



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Nephrocentric vs Nephrotolerant: When is it Safe to Rechallenge?

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DISCLOSURES

Please state any/all financial disclosures for past 24 months.

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Scientific Advisory Board: Vera Therapeutics, Travers Therapeutics, Alexion, Vertex

Astrid Weins, MD, PhD

Scientific Advisory Board: Vera Therapeutics

Speaker: Genentech, Travers Therapeutics

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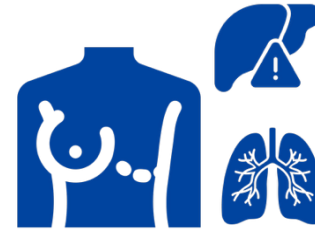
Learning Objective

Understand the timing and strategies for the re-challenge of oncology medications associated with AKI through a case-based scenario.





73F



Metastatic Breast Cancer



Paclitaxel +Pembrolizumab

Sacituzumab

Complications:

Neutropenic Fever

Soft Tissue infections

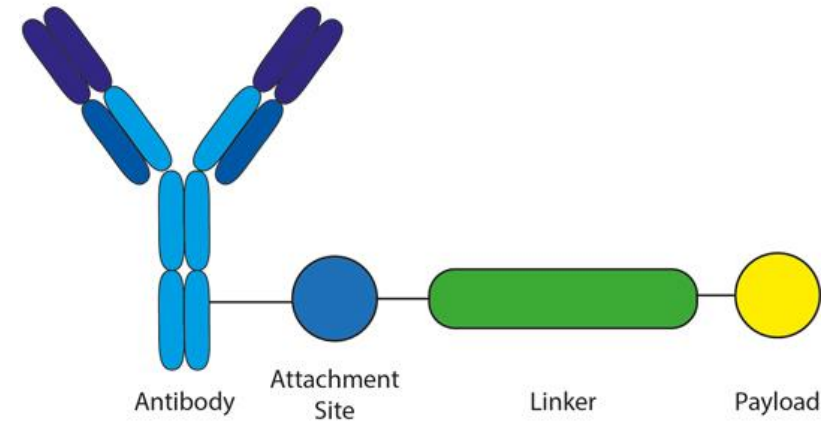


Progression of Disease (2 years in)
(Intracranial mets)



Clinical Trial enrollment
'Study Drug'

Antibody-Drug Conjugate
Aka 'Biological Missile'





Hypertension: 20 + years

SBP 120s at home previously, now 130-140s

Valsartan (long-term)

Started on amlodipine

No other **PMH**

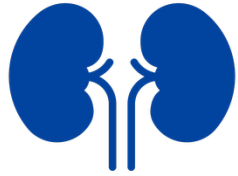
Never smoked

No family history of kidney disease

Meds: Bupropion, Tylenol, Docusate, Gabapentin, Valsartan

Physical Exam: 2+ Edema





Baseline Cr 0.6-0.8

AKIs prior (peak Cr 1-1.2)



Baseline proteinuria = none

1+ to 2+ on UA 1 month after starting the medication

No hematuria



Other Labs:

Hb **9-10 g/dL**

Platelets >250k/uL

Electrolytes (including Ca, Ph, Mg) = normal

LFTs: AST/ALT mildly elevated, Alk Phos chronically 150-200

LDH **500s → 1400s**

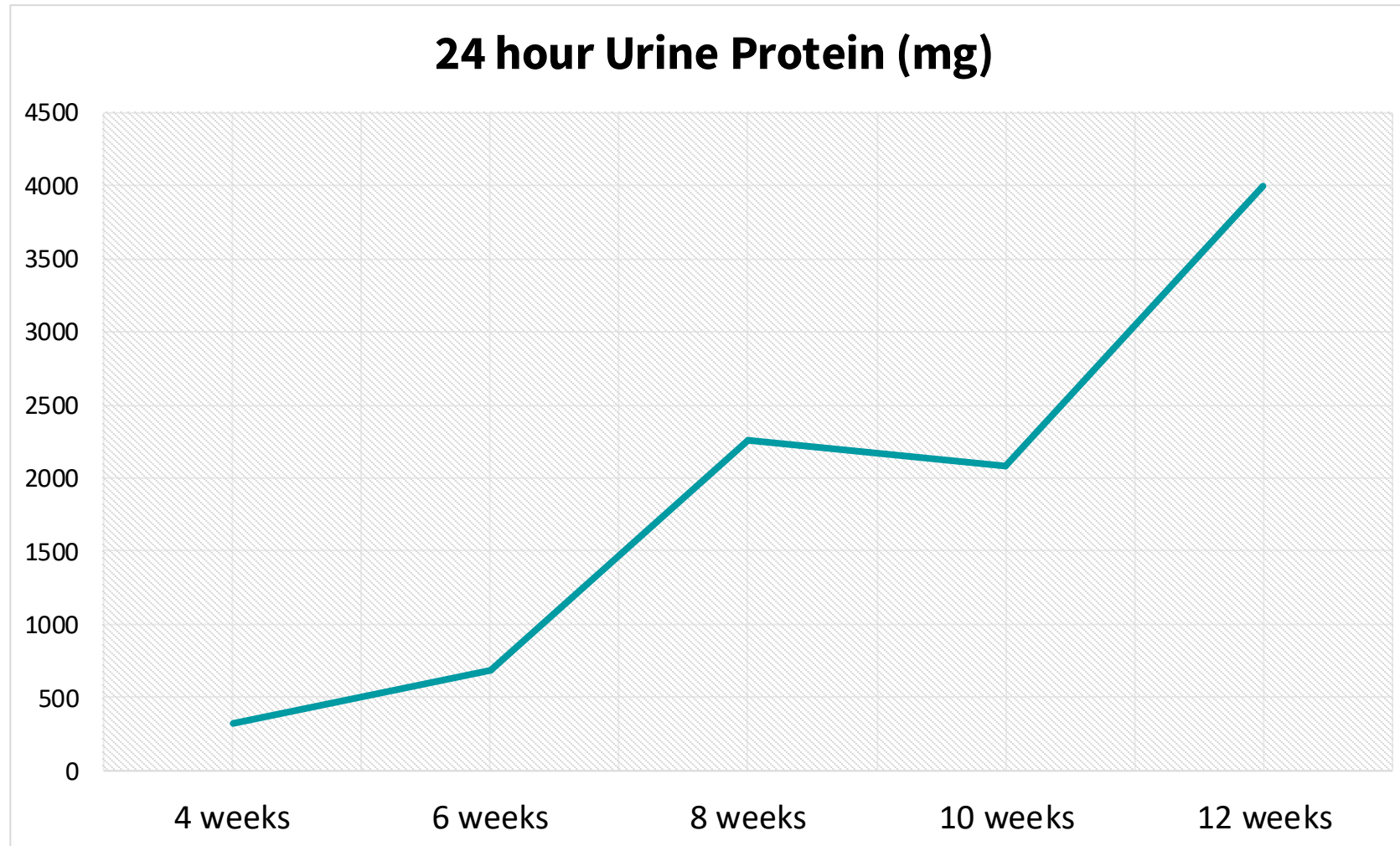
sIL2R: **1985 pg/mL** (175-858)



Initial Thoughts

Assuming you see the patient at this time, what are your initial thoughts?





Initial Thoughts

Proteinuria is obviously rising. Cr is stable.

What's the next step? What work up are you sending?
(Focused or Everything)





Workup

ANA, dsDNA

C3, C4

ANCA

Cryoglobulins

Anti-PLA2R

HbA1c

Hep serologies

Started on empagliflozin

Kidney Biopsy

Is a Kidney Biopsy important in this patient?

Why not assume it's a drug effect on the podocytes?

Is there a role for genetic testing?



Genetic Testing

Kidney Biopsy



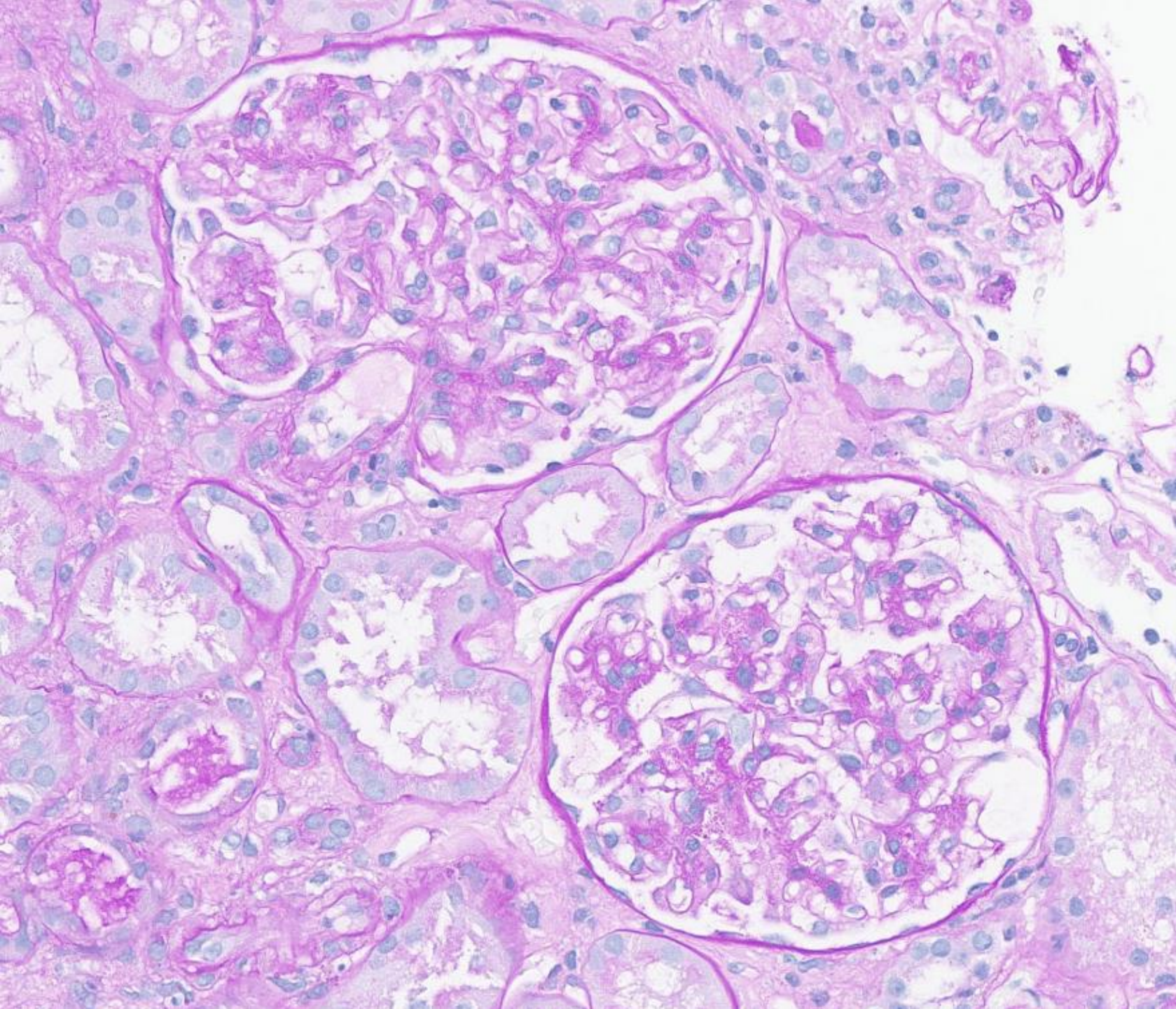
Renasight IQ™
Clinicogenomic Database

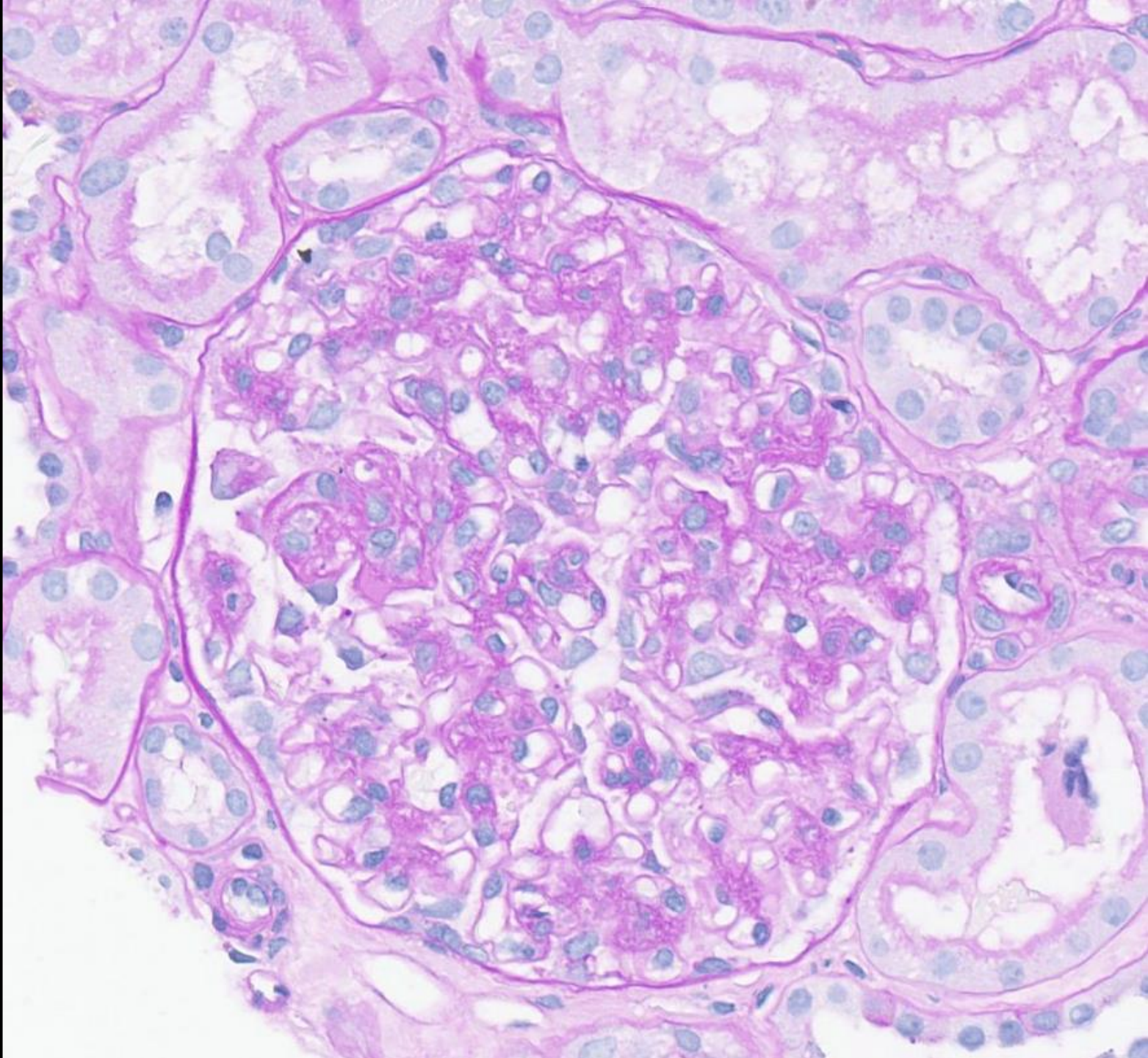


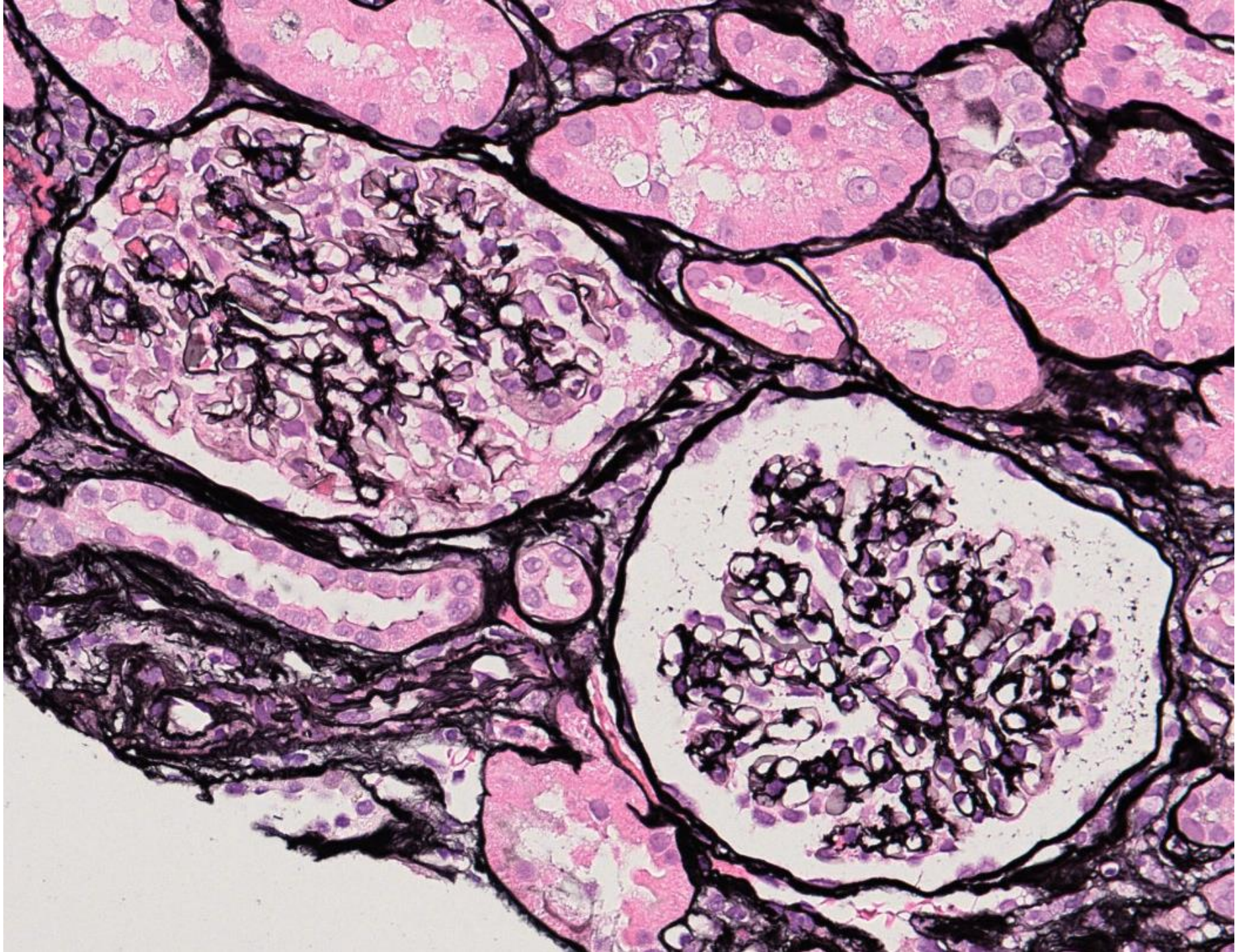
— Negative

Test Interpretation: No clinically significant variants were identified for the primary indication for testing. The absence of identifying clinically significant variants neither confirms nor rules out a genetic cause for this individual's clinical presentation. Clinical correlation of these results is recommended.

Additional Results: None detected





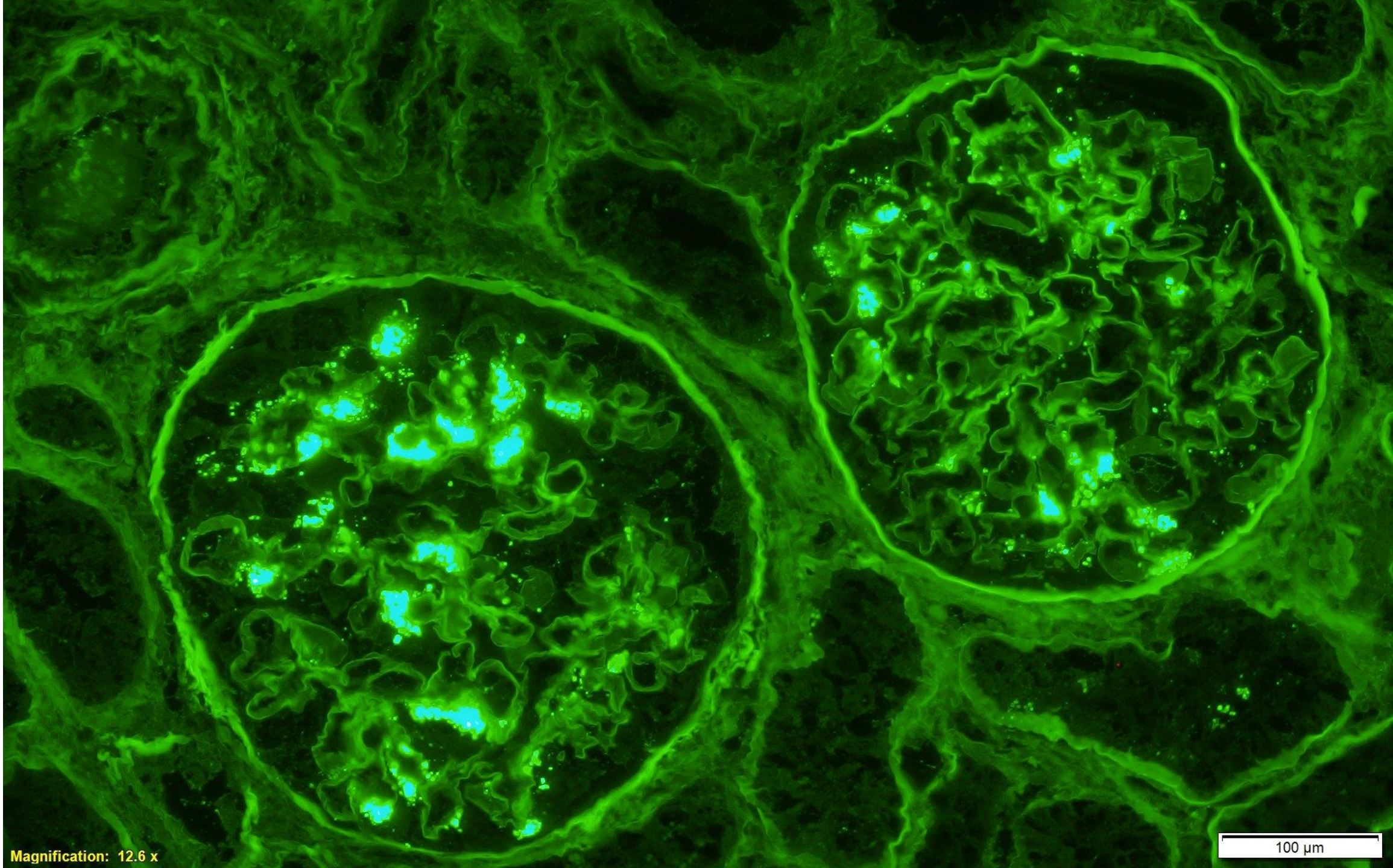


Albumin

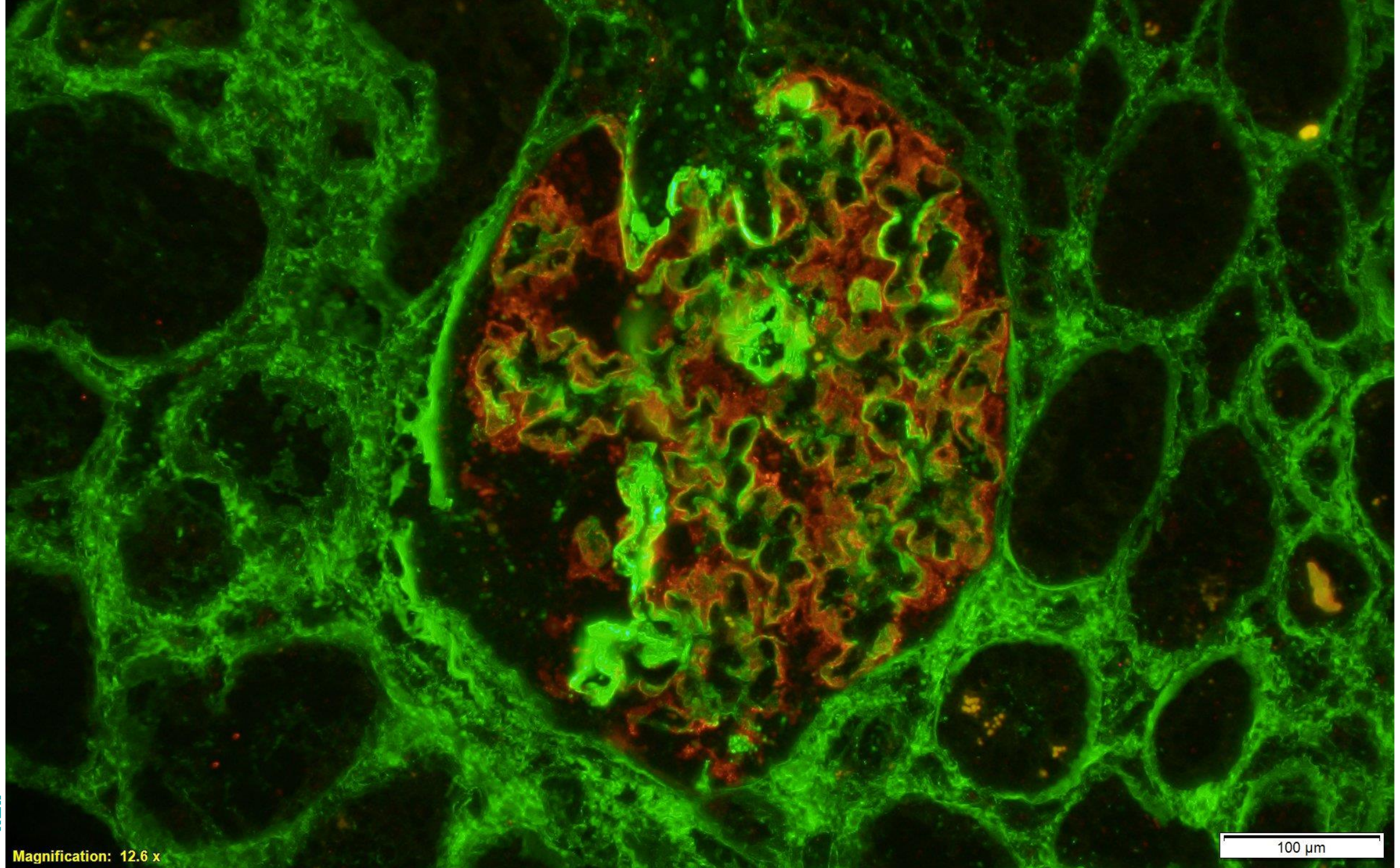


Magnification: 12.6 x

100 μ m



IgG



Magnification: 12.6 x

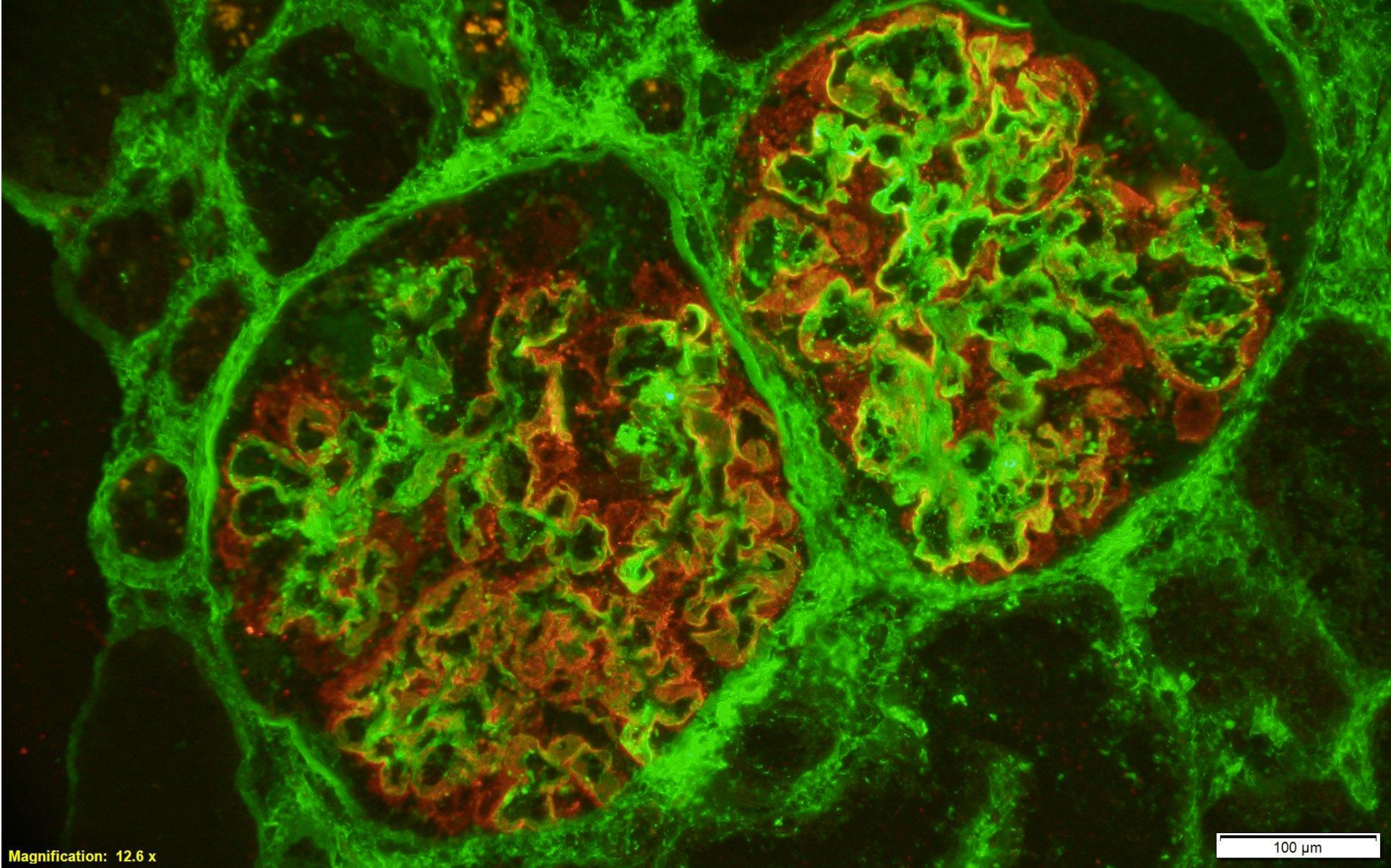
100 μ m

IgG

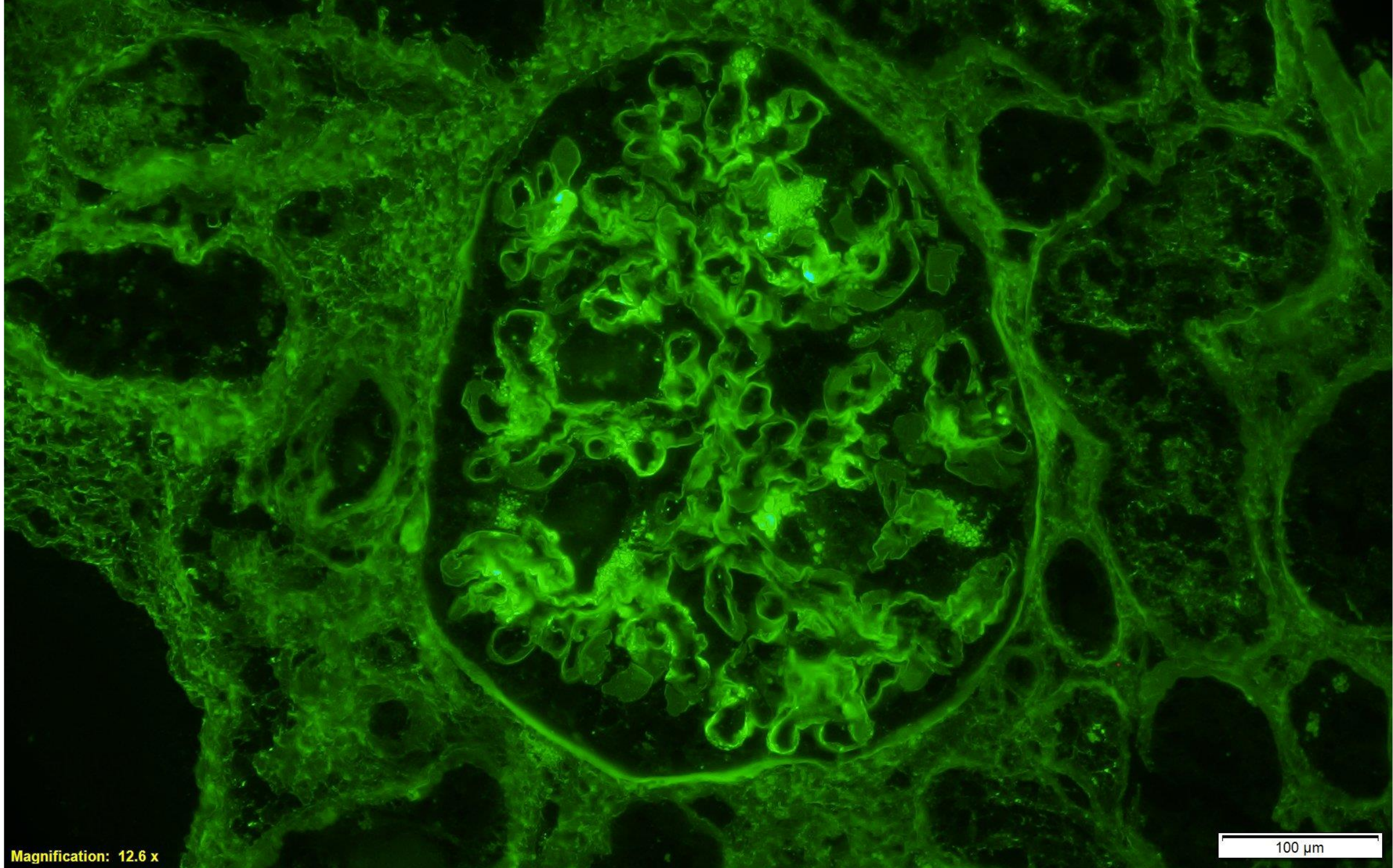


Magnification: 12.6 x

100 μ m

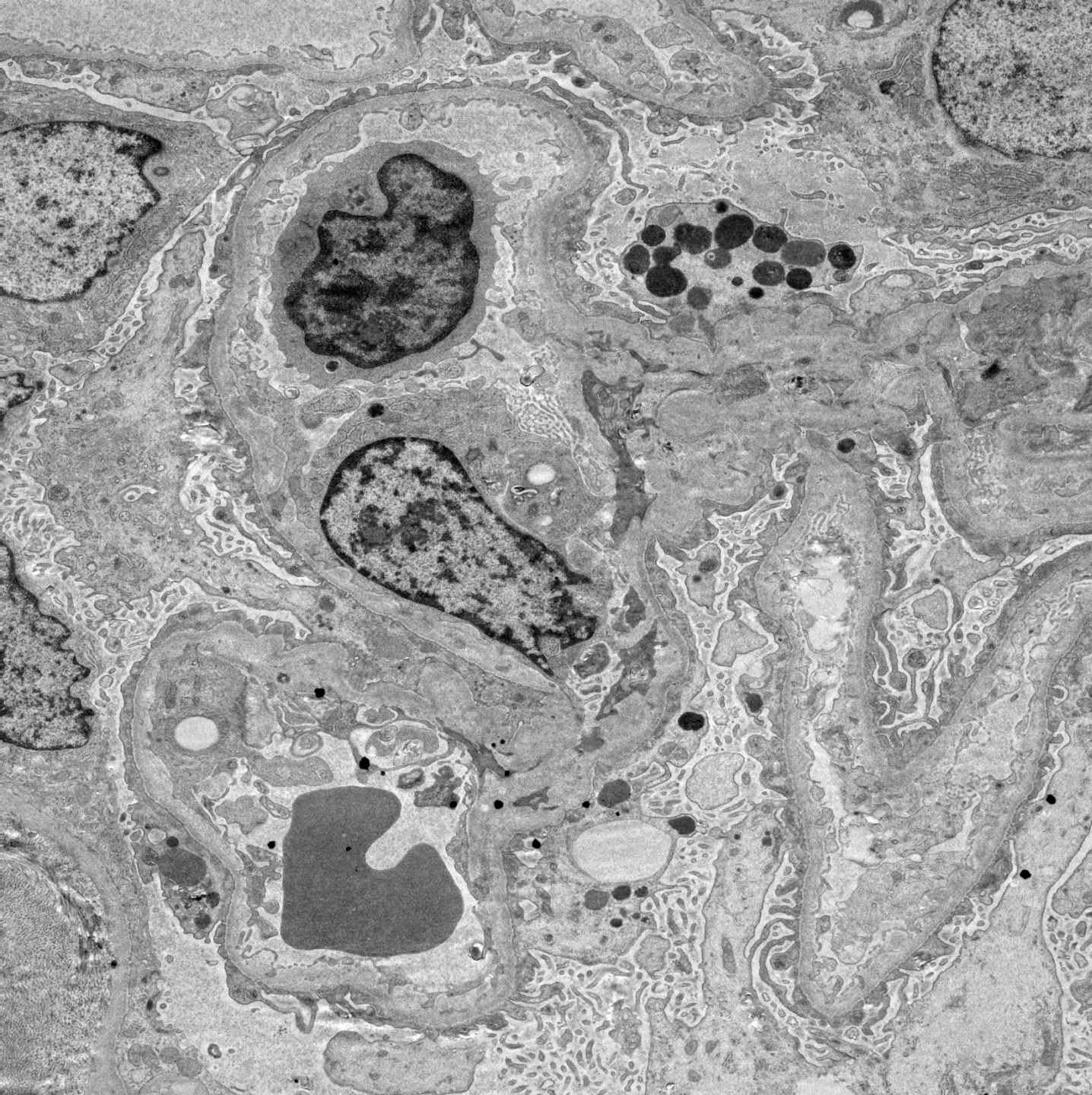


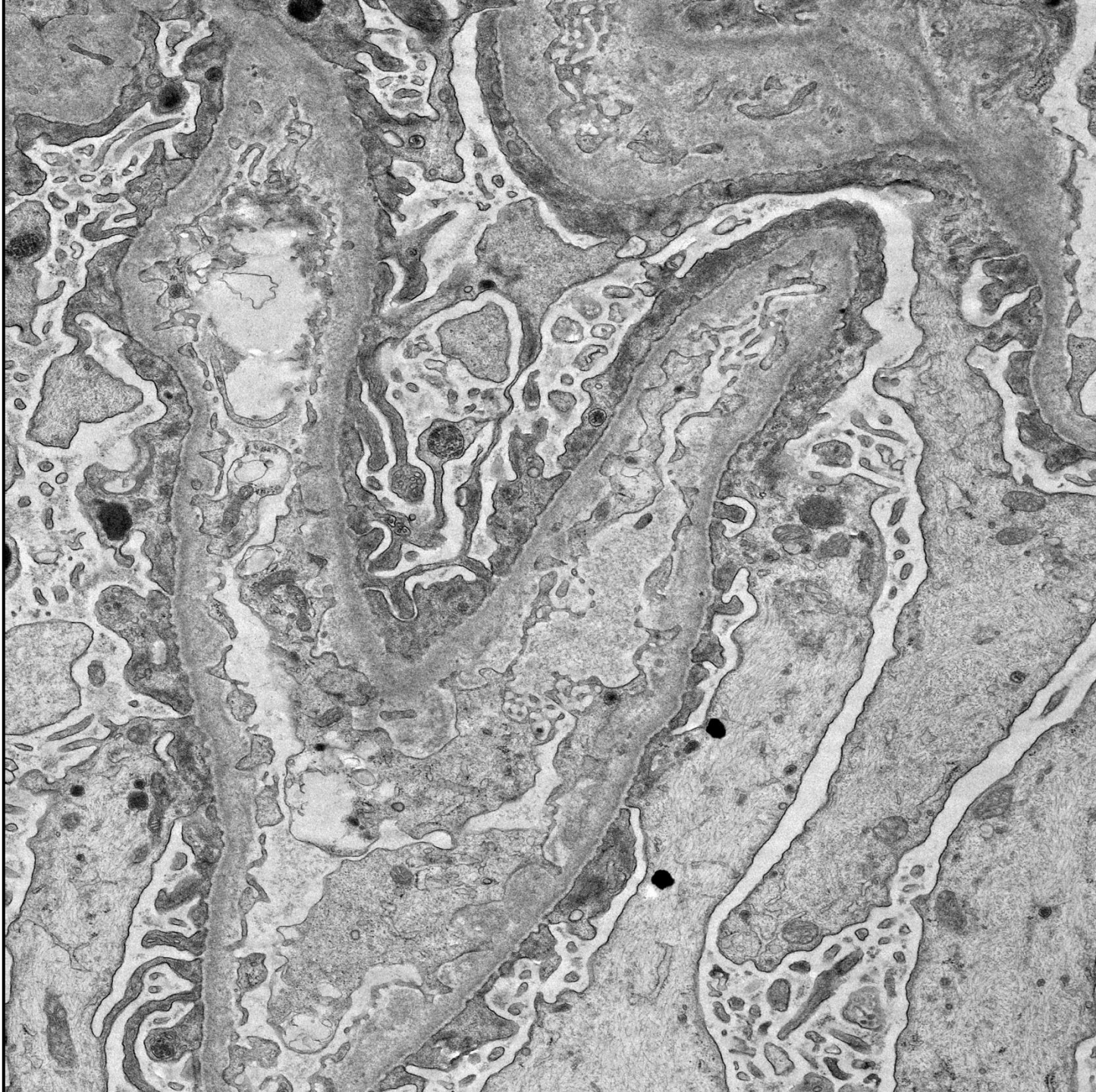
IgG

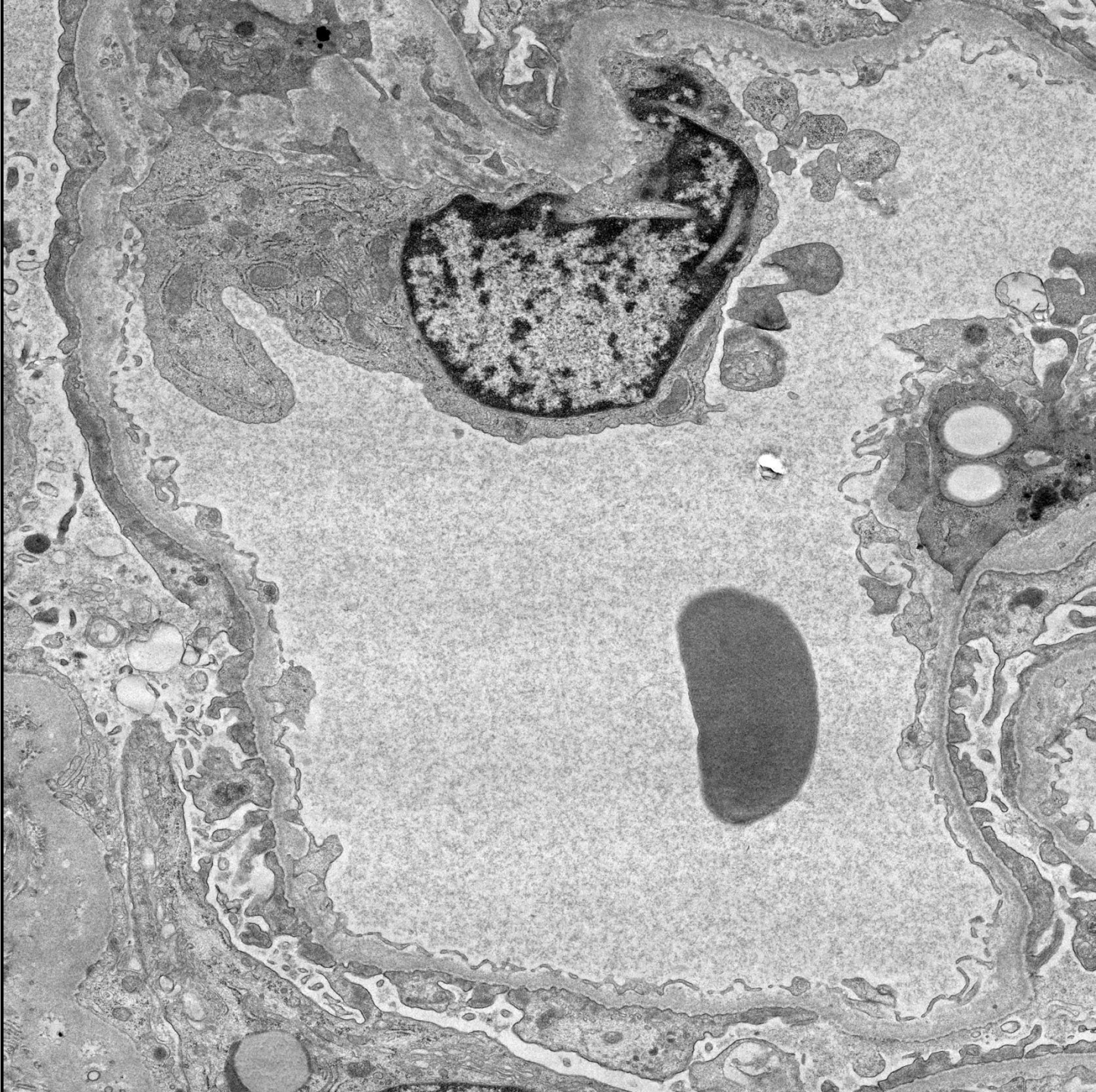


Magnification: 12.6 x

100 μm







Final Diagnosis

Extensive foot process effacement, suggestive of a **Toxic Podocytopathy**

- At least focal preservation of podocyte foot processes, ruling out a currently active diffuse podocytopathy ('minimal change disease')
- No significant overlapping staining of IgG with Nephryn
- We have seen similar cases in patients receiving cancer treatment with XMT-1660 and other auristatin-based microtubule assembly blockers

No evidence of immune complex-mediated disease or paraprotein deposition disease

Mild chronic changes of the parenchyma

- Global glomerulosclerosis (4% of glomeruli)
- Mild tubular atrophy & interstitial fibrosis (5-10% of the cortex)
- Mild arterial and arteriolar sclerosis



Discussion Questions Post Biopsy

Knowing what you know now, how would you manage her?
Stop the drug (assume last option)? Steroids? Something else?

Re-challenge Question:
Would you re-challenge her if proteinuria improves?



Follow-Up

Taken off trial

Treated with ARB, SGLT2i, steroids

After coming off study, within 2-3 weeks, serum albumin normalized, BPs and proteinuria improved

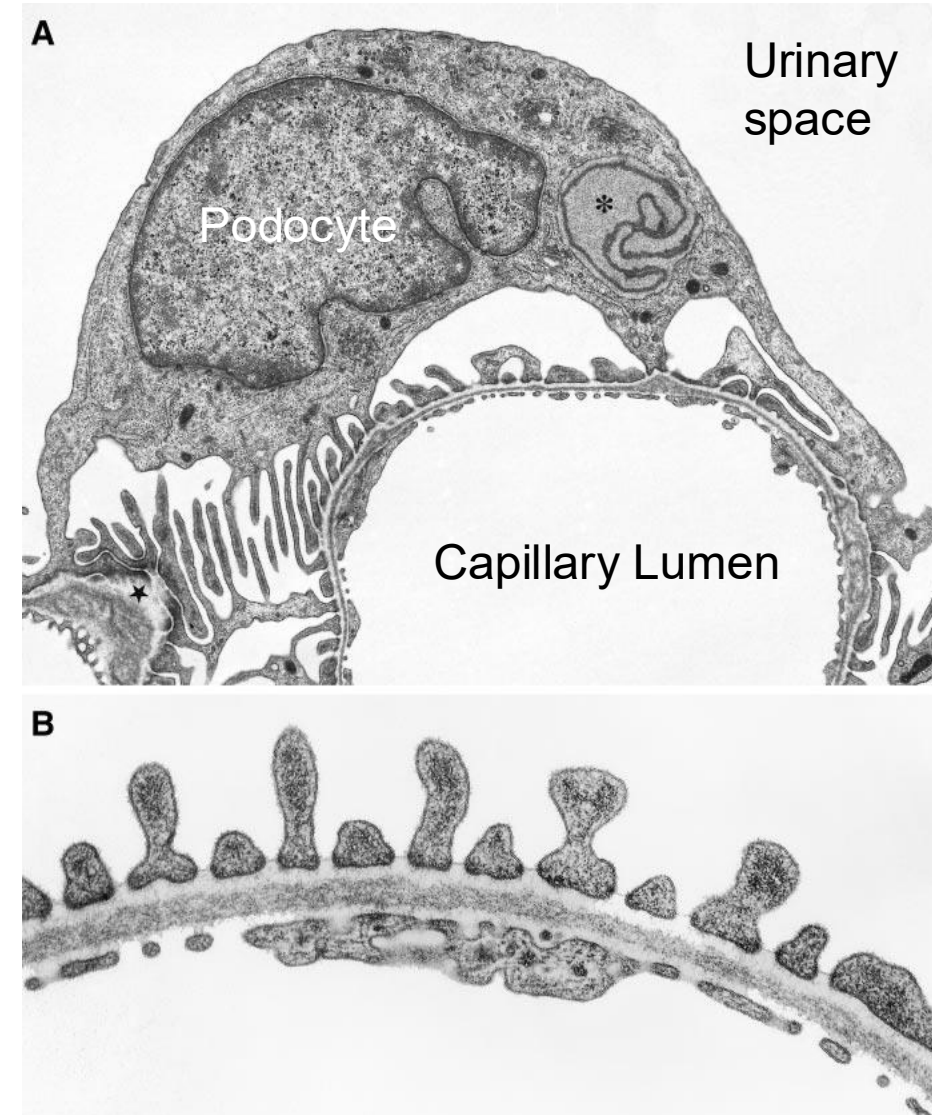
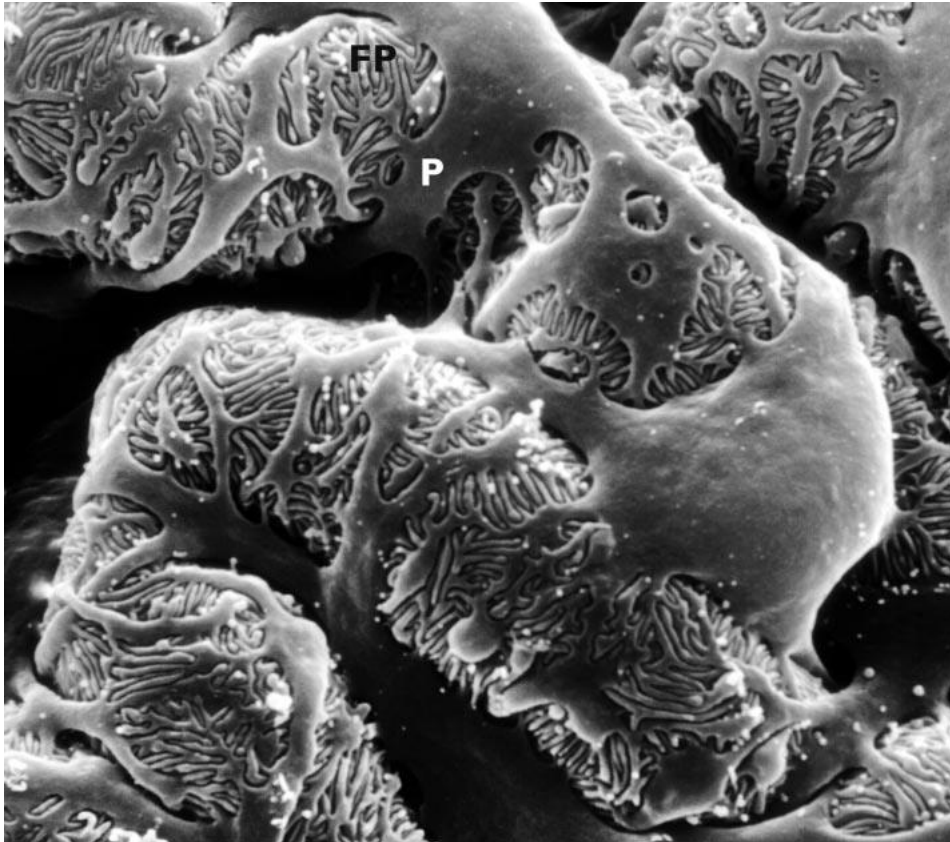
Had disease progression on scans, and passed away on hospice 6 months after starting trial



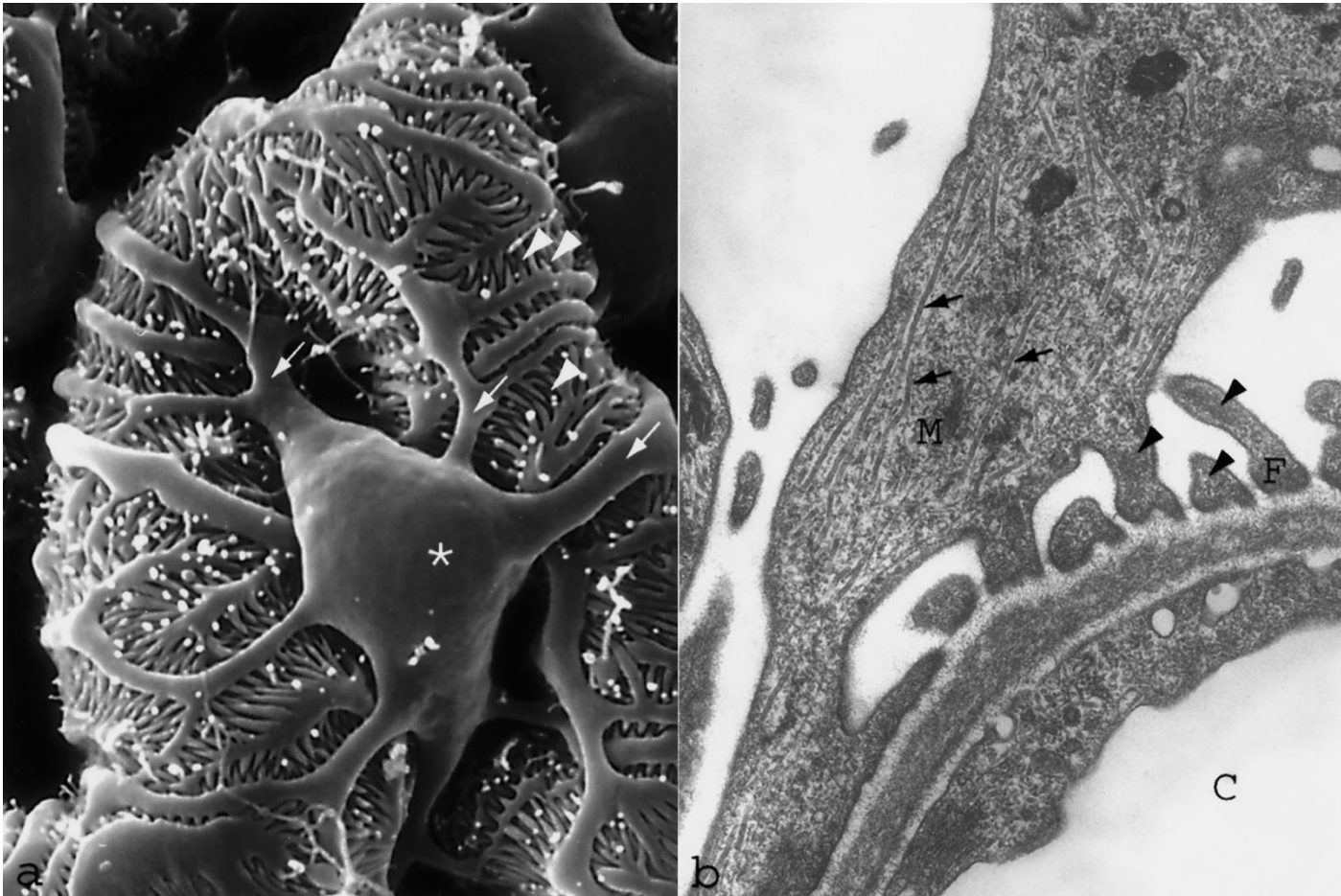
Potential causes of Proteinuria after Microtubule Disruption



Podocyte Structure



The arborized structure of podocytes relies on a specialized cytoskeleton



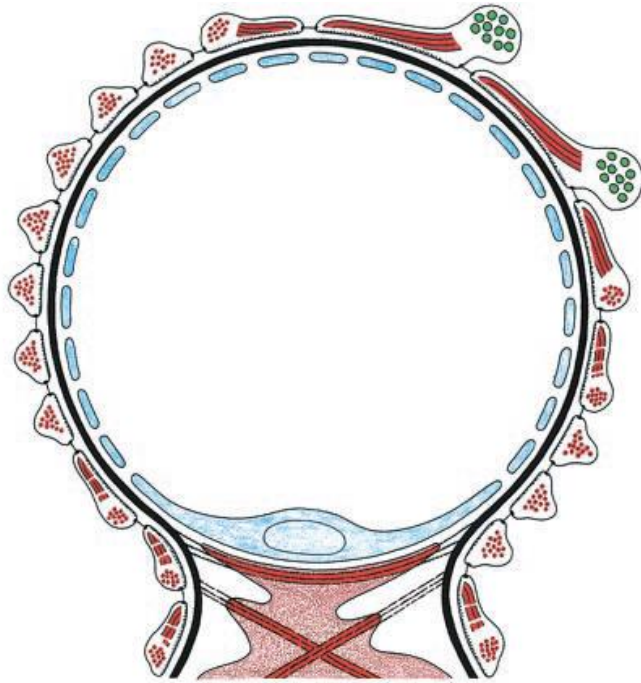
Asterisk: Podocyte cell body

Arrows: Microtubules in major processes

Arrowheads: Actin filament bundles in foot processes

Kobayashi et al, 2001

Cytoskeletal organization of podocyte processes



Major processes:

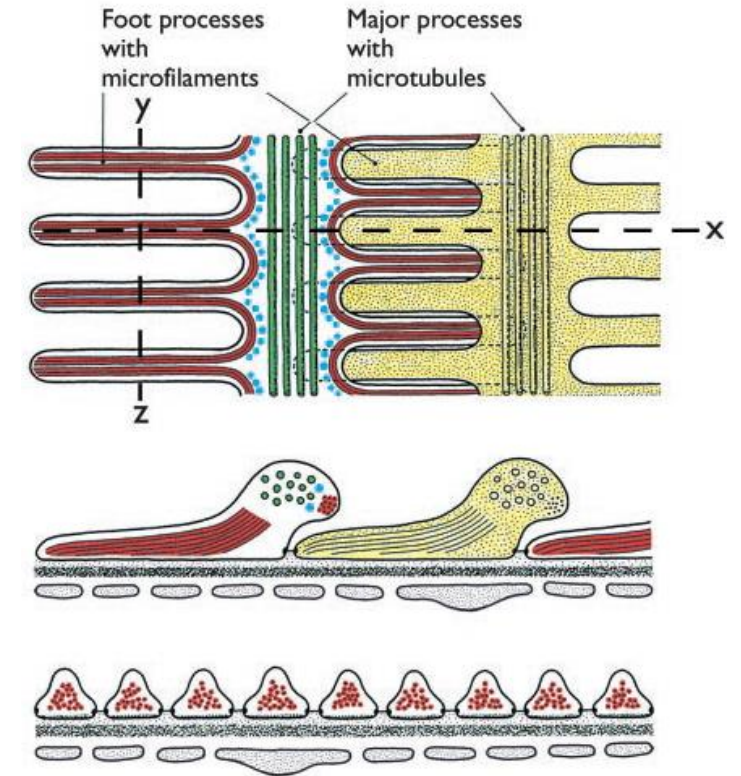
- Microtubules (tubulin)
- Intermediate filaments (vimentin, plectin)

Foot processes:

- Microfilaments (actin)

Dynamic response to outside forces happens mostly in foot processes by rearrangement of their actin cytoskeleton (Ca^{2+} /Rho-K).

Major processes remain mostly static.



Pavenstaedt et al, 2001

Role of microtubules in podocytes

- Microtubules **facilitate intracellular transport of organelles, proteins (including nephrin!), molecules (including ATP!) and vesicles** along the length of the process to and from the foot processes via kinesin, Rab8, and dynein. Disruption of microtubule-based transport (e.g., via altered APC protein or dynamin) is associated with proteinuria, reduced podocyte adhesion, and foot process effacement. (*Gibbs et al, 2015*)
- They are **crucial for maintaining cell shape, polarity and structural integrity**. Disruption of microtubules in podocytes *in vitro* by application of the MT-depolymerizing drug vinblastine inhibited process formation, in a dose-dependent and transient manner, with full cytoskeletal recovery 3-7 days after the drug was removed. (*Kobayashi et al, 2001*)
- **Podocyte foot process formation and maintenance** is dependent on microtubule assembly. Actin filaments and intermediate filaments alone are not able to maintain podocyte structure. (*Kobayashi et al, 2001*)
- A **synergistic detrimental effect of MT destabilization with genetic mutations** on podocyte integrity and survival is likely, especially those mutations affecting podocyte adhesion to the GBM.



How does the drug enter the podocyte?

nephron
Experimental
Nephrology

Original Paper
Nephron Exp Nephrol 2010;116:e72–e83
DOI: [10.1159/000319320](https://doi.org/10.1159/000319320)

The Cytoplasmic Domain of Tissue Factor Restricts Physiological Albuminuria and Pathological Proteinuria Associated with Glomerulonephritis in Mice

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Centre for Inflammatory Diseases

Key Words

Tissue factor · Podocyte · Albuminuria · Proteinuria · Glomerulonephritis

Abstract

Background/Aims: Tissue factor (TF) is a transmembrane protein that is essential for coagulation. TF is expressed on podocytes and its cytoplasmic domain has cell signalling functions in epithelial cells. **Methods:** Mice lacking the cyto-

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The Journal of Translational Immunology

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12452

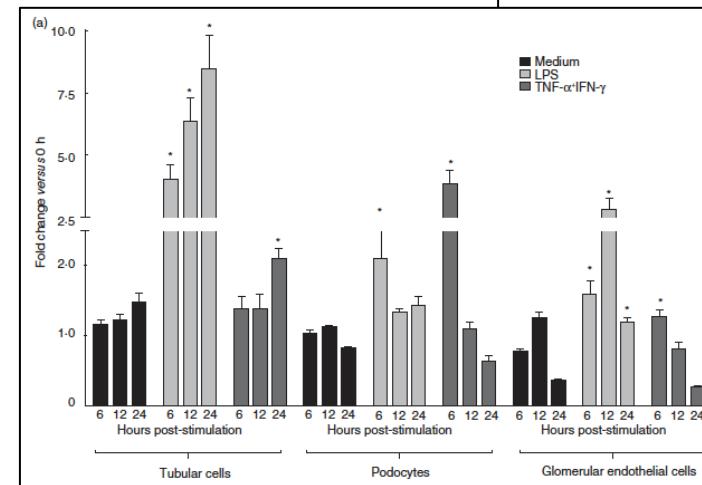
B7x/B7-H4 modulates the adaptive immune response and ameliorates renal injury in antibody-mediated nephritis

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Summary

Kidney disease is one of the leading causes of death in patients with lupus and other autoimmune diseases affecting the kidney, and is associated with deposition of antibodies as well as infiltration of T lymphocytes and macrophages, which are responsible for initiation and/or exacerbation of inflammation and tissue injury. Current treatment options have relatively limited efficacy; therefore, novel targets need to be explored. The co-inhibitory molecule, B7x, a new member of the B7 family expressed predominantly by non-lymphoid tissues, has been shown to inhibit the proliferation, activation and functional responses of CD4 and CD8 T cells. In this study, we found that B7x was expressed by intrinsic renal cells, and was up-regulated upon stimulation with inflammatory triggers. After passive administration of antibodies against glomerular antigens, B7x^{-/-} mice developed severe renal injury accompanied by a robust adaptive immune response and kidney up-regulation of inflammatory mediators, as well as local infiltration of T cells and macrophages. Furthermore, macrophages in the spleen of B7x^{-/-} mice were polarized to an inflammatory phenotype. Finally, treatment with B7x-immunoglobulin (Ig) in this nephritis model decreased kidney damage and reduced local inflammation. We propose that B7x can modulate kidney damage in autoimmune diseases including lupus nephritis and anti-glomerular basement membrane disease. Thus, B7x mimetics may be a novel therapeutic option for treatment of immune-mediated kidney disease.

Keywords: B7x, co-inhibition, co-stimulation, nephritis, T cells



List of approved ADCs that are microtubule inhibitors

Table 1. Approved Antibody–Drug Conjugates (ADCs) and Their Key Characteristics.

No.	Antibody–Drug Conjugate (Developer)	Trade Name	Target Antigen	Linker	Cytotoxic Payload	Payload Action	Drug Antibody Ratio (DAR)
1	Ado-trastuzumab emtansine	Kadcyla	HER2	SMCC	DM1	Microtubule Inhibitor	3.5
2	Mirvetuximab soravtansine (ImmunoGen)	Elahere	FR α	sulfo-SPDB	DM4	Microtubule Inhibitor	3.4
3	Brentuximab vedotin (Seagen)	Adcetris	CD30	mc-VC-PABC	MMAE	Microtubule Inhibitor	4
4	Polatuzumab vedotin	Polivy	CD79B	mc-VC-PABC	MMAE	Microtubule Inhibitor	3.5
5	Enfortumab vedotin (Seagen)	Padcev	Nectin-4	mc-VC-PABC	MMAE	Microtubule Inhibitor	3.8
6	Disitamab vedotin	Aidixi	HER2	mc-VC-PABC	MMAE	Microtubule Inhibitor	4
7	Tisotumab vedotin (Genmab/Seagen)	Tivdak	TF	mc-VC-PABC	MMAE	Microtubule Inhibitor	4
8	Belantamab mafodotin (GSK)	Blenrep	BCMA	mc	MMAF	Microtubule Inhibitor	4
9	Loncastuximab tesirine (ADC Therapeutics)	Zynlonta	CD19	dipeptide	PBD dimer	DNA Cleavage	2.3
10	Gemtuzumab ozogamicin	Mylotarg	CD33	hydrazone	N-acetyl- γ -calicheamicin	DNA Cleavage	2~3
11	Inotuzumab ozogamicin	Besponsa	CD22	hydrazone	N-acetyl- γ -calicheamicin	DNA Cleavage	5~7
12	Fam-trastuzumab deruxtecan	Enhertu	HER2	tetrapeptide	DXd	TOP1 Inhibitor	7~8
13	Sacituzumab tirumotecan	Jla	Trop-2	methyl sulfonyl pyrimidine	KL610023	TOP1 Inhibitor	7.4
14	Sacituzumab govitecan (Immunomedics)	Trodelvy	Trop-2	CL2A	SN38	TOP1 Inhibitor	7.6
15	Cetuximab sarotalocan	Akalux	EGFR	NA	IRDye700DX	Membrane damage	1.3~3.8
16	Moxetumomab pasudotox	Lumoxiti	CD22	mc-VC-PABC	PE38	Protein synthesis inhibition	NA



FDA-approved ADCs that contain auristatins

These are the agents for which toxic podocytopathy is biologically most plausible because MMAE inhibits microtubule polymerization

ADC	Payload
Brentuximab vedotin	MMAE
Enfortumab vedotin	MMAE
Polatuzumab vedotin	MMAE
Tisotumab vedotin	MMAE



Take Home Points

Proteinuria with stable Cr on an auristatin ADC = toxic podocytopathy

Biopsy may be useful even with preserved kidney function

Injury is dose-dependent and reversible; supports rechallenge if proteinuria resolves



DISCUSSION AND QUESTIONS

