017

➤ Am J Kidney Dis. 2018 Sep;72(3):325-336. doi: 10.1053/j.ajkd.2018.03.017. Epub 2018 Jun 14.

## Congophilic Fibrillary Glomerulonephritis: A Case Series

Mariam P Alexander<sup>1</sup>, Surendra Dasari<sup>2</sup>, Julie A Vrana<sup>3</sup>, Julie Riopel<sup>4</sup>, Anthony M Valeri<sup>5</sup>, Glen S Markowitz<sup>6</sup>, Aviv Hever<sup>7</sup>, Vanesa Bijol<sup>8</sup>, Christopher P Larsen<sup>9</sup>, Lynn D Corneli<sup>3</sup>, Mary E Fidler<sup>3</sup>, Samar M Said<sup>3</sup>, Sanjeev Sethi<sup>3</sup>, Loren Paola Herrera Hernandez<sup>3</sup>, Joseph P Grande<sup>3</sup>, Stephen B Erickson<sup>10</sup>, Fernando C Fervenza<sup>10</sup>, Nelson Leung<sup>10</sup>, Paul J Kurtin<sup>3</sup>, Samih H Nasr<sup>3</sup>

Affiliations + expand

PMID: 29866458 DOI: 10.1053/j.ajkd.2018.03.017



EDITORIAL | VOLUME 72, ISSUE 3 | P315-317, SEPTEMBER 01, 2018

## The Interpretation of Congophililia in Tissue Biopsies: Caution Required

Maria M. Picken  

DOI: <https://doi.org/10.1053/ajkd.2018.05.000>  Check for updates

When diagnosis of amyloid is made, look for other clues as to type, specifically, signs of underlying myeloma; and type with IHC if possible – kappa, lambda, and serum amyloid A:

- Acute tubular injury, including granular expansion of the tubular epithelial cell cytoplasm
  - Check for light chain tubulopathy;
  - Note, no myeloma-type casts;
  - Note, no plasma cell infiltrate.
- Amyloid in interstitium and around tubular basement membranes and in vessel walls.

# Immunohistochemistry in amyloid

- (C3 and possibly heavy chain restriction)
- Kappa and lambda
  - Immunofluorescence may be better than immunoperoxidase, with caution for masked deposits;
  - Clinical correlation with serum electrophoresis essential.
- Serum amyloid A
  - DNAJB9 (DNAJ homolog subfamily B member 9)
- The patient will be referred to the National Amyloidosis Centre at the Royal Free, with block.

clinical investigation

<http://www.kidney-international.org>

© 2014 International Society of Nephrology

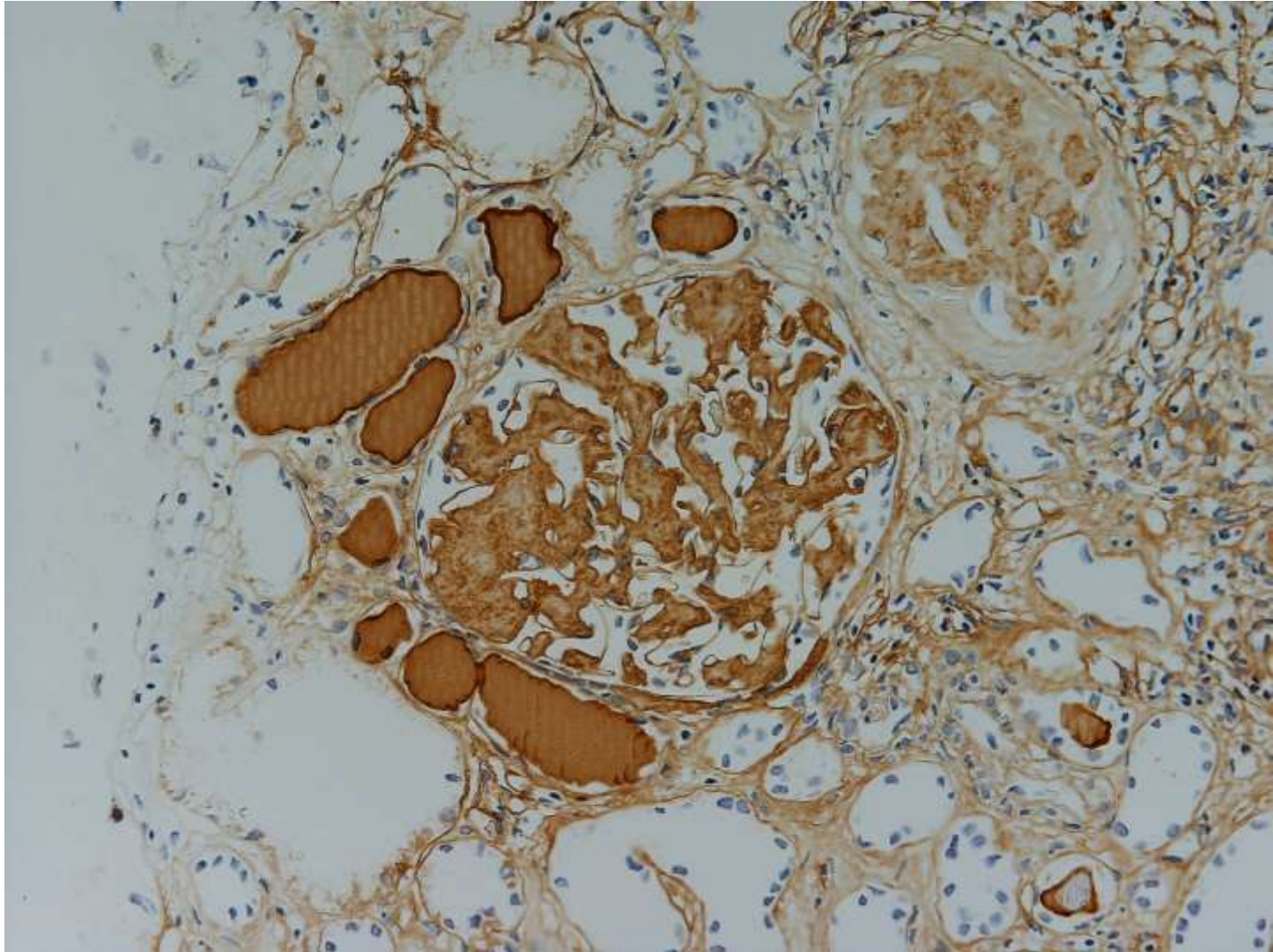
see commentary on page 13

## Membranous-like glomerulopathy with masked IgG kappa deposits

Christopher P. Larsen<sup>1</sup>, Josephine M. Ambruzs<sup>1</sup>, Stephen M. Bonsib<sup>1</sup>, Christie L. Boils<sup>1</sup>, Larry N. Cossey<sup>1</sup>, Nidia C. Messias<sup>1</sup>, Fred G. Silva<sup>1</sup>, Yihan H. Wang<sup>1</sup>, Neriman Gokden<sup>2</sup> and Patrick D. Walker<sup>1</sup>

<sup>1</sup>Nephropath, Little Rock, Arkansas, USA and <sup>2</sup>University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

An example of serum amyloid A positive case



# Amyloidosis

- Defined by accumulation of proteins, extracellular sites, characteristic form that causes positive staining with Congo Red, and apple-green birefringence when examined using cross-polarized light
- Previously felt that nothing but amyloid shows these staining qualities, however Fibrillary GN arguably can.

# The list of potential monotypic polypeptides that constitute amyloid

- Immunoglobulin light chains
  - Immunoglobulin heavy chains
  - Amyloid A protein
  - Beta-2-microglobulin
  - Prealbumin
  - Procalcitonin
  - Islet amyloid polypeptide
  - Atrial natriuretic peptides
  - Beta amyloid protein
  - Cystatin C
  - Gelsolin
  - Apolipoprotein A I or A II
  - lysozyme
- Same morphology
  - Same ultrastructural appearances
    - 10nm diameter randomly orientated non-branching fibrils
    - Molecular configuration – antiparallel beta-pleated sheet
  - Immunohistochemistry differentiates AL from AA amyloid; clinically different
    - AL and AA amyloid are the usual types to affect the kidneys

# Clinical presentation

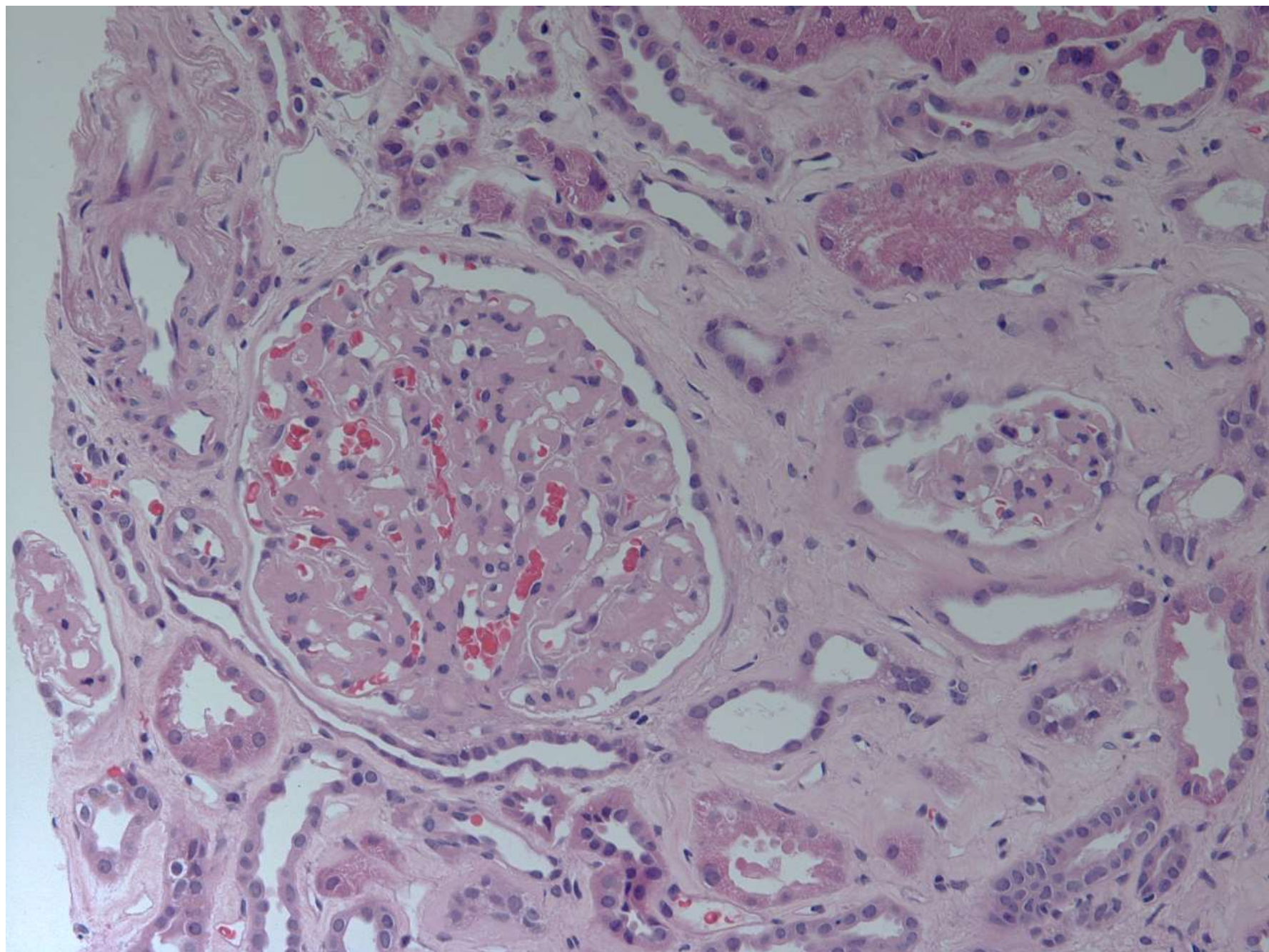
- Adult onset proteinuria, often nephrotic range
- May have haematuria
- Two thirds – renal insufficiency at diagnosis
- May have extrarenal manifestations
  - Congestive cardiac failure
  - Orthostatic hypertension, bladder dysfunction, dysesthesias, hepatosplenomegaly, macroglossia
  - Other features of underlying cause – AA / AL

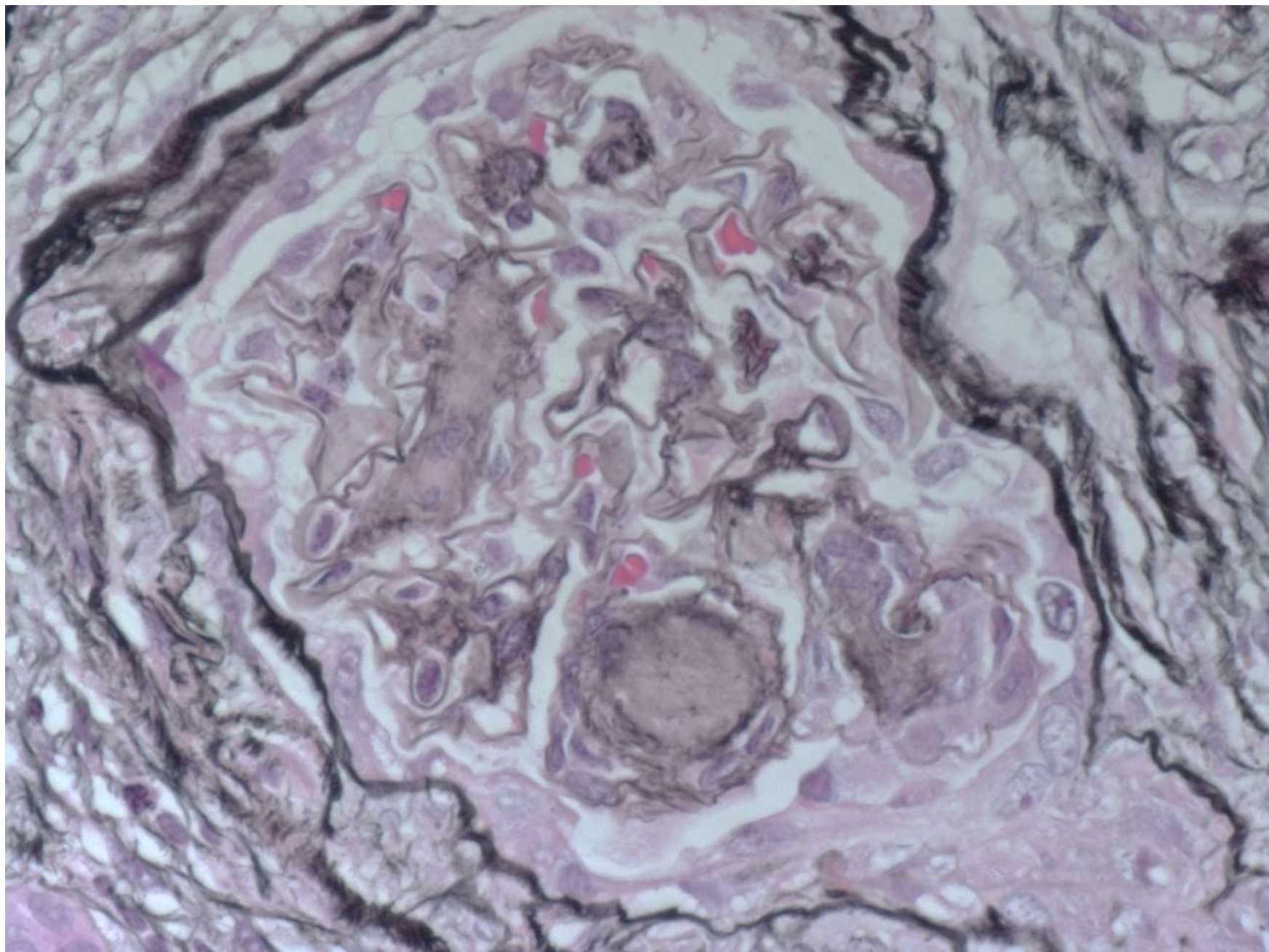
# Secondary amyloid

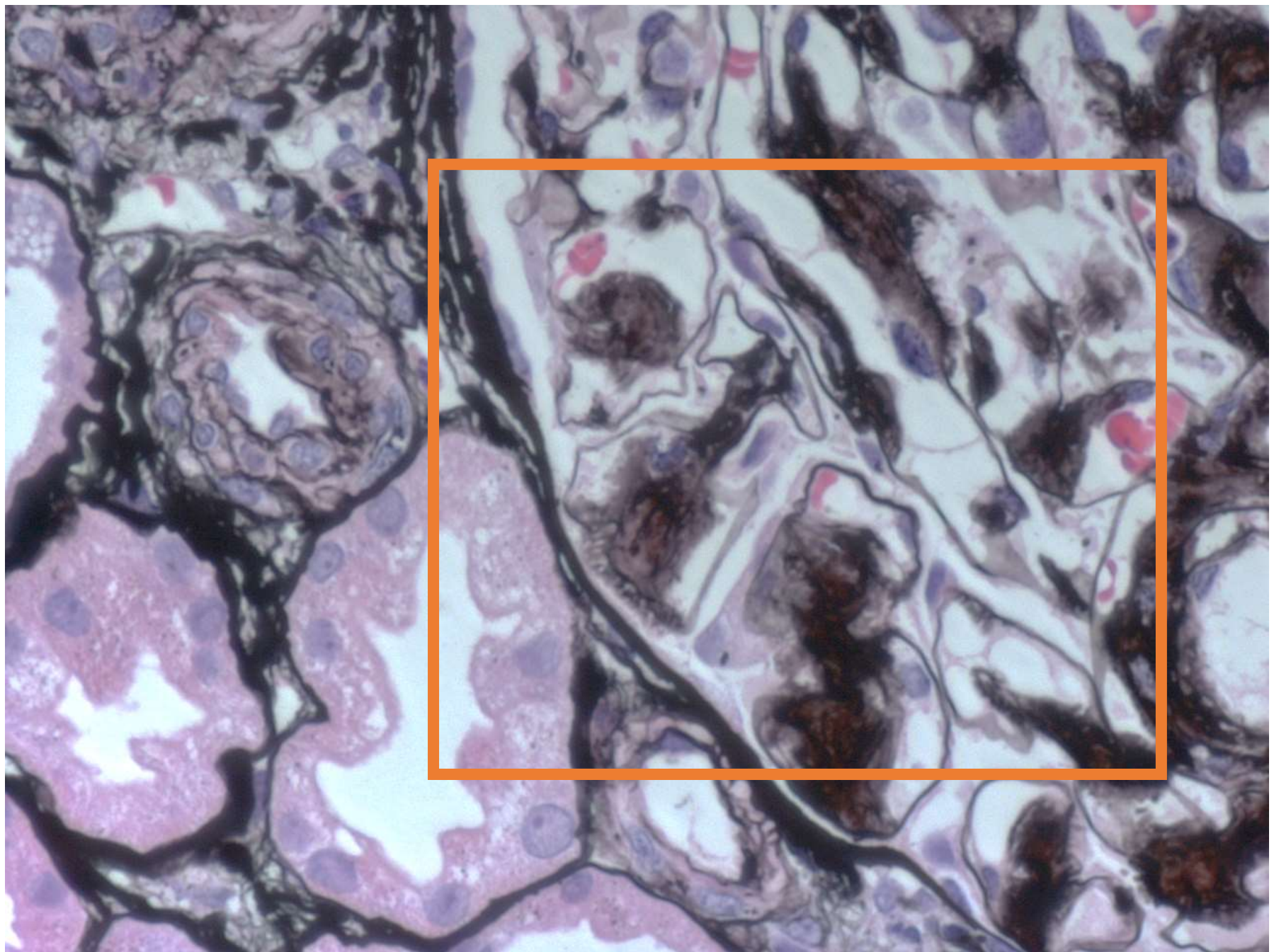
- Clinically the diagnosis of renal AA-amyloid is suspected
- Setting of chronic inflammatory disorder
- Chronic auto-immune disease [RA]
- Chronic infective processes [TB, osteomyelitis, chronic skin infections in IVDU]
- Serum Amyloid A

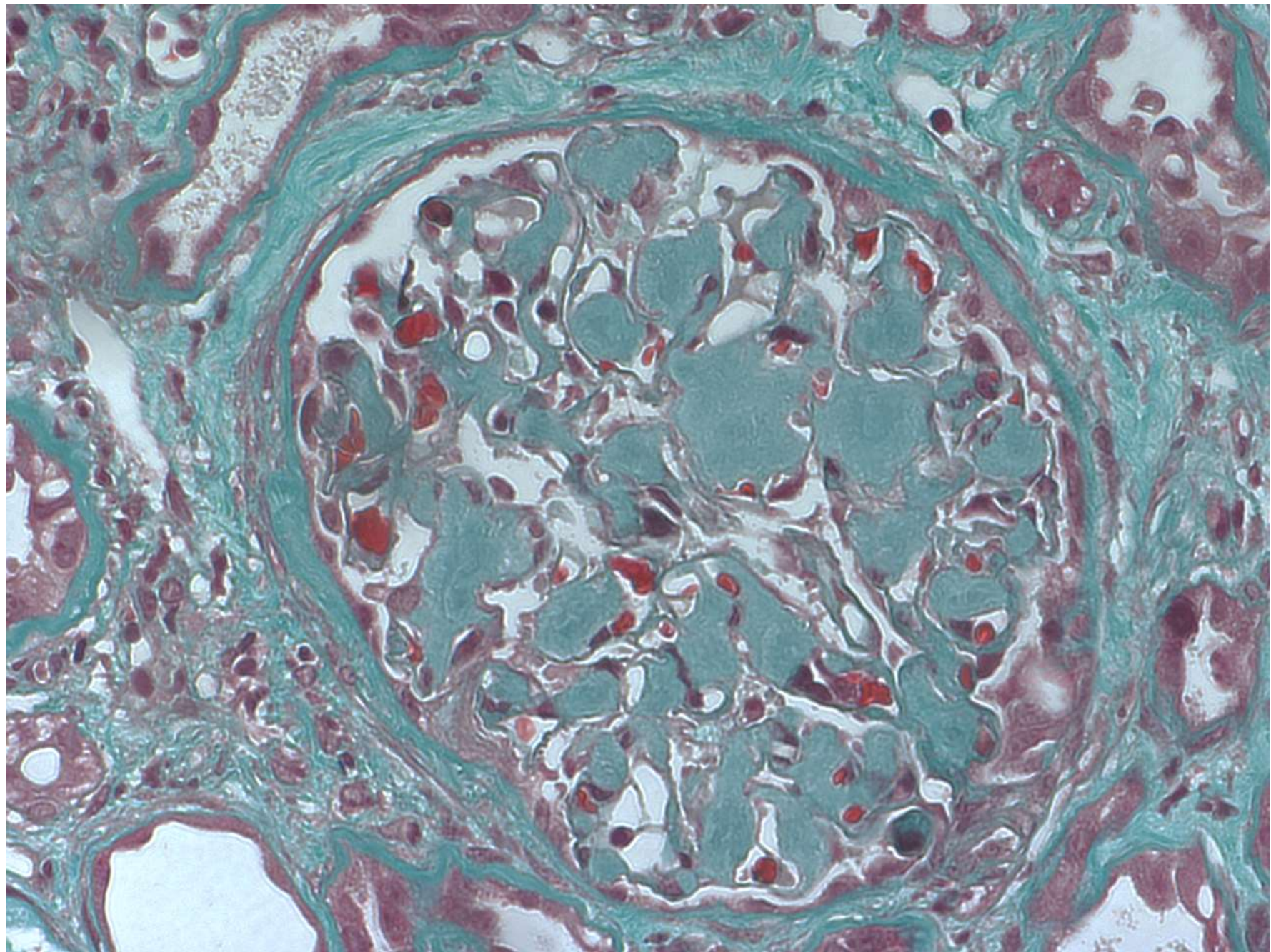
# Primary amyloid

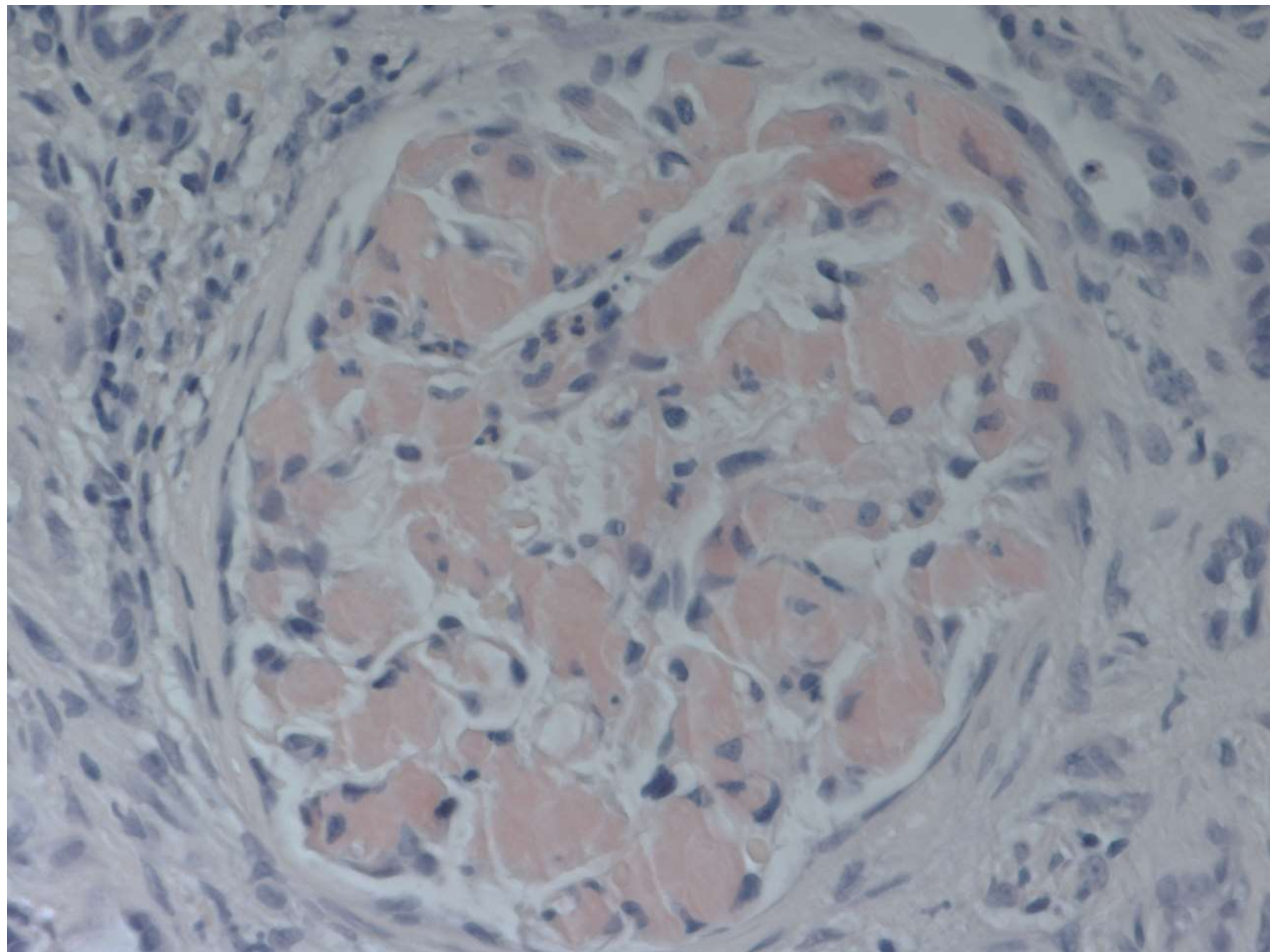
- AL amyloid
- Is never clinically suspected – ie. The underlying plasma cell dyscrasia is not known about
- 90% will have abnormal monoclonal population in BMT; occasionally clinically apparent later

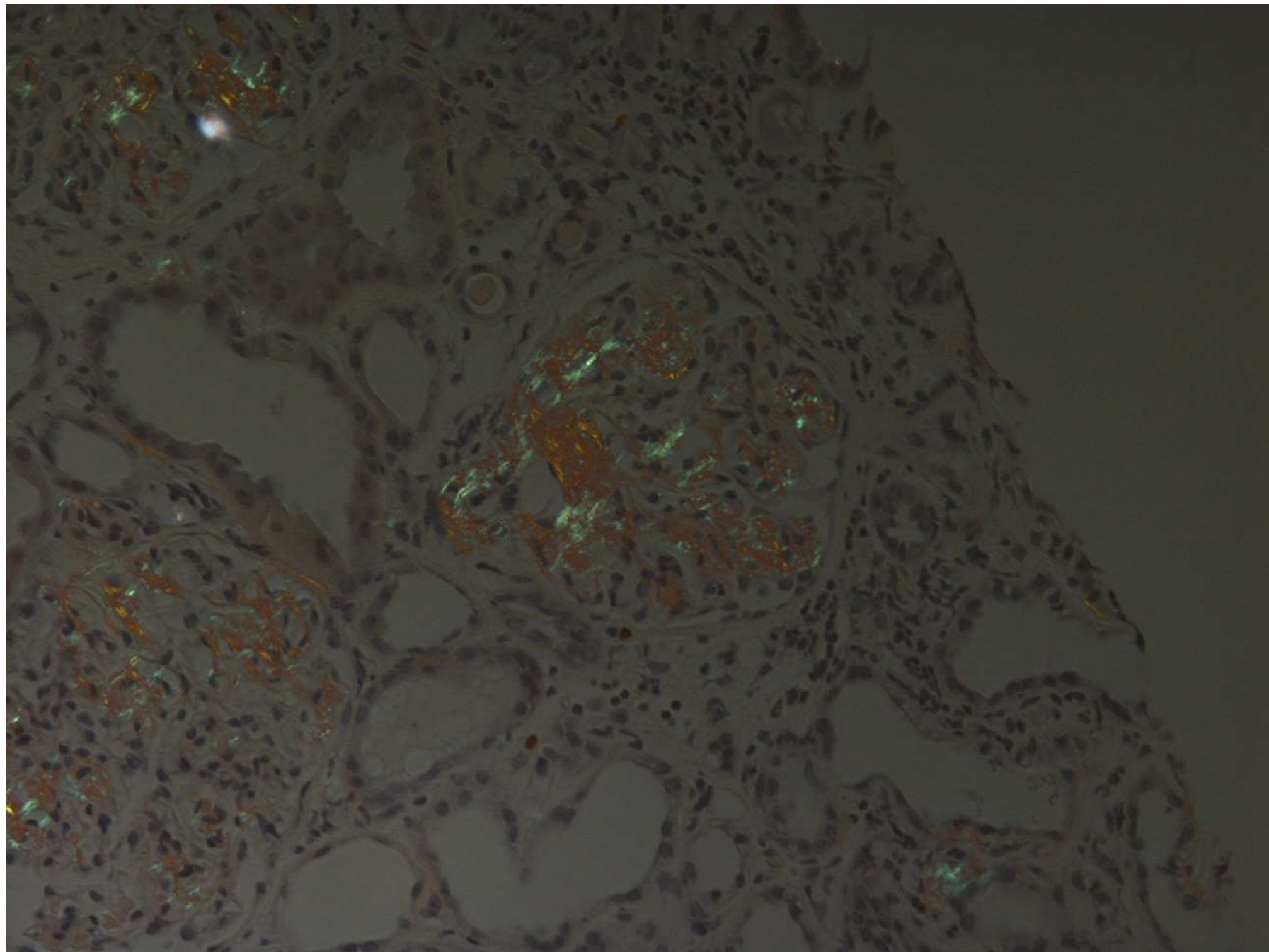












# Differential diagnosis of nodular glomerulopathy

- Diabetes
- Amyloid
- Monoclonal Immunoglobulin Deposition Disease
- Advanced MPGN/other chronic GN
- Fibrillary GN
- Immunotactoid GN
- Fibronectin glomerulopathy
- Collagenofibrotic glomerulopathy

# Summary – Nephrotic Syndrome

Always essential to interpret the morphology in the context of the clinical scenario.

- Children :
  - MCD > FSGS >> Membranous (consider secondary Membranous causes)
- Adults :
  - Membranous (Primary – AntiPLA2R, and the more recently described antibodies; Secondary causes – drugs; malignancy; infections)
  - > FSGS
  - >> MCD (secondary causes; drugs; malignancy; allergies)
- Diabetes
- Amyloid.

- Any Questions?

