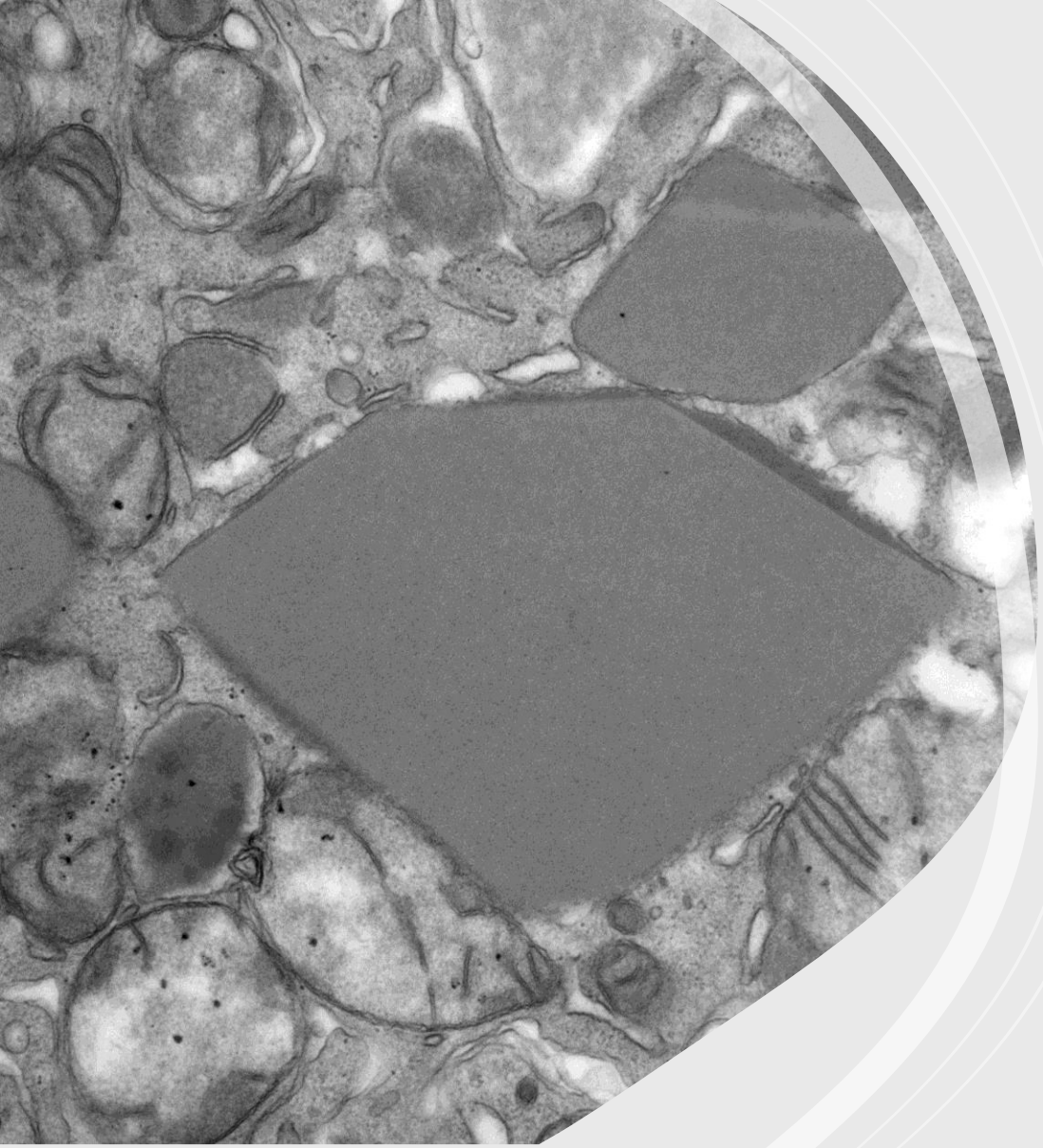


Electron Microscopy Beyond The Glomerulus

Liverpool Clinical Laboratories

Dr. Aml Mousa, MD. FRCPath.

Associate specialist, Royal Liverpool and Broadgreen Hospital

Introduction

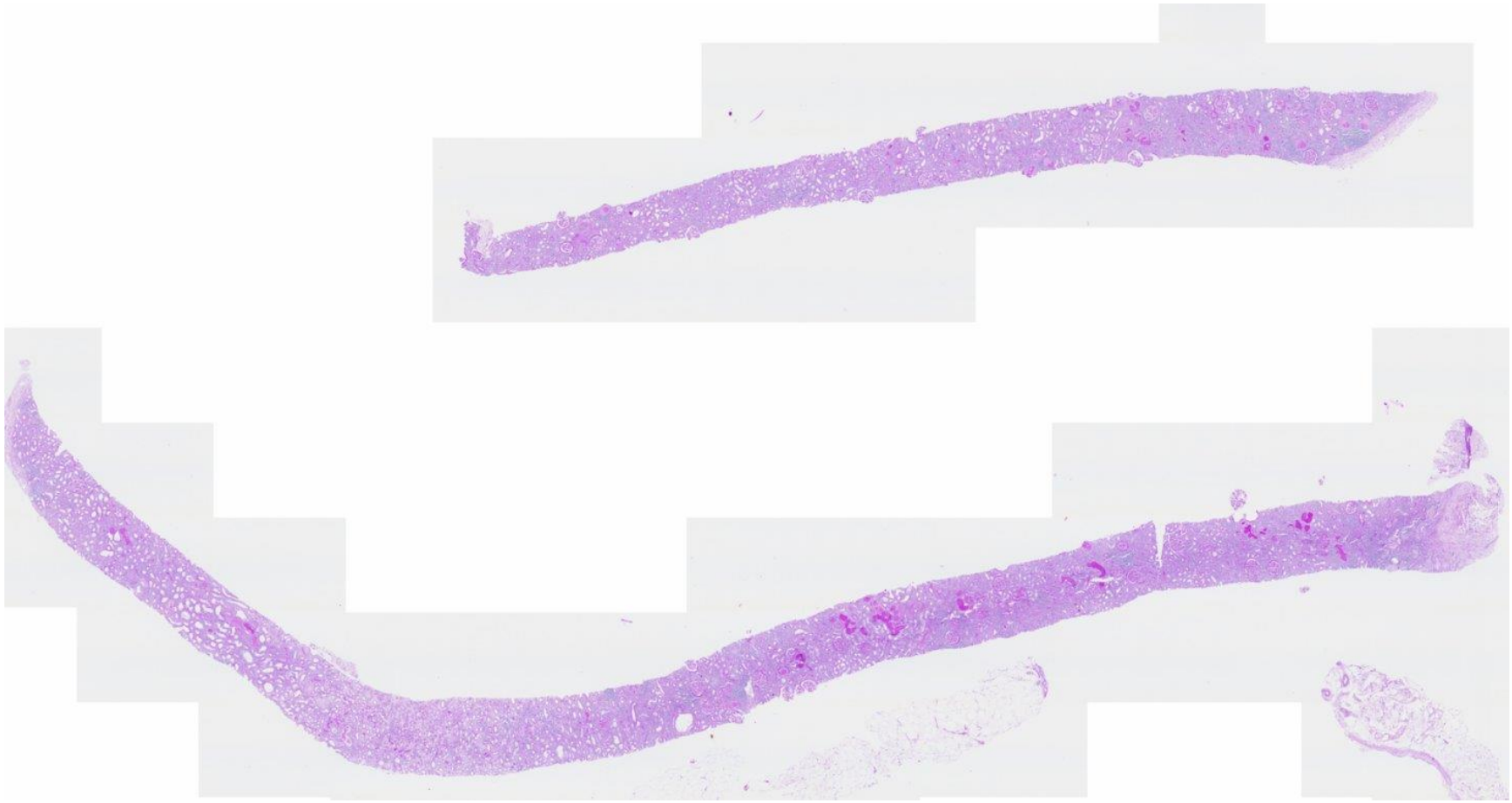
- Electron microscopy (EM) is pivotal in renal pathology, yet its diagnostic power beyond the glomerulus remains at times underutilised and overlooked.

- Although EM is routinely associated with glomerular disease, it is uniquely positioned to identify critical ultrastructural abnormalities within tubulointerstitial and vascular compartments, findings that frequently determine diagnosis, refine classification, and directly influence clinical management.

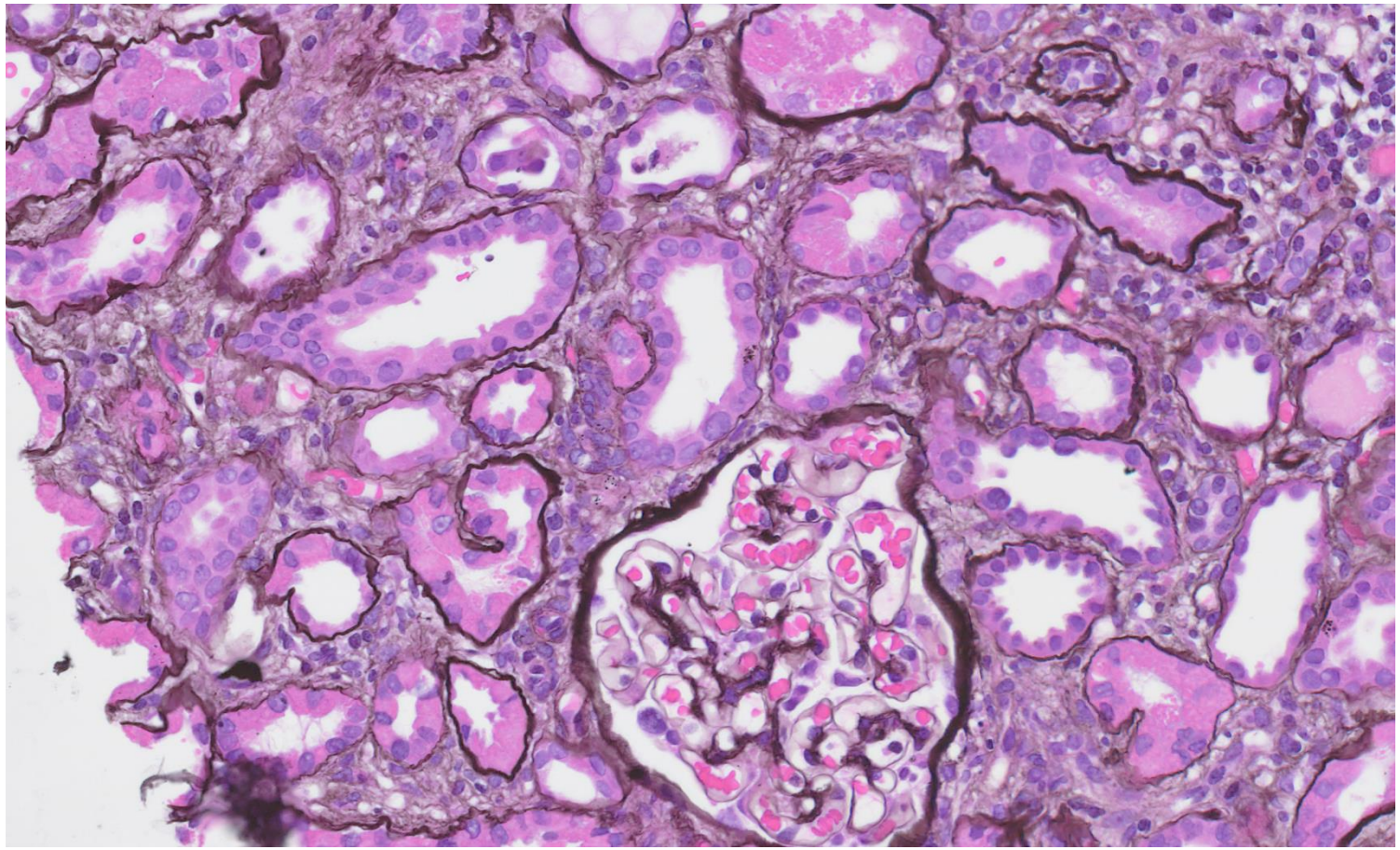
- This presentation challenges the glomerulocentric paradigm by highlighting the role of EM in non-glomerular renal pathology

Case 1

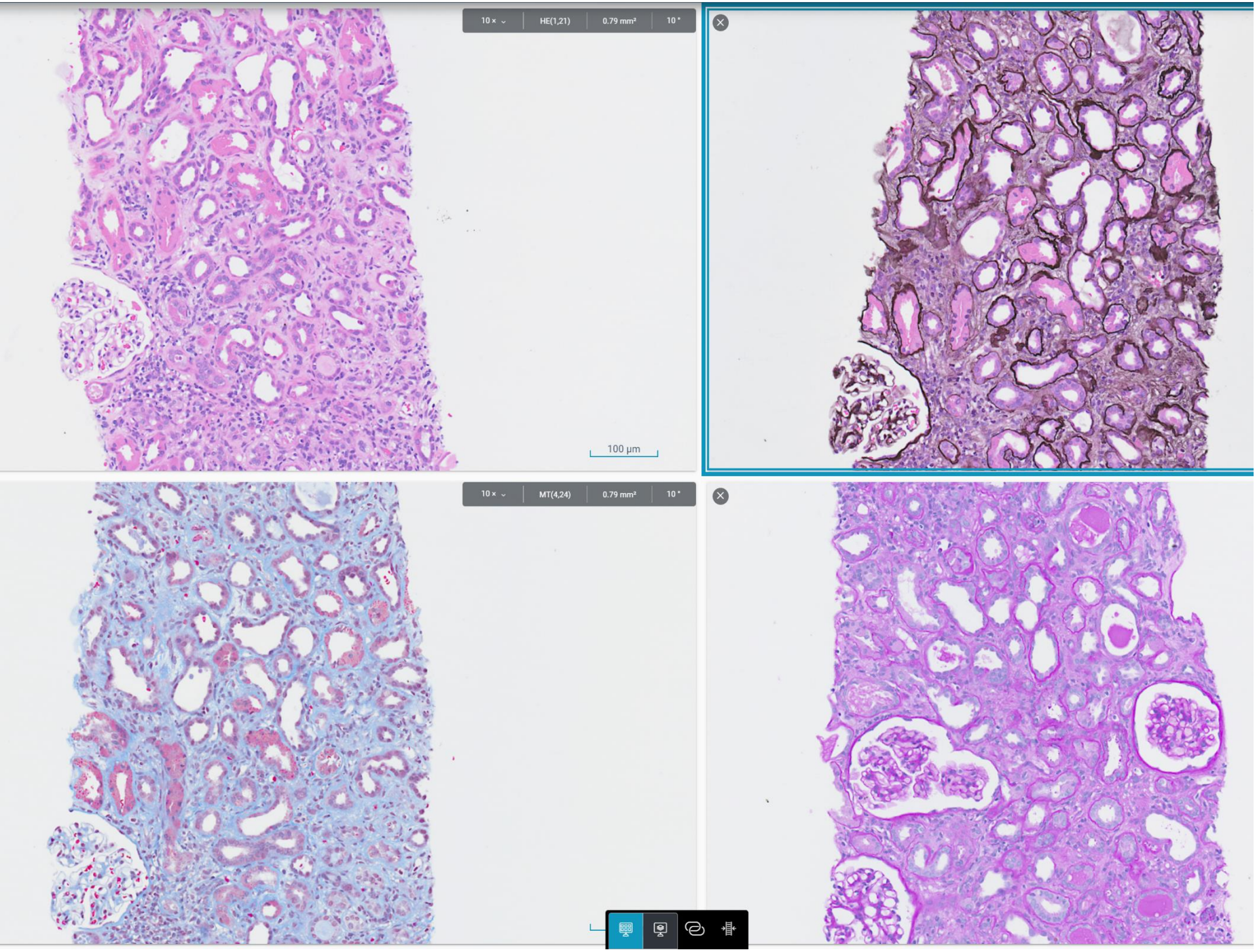
- 70 years old female patient
- **Presentation**
  - AKI after diarrhoeal illness, dialysis dependent
  - Confusion, ESRF, creatinine >2000 µmol/L
- **Background**
  - CKD known since 2021, prior eGFR ~50
  - No renal follow-up for 5 year
- **Myeloma/paraprotein screen**
  - Kappa 704.0, lambda 57.4, ratio 12.26
  - Hb 98, beta-2 microglobulin 9.1, calcium normal



Two cores of renal cortex and medulla



Two cores of renal cortex and medulla
Glomeruli: 35
9/35 Global sclerosis
No hypercellularity
No mesangial expansion
Unremarkable GBM



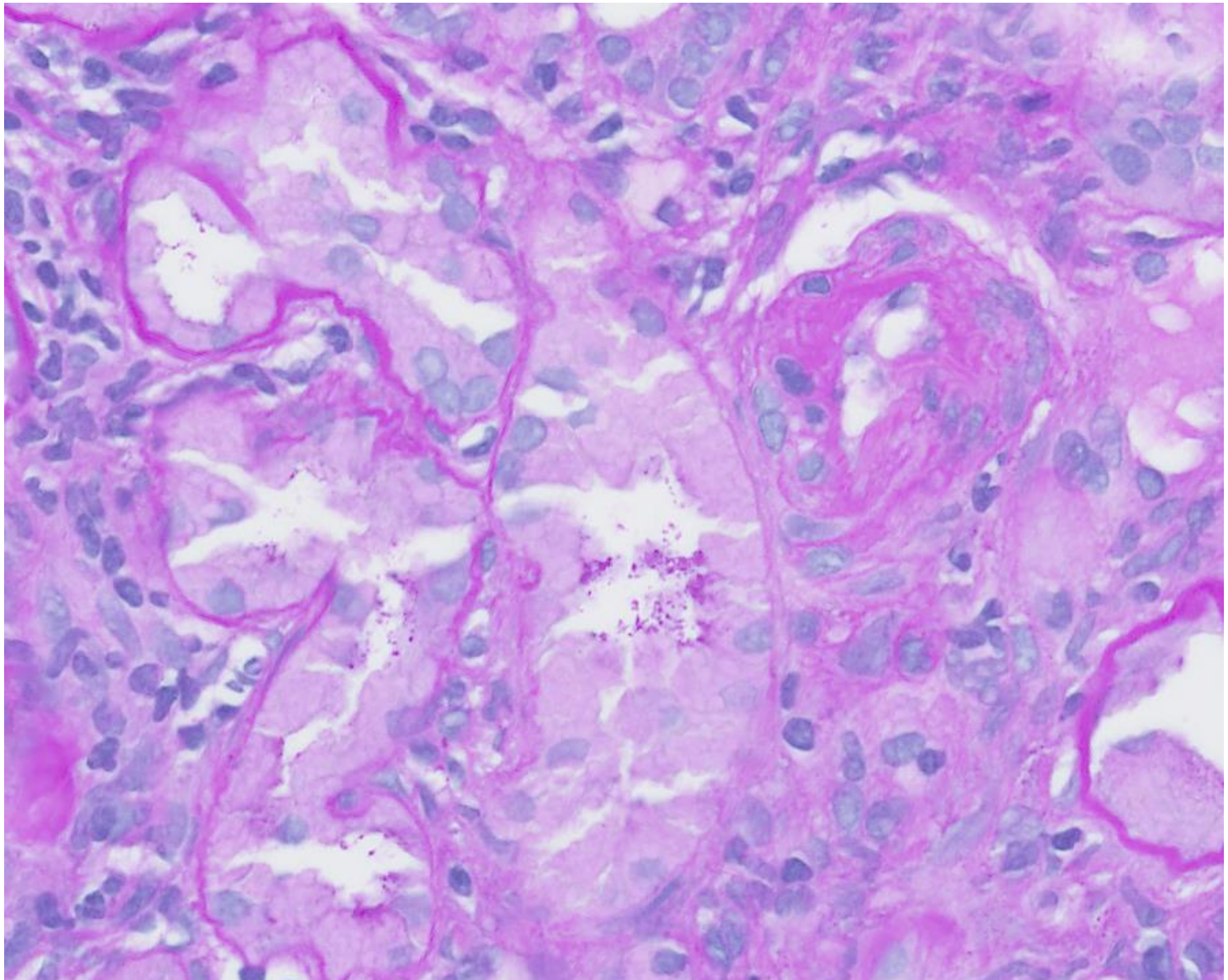
Two cores of renal cortex and medulla

Glomeruli: 35

- 9/35 Global sclerosis
- No hypercellularity
- No mesangial expansion
- Unremarkable GBM

Tubulointerstitium:

- marked chronic damage.
- Acute tubular injury



Two cores of renal cortex and medulla

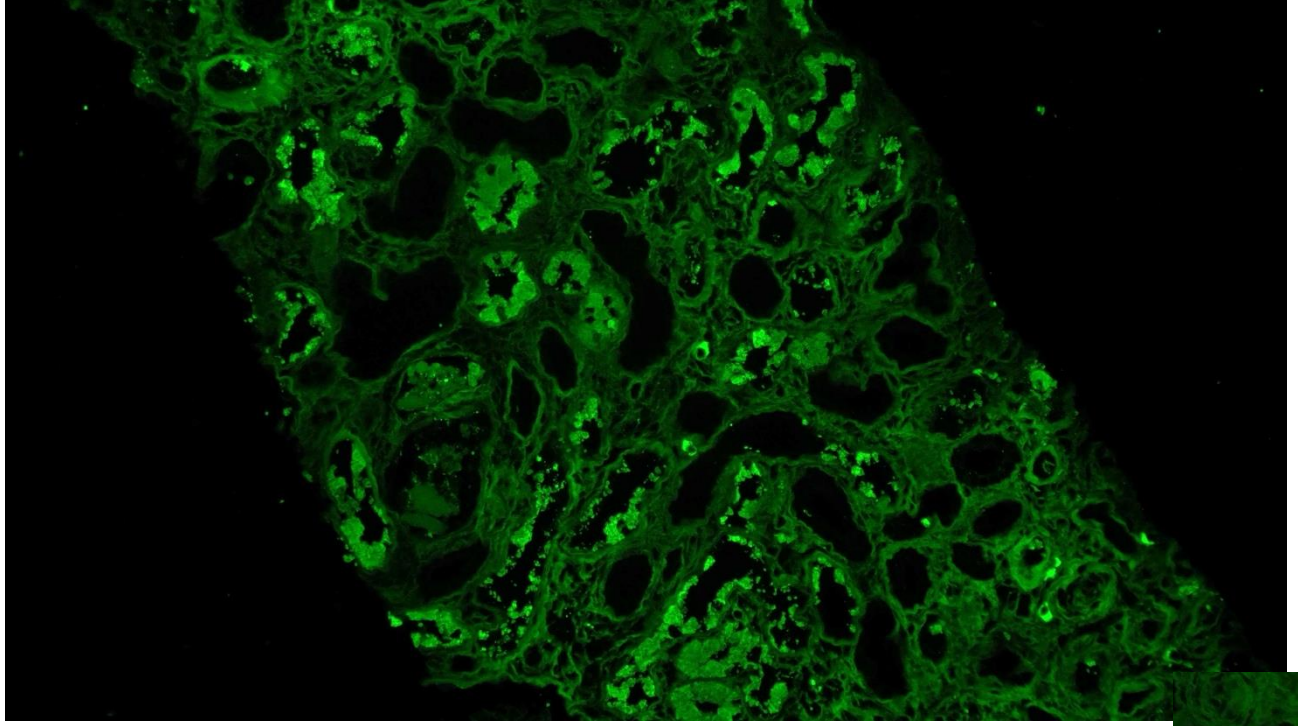
Glomeruli: 35

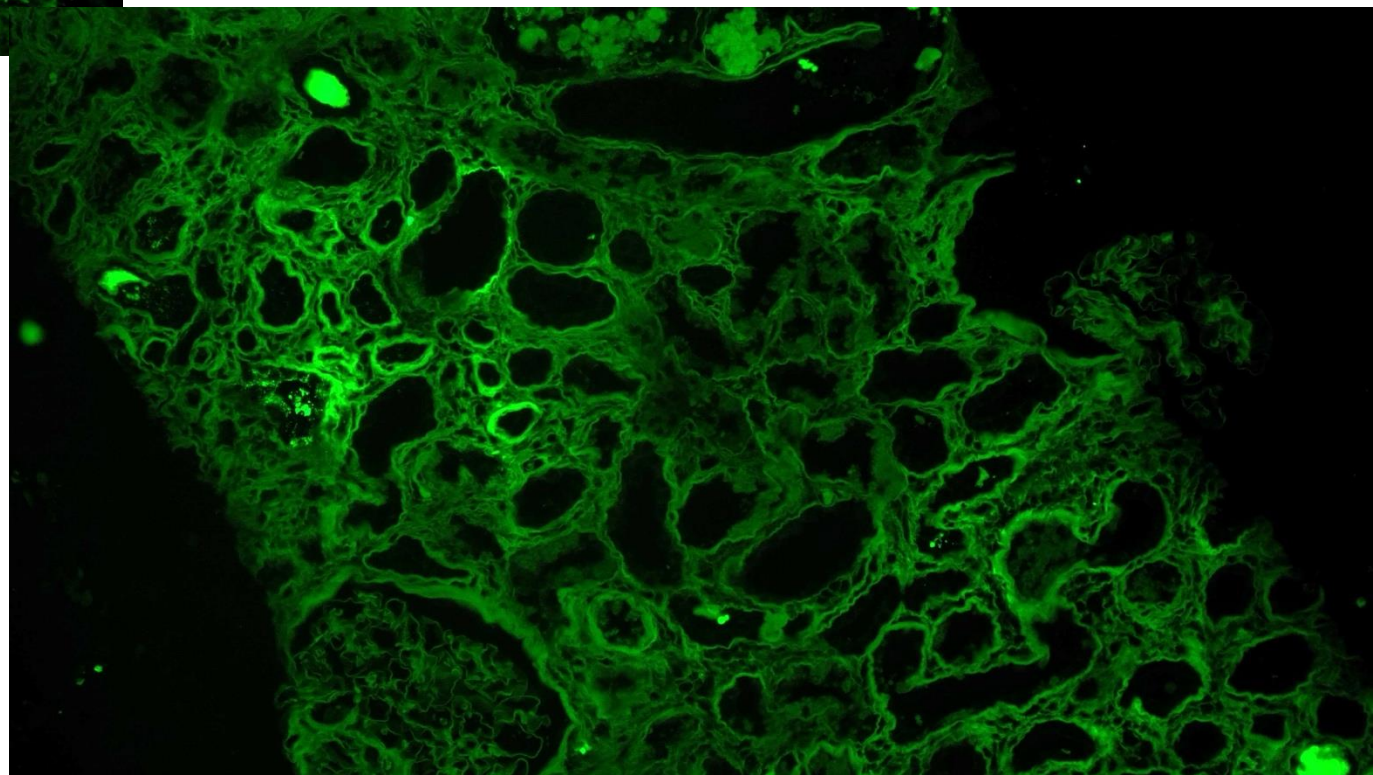
- 9/35 Global sclerosis
- No hypercellularity
- No mesangial expansion
- Unremarkable GBM

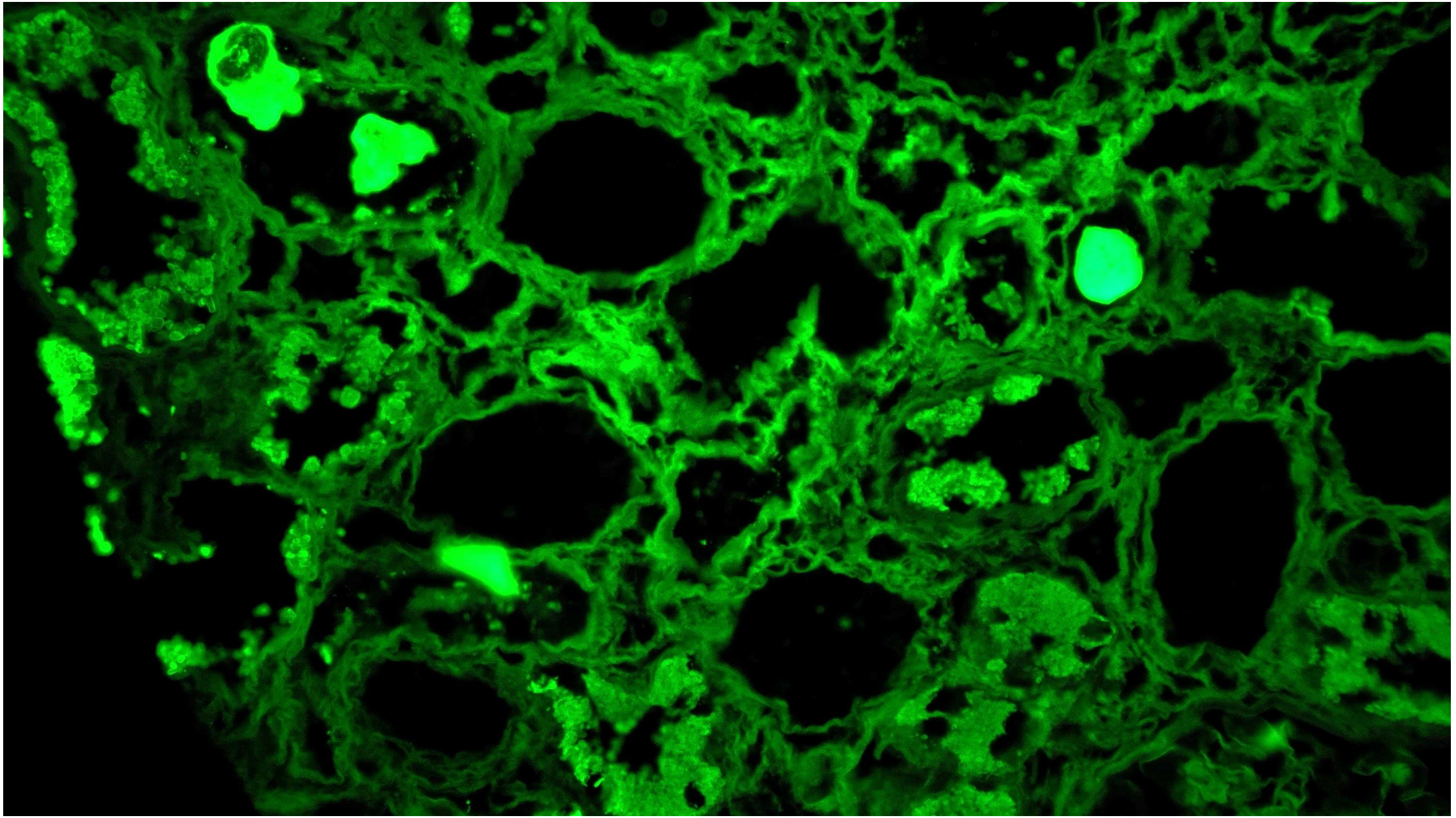
Tubulointerstitium:

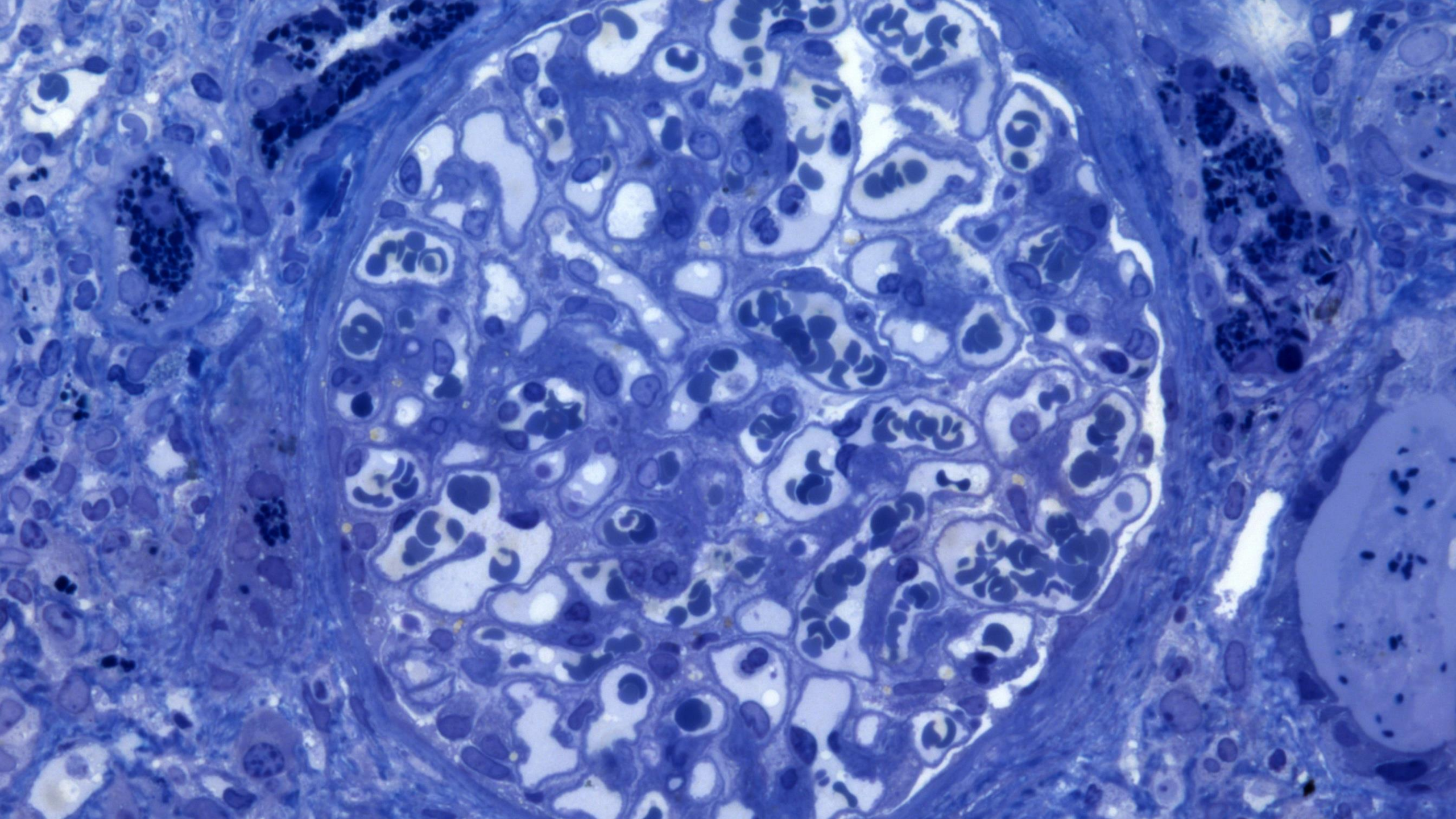
- Marked chronic damage

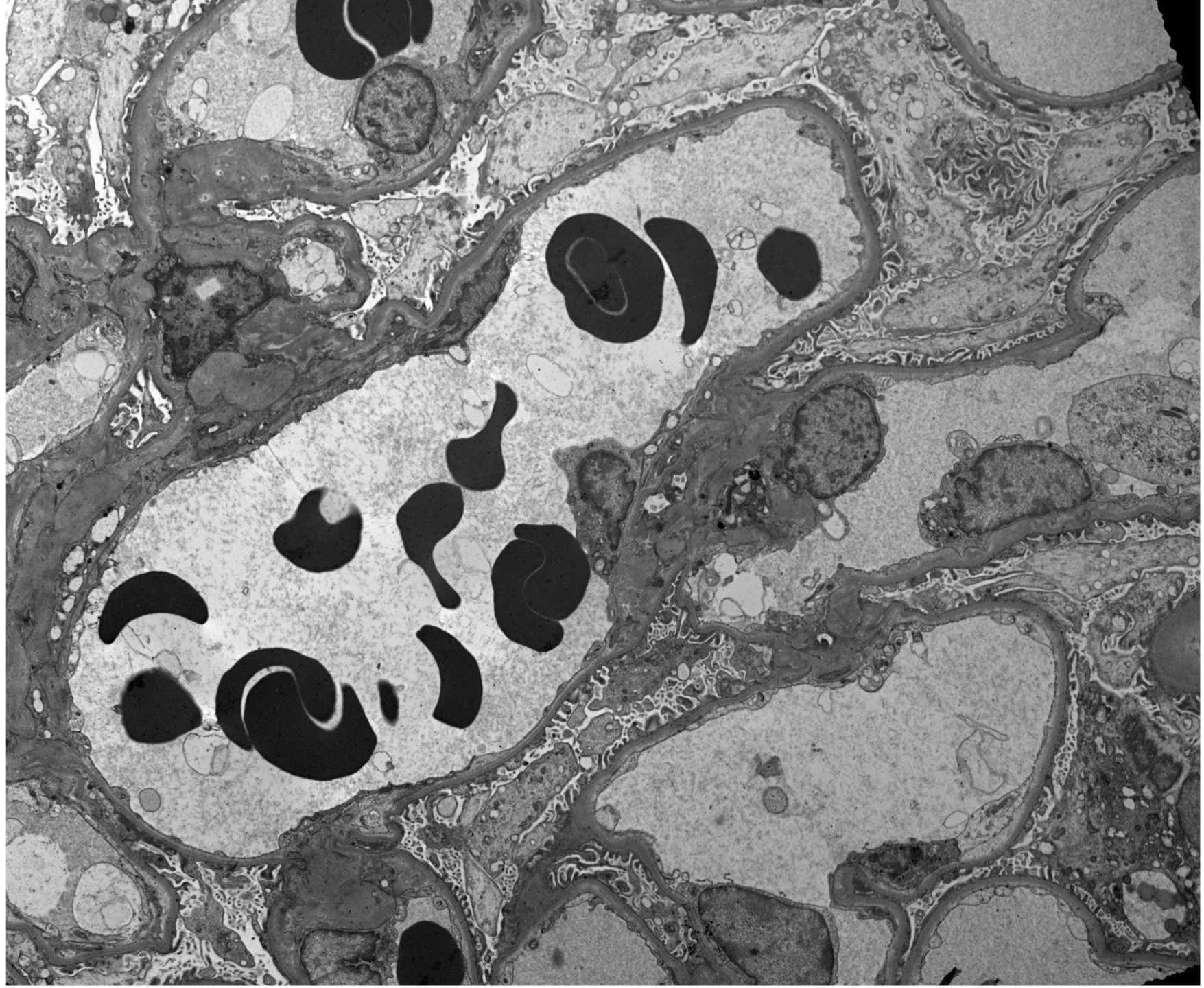
-TC show eosinophilic intracellular inclusions that are PAS negative silver negative and appear fuchsinophilic on trichrome stain.

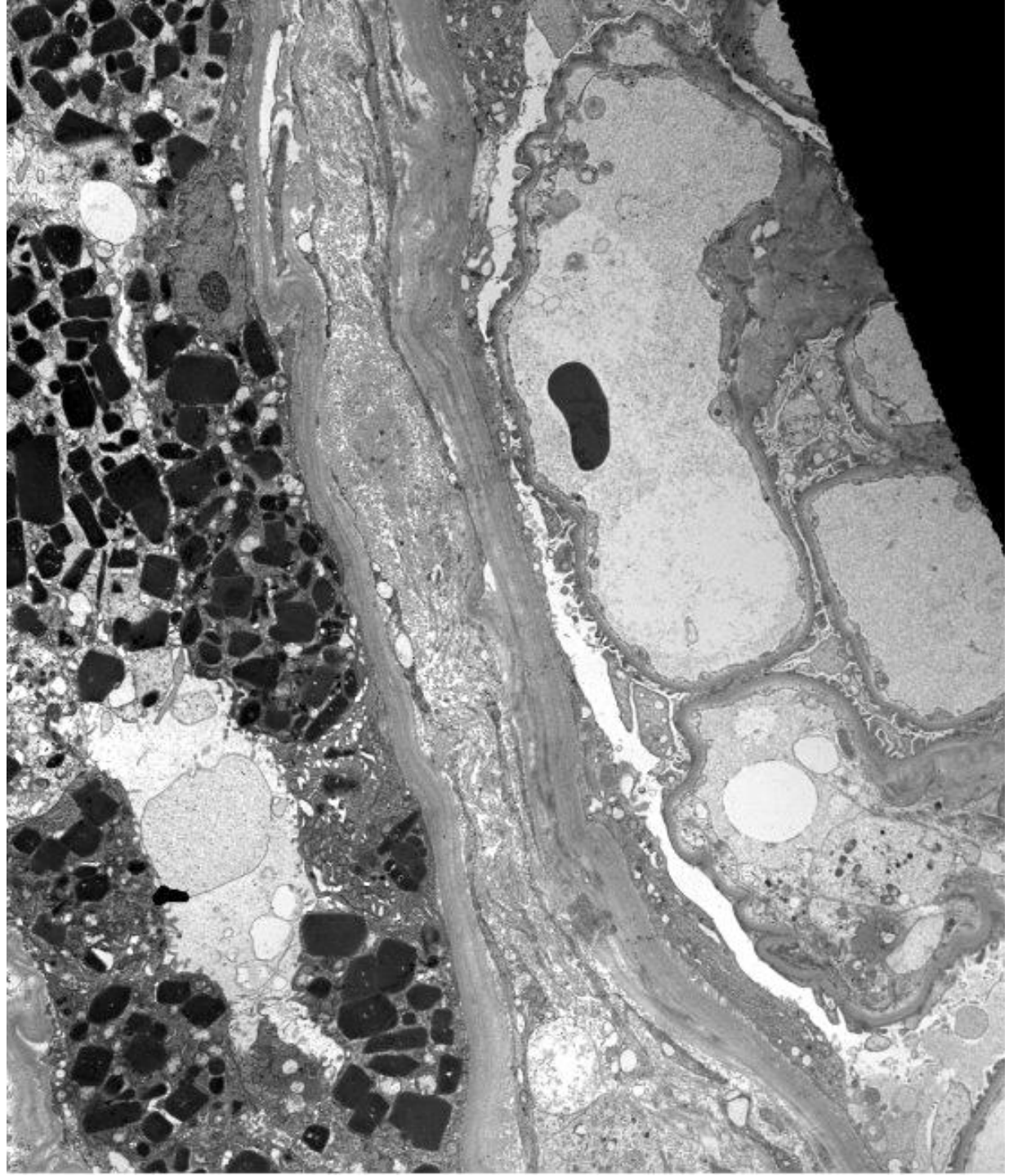


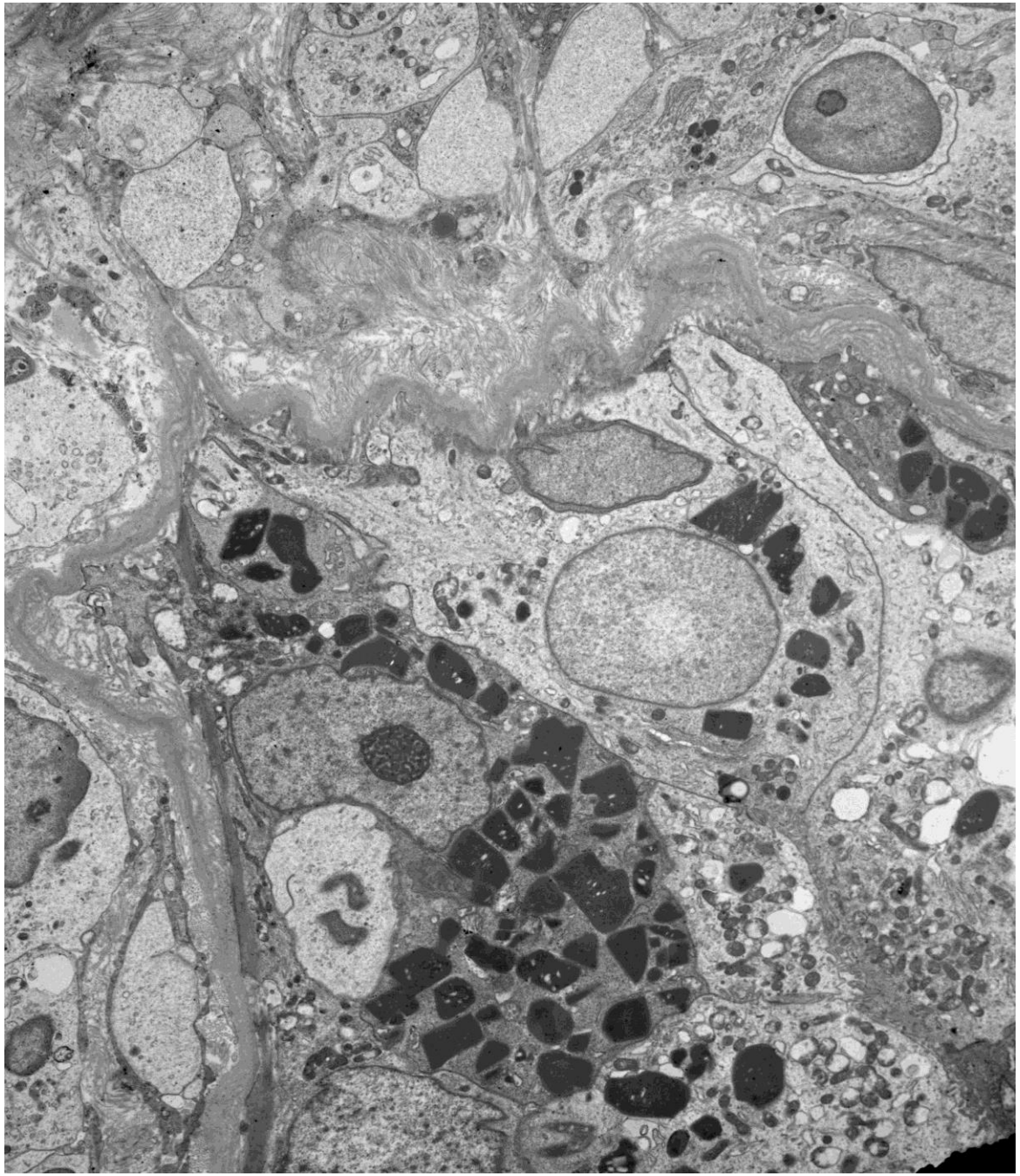


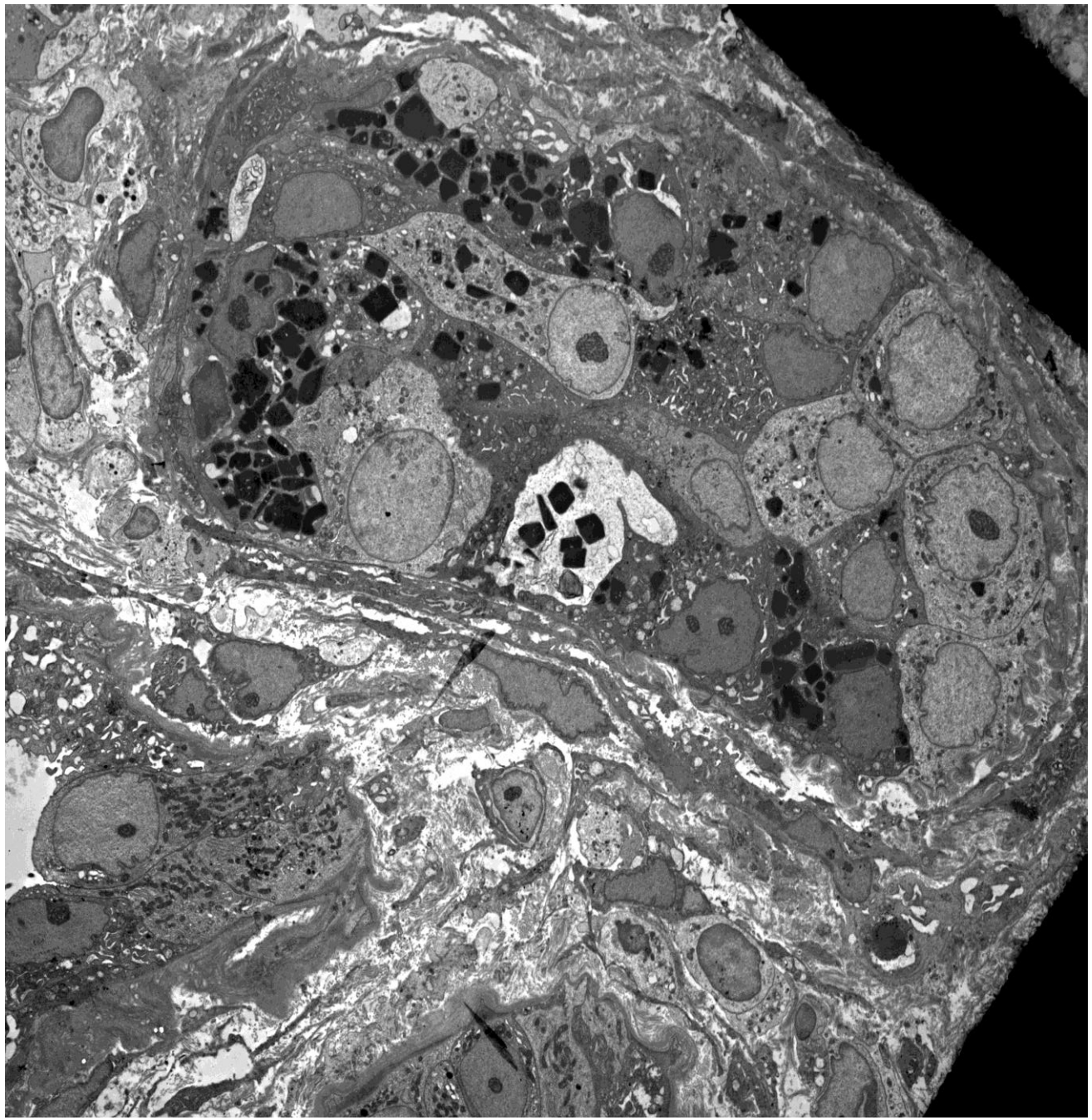


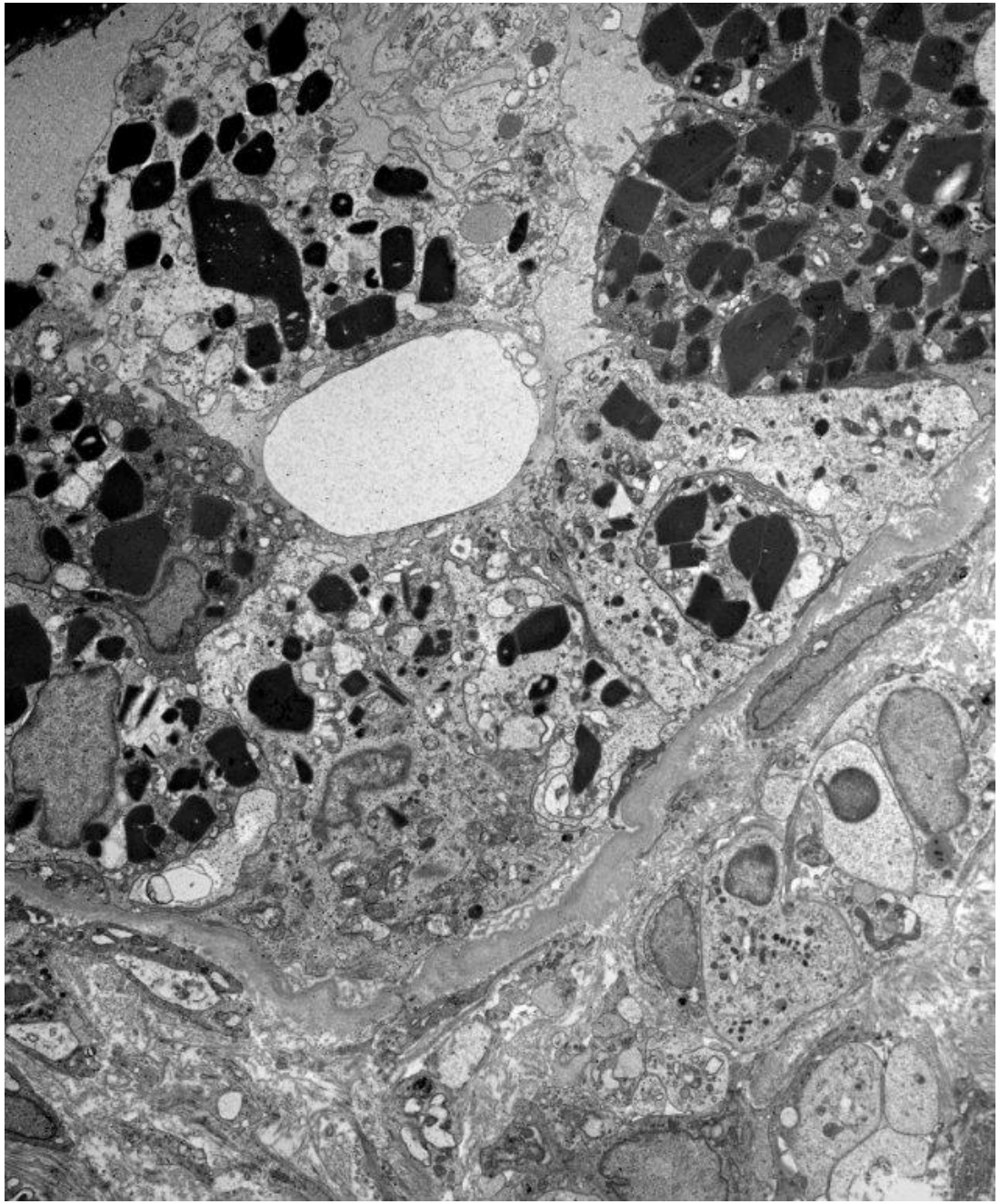


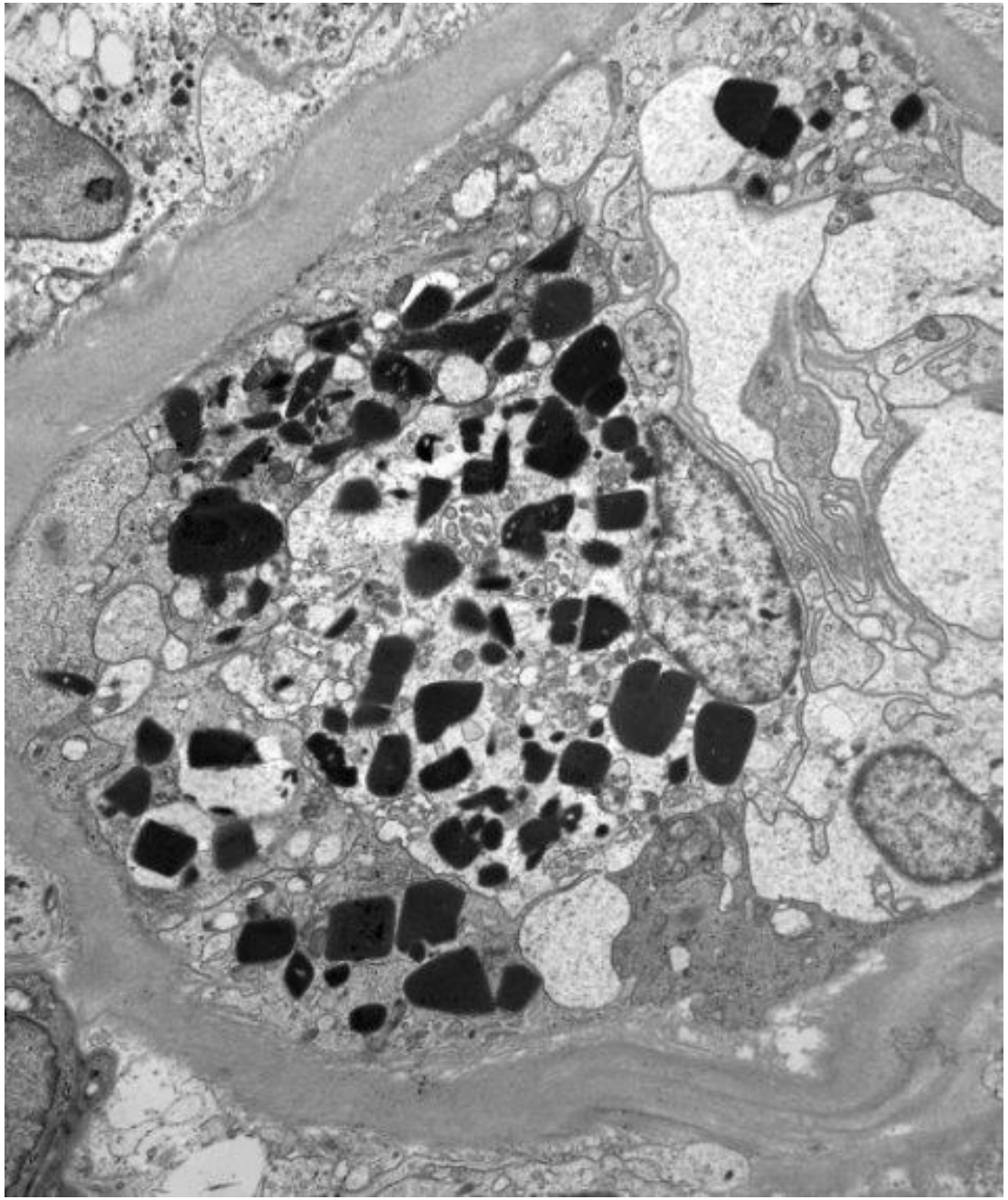












Diagnosis:

- Light chain proximal tubulopathy, crystalline

Follow up:

- BONE MARROW BIOPSY: scattered plasma cells <3% of nucleated cells with possible excess of kappa light chain , so not consistent with a myeloma diagnosis.
- The PETCT did not show any suspicious lesions, would all be more consistent with a diagnosis of MGRS.

CLINICAL RESEARCH www.jasn.org

Light Chain Proximal Tubulopathy: Clinical and Pathologic Characteristics in the Modern Treatment Era

Michael B. Stokes,* Anthony M. Valeri,† Leal Herlitz,‡ Abdullah M. Khan,§ David S. Siegel,§ Glen S. Markowitz,* and Vivette D. D'Agati*

*Departments of Pathology and †Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; ‡Department of Pathology, Cleveland Clinic, Cleveland, Ohio; and §Department of Medicine, Hackensack University Medical Center, Hackensack, New Jersey

Table 2. Pathologic findings in LCPT

	Number (%)
Total no. of participants	46
Crystalline	40[c]
Noncrystalline	6
κ LC	43/45 (96)[d]
Detection by IF-frozen	15/43 (35)
Detection by IF-pronase	37/38 (97)
ATI score[a]	
Absent	4
Mild/patchy	6
Severe/diffuse	36
Interstitial fibrosis/tubular atrophy score[b]	
0	11
1	17
2	15
3	3
Interstitial inflammation[b]	
0	13
1	28
2	5
3	0
Tubular casts	
Absent	37
Focal	9

LC, light chain.
[a]0=absent, 1=mild, 2=moderate, 3=severe.
[b]Scores: 0 (absent), 1 (<25% of cortical area), 2 (25%–49% of cortical area), and 3 (≥50% of cortical area).
[c]Five patients showed crystals by EM only.
[d]One case that did not stain for κ or λ light chain by IF performed on both frozen and pronase-digested paraffin tissue was known to have monoclonal κ light chain in urine.

ABSTRACT

Light chain proximal tubulopathy (LCPT) is char within proximal tubular cells. The significance of crystalline versus noncrystalline LCPT and the effect of modern therapies are unknown. We reported the clinical-pathologic features of 40 crystalline and six noncrystalline LCPT patients diagnosed between 2000 and 2014. All crystalline LCPTs were κ-restricted and displayed acute tubular injury. One-third of noncrystalline LCPT patients displayed λ-restriction or acute tubular injury. Only crystalline LCPT frequently required antigen retrieval to demonstrate monoclonal LC by immunofluorescence. In five of 38 patients, crystals were not detectable by light microscopy, but they were visible by electron microscopy. Hematolymphoid neoplasms, known before biopsy in only 15% of patients, included 21 monoclonal gammopathies of renal significance; 15 multiple myelomas; seven smoldering multiple myelomas; and three other neoplasms. Biopsy indications included Fanconi syndrome (38%; all with crystalline LCPT), renal insufficiency (83%), and proteinuria (98%). Follow-up was available for 30 (75%) patients with crystalline LCPT and all six patients with noncrystalline LCPT, of whom 11 underwent stem cell transplant, 16 received chemotherapy only, and nine were untreated. Complete or very good partial hematologic remissions occurred in six of 22 treated crystalline LCPT patients. By multivariable analysis, the only independent predictor of final eGFR was initial eGFR, highlighting the importance of early detection. All patients with crystalline LCPT treated with stem cell transplant had stable or improved kidney function, indicating the effectiveness of aggressive therapy in selected patients.

J Am Soc Nephrol 27: 1555–1565, 2016. doi: 10.1681/ASN.2015020185

Stokes, Michael B.*; Valeri, Anthony M.; Herlitz, Leal; Khan, Abdullah M.; Siegel, David S.; Markowitz, Glen S.*; D'Agati, Vivette D.*. Light Chain Proximal Tubulopathy: Clinical and Pathologic Characteristics in the Modern Treatment Era. Journal of the American Society of Nephrology 27(5):p 1555-1565, May 2016. | DOI: 10.1681/ASN.2015020185

Clinicopathological characteristics of light chain proximal tubulopathy: a multicentre case series

Yao Lin,[1,2] Guolan Xing,[3] Ruimin Hu,[3] Shaojun Liu,[4] Guisen Li,[5] Ping Zhang,[5] Feng Xu,[6] Dandan Liang,[6] Xiaodong Zhu,[6] Mingchao Zhang,[6] Fan Yang,[6] Xinchen Yao,[6] Feng Liu,[6] Yujie Wang,[6] Shihui Dong,[6] Shaoshan Liang,[1] Caihong Zeng [1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jcp-2024-209620).

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ABSTRACT

Aims Light chain proximal tubulopathy (LCPT) is a rare complication of paraprotein-related diseases. We report a case series to present the clinicopathological characteristics and outcomes of LCPT.

Methods A multicentre retrospective case series of 47 patients with LCPT, consisting of 36 crystalline, three non-crystalline, and eight mixed LCPTs, was studied between January 2007 and December 2023.

Results The median age at diagnosis was 57 years. Presentations included proteinuria (100%), renal insufficiency (62%) and Fanconi syndrome (68%). The underlying haematological diagnoses were monoclonal gammopathy of renal significance in 81% and multiple myeloma in 19%. Monoclonal light chain (LC) was detected in all cases using serum/urine-free LC assays or immunofixation electrophoresis. Among 36 crystalline LCPTs, 34 were κ-restricted and 2 λ-restricted. Three non-crystalline LCPTs were all λ-restricted. In mixed LCPTs, seven were κ-restricted and one was λ-restricted. Notably, 66% frozen-section immunofluorescence failed to reveal restricted LC, requiring paraffin-immunofluorescence or immunoelectron microscopy. The appearance of inclusions displayed intraindividual homogeneity but interindividual heterogeneity in 42 patients and notable intraindividual heterogeneity in the remaining 5 patients. Haematological complete response, very good partial response and partial response occurred in 61%. Kidney function improved or remained stable in 84%, worsened in 8% and progressed to end-stage renal disease in 8%.

Conclusions Proteinuria and kidney dysfunction are the most common but less-specific renal manifestations of LCPTs, with most featuring Fanconi syndrome. Crystalline LCPT, primarily associated with κ-LC, is the predominant form. Most inclusions displayed intraindividual homogeneity and interindividual heterogeneity by electron microscopy. Most achieved haematological responses and favourable renal outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Light chain proximal tubulopathy (LCPT) is a rare complication of paraprotein-related diseases characterised by the presence of monoclonal light chain inclusions within proximal tubular cells and occurs traditionally in two main histopathological forms: crystalline and non-crystalline.

WHAT THIS STUDY ADDS

⇒ Under electron microscopy, the majority of inclusions exhibit intraindividual homogeneity and interindividual heterogeneity, and a minority display significant intraindividual heterogeneity in electron densities and morphologies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This detailed description of LCPT highlights the intraindividually heterogeneous inclusions confirmed by immunoelectron microscopy.

LCPT with involvement of multiple cell types from 2007 to 2014.[2] The biopsy-proven LCPT has recently increased, prompting us to pay close attention to this issue. We retrospectively analysed multicentre Chinese patients with LCPT.

MATERIALS AND METHODS

Patients and clinical data

The diagnostic criteria for LCPT were as follows: (1) abnormal cytoplasmic inclusions in PTCs or proximal tubular injury observed by light microscopy (LM); (2) LC-restricted staining in PTCs observed by immunofluorescence (IF); (3) crystals or increased abnormal lysosomal inclusions observed by electron microscopy (EM).[2] Patients' medical records were

J Clin Pathol: first published as 10.1136/jcp-2024-209620 on 12 December 2024. Downloaded from http://jcp.bmj.com/ on June 19, 2026 a
Protected by copyright, including for uses related to text and data mining, AI training, and similar technol
Trust (NHS).

Table 3 Pathological characteristics of 47 cases of LCPT

Parameter	Value
Light microscopy	
Semiquantitative intracytoplasmic inclusions:	
0/1/2/3	3/16/14/14
Characteristics of inclusions staining	
H&E visibility	29/47 (62%)
PAS visibility	41/47 (87%)
PASM visibility	2/47 (4%)
Trichrome visibility	37/47 (79%)
TB visibility	16/28 (57%)
ATI: 0/1/2/3	14/25/7/1
IF/TA: 0/1/2/3	17/26/2/2
Interstitial inflammation: 0/1/2/3	10/26/8/3
Immunofluorescence	
Monoclonal immunoglobulin type: κ/λ	40/6*
Detection by IF-F	16/47 (34%)
Detection by IF-P	36/38 (95%)
Detection by IE	17/17 (100%)
Electron microscopy	
Crystalline/non-crystalline/mixed type	36/3/8
Location of intracytoplasmic crystals by electron microscopy or light microscopy	
PTCs	44
Glomeruli (Podos/MCs/Endos/PECs)	8 (6/6/4/4)
IHs	9
PCECs	3

Values are presented as number (percentage) or mean±SD.
Interstitial inflammation; semiquantitative intracytoplasmic inclusions: 0, no/minimal; 1, ≤25%; 2, 26%–50%; 3, >50%.
*One case that did not stain for κ or λ light chain by IF performed on both frozen and pronase-digested paraffin tissue was known to have monoclonal κ light chain in serum.
ATI, acute tubular injury; Endos, endothelial cells; IE, immunoelectron microscopy; IF-F, immunofluorescence on frozen tissue; IF-P, immunofluorescence on paraffin tissue; IF/TA, interstitial fibrosis and tubular atrophy; IHs, interstitial histiocytes.; LCPT, light chain proximal tubulopathy; MCs, mesangial cells; PAS, periodic acid Schiff; PASM, periodic acid-silver methenamine; PCECs, peritubular capillary endothelial cells; PECs, parietal epithelial cells; Podos, podocytes; PTCs, proximal tubular cells; TB, toluidine blue; trichrome, Masson trichrome.

Lin Y, Xing G, Hu R, et al. J Clin Pathol 2025;78:562–568.

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www.kidney-international.org

meeting report

Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions

Samih H. Nasr[1], Virginie Royal[2], Alejandro Best Rocha[3], Maike Büttner-Herold[4], Candice Roufosse[5], Frank Bridoux[6], Wesam Ismail[7], Lihong Bu[1], Lynn D. Cornell[1], Amélie Dendooven[8], Rajib K. Gupta[9], Shigeo Hara[10], Vincent Javaugue[6], Nicolas Kozakowski[11], Satoru Kudose[12], Gonzalo P. Méndez[13], Kimberley Oliver[14], Maria M. Picken[15], Dominick Santoriello[12], Sanjeev Sethi[1], Akira Shimizu[16], Geetika Singh[17], M. Barry Stokes[12], Su-xia Wang[18], Nelson Leung[19,20], Glen S. Markowitz[12] and Vivette D. D'Agati[12]

Nasr S et al. **Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions.** Kidney International, 2025; 108, 184-19

Five distinct mechanisms of monoclonal Ig kidney damage

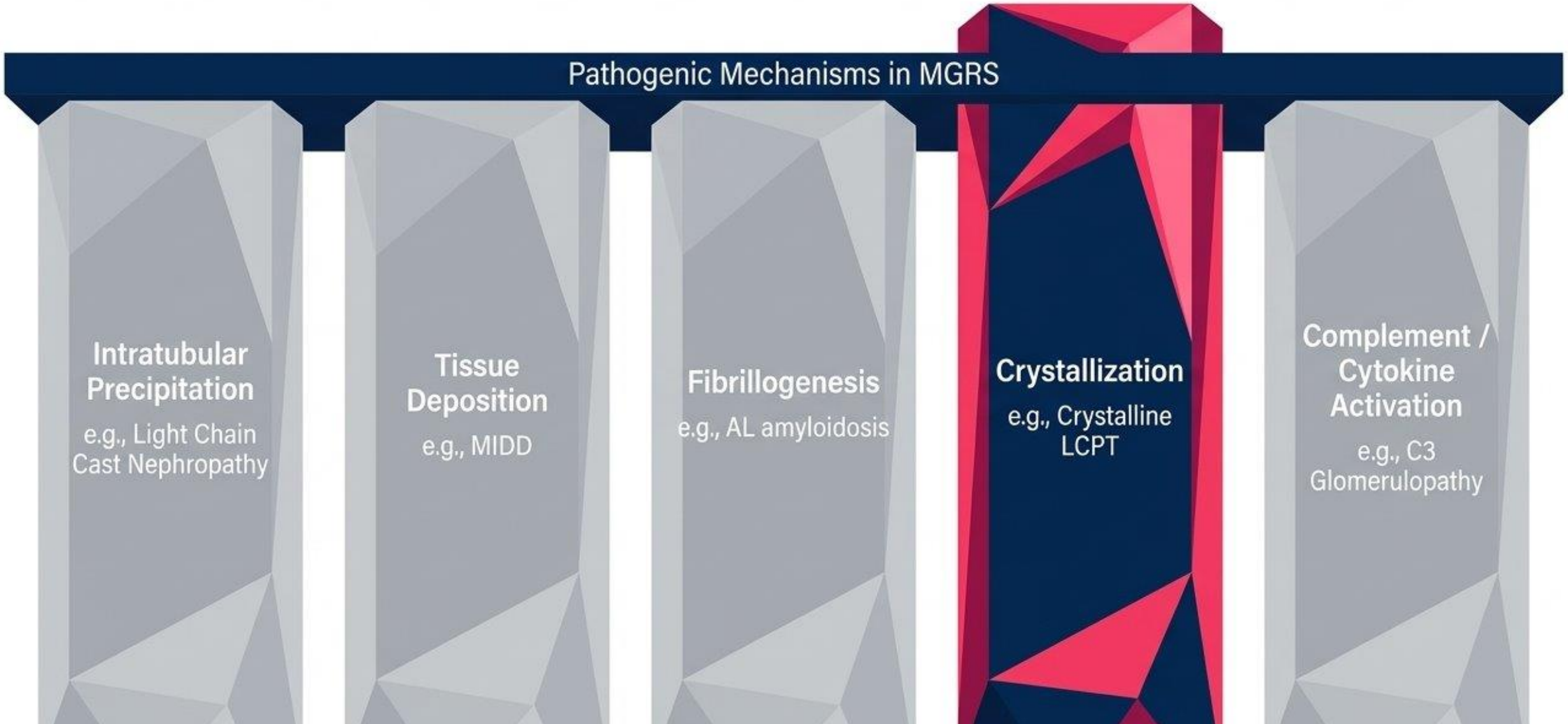


Table 5 | Proposed diagnostic criteria for monoclonal gammopathy–associated crystalline nephropathies

Lesion	Abbreviations	Prerequisite diagnostic criteria (all must be met)	Supportive features
Crystalline light chain proximal tubulopathy	Crystalline LCPT	• Crystals within proximal tubular cell cytoplasm by EM and/or LM • Monotypic Ig LC staining[a]	• κ in >95% • Fanconi syndrome • Tubular proteinuria • MGRS
Light chain crystalline podocytopathy	LCCP	• Abundant crystals within podocytes by EM and/or LM • Monotypic Ig LC staining[a]	• κ in 87% • FSGS (particularly collapsing variant) • Significant albuminuria • MGRS • LC crystalline keratopathy
Light chain crystal-storing histiocytosis	CSH	• Crystals within interstitial or glomerular histiocytes by LM and/or EM (not adjacent to ruptured tubules) • Monotypic Ig LC staining[a]	• κ in ∼80% • Crystal-laden histiocytes in bone marrow or other organs • MGRS in majority
Crystalglobulin-induced nephropathy	CIN	• Intravascular (extracellular) crystals (in glomerular and/or vascular lumina) visible by LM and EM, with/without thrombosis, mild glomerular proliferative response, or arteritis • Uninvolved glomeruli unremarkable • No granular EDD by EM • Monotypic intact[c] Ig or Ig LC staining[a]	• IgGκ in 65% • Paracrystalline[b] substructure on EM • Cutaneous (e.g., rash/ulcers) and/or rheumatologic manifestations • Negative serum cryoglobulin
Crystalline cryoglobulinemic glomerulonephritis type I	Crystalline CryoGN type I	• Glomerular crystals: intracellular (within macrophages or endothelial cells) and extracellular (intraluminal, subendothelial, or mesangial) • Macrophage-rich MPGN or proliferative GN • Monotypic intact[c] Ig staining[a]	• Intraluminal pseudothrombi • Granular EDD by EM • Positive serum cryoglobulin

CIN, crystalglobulin-induced nephropathy; CryoGN, cryoglobulinemic glomerulonephritis; CSH, crystal-storing histiocytosis; EDD, electron-dense deposit; EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; Ig, immunoglobulin; LC, light chain; LCCP, light chain crystalline podocytopathy; LCPT, light chain proximal tubulopathy; LM, light microscopy; MGRS, monoclonal gammopathy of renal significance; MPGN, membranoproliferative glomerulonephritis.

[a]By immunofluorescence, immunoperoxidase technique, or immunoelectron microscopy. Many of these lesions require immunofluorescence on paraffin tissue after antigen retrieval by a protease (e.g., pronase, proteinase K) or by the immunoperoxidase technique for detection.

[b]Parallel linear arrays with periodicity ranging from 13–31 nm.

[c]Composed of both light chain and heavy chain.

A proposed pathologic definition of *crystal* is an inclusion having at least 1 straight edge.

Nasr S et al. **Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions.** Kidney International, 2025; 108, 184-19

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www.kidney-international.org meeting report

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Samih H. Nasr[1], Virginie Royal[2], Alejandro Best Rocha[3], Maike Büttner-Herold[4], Candice Roufosse[5], Frank Bridoux[6], Wesam Ismail[7], Lihong Bu[1], Lynn D. Cornell[1], Amélie Dendooven[8], Rajib K. Gupta[9], Shigeo Hara[10], Vincent Javaugue[6], Nicolas Kozakowski[11], Satoru Kudose[12], Gonzalo P. Méndez[13], Kimberley Oliver[14], Maria M. Picken[15], Dominick Santoriello[12], Sanjeev Sethi[1], Akira Shimizu[16], Geetika Singh[17], M. Barry Stokes[12], Su-xia Wang[18], Nelson Leung[19,20], Glen S. Markowitz[12] and Vivette D. D'Agati[12]

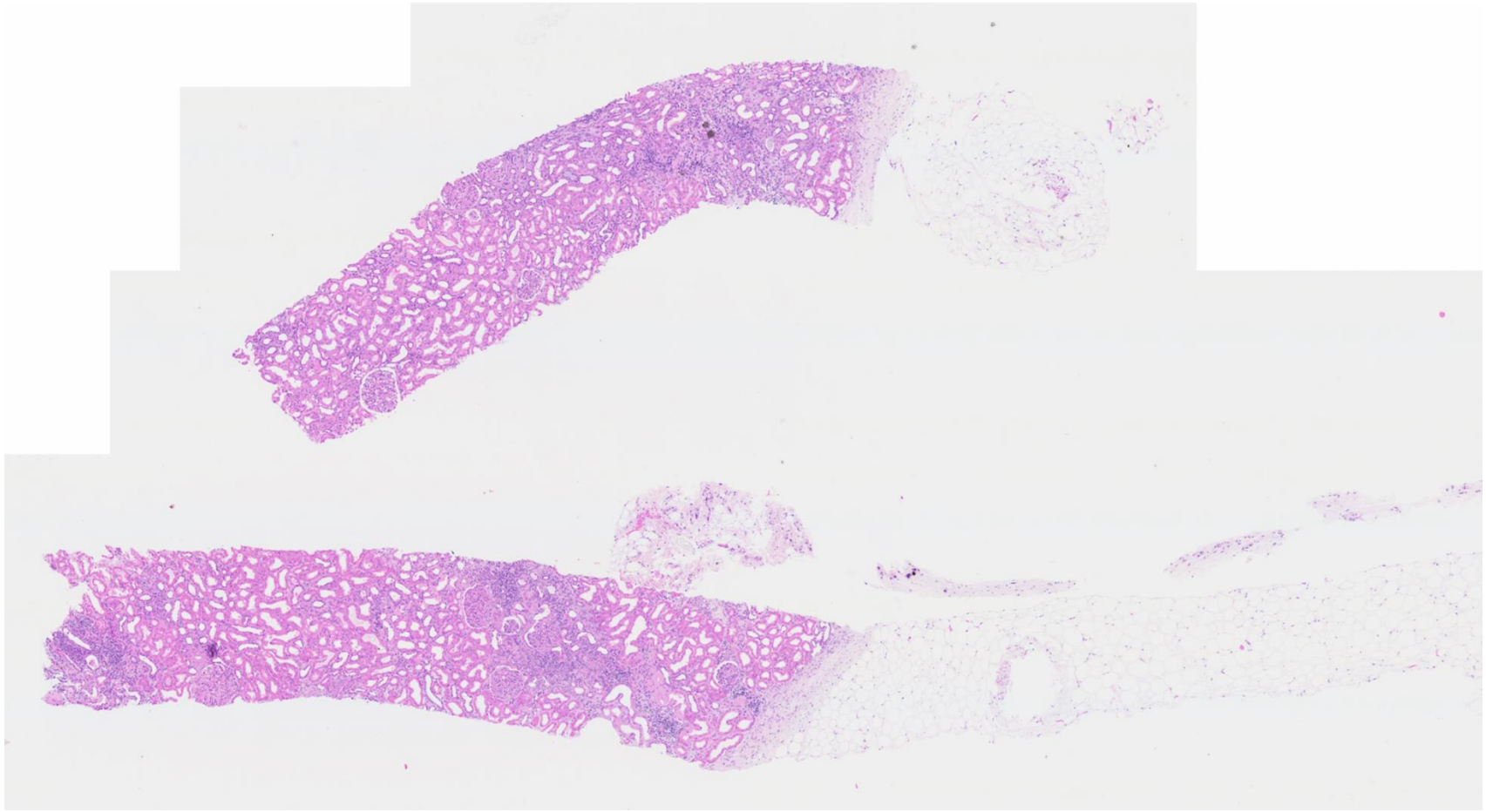
MG-associated crystalline nephropathies. The group adopted the pathologic definition of crystal proposed by Stokes *et al.* "an inclusion having at least one straight edge."[38(p1564)] In crystalline LCPT, intratubular crystals are not always visible by light microscopy but are always identifiable by electron microscopy. Therefore, the definition is worded as *crystals within proximal tubular cell cytoplasm by electron microscopy and/or light microscopy*. The group debated how to classify cases of LCPT in which the intracytoplasmic inclusions are highly organized with repeating substructures (e.g., forming unusual feather-like or rope-like structures) but lack the classic appearance of densely packed, geometric crystals. Because these structures suggest formation by a highly ordered pattern of molecular alignment, the consensus opinion was to include them within crystalline LCPT.

In addition to the old lesions—crystalline LCPT (formerly *light chain Fanconi syndrome*) and crystal-storing histiocytosis—the spectrum of MG-associated crystalline nephropathies (Table 5) has expanded over the past decade to include light chain crystalline podocytopathy, crystalglobulin-induced nephropathy, crystalline cryoglobulinemic GN type I, and a glomerular variant of crystal-storing histiocytosis.[10,34,59,60] The working group emphasizes that the diagnosis of most of these lesions requires IF-P to demonstrate the monotypic Ig composition of crystals,[10,34,38] and advocates establishing this test in nephropathology laboratories that currently do not perform this procedure, or ensuring its availability as a send-out test. Published protocols for IF-P on formalin-fixed, paraffin-embedded tissue after antigen retrieval by pronase or proteinase K are available.[61,62]

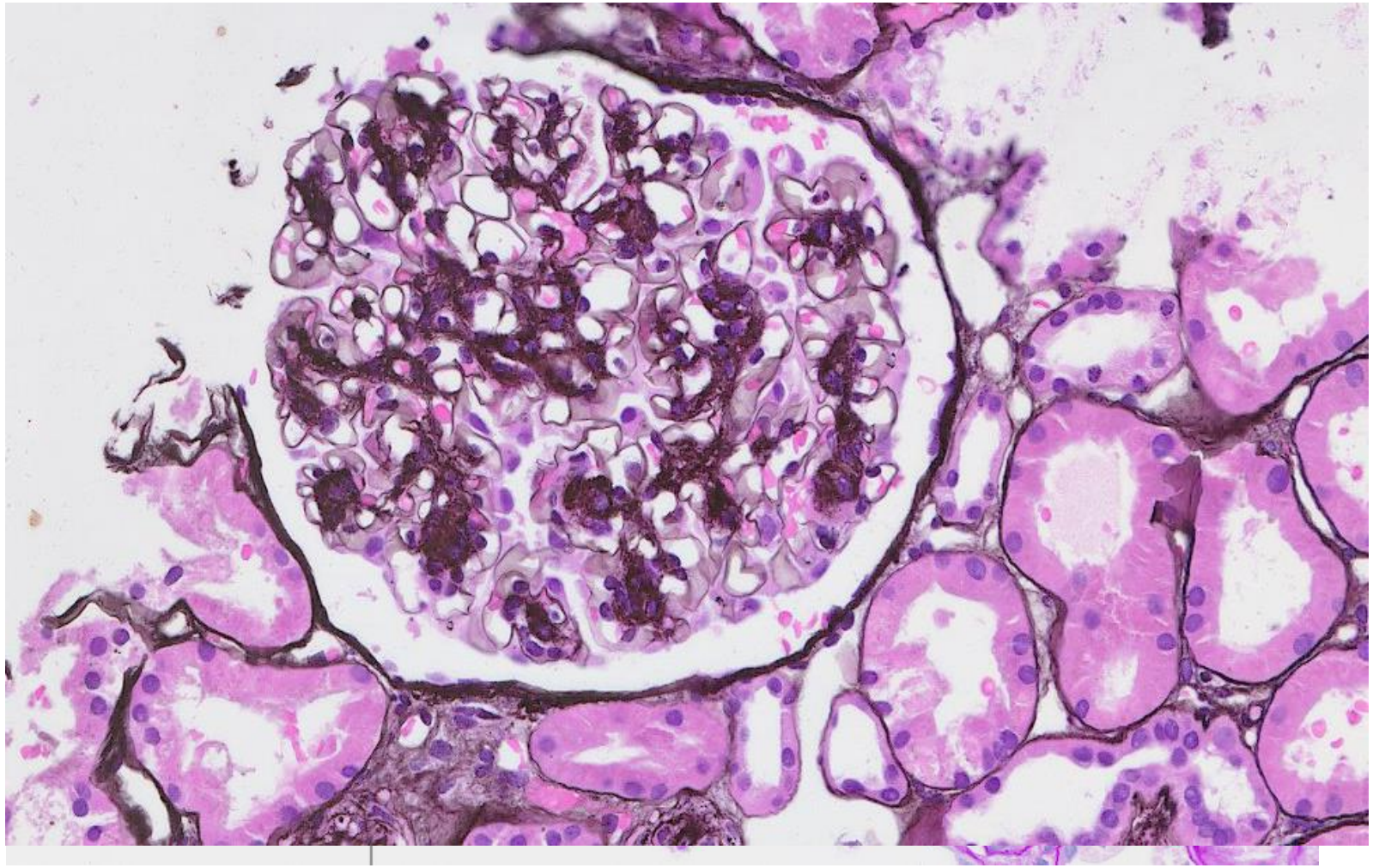
Nasr S et al. **Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions.** Kidney International, 2025; 108, 184-19

Case 2

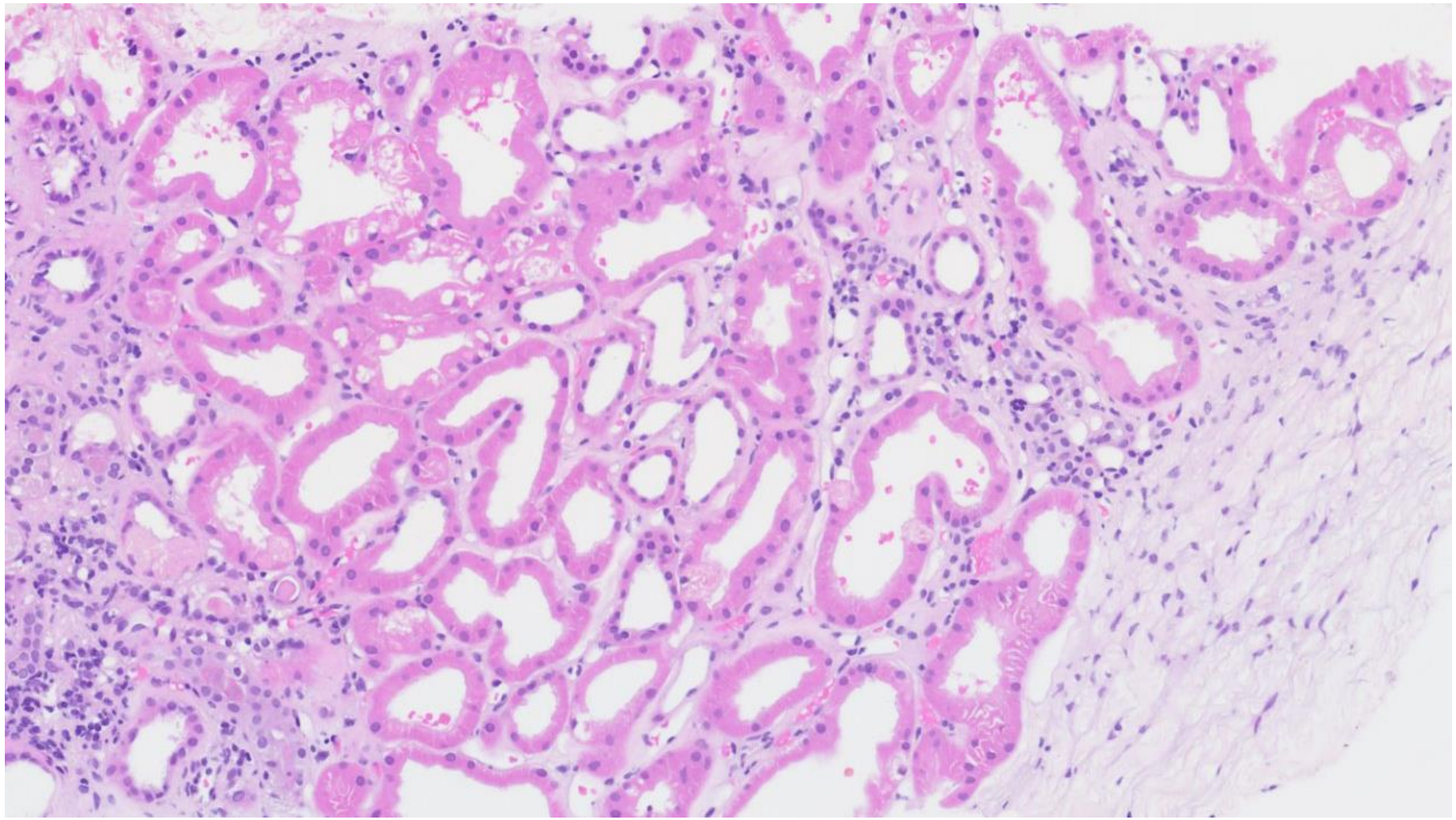
- **Presentation**
  - Worsening renal function of unclear cause
  - Creatinine 170 µmol/L
  - uACR 76
- **Background**
  - Type 2 diabetes since 2005
  - Diabetic retinopathy
  - Right upper lobectomy for T1bN0 lung adenocarcinoma in 2018
- **Paraprotein work-up**
  - IgG paraproteinaemia
  - Raised kappa:lambda ratio
  - Query diabetic nephropathy versus monoclonal renal disease



Two cores of renal cortex



Two cores of renal cortex
Glomeruli: 15
- 6/15 global sclerosis
- 5/15 mesangial expansion with nodule formation
- GBM: focal thickening



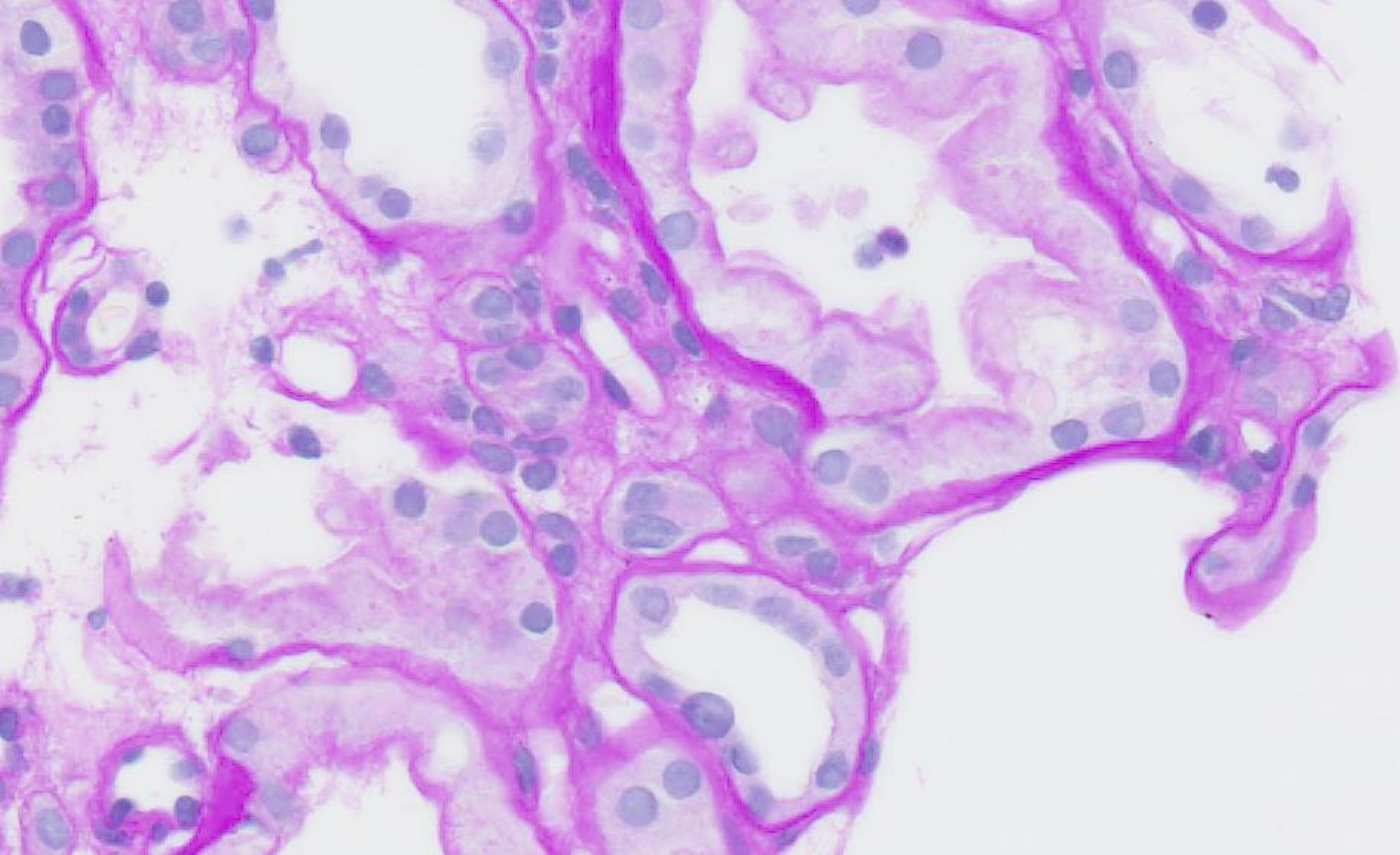
Two cores of renal cortex

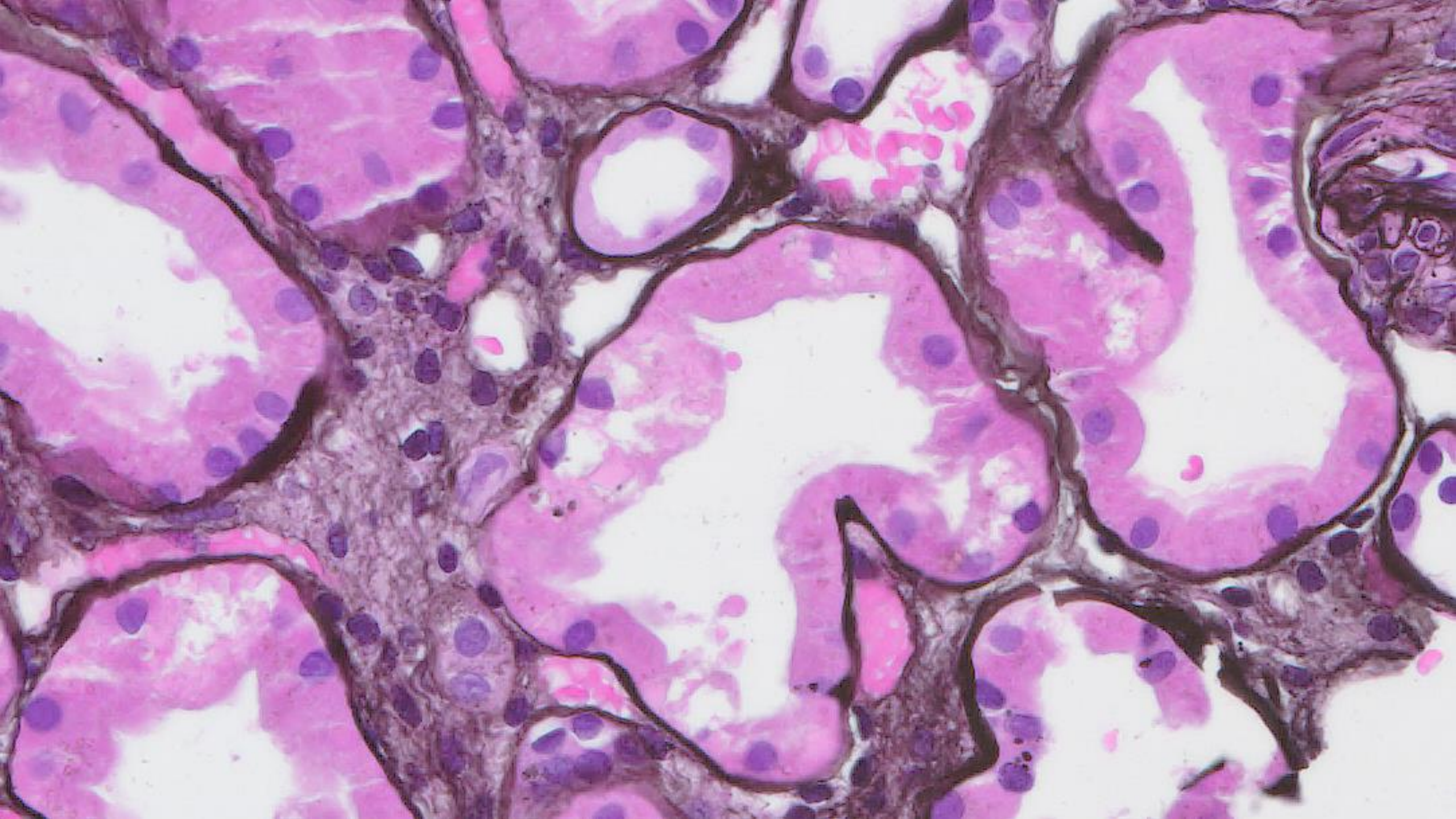
Glomeruli: 15

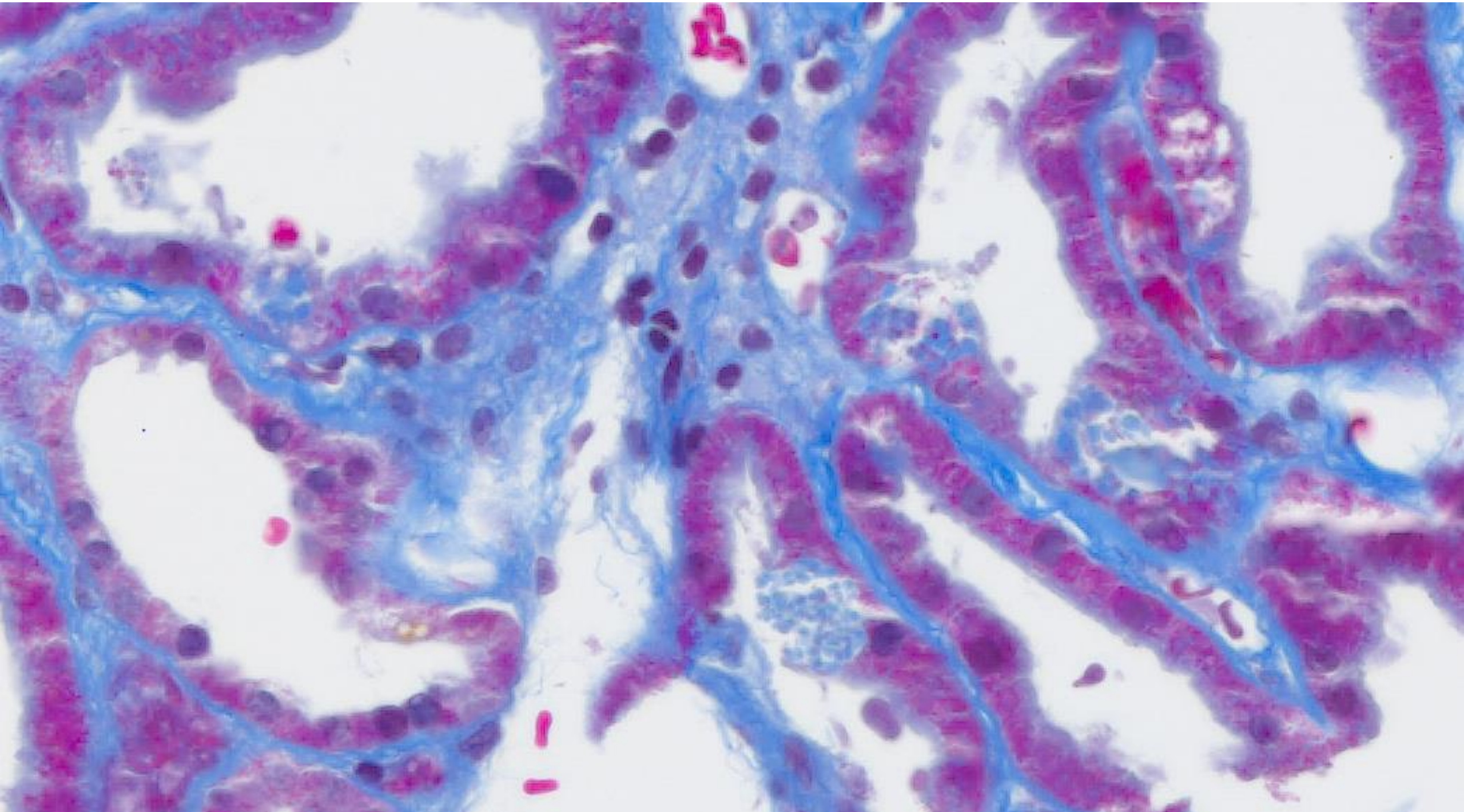
- 6/15 global sclerosis
- 5/15 mesangial expansion with nodule formation
- GBM: focal thickening

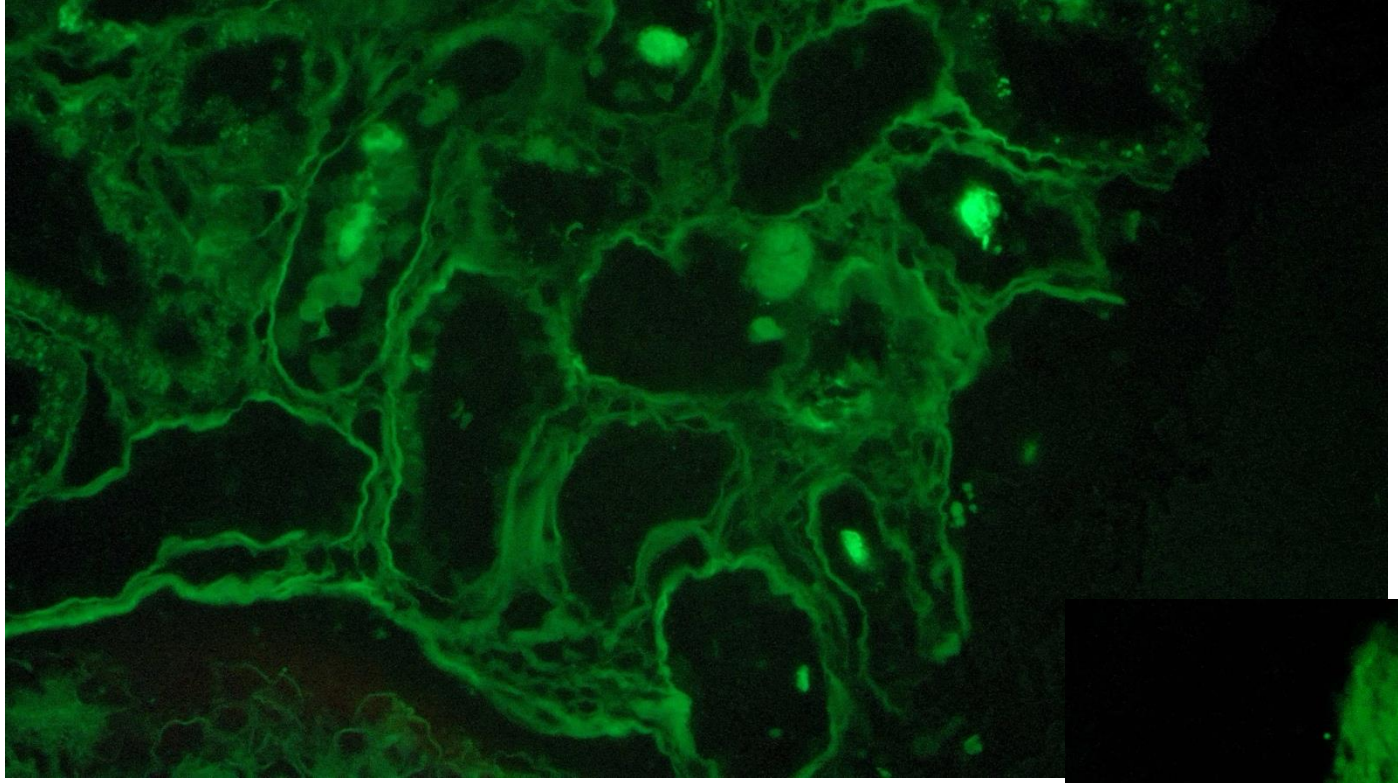
Tubulointerstitium:

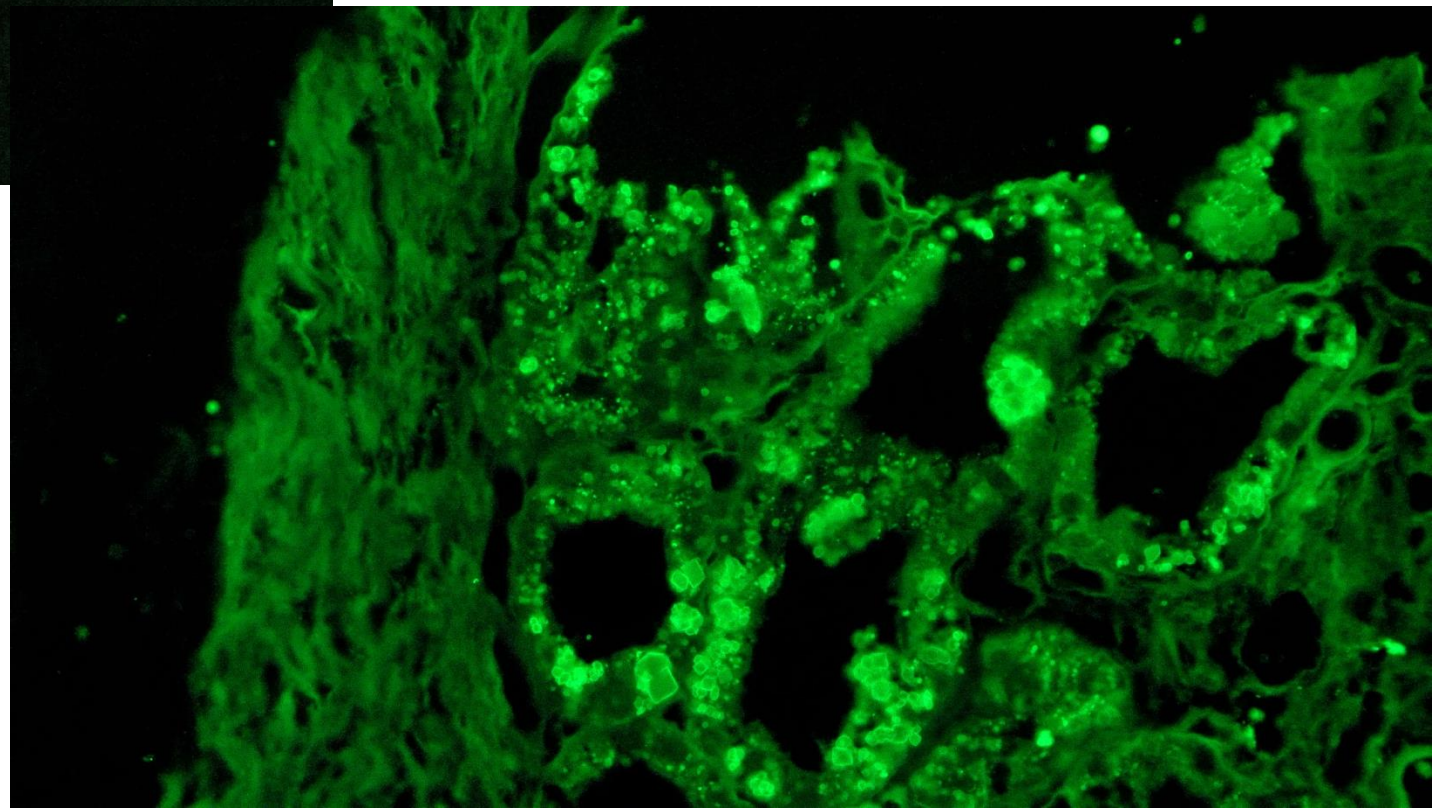
- There is acute tubular injury.
- Mild chronic damage

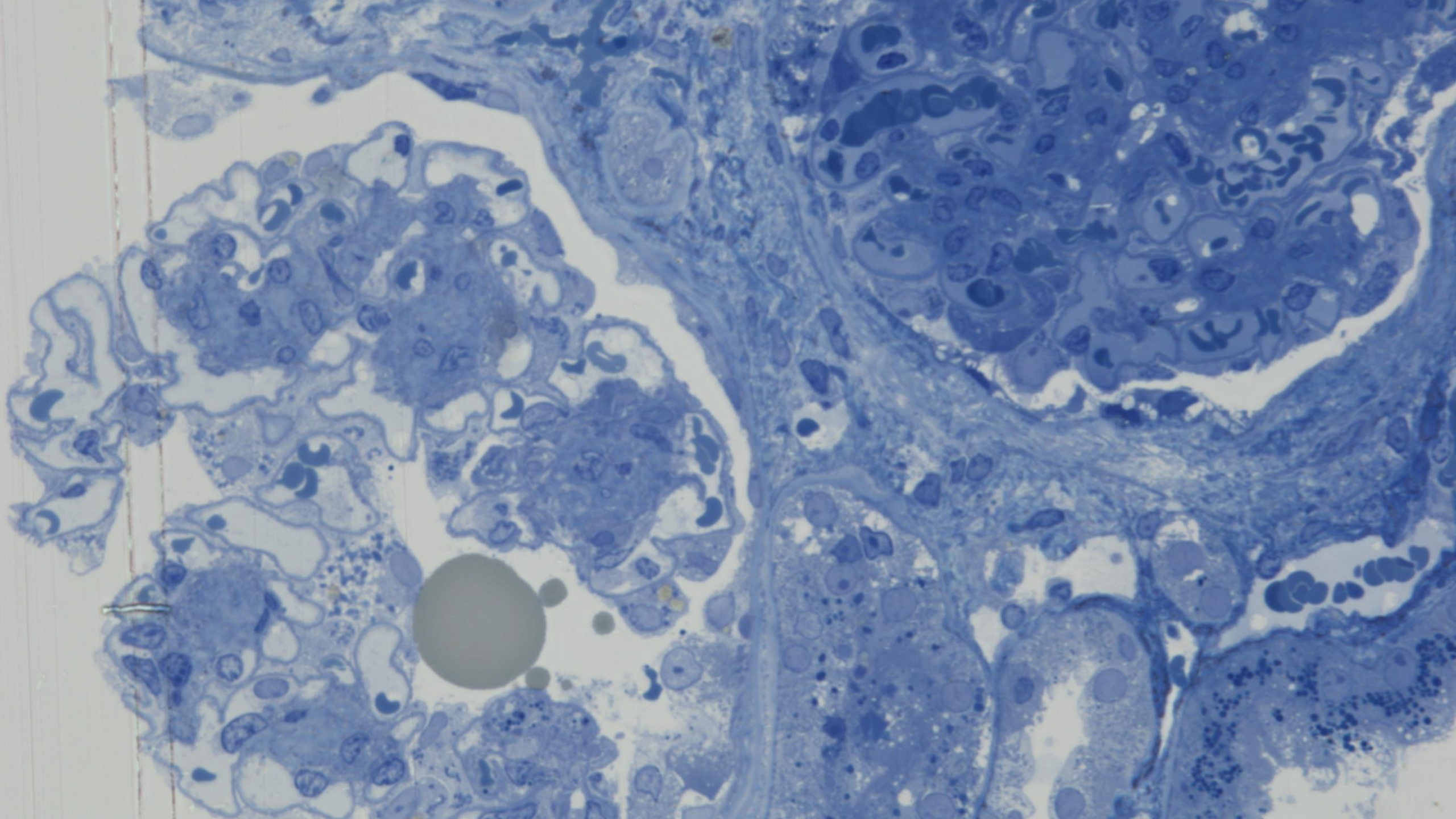


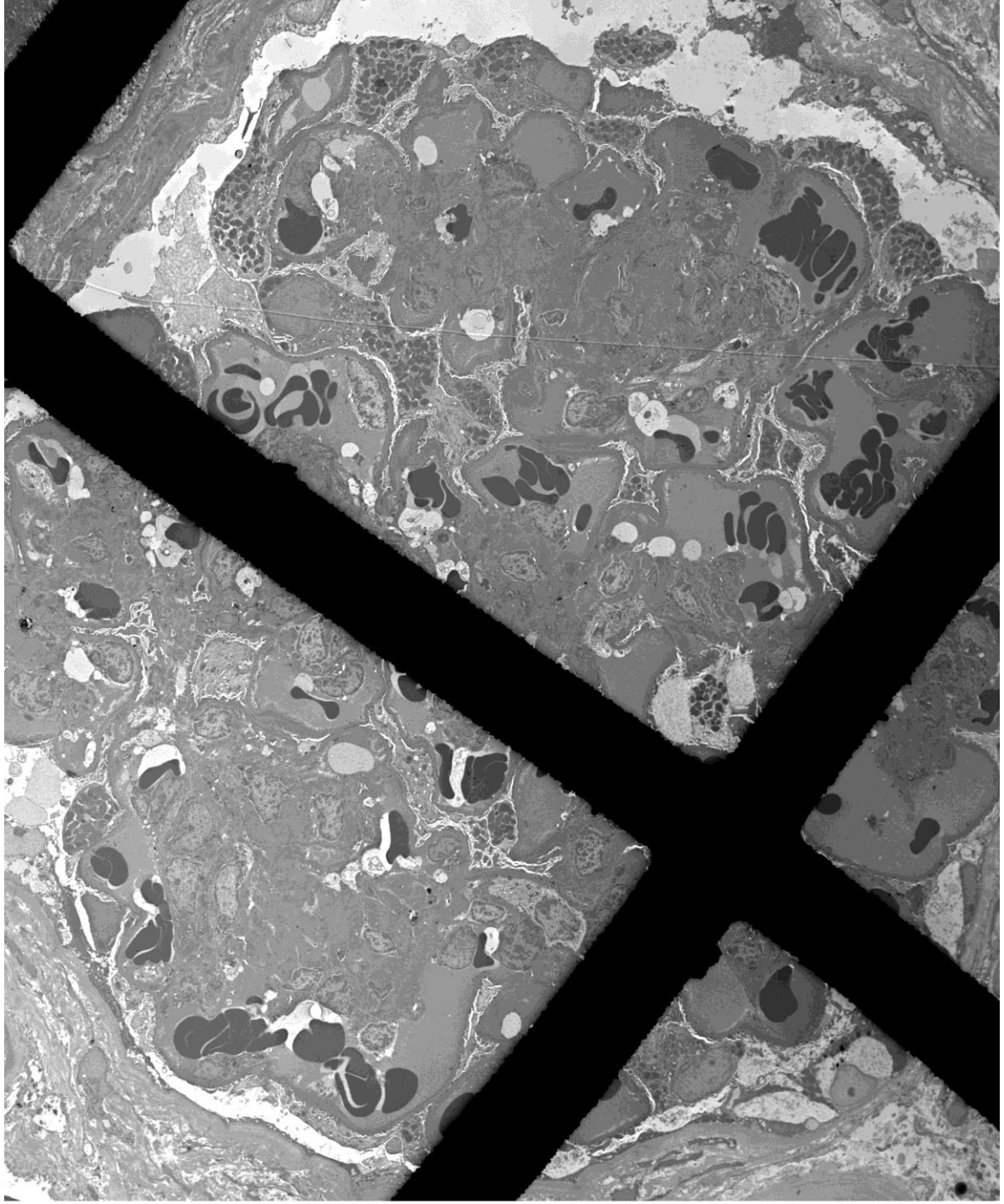


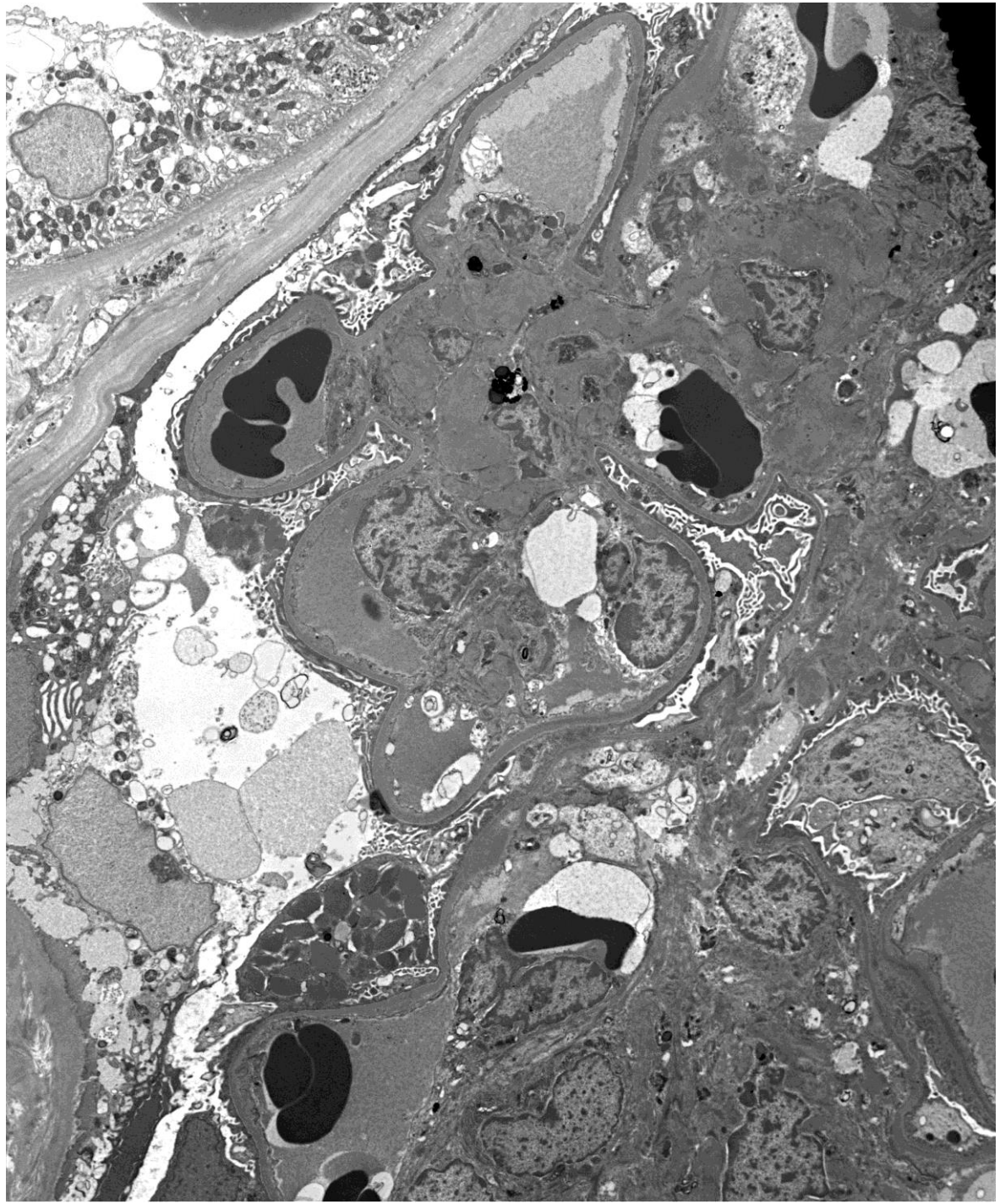


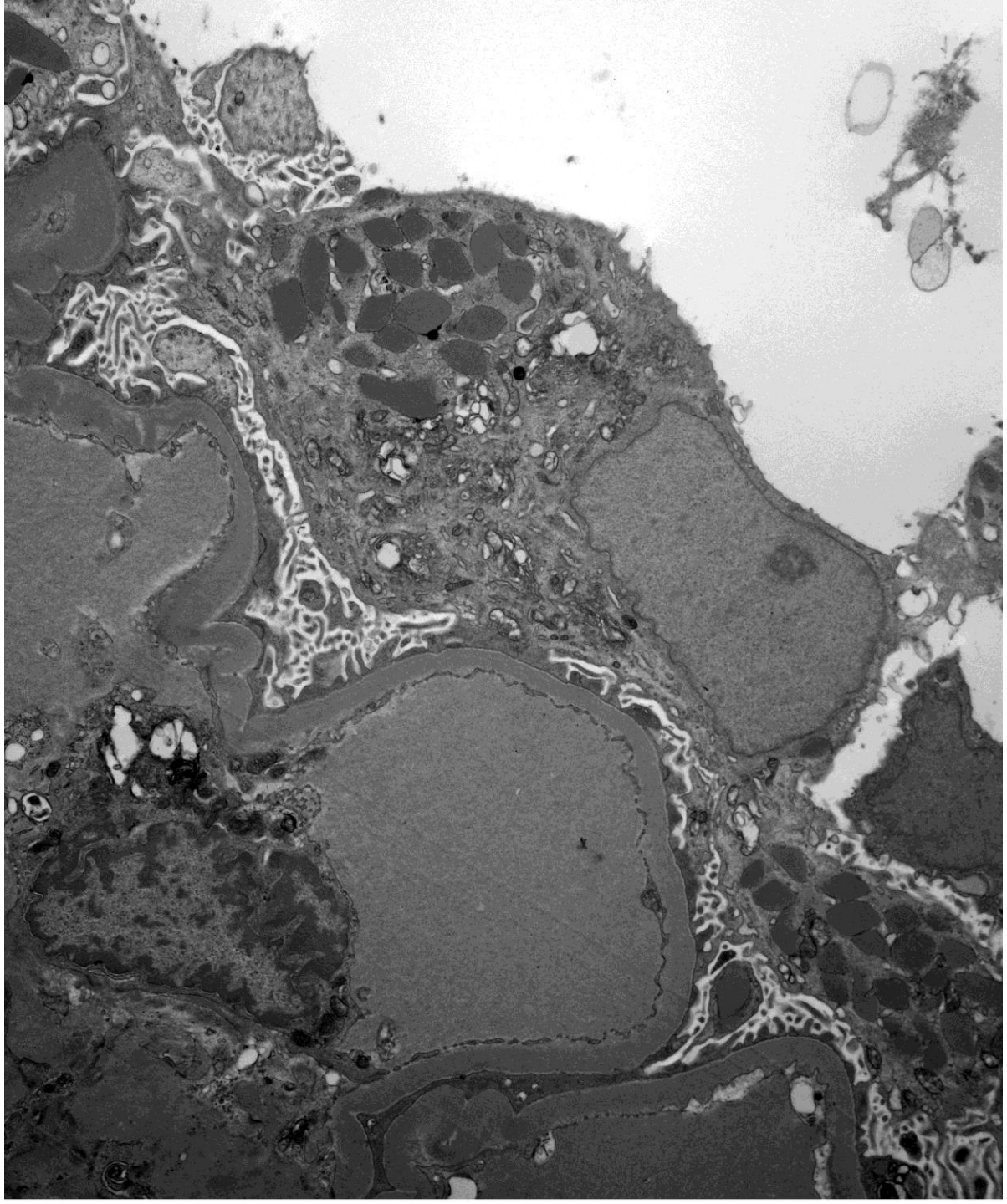


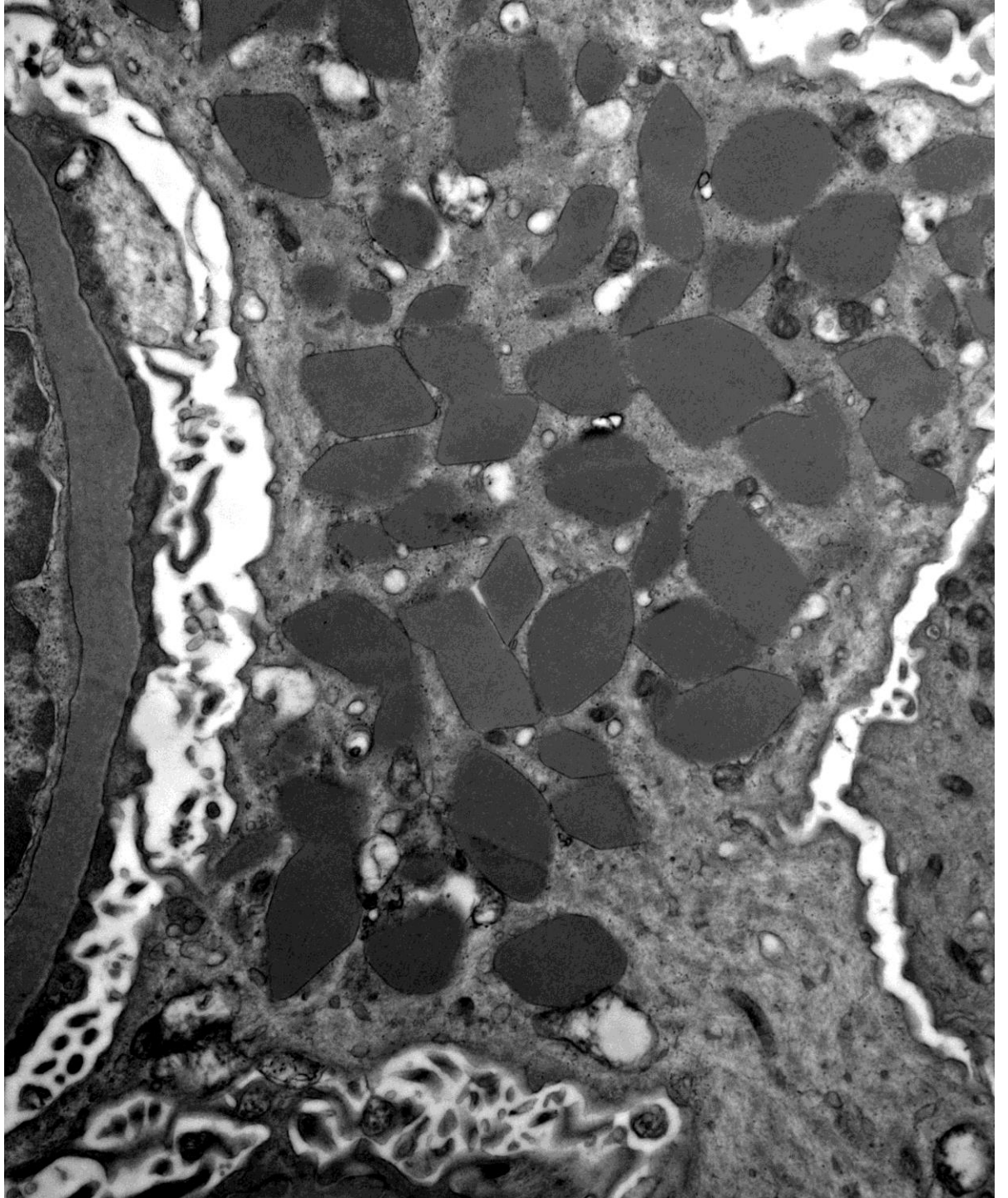


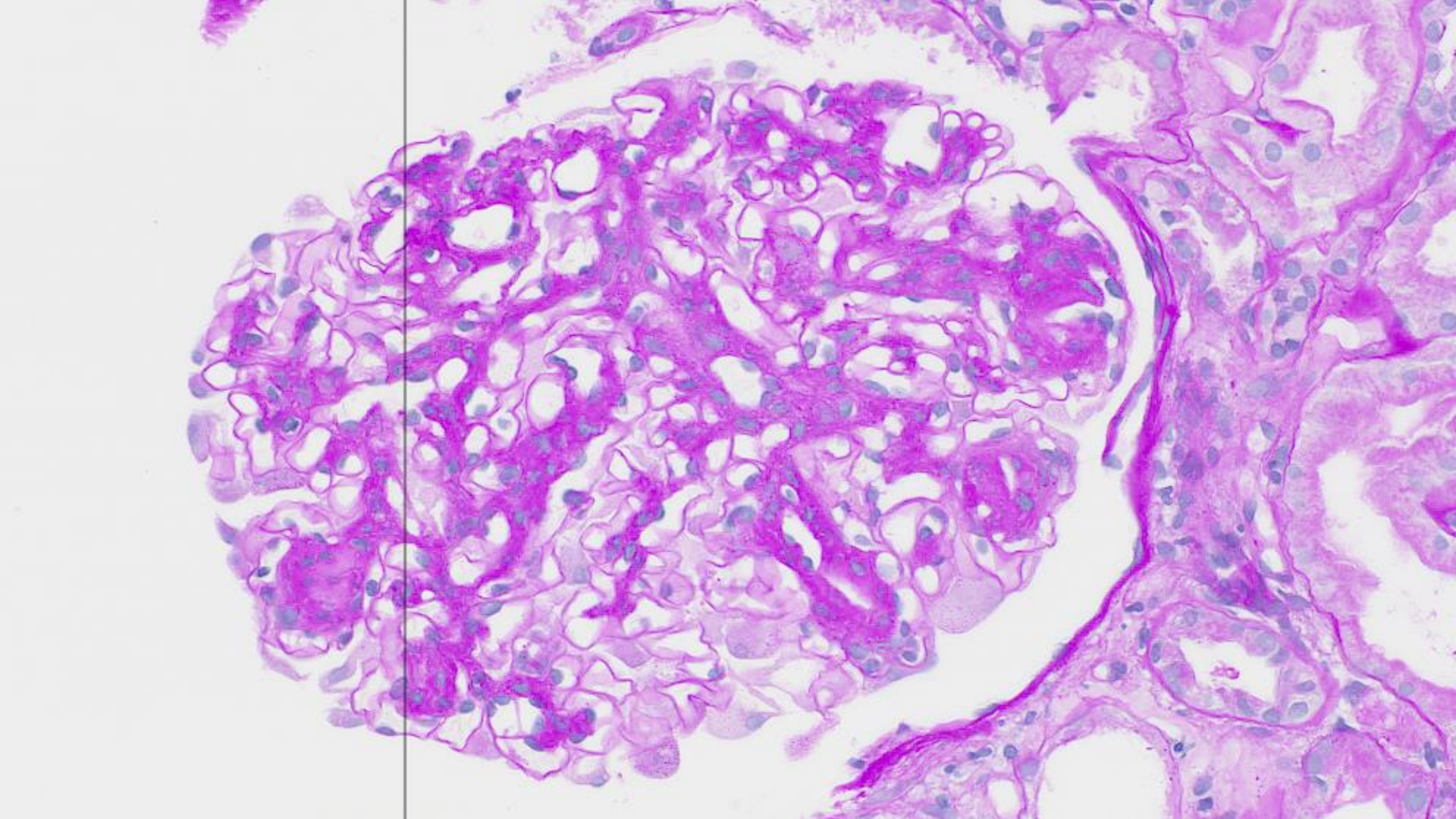


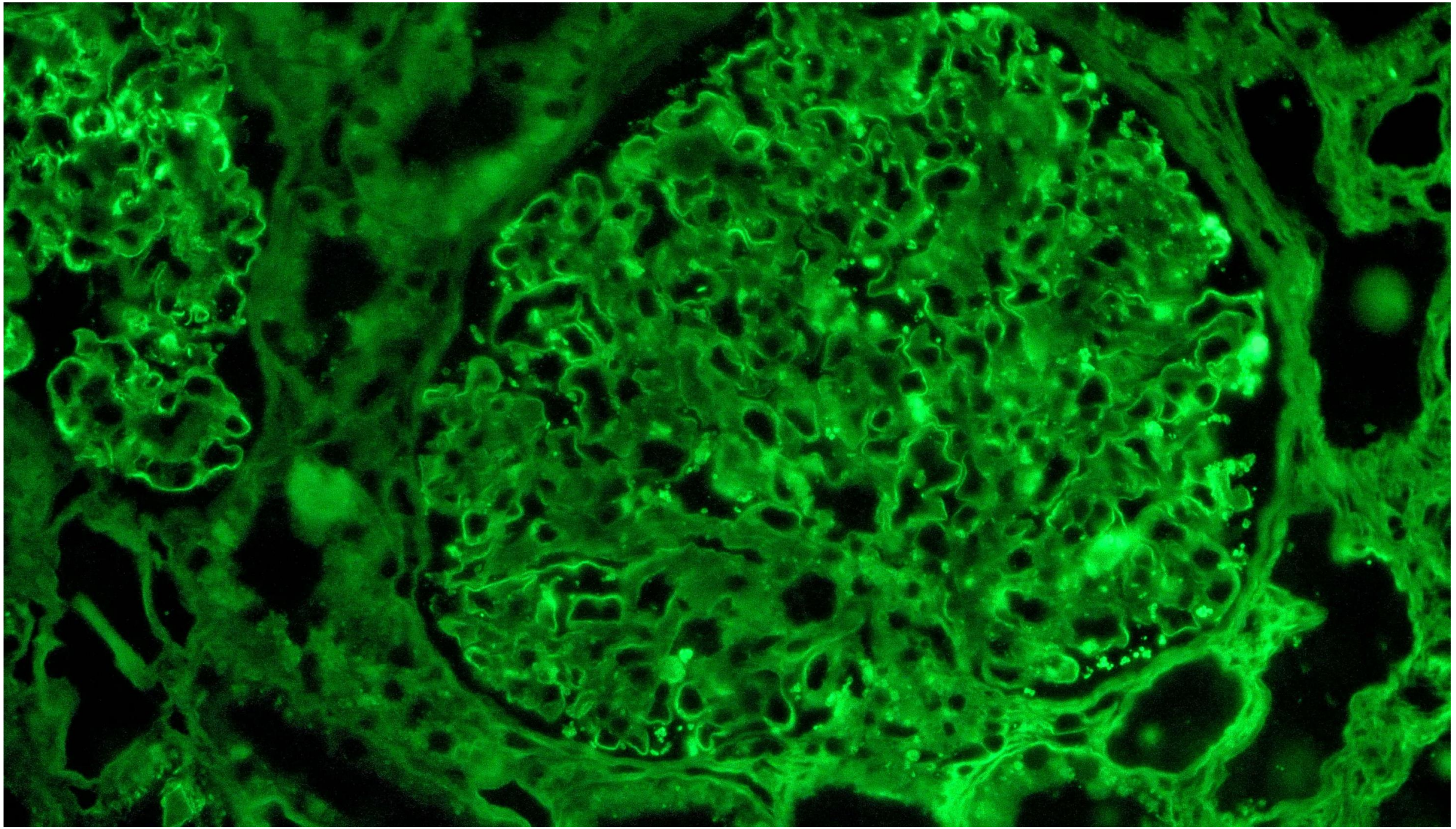


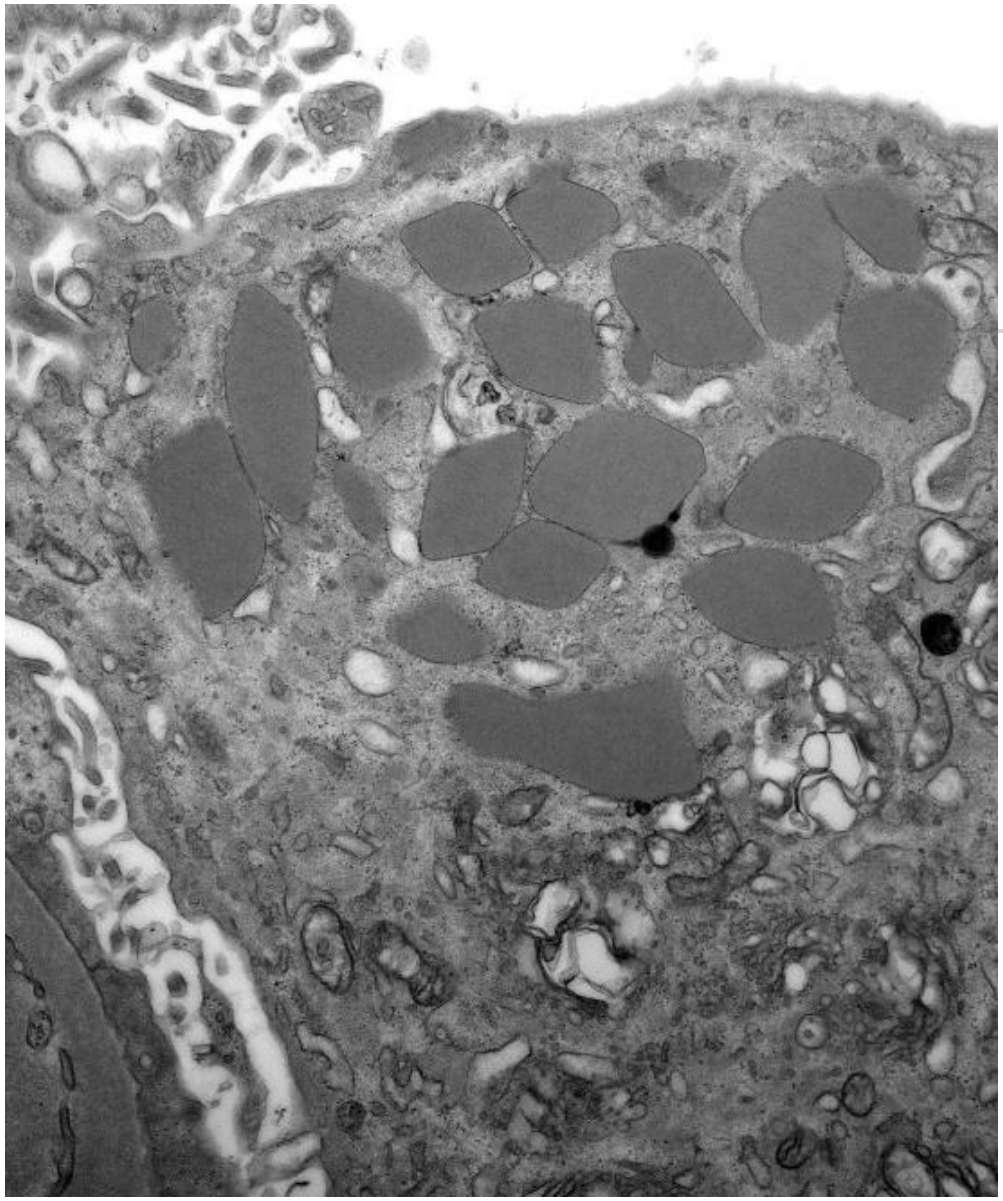


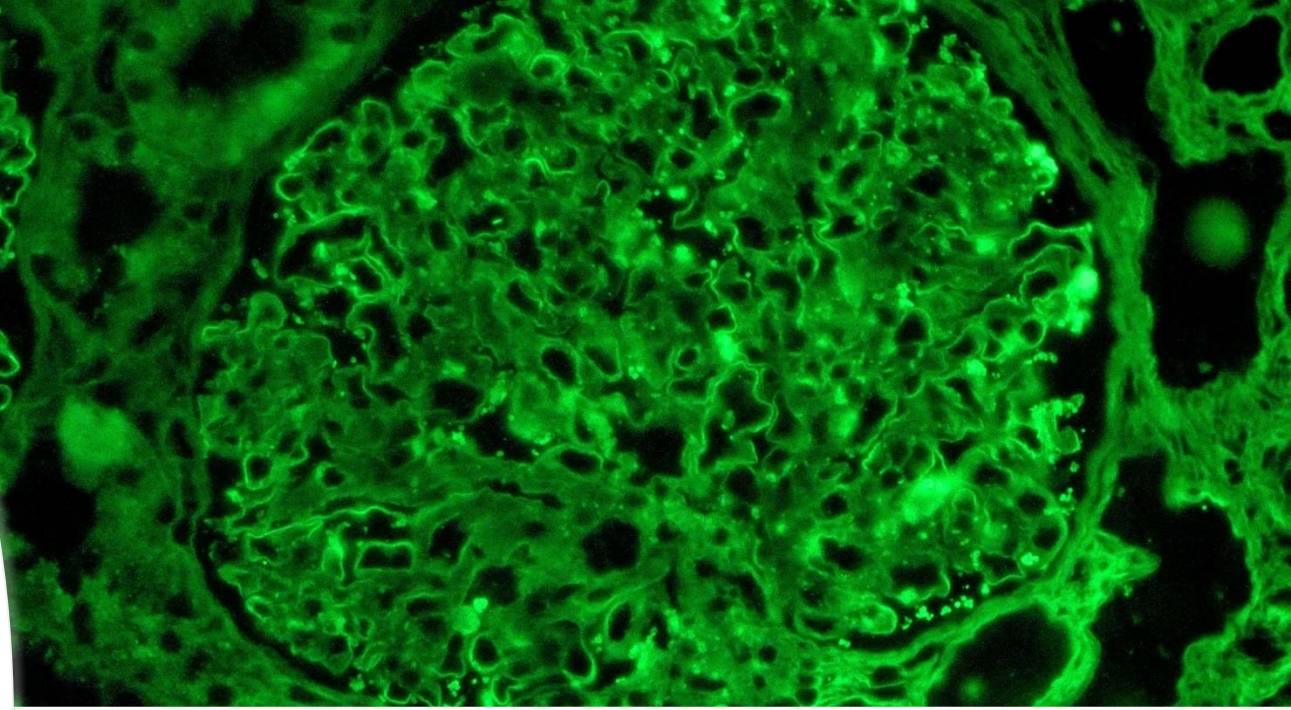


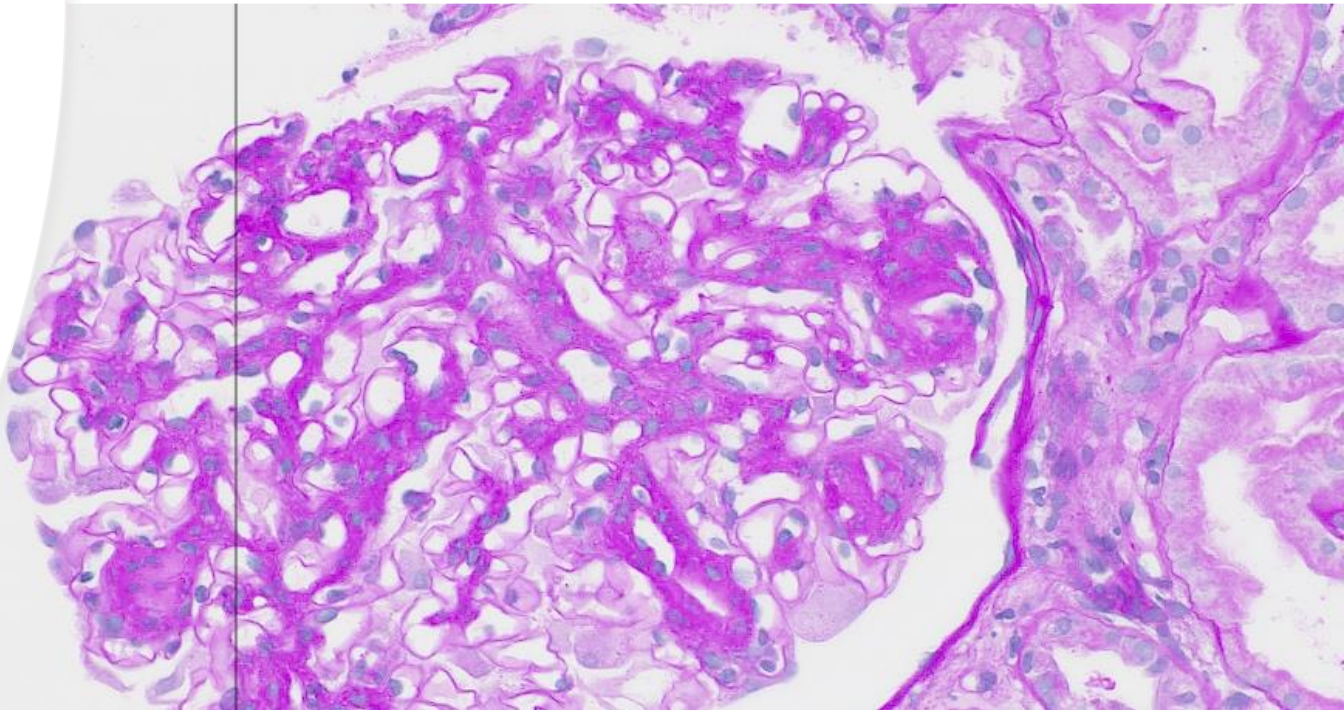


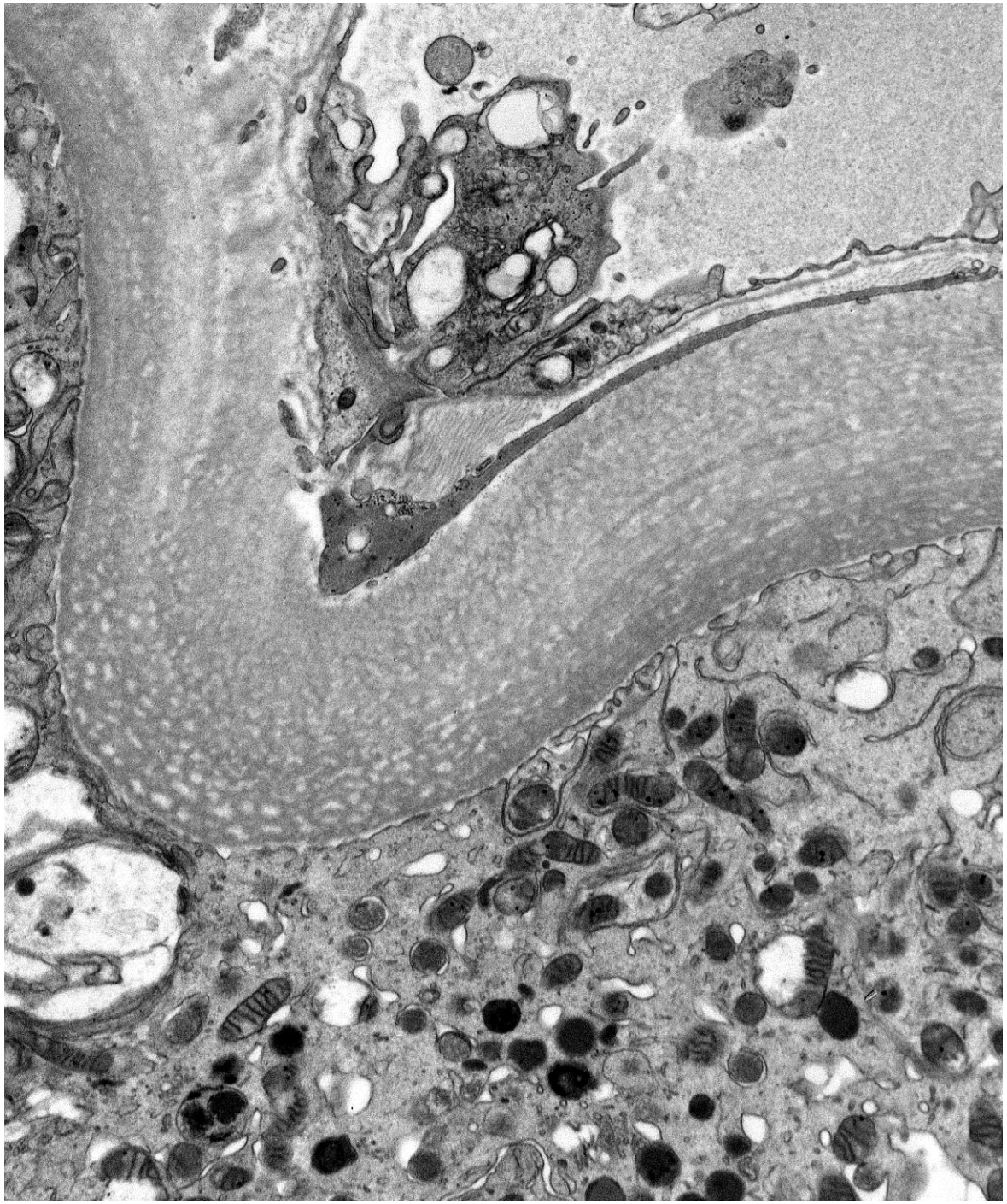


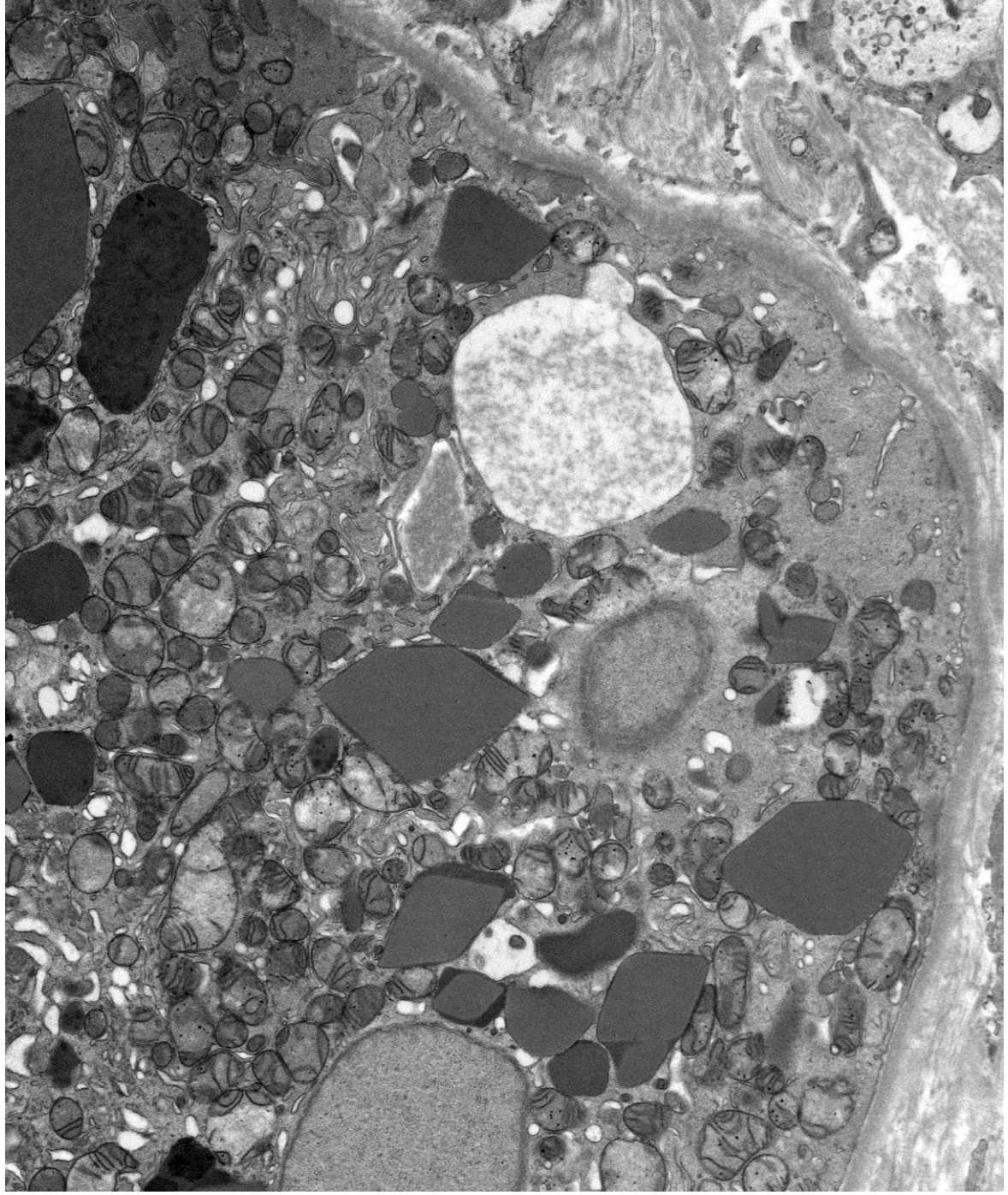


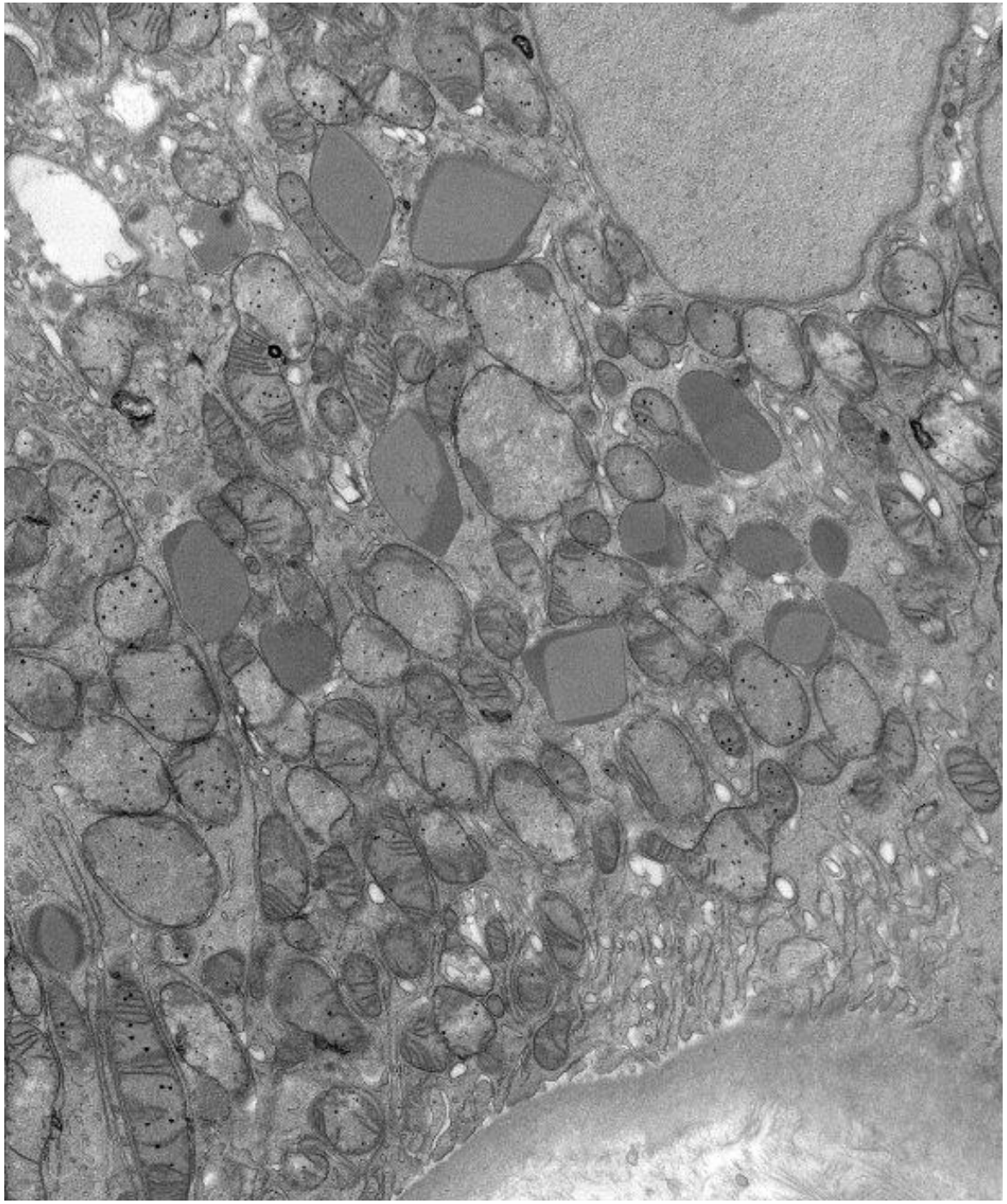


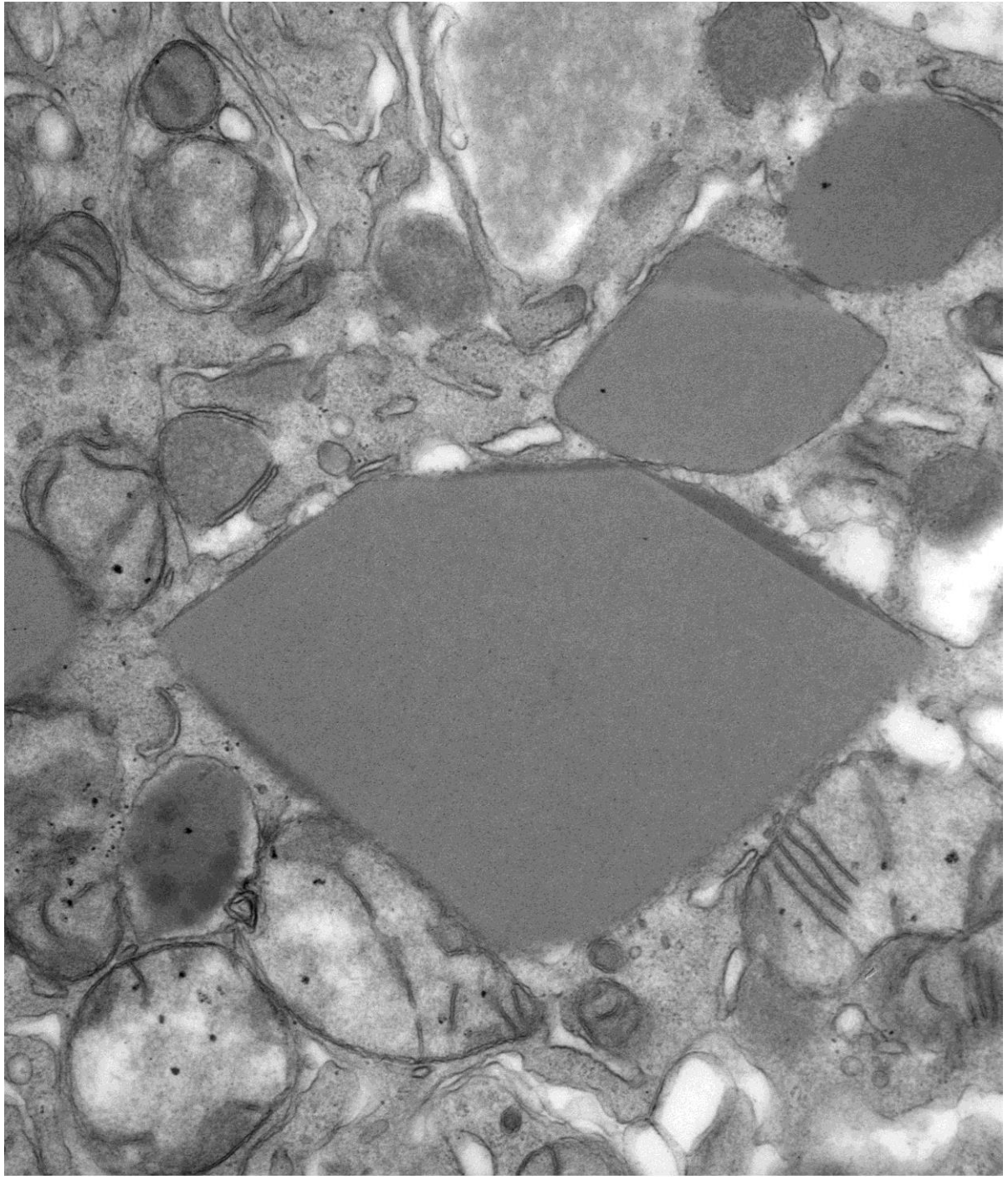








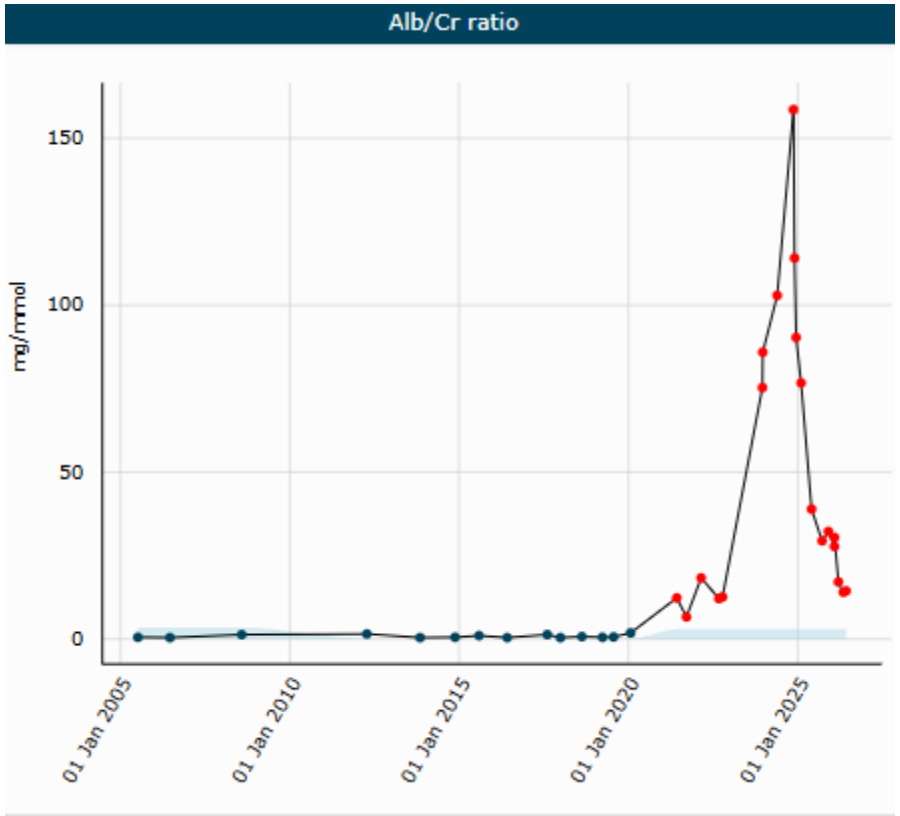


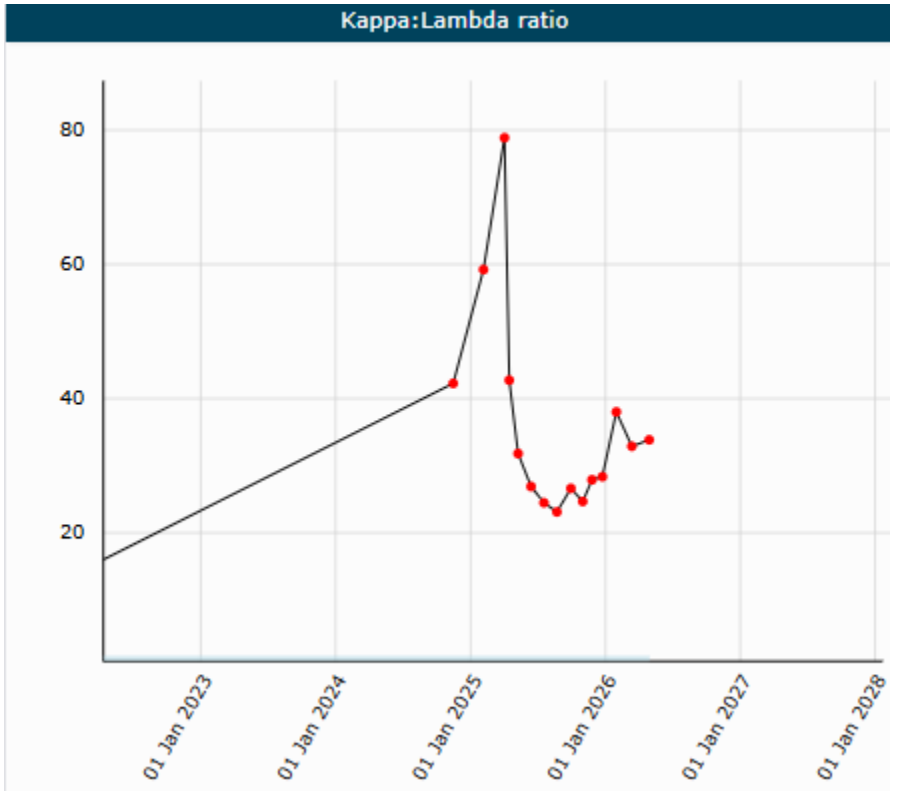


Diagnosis

- Diabetic Nephropathy
- Light Chain Podocytopathy
- Light Chain Proximal Tubulopathy, Crystalline.

Follow up
Bone marrow biopsy have shown <10% plasma cells, so not consistent with a myeloma diagnosis. The PETCT did not show any suspicious lesions, would all be more consistent with a diagnosis of MGRS


Alb/Cr ratio
mg/mmol
150
100
50
0
01 Jan 2005
01 Jan 2010
01 Jan 2015
01 Jan 2020
01 Jan 2025

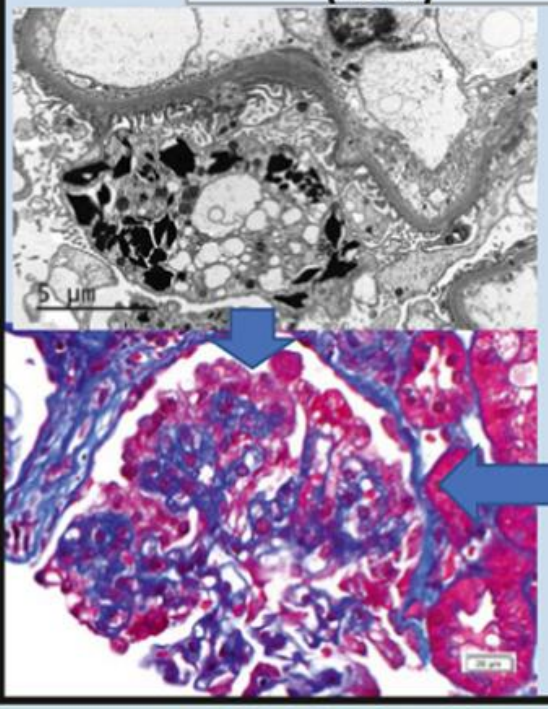

Kappa:Lambda ratio
80
60
40
20
01 Jan 2023
01 Jan 2024
01 Jan 2025
01 Jan 2026
01 Jan 2027
01 Jan 2028

Pathological characteristics of light chain crystalline podocytopathy.

kidney INTERNATIONAL

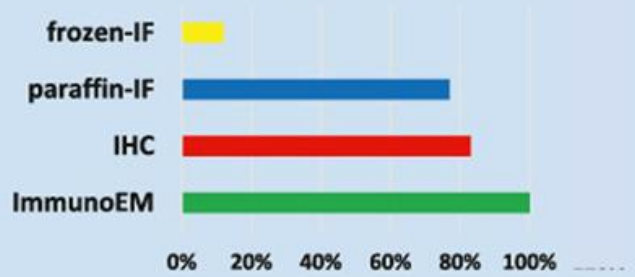
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

25 cases of LC crystalline podocytopathy (LCCP)



Pathologic & molecular characteristics

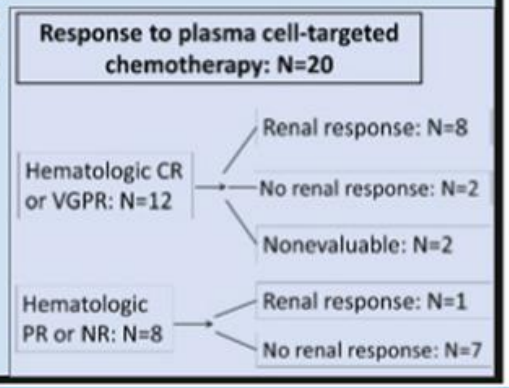
- ✓ EM: LC crystals in podocytes (100%); concurrent LCPT (80%) & CSH (36%)
- ✓ Detection of LC



- ✓ LM: FSGS in 60% (collapsing variant in 2/3)
- ✓ Proteomic analysis: *IGKV1-33* (n=4), *IGKV3-20* (n=1)

Clinical characteristics & outcome

- ➢ Proteinuria and CKD, with NS in 28%
- ➢ Hematologic condition: MGRS in 55% and MM in 45% (IgGK M-protein in 86%)
- ➢ Crystalline keratopathy in 22%; FS in only 10%
- ➢ ESKD-free survival 58 months (worse in patients with FSGS)
- ➢ Kidney response depended on hematologic response



Nasr, Kudose, & Javaugue et al, 2022

CONCLUSION

LCCP is mostly associated with IgGκ MGRS. Despite frequently concurrent LCPT, FS is uncommon. Paraffin-IF and EM are essential for diagnosis. Kidney survival depends on early diagnosis and clone-directed therapy.

www.kidney-international.org meeting report

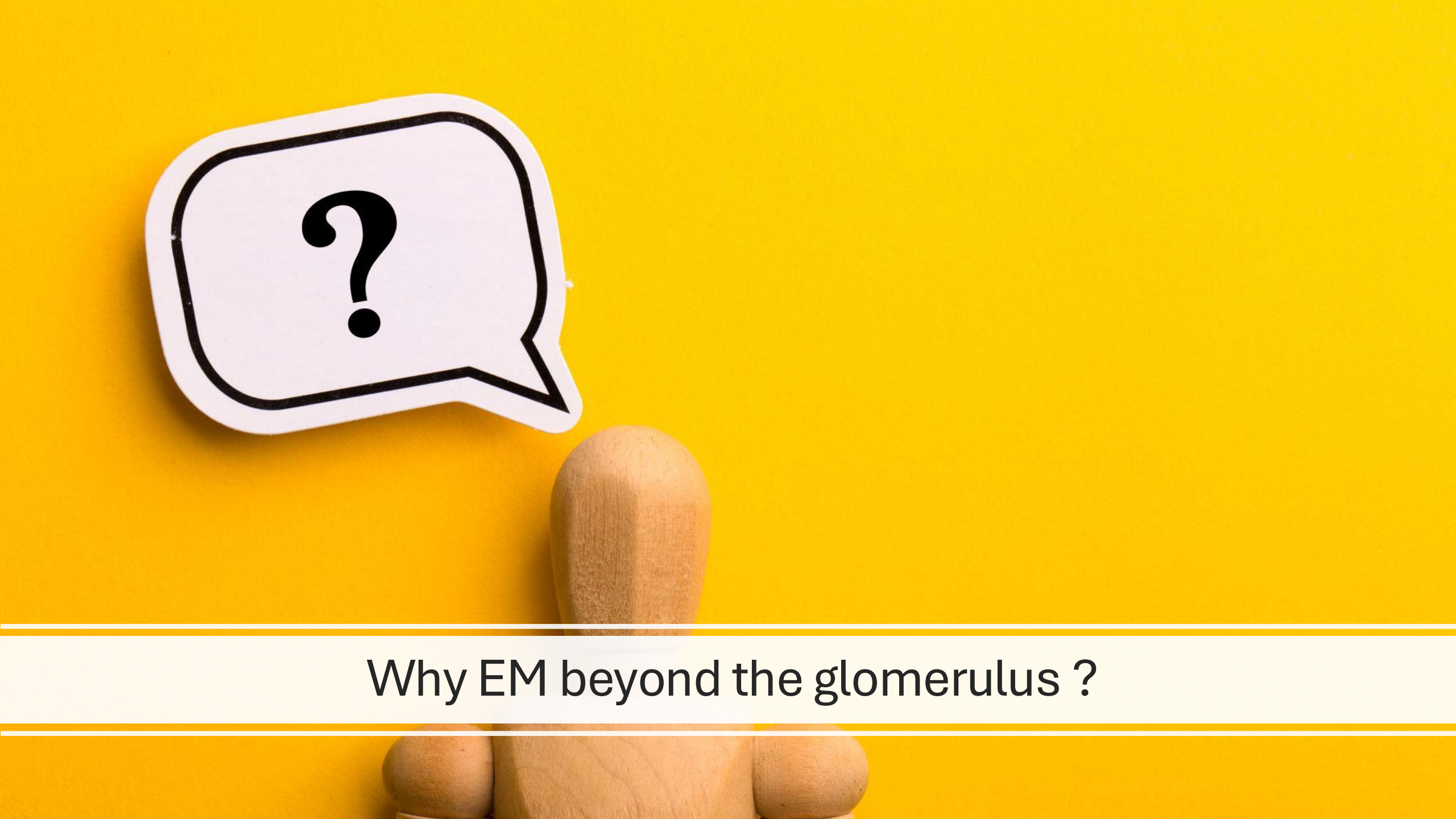
Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions

Samih H. Nasr[1], Virginie Royal[2], Alejandro Best Rocha[3], Maike Büttner-Herold[4], Candice Roufosse[5], Frank Bridoux[6], Wesam Ismail[7], Lihong Bu[1], Lynn D. Cornell[1], Amélie Dendooven[8], Rajib K. Gupta[9], Shigeo Hara[10], Vincent Javaugue[6], Nicolas Kozakowski[11], Satoru Kudose[12], Gonzalo P. Méndez[13], Kimberley Oliver[14], Maria M. Picken[15], Dominick Santoriello[12], Sanjeev Sethi[1], Akira Shimizu[16], Geetika Singh[17], M. Barry Stokes[12], Su-xia Wang[18], Nelson Leung[19,20], Glen S. Markowitz[12] and Vivette D. D'Agati[12]

Nasr S et al. **Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions.** Kidney International, 2025; 108, 184-193

Defining the expanded crystalline spectrum





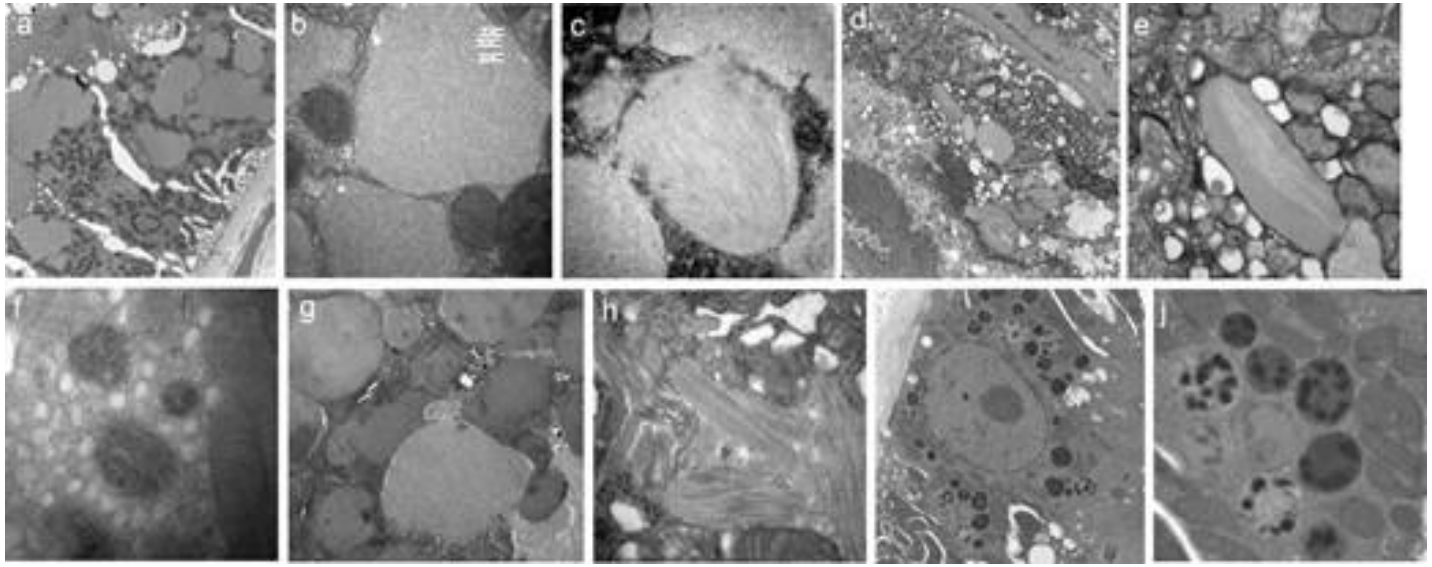
Why EM beyond the glomerulus ?

Tubules

Light chain tubulopathy

In **light chain proximal tubulopathy**

- Crystalline LCPT shows **angular, rhomboid, rectangular, or needle-like electron-dense inclusions**, usually within lysosomes; some cases also show similar inclusions in podocytes or interstitial cells.
- Non-crystalline LCPT may show only **prominent phagolysosomes, dense vacuolar accumulation or vacuolar degeneration**, which can be missed or mistaken for nonspecific protein reabsorption on LM.



JOURNAL ARTICLE

Non-crystalline light chain proximal tubulopathy, a morphologically protean entity

Andreas Kousios, Sarah Blakey, Linda Moran, Maria Atta, Rawya Charif, Neill Duncan, Andrew Smith, Frederick W K Tam, Jeremy B Levy, Aristeidis Chaidos ... Show more

Nephrology Dialysis Transplantation, Volume 38, Issue 11, November 2023, Pages 2576–2588, https://doi.org/10.1093/ndt/gfad085

Published: 29 April 2023 **Article history** ▾

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ABSTRACT

Background

Light chain proximal tubulopathy (LCPT) is a rare form of paraprotein-related disease, occurring in two main histopathological forms: crystalline and non-crystalline. The clinicopathological features, treatment strategies and outcomes, especially of the non-crystalline form, are not well described.

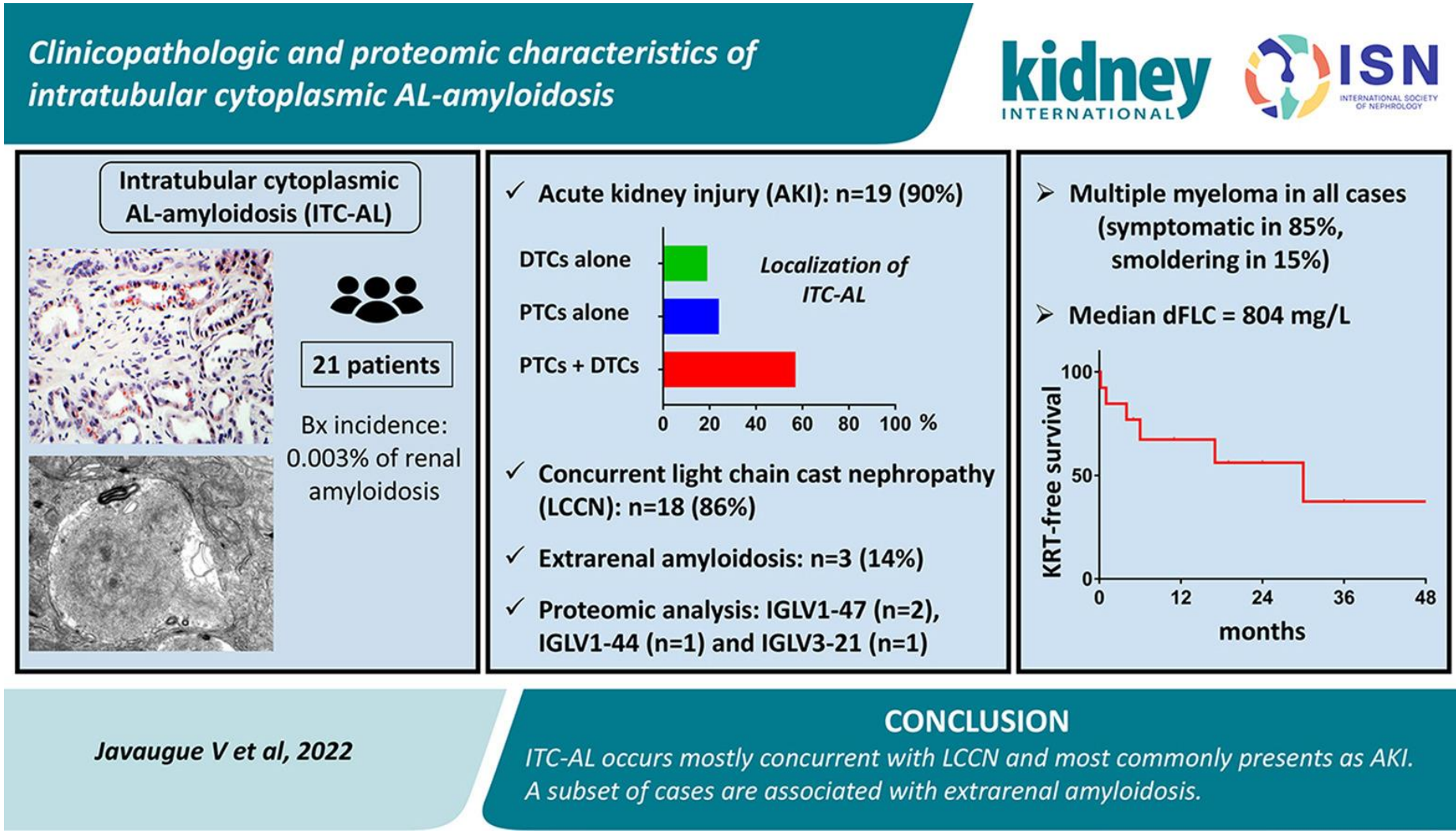
Methods

We conducted a single-centre retrospective case series of 12 LCPT patients, 5 crystalline and 7 non-crystalline, between 2005 and 2021.

Andreas Kousios, Sarah Blakey, Linda Moran, Maria Atta, Rawya Charif, Neill Duncan, Andrew Smith, Frederick W K Tam, Jeremy B Levy, Aristeidis Chaidos, Candice Roufosse, Non-crystalline light chain proximal tubulopathy, a morphologically protean entity, *Nephrology Dialysis Transplantation*, Volume 38, Issue 11, November 2023, Pages 2576–2588, https://doi.org/10.1093/ndt/gfad085

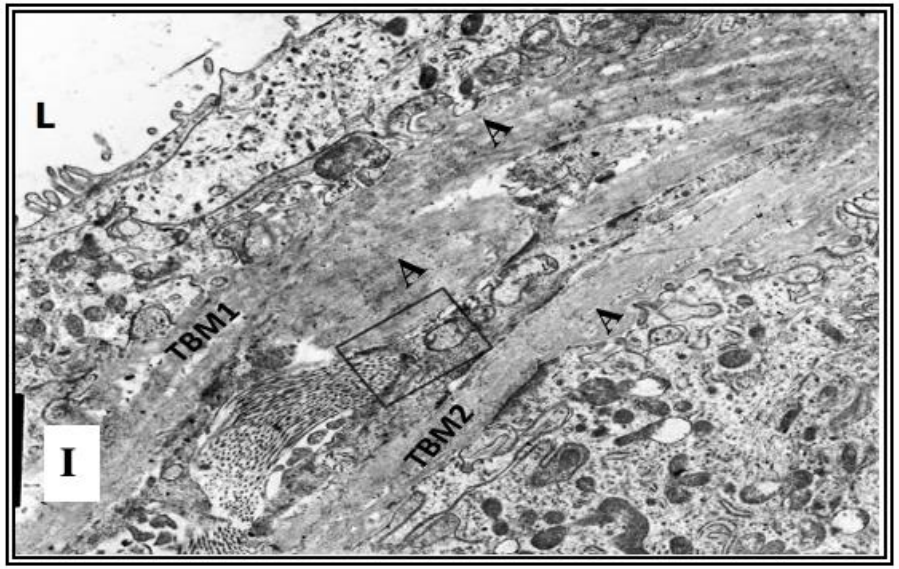
Tubules

Intratubular cytoplasmic AL –amyloidosis



Tubules

Organized deposits:
e.g. amyloidosis



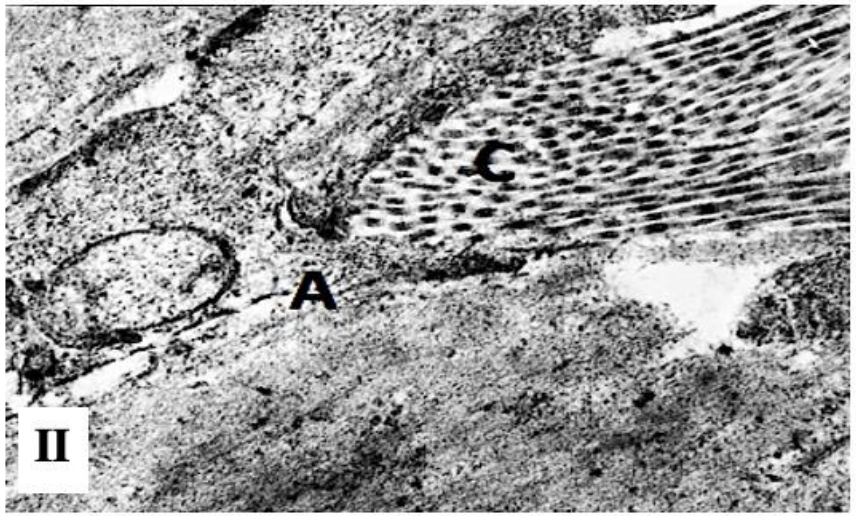


Figure 14: An *electron micrograph showing amyloid deposition A in relation to tubular basement membranes (TBM1, TBM2) and interstitial tissue; L: tubular lumen; C; collagen fibers.*
(negative mag. of I: 8000; negative mag. of II: 28000)

Tubules

Inherited Mitochondrial diseases

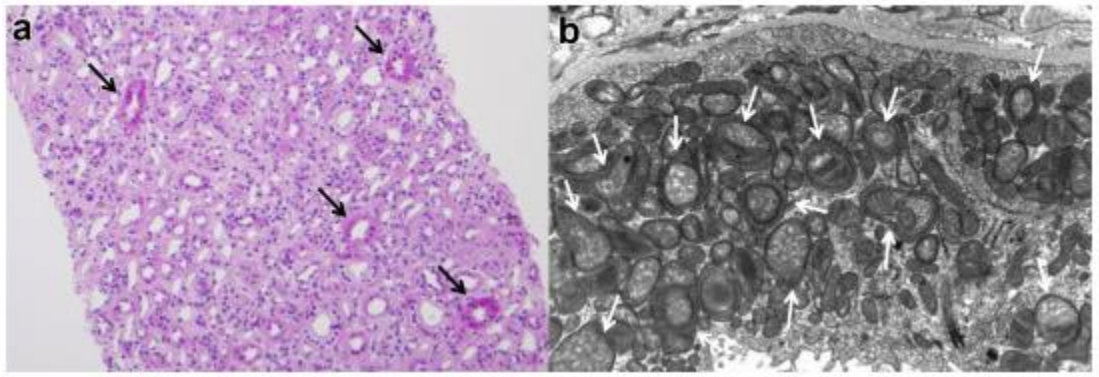


Figure viewer

Figure 2 Kidney biopsy findings of patient (proband). (a) Light microscopy of this hematoxylin-and-eosin slide shows mild interstitial inflammation of this segment of the renal medulla. Scattered distal tubules show more eosinophilic and granular epithelial cells (arrows). These findings are nonspecific. (b) Electron microscopy shows numerous enlarged abnormal mitochondria, with circularly arranged cristae and electron-dense, parallel linear inclusions (arrows).

Buglioni A, et al. Mitochondriopathy Manifesting as Inherited Tubulointerstitial Nephropathy Without Symptomatic Other Organ Involvement.Kidney International Reports, 2021; 6, 2514-2518

Tubules

In **BK virus nephropathy**, EM may reveal **packed viral particles within tubular epithelial nuclei**, supporting viral cytopathic change when inclusions are atypical.

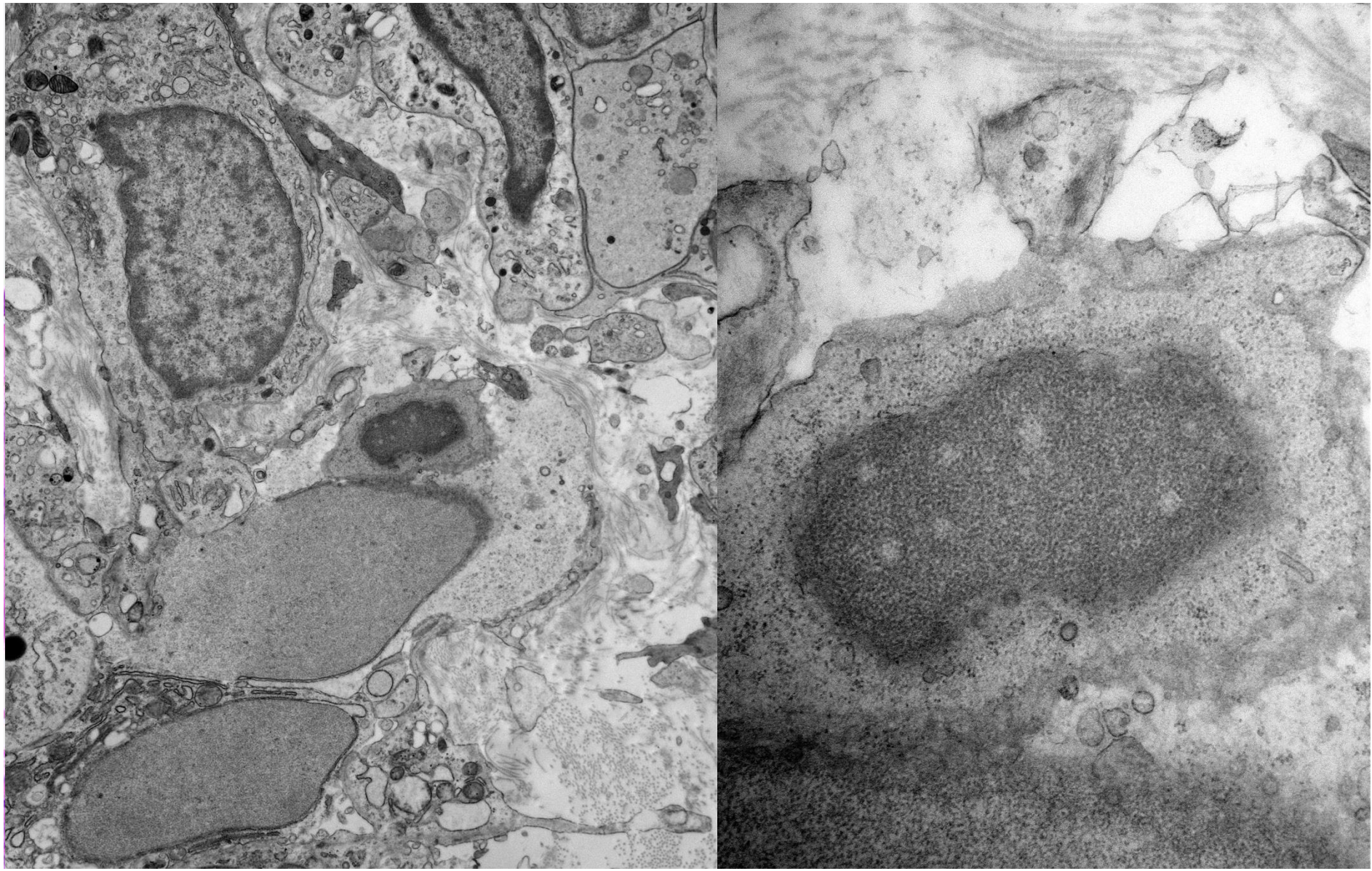
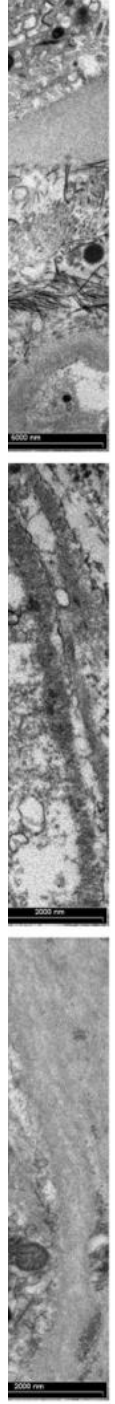


TABLE 1. Numbers of cases with positive immunostaining with corresponding EM findings.

Primary diagnosis	Cases	Glomeruli IF Immunoglobulin or light chain	Glomeruli IF Complement	Tubules IF Immunoglobulin or light chain	Tubules IF Complement	Tubules EM Granular deposits in TBM	Tubules EM Vesicular deposits in TBM	Tubules EM Vacuolar changes in TBM
Normal aged (within normal limits)	5	2	2	1	0	0	5	1
Amyloid	1	1	1	0	0	0	1	0
Diabetes	7	6	4	2	2	2	4	1
Focal and segmental glomerulosclerosis, necrotising glomeruolonephritis	11	5	5	1	1	3	6	2
Immunoglobulin deposition (including IgA, IgG, and IgM), light chain disease, immune complex tubular basement membrane disease	41	40	29	6	6	8	9	5
Lupus nephritis (SLE)	8	8	8	1	1	8	4	3
Minimal change nephropathy	5	0	0	0	0	0	1	2
Scleroderma	1	1	0	0	0	0	1	0
Tubulointerstitial nephritis, tubular atrophy, and transplant glomerulopathy	6	2	2	1	1	6	0	0
Drug toxicity	2	0	0	0	0	0	0	0
TOTAL	87	65	51	12	11	27	31	14

Renal biopsy cases grouped into main disease entities based on the primary diagnosis. Types of deposits seen in the glomerulus and tubules by immunofluorescence (IF) with corresponding deposits associated with tubular basement membrane (TBM) identified by transmission electron microscopy (EM).



Interstitium

Interstitial EM is most useful for **storage disease and extracellular deposits** rather than routine fibrosis alone.

- In **crystal-storing histiocytosis**, interstitial histiocytes contain **elongated, rhomboid, or needle-shaped intracytoplasmic crystals**, usually related to monoclonal immunoglobulin accumulation.
- Crystal-storing lesions may overlap with other paraprotein-associated patterns, so EM can help show **shared crystal morphology across compartments**.

- In **interstitial amyloid**, EM demonstrates **extracellular non-branching fibrils** in the interstitial matrix and around vessels, even when Congo red is focal or limited.

Wu *et al. BMC Nephrology* (2017) 18:170
DOI 10.1186/s12882-017-0584-8

BMC Nephrology

CASE REPORT Open Access

Combined proximal tubulopathy, crystal-storing histiocytosis, and cast nephropathy in a patient with light chain multiple myeloma

Chung-Kuan Wu[1,2], An-Hang Yang[3], Hung-Chih Lai[4] and Bing-Shi Lin[1,5*]

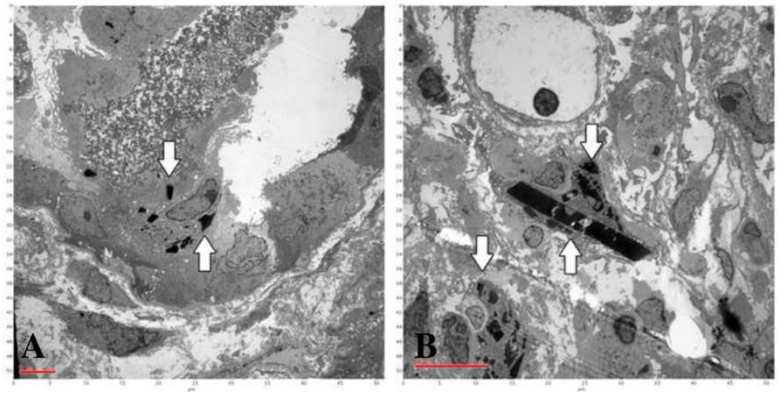


Fig. 3 Electron microscopy showing crystalline inclusions in proximal tubular epithelial cells and histiocytes. **a** Cuboid- and rhomboid-shaped crystalline inclusions (*arrows*) in proximal tubular epithelial cells. **b** Needle- and rhomboid-shaped crystalline inclusions (*arrows*) in histiocytes

Blood vessels

- In **lupus nephritis**, small arteries and arterioles may show **granular electron-dense immune deposits** in the intima and vessel wall matrix.
- In **amyloidosis**, vascular involvement shows **randomly arranged non-branching fibrils**measuring about 8–12 nm, often within arteriolar walls and sometimes around peritubular capillaries.
- In **monoclonal immunoglobulin deposition disease (MIDD)**, vascular basement membranes contain **finely granular "powdery" electron-dense deposits**, contrasting with the fibrillar pattern of amyloid.

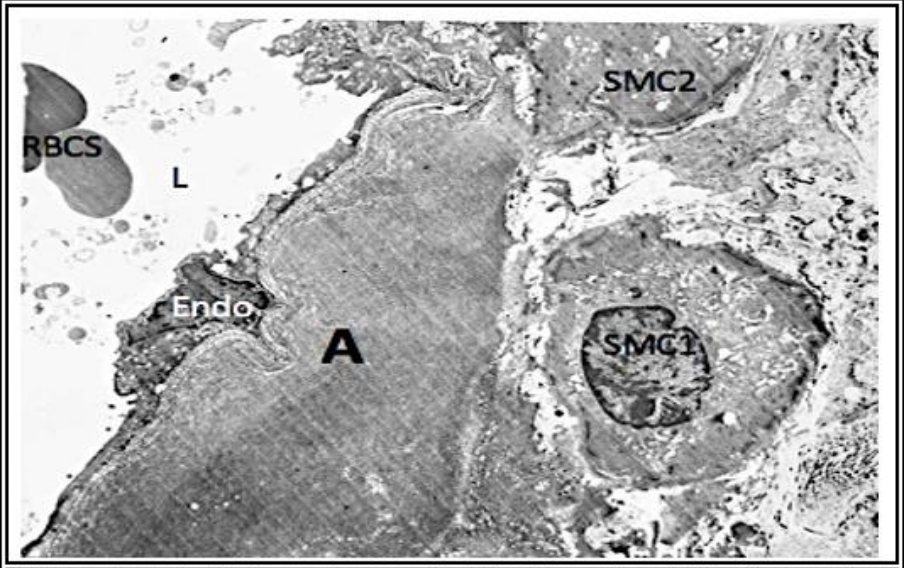


Figure 15: An *electron micrograph of blood vessel wall showing amyloid deposition **A** in subendothelial space (L: lumen; ENDO: endothelial cells; SMC: smooth muscle cells of the media (negative mag:2800)*

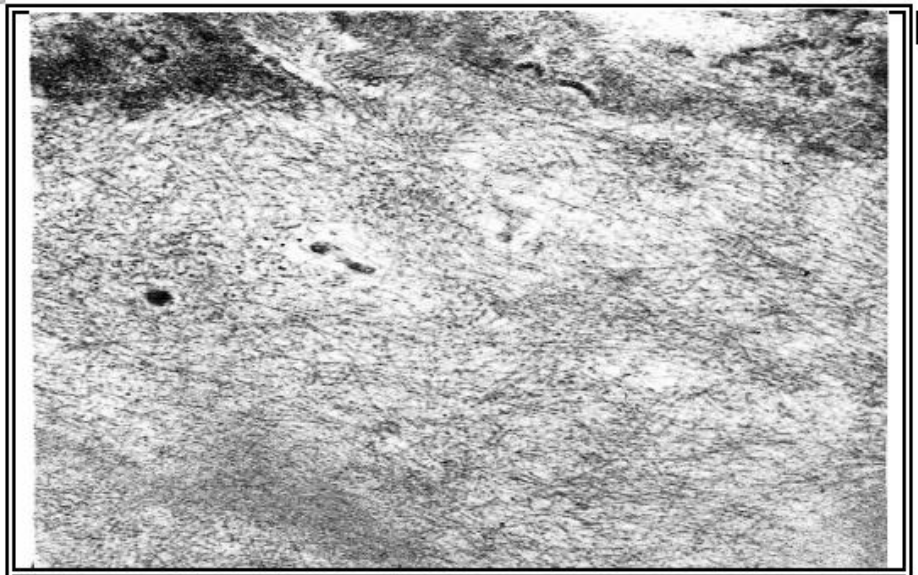


Figure 16: Amyloid fibrils *randomly arranged non branching fibrils measured 12 nm. (negative mag: 28000)*

Blood vessels

- **Transplant setting**

- Transplant-type microvascular injury (In chronic **thrombotic microangiopathy**), EM may show **multilayering of capillary basement membranes**.

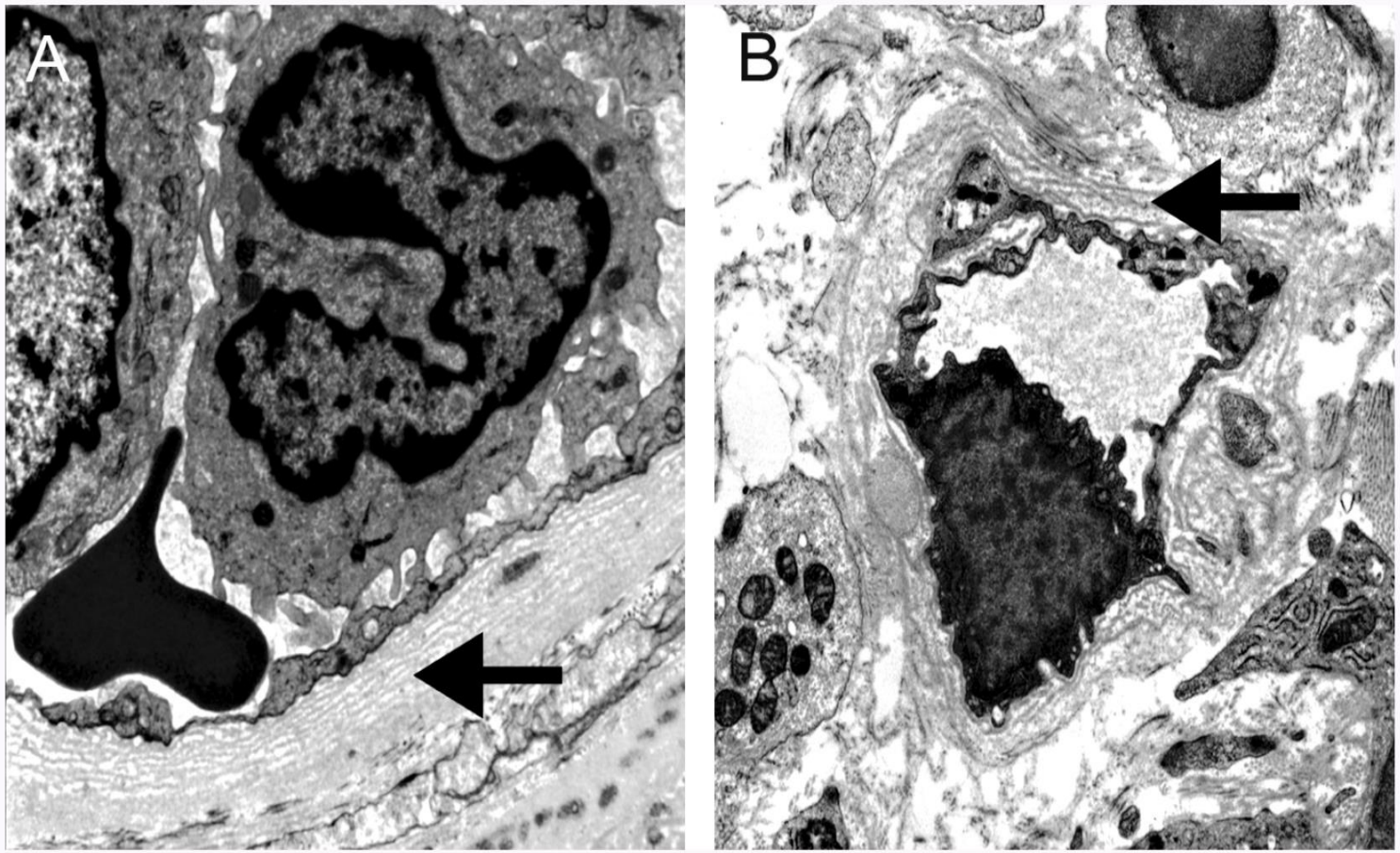


Figure 18. Banff Additional Diagnostic Parameter ptcml (peritubular capillary basement membrane multilayering) is only demonstrable by EM. A, This Additional Diagnostic Parameter is a criterion for AMR chronicity. It is defined as 7 or more layers of basement membrane in at least a single cortical peritubular capillary and 5 or more in at least 2 additional capillaries. This particular capillary shows 8 layers (arrow). Transmission EM, original magnification x14,000. B, this image demonstrates a peritubular capillary with 5 layers of basement membrane (arrow). Transmission EM, original magnification x10,000.

Reference Guide to the Banff Classification - BANFF

Take home message

- **Think beyond glomeruli:** EM adds value in tubules, vessels, and interstitium. Tubular EM is especially helpful when proximal tubular injury is subtle, overlapping (Mixed lesions are real), or compartment-specific.

- **LCPT** may be subtle on LM and routine IF; EM can secure the diagnosis. Diagnosis by EM can change downstream haematology and renal management.



- Thanks to:
- Dr. Howida Shawki Consultant histopathology, Royal Liverpool Hospital
- EM unit, New Castle .
- Clinical team at Royal Liverpool Hospital