

Immune Checkpoint Inhibitor–Associated Glomerulonephritis: Navigating a Clinical Conundrum

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Meet Our Experts



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Patient Presentation

HPI:

A 69-year-old man presents for evaluation of worsening kidney function.

He recently initiated **Cycle 1** of **ipilimumab/nivolumab** approximately **3 weeks** prior to admission and has had a progressive rise in serum creatinine over several weeks:

1.0 mg/dL (baseline) → 1.5 mg/dL → 1.9 mg/dL (on admission)



Medical Hx

- Hypertension
- Diabetes mellitus
- GERD
- Nephrolithiasis

Medications

- Amlodipine, Dasatinib, Jardiance, Levothyroxine, Losartan, Metformin, Spironolactone

Oncologic Hx:

- **Chronic Myeloid Leukemia**
- **Hurthle Cell Thyroid Cancer**
 - **Lenvatinib** for 1 year → switched to **cabozantinib** for 1 year (frequent treatment interruptions due to diarrhea)
 - Cabozantinib stopped due to severe cutaneous toxicity
 - Started cycle 1 of **ipilimumab/nivolumab** 3 weeks ago



CLINICAL SUMMARY



VITALS



Temperature **36.9 °C**



Heart Rate **69 bpm**



Blood Pressure **137/71 mmHg**



SpO₂ **97 %**



LABS



- Hgb **10.7 g/dL**
- Platelets **257 k/uL**
- No eosinophilia



Serum creatinine:
1.9 mg/dL



Serum albumin:
4.7 g/dL



Urine Protein/Creatinine
ratio
2 g/g Cr



24 hour total urine protein
4.4 g
(2.3 g albumin)



Bland UA,
no casts



IMAGING



No hydronephrosis
or renal stones



ADDITIONAL SEROLOGIES



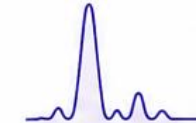
C3: 149 mg/dL
C4: 37 mg/dL



ANA, ANCA,
dsDNA Ab,
Cryoglobulin:
Negative



Hepatitis B/C,
HIV
Negative



SPEP
without
M spike

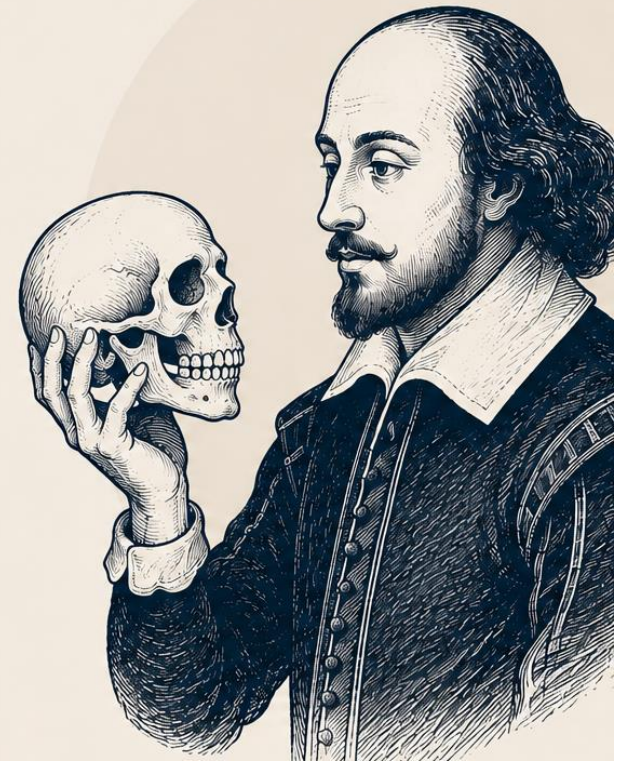


FLC:
Kappa/Lambda
1.51

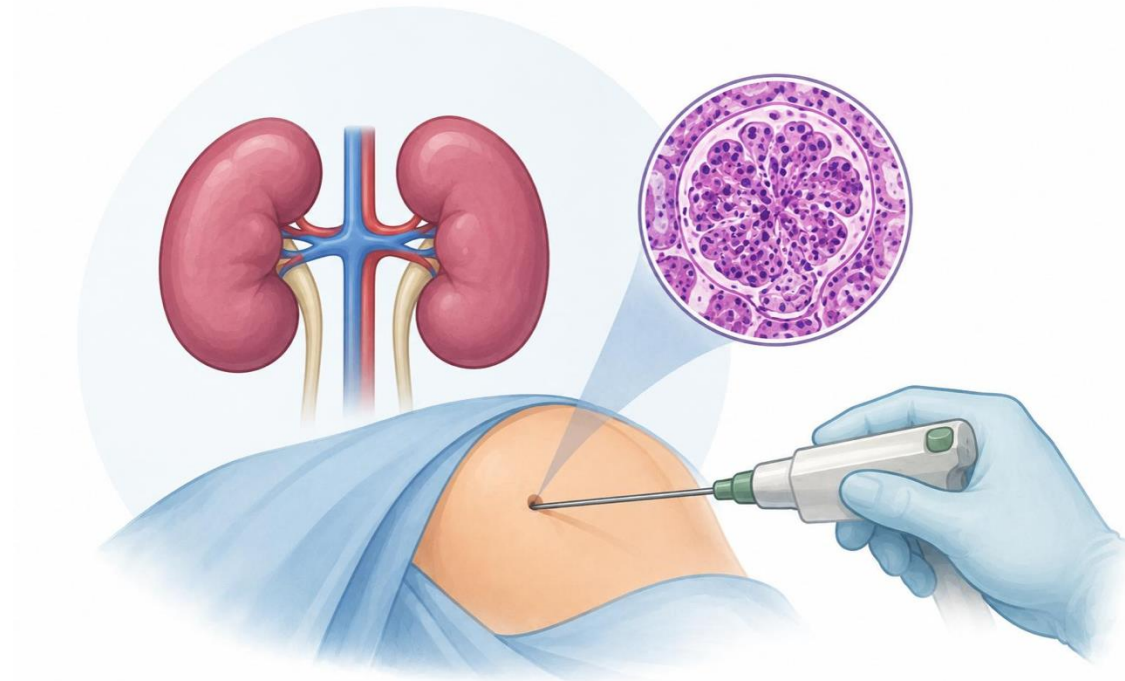


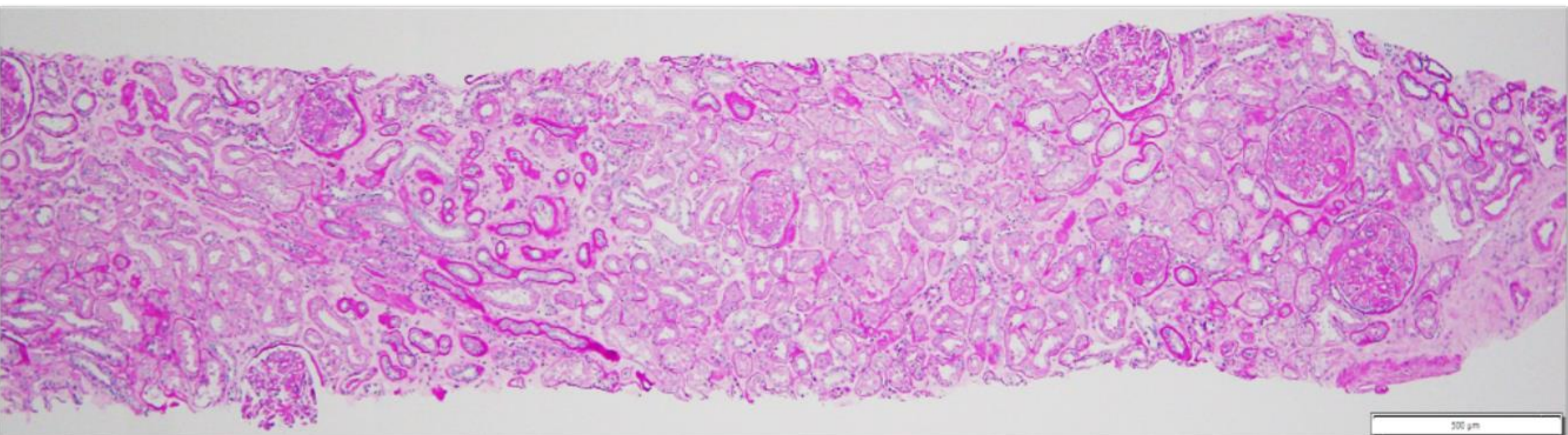
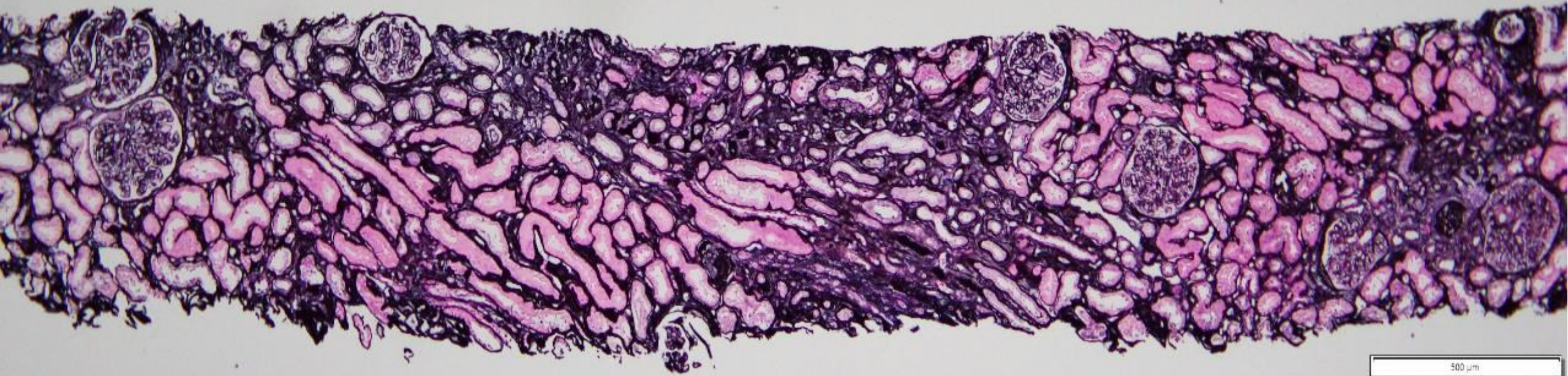
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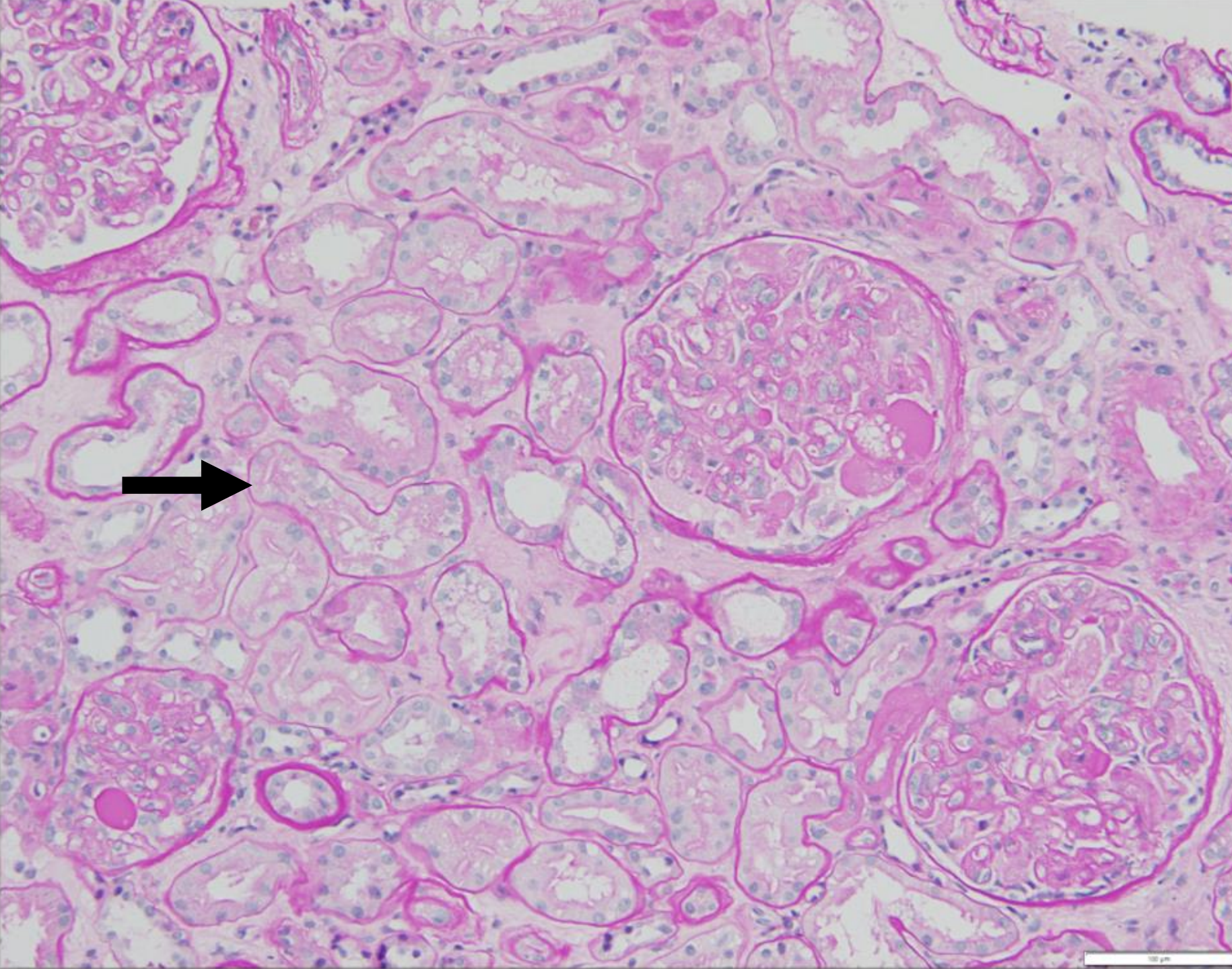
To biopsy
or not to biopsy...
that is the question

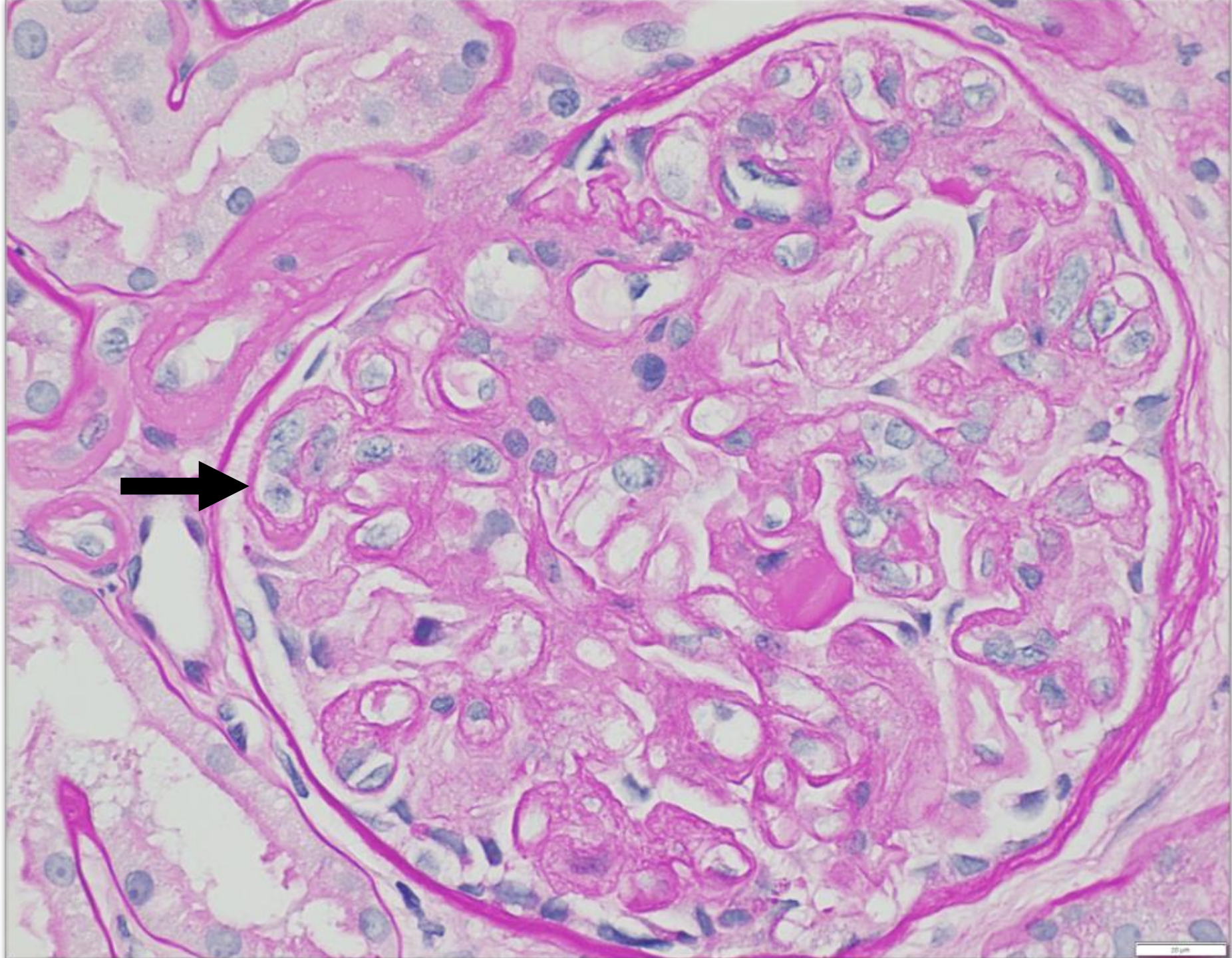


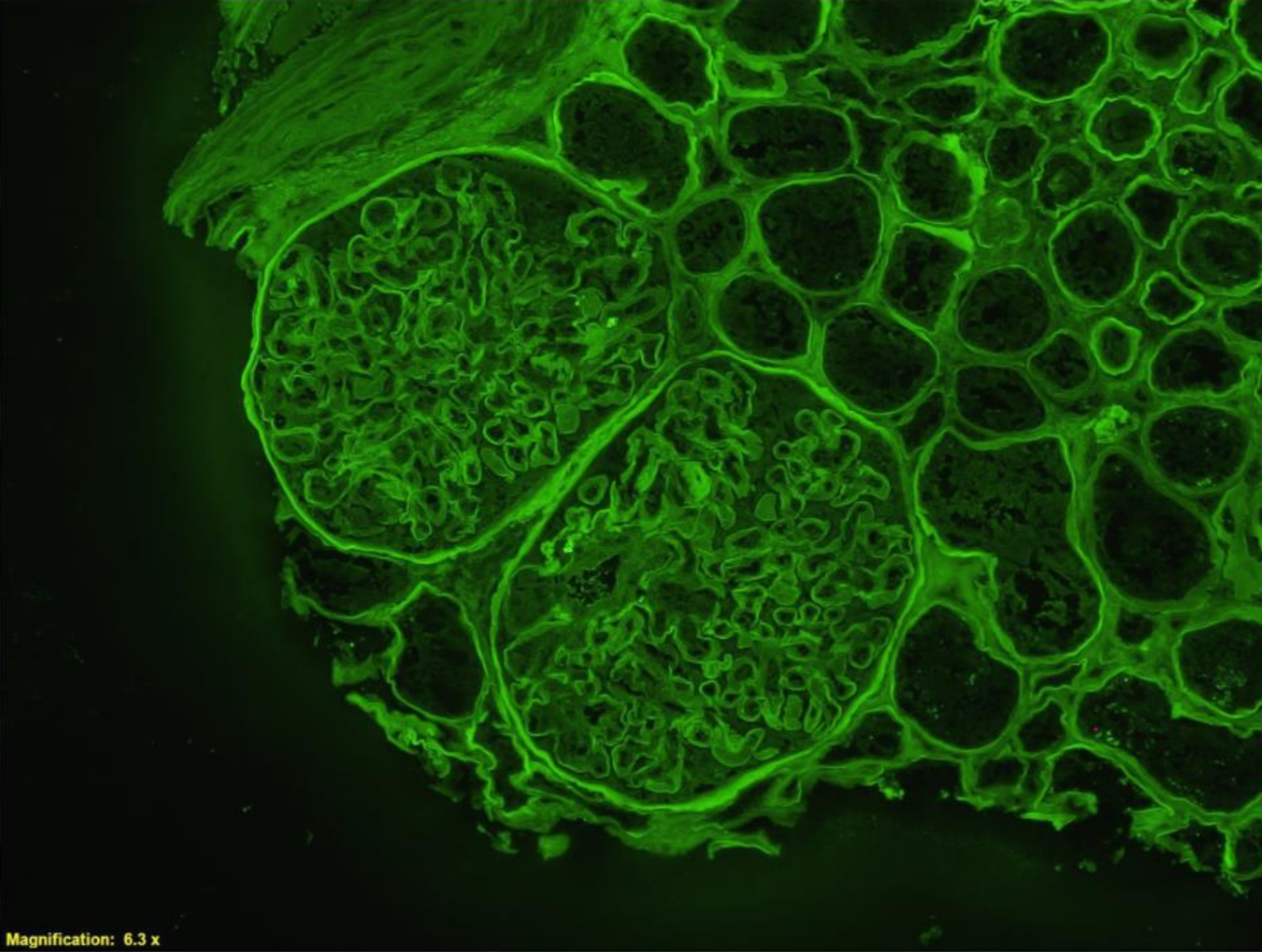
A Renal Biopsy was performed





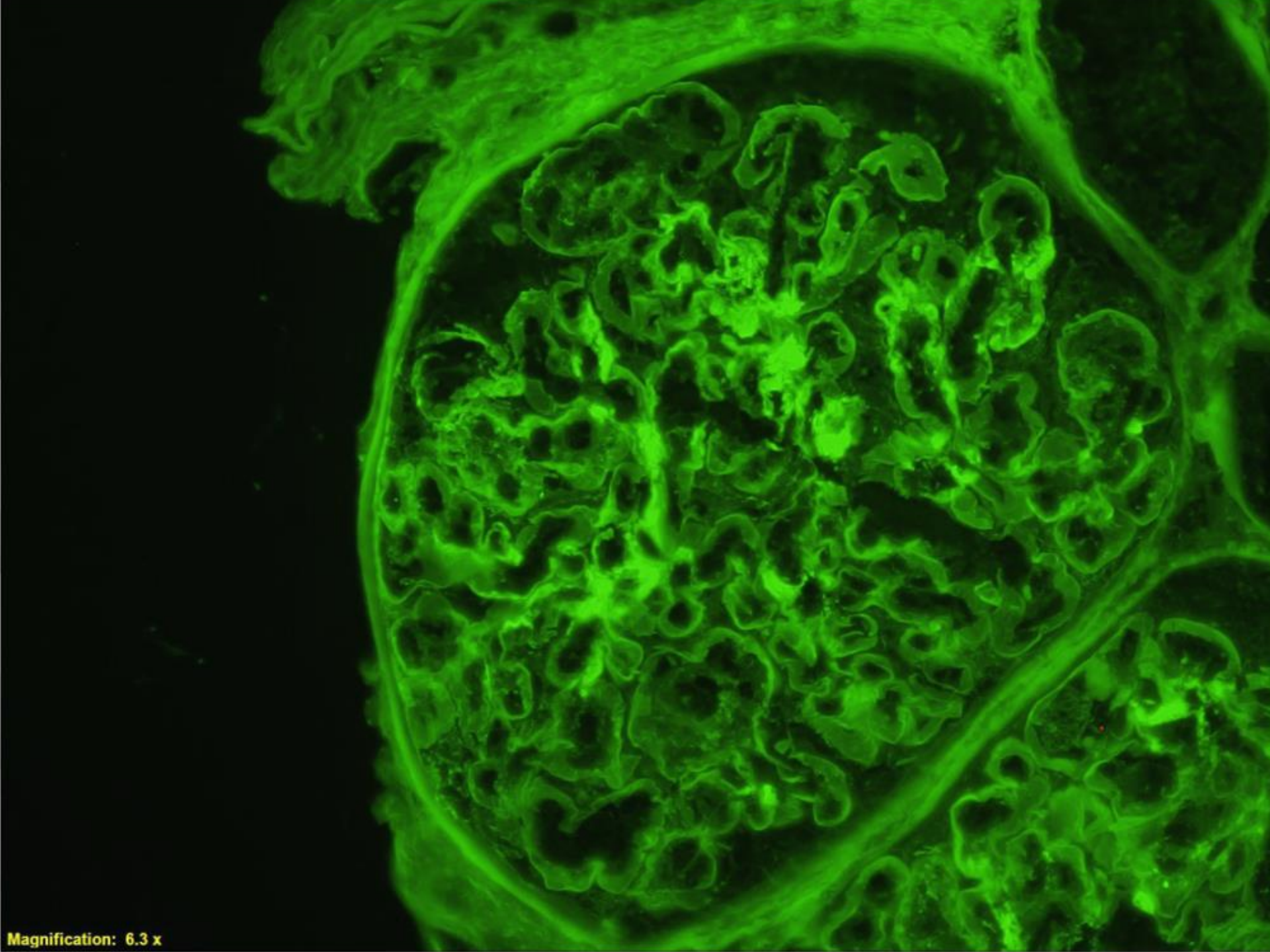




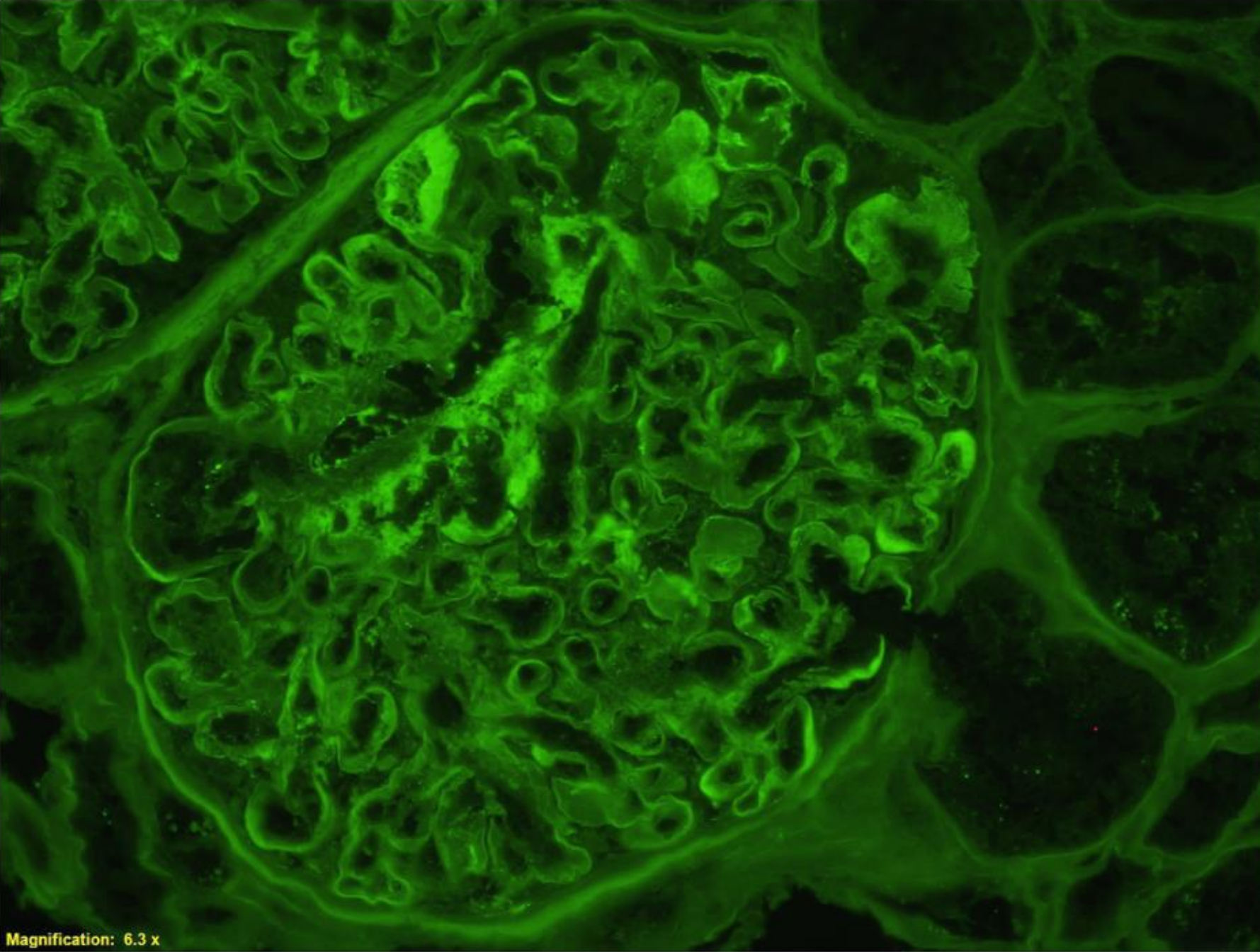


Magnification: 6.3 x



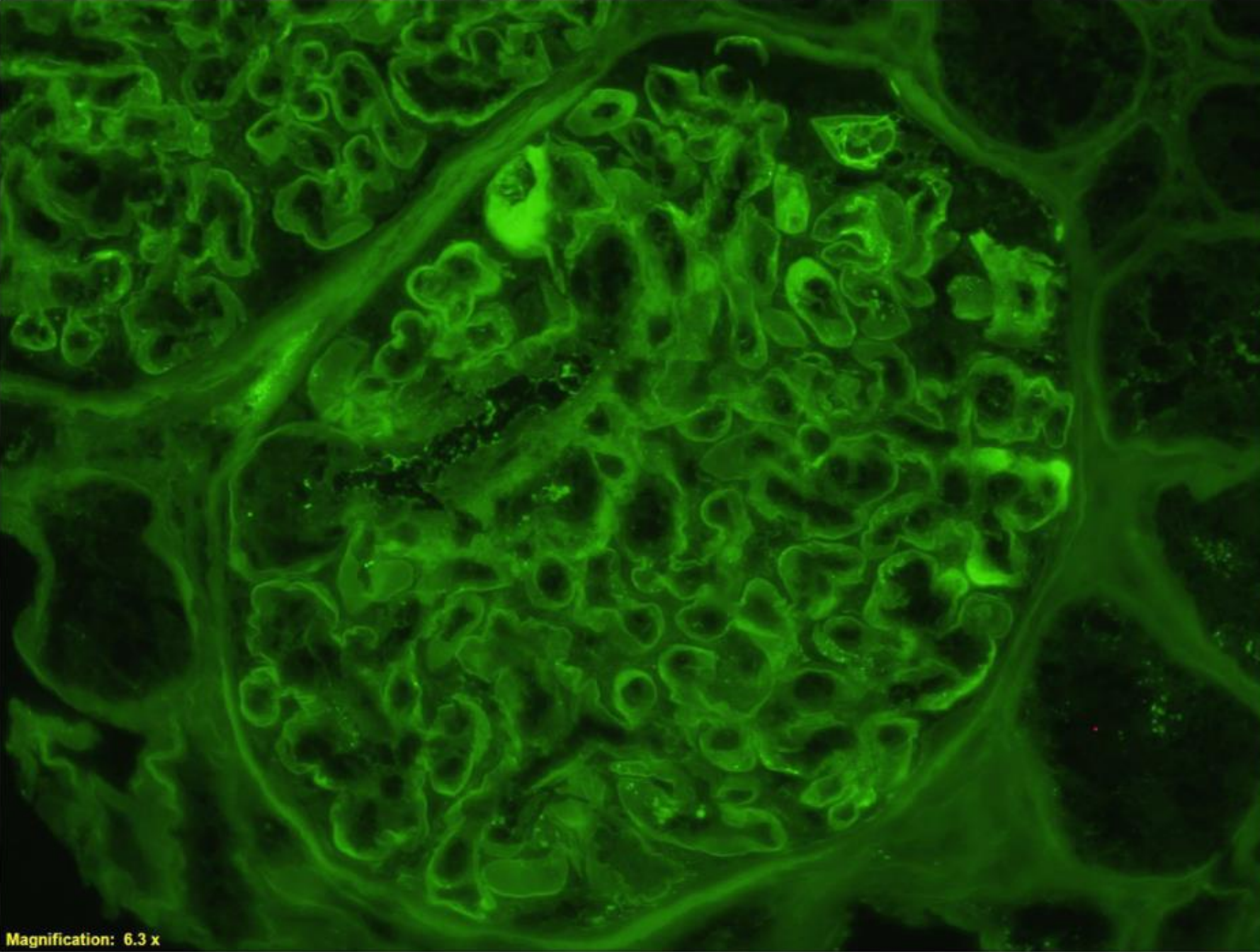


Magnification: 6.3 x



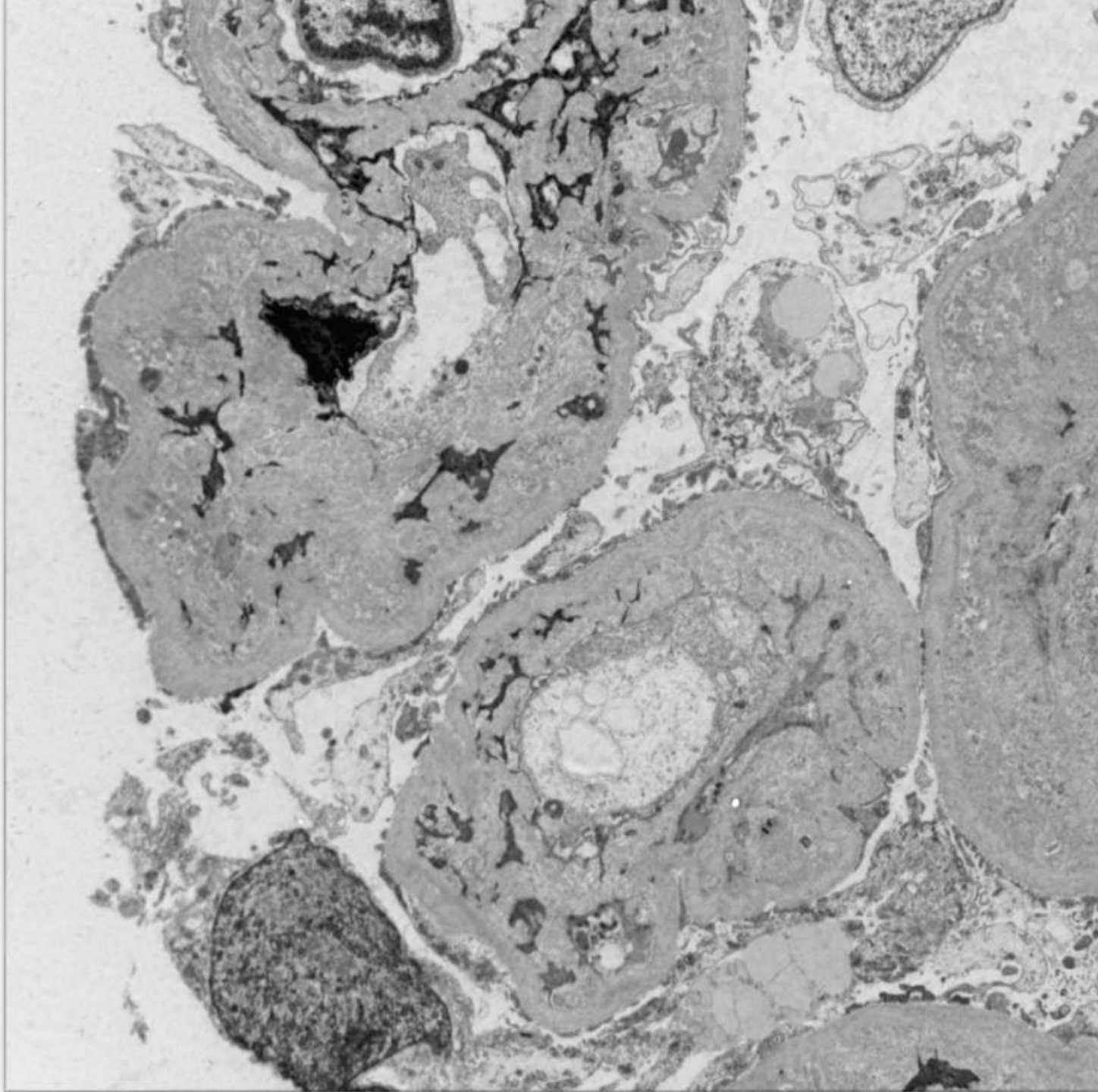
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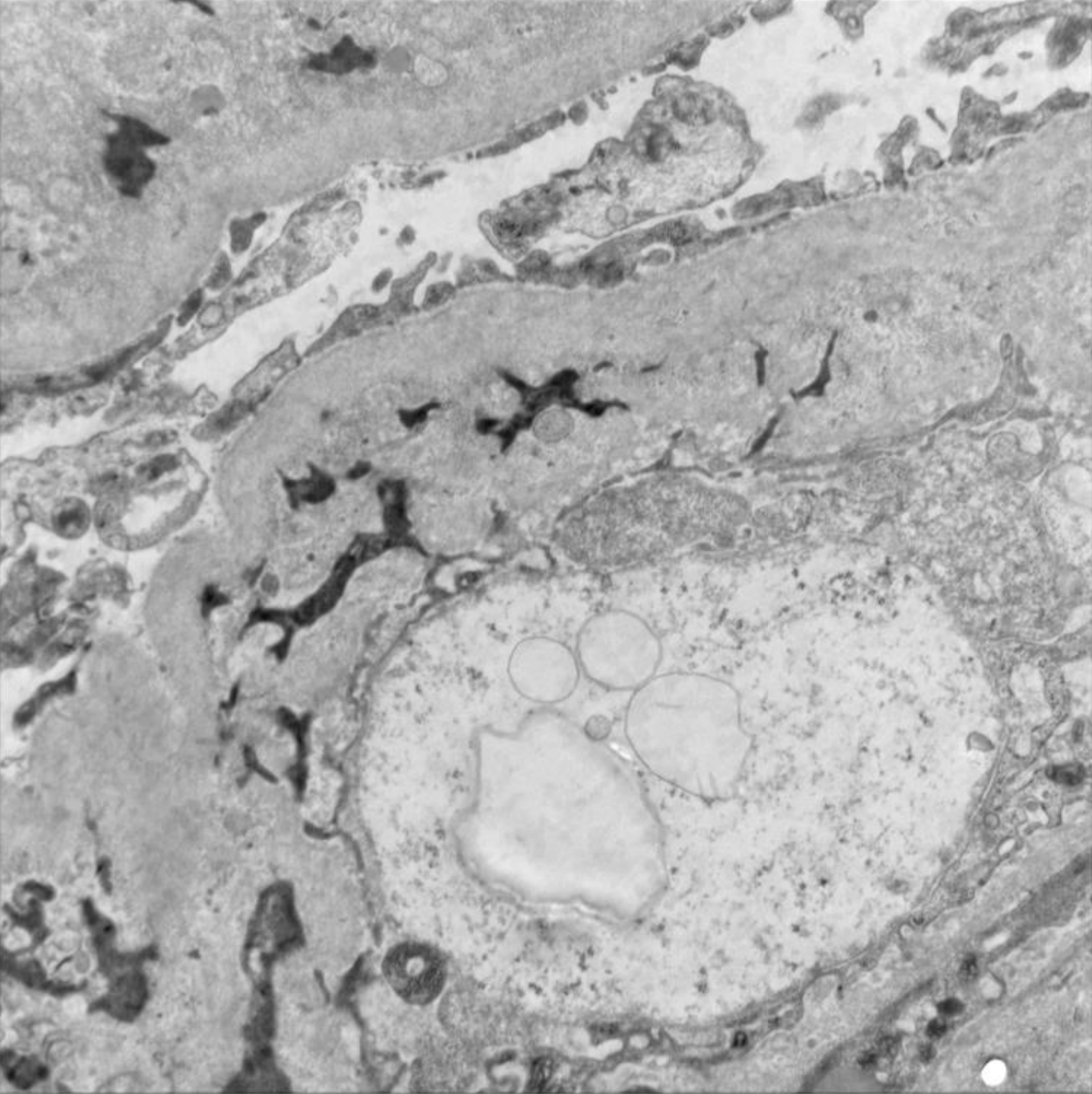


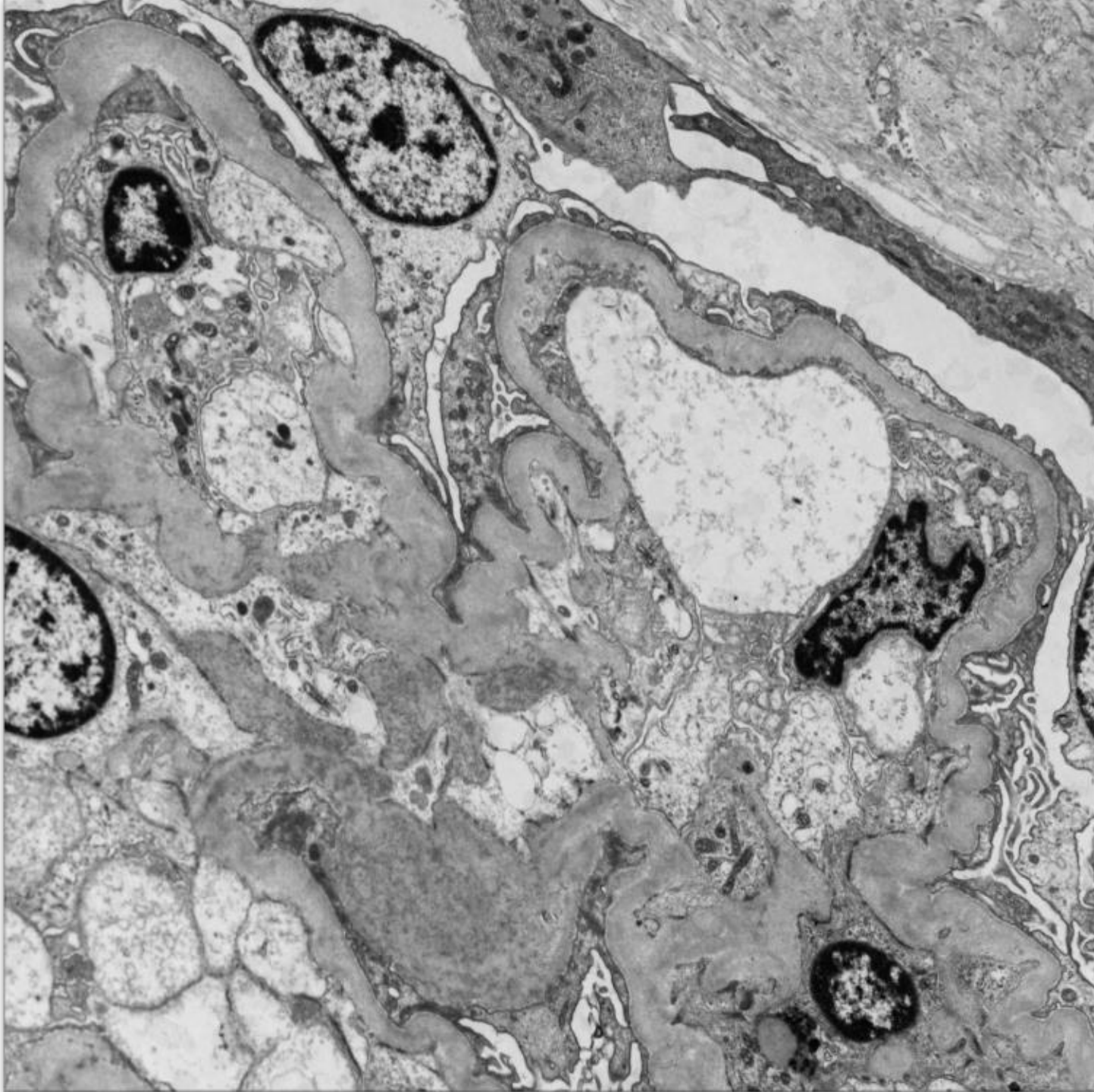


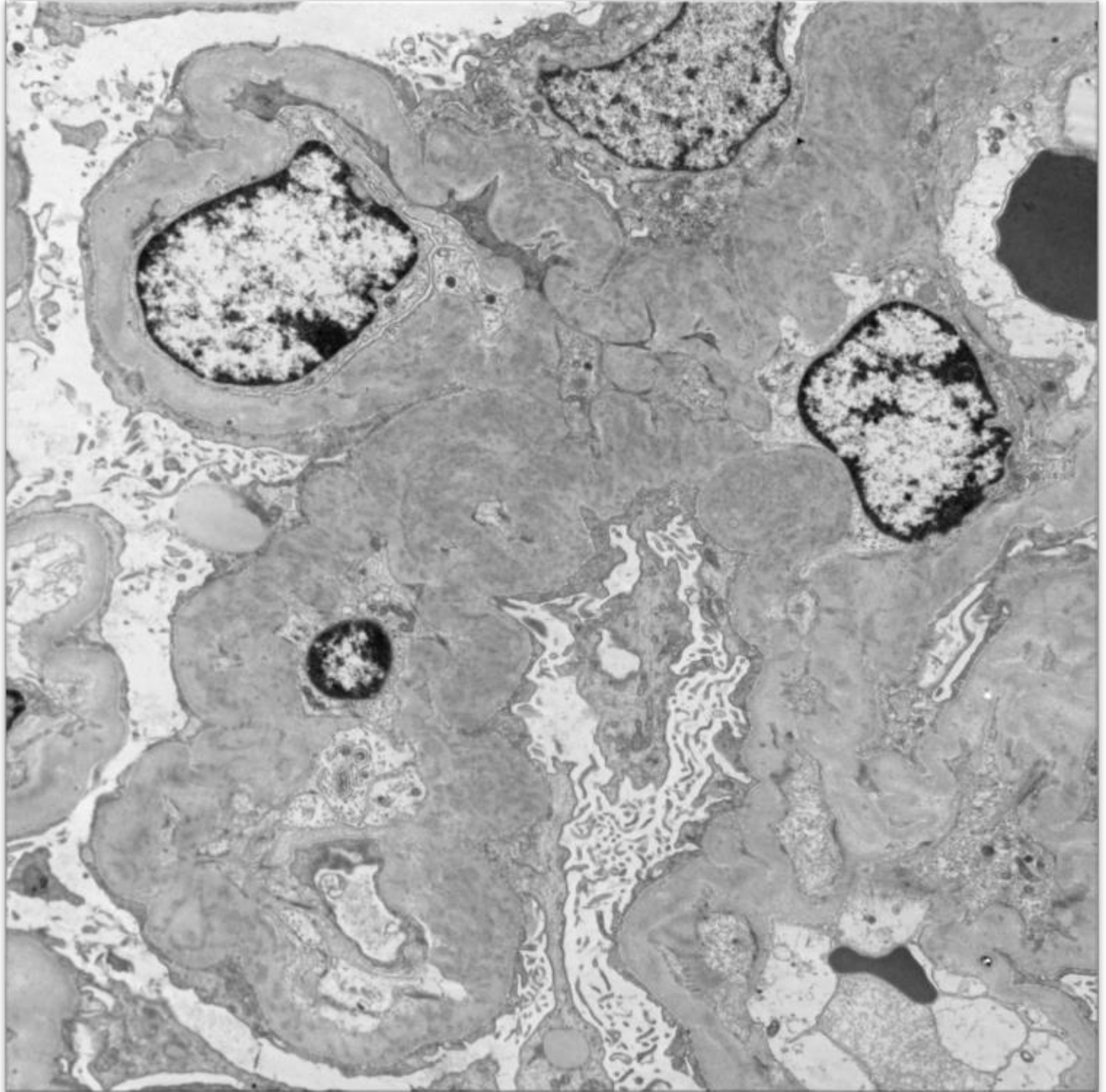
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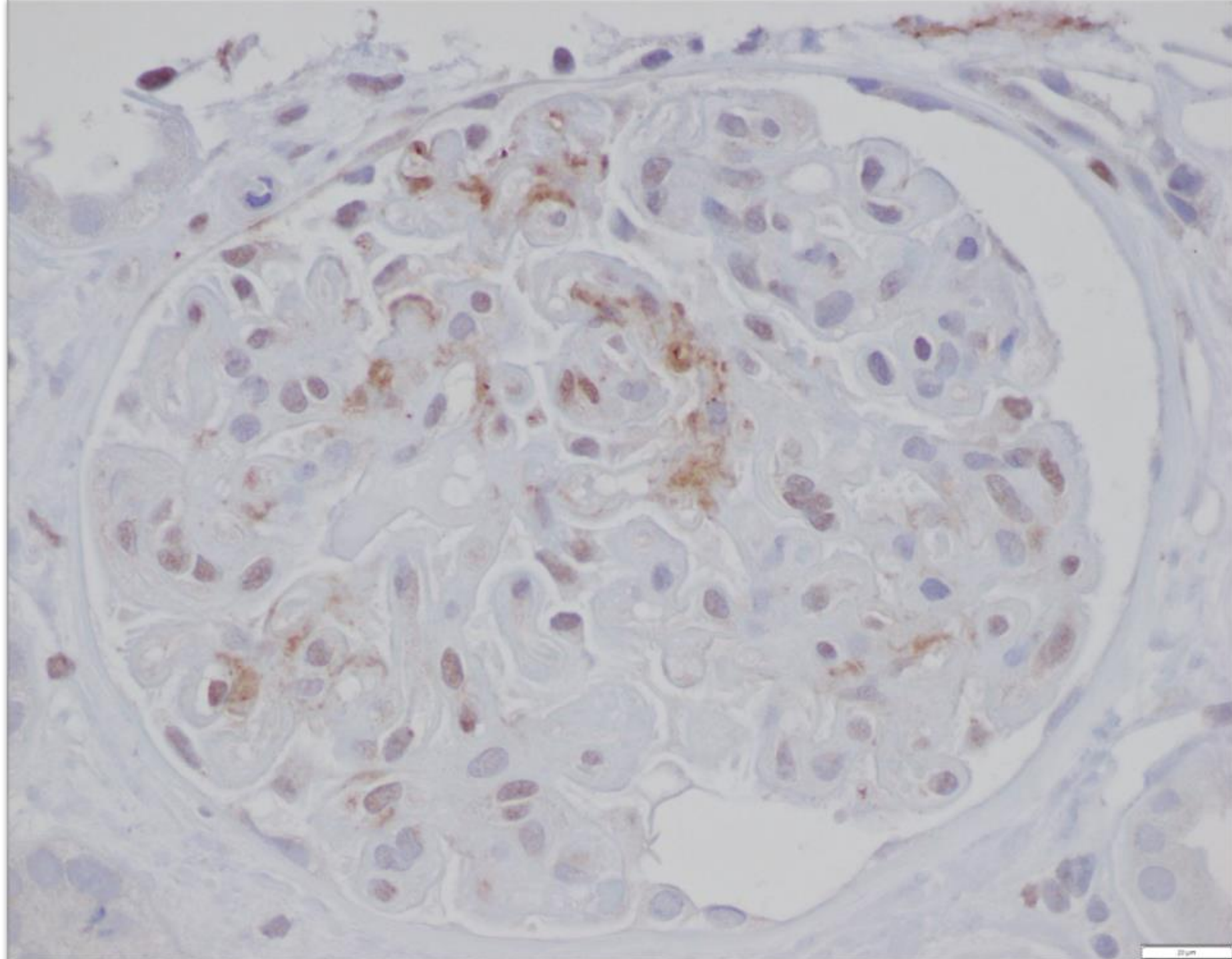






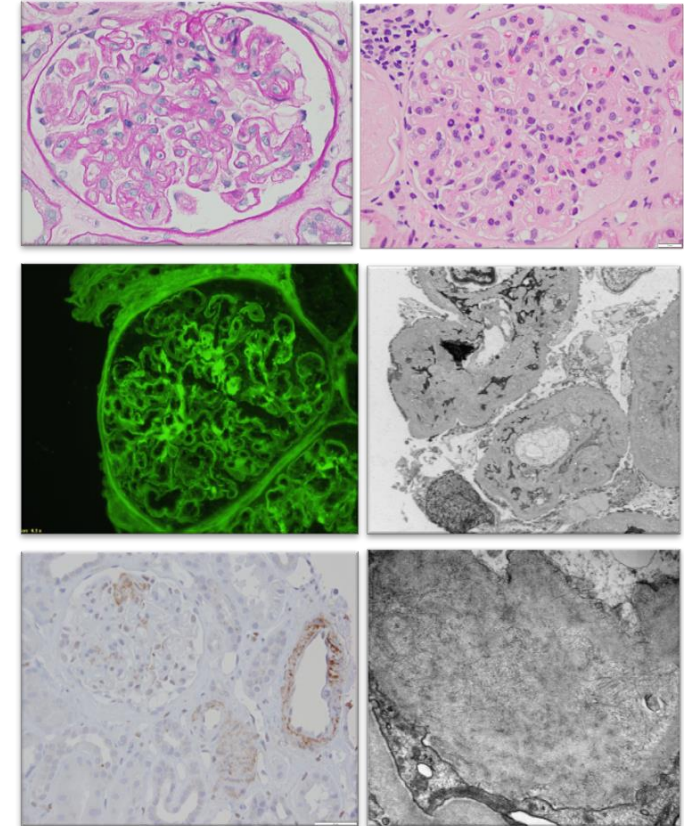






Final Diagnosis

- **Chronic thrombotic angiopathy**, with endothelial injury and extensive signs of remodeling of the glomerular capillary walls
- **Fibrillary glomerulonephritis**, with focal and segmental glomerular involvement and sparsely distributed deposits (18nm in diameter)
 - IHC for **DNAJB9 is positive** in glomeruli and focally along tubular basement membranes and vascular walls
 - Reactive for polyclonal IgG, C3, and C1q
 - **Congo red stain is negative**
- **Acute Tubular Injury**
- Chronic changes: 21% global sclerosis; 20% IFTA; mild vascular sclerosis





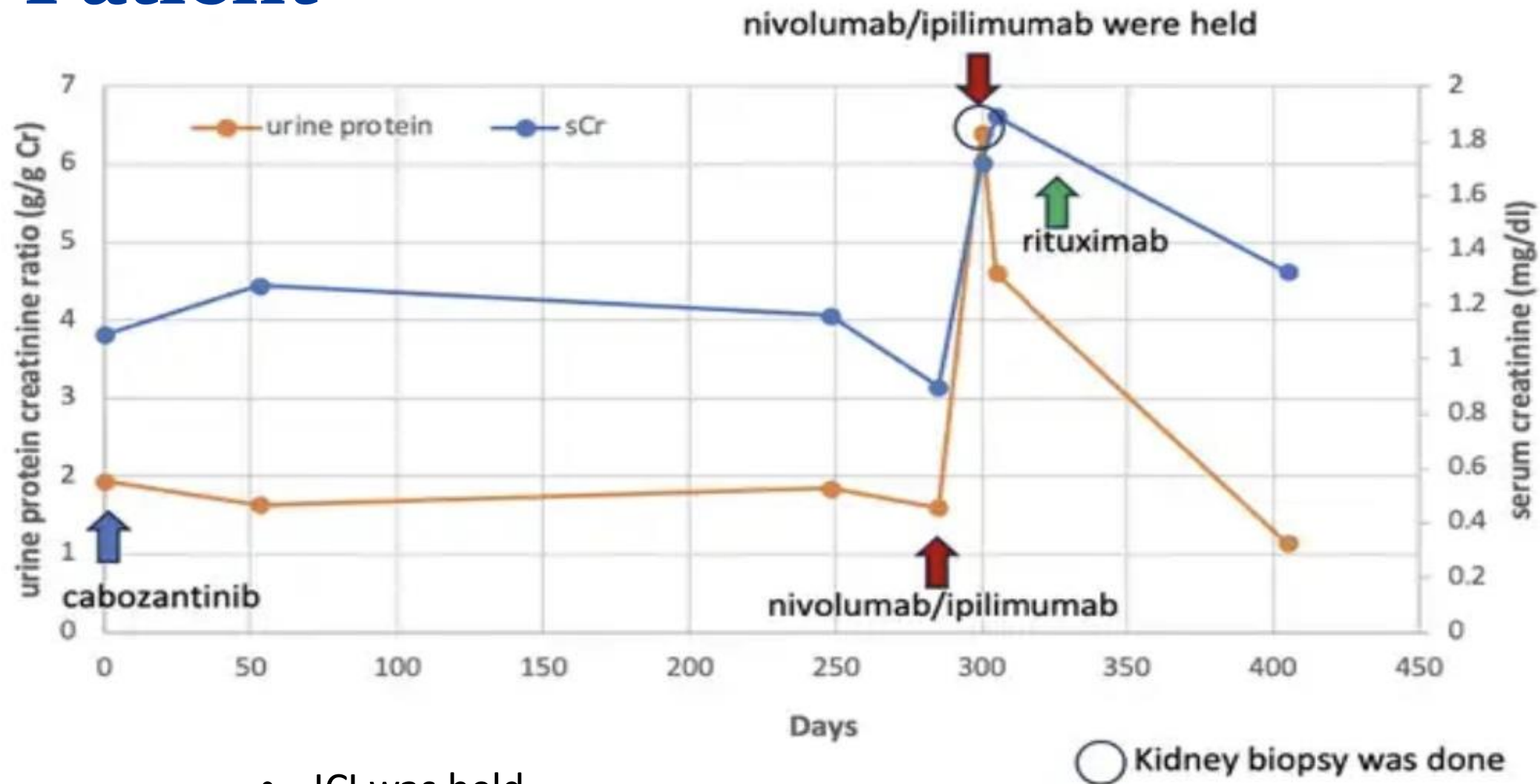
**What are the likely etiologies
of these glomerular disorders?**



What is the next step in management?

What therapeutic options should be considered?

Our Patient



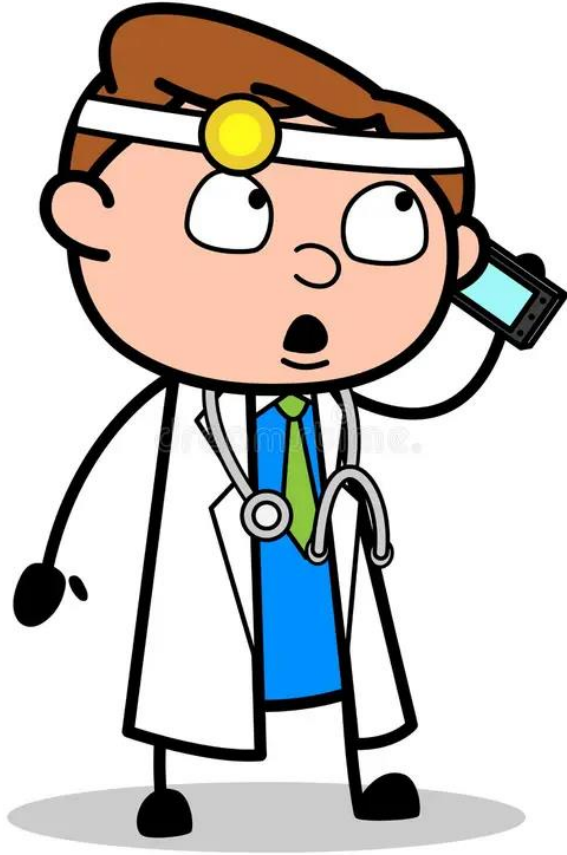
- ICI was held
- Rituximab x2 doses
- sCr decreased 1.9 > 1.2 mg/dL
- UPCR decreased 2 > 0.18 g/g Cr



**Two
Years
Later...**

The Oncologist Calls





The cancer is progressing!!!

**Can I rechallenge with
immune checkpoint
inhibitor therapy?**

Would you rechallenge with immune checkpoint inhibitor therapy?



Our patient

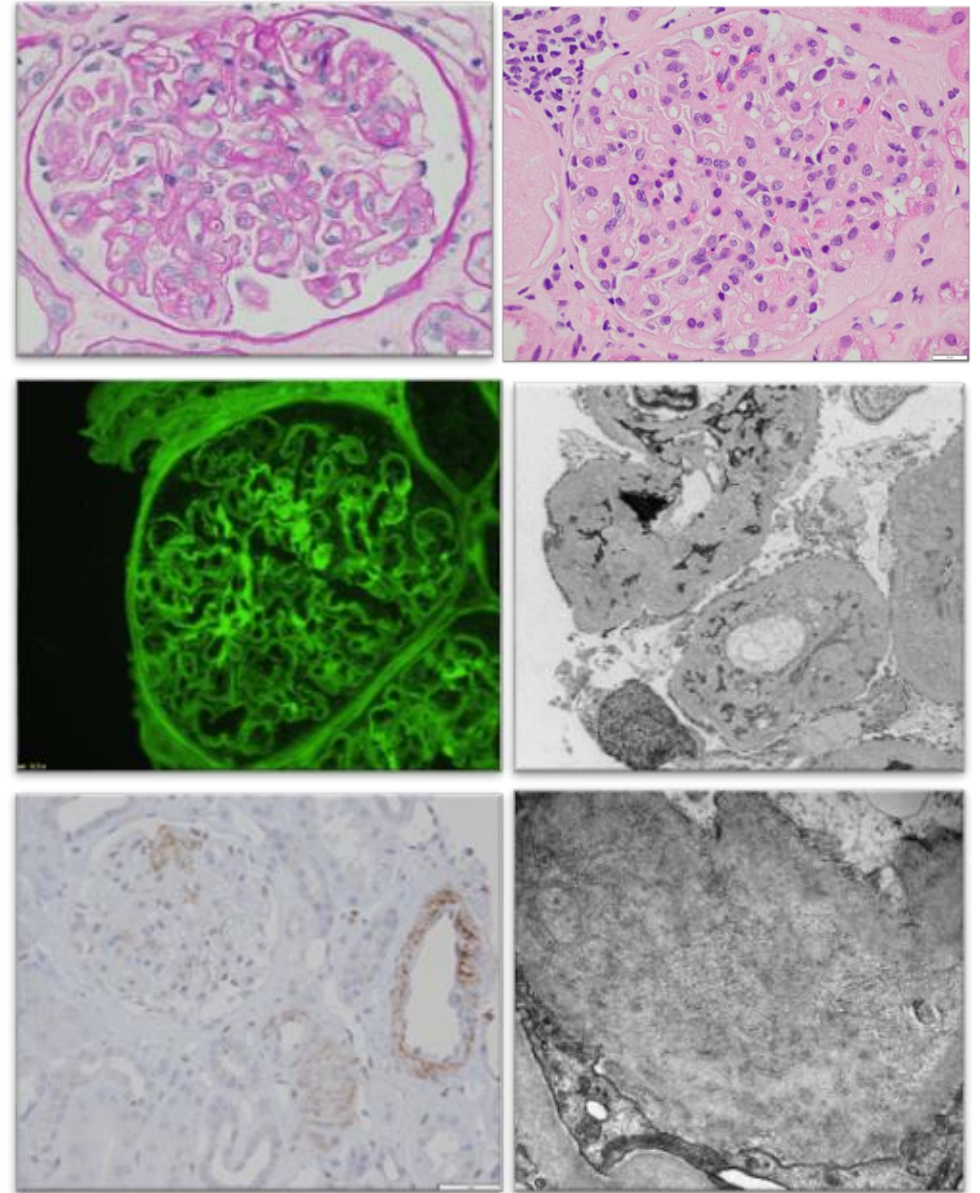
- Received a total of Rituximab **x4 doses** over ~12 months
- 2 years of surveillance/treatment break until disease progression
- **Rechallenged on NIVOLUMAB for 1 year with stable creatinine and no proteinuria**
- Added **IPILIMUMAB** recently for disease progression
- Currently
 - Serum Creatinine **1.32 mg/dl**
 - Microalbumin/creatinine **14 mg/g Cr**



Fibrillary Glomerulonephritis

Characterized by glomerular deposition of:

- **randomly arranged fibrils: 15-25 nm** in thickness
- **Congo red negative, DNA JB9+**
- IF staining typically IgG with C3, κ , and λ
- Polyclonal in 90%, Monotypic 7-10%
- DDx:
 - Amyloidosis
 - Immunotactoid Glomerulopathy
 - Diabetic glomerulosclerosis
 - Cryoglobulinemic glomerulonephritis



Patient Clinical Characteristics and Main Associated Conditions in the Largest International Case Series of FGN

	Rosenstock and Colleagues, 2003 ⁴	Javaugue and Colleagues, 2013 ⁶	Payan Schober and Colleagues, 2017 ⁹	Nasr and Colleagues, 2018 ⁷	Andeen and Colleagues, 2019 ⁵	Gambella and Colleagues, 2022 ⁸
N	61	27	42	84	266	77
Mean age (y) (range or SD)	57 (28-81)	59 (25-82)	54 (11)	59 (21-80)	61 (24-87)	56 (16-80)
Female (%)	61	41	60	74	65	40
White race (%)	92	NR	71	NR	87	NR
Serum creatinine at presentation (mg/dL), mean (range or SD)	3.1 (0.5-14)	NR	3.2 (4)	2.5 (0.4-12.8)	2.1 (1.5-3.5)	2 (1.5)
Mean eGFR (mL/min/1.73 m ²) (range or SD)	NR	49 (20-115)	35 (20)	NR	27 (14-134)	NR
Hypertension (%)	77	70	NR	62	54	44
Hematuria (%)	60	73	95	90	39	39
Proteinuria (%)	100	100	97	NR	59	NR
Nephrotic range proteinuria (%)	NR	NR	NR	65	35	49.4
Nephrotic syndrome at presentation (%)	52	41	NR	25	15	NR
Mean 24-h proteinuria at biopsy (g/day) (range or SD)	6.5 (0.8-25)	3.2 (0.5-17)	5.7 (5)	5.1 (0-20)	NR	4.8 g/dL (2.8)

PMID: 39084762

Epidemiology:

- ~1.2 of all kidney biopsies
- Mean Age: 6th decade
- Caucasian
- Gender?

Clinical Features

- Nephrotic range proteinuria
- Hematuria
- Hypertension

Diagnosis

- Renal Biopsy



Associations:

- Autoimmune diseases (ie. RA, SLE, Sarcoidosis)
- Dysproteinemias
- Solid and hematologic malignancies
- Viral Infections (Hep B/C, HIV)

Prognosis:

- ~50% of patients progress to ESRD within 2-4 years

Management:

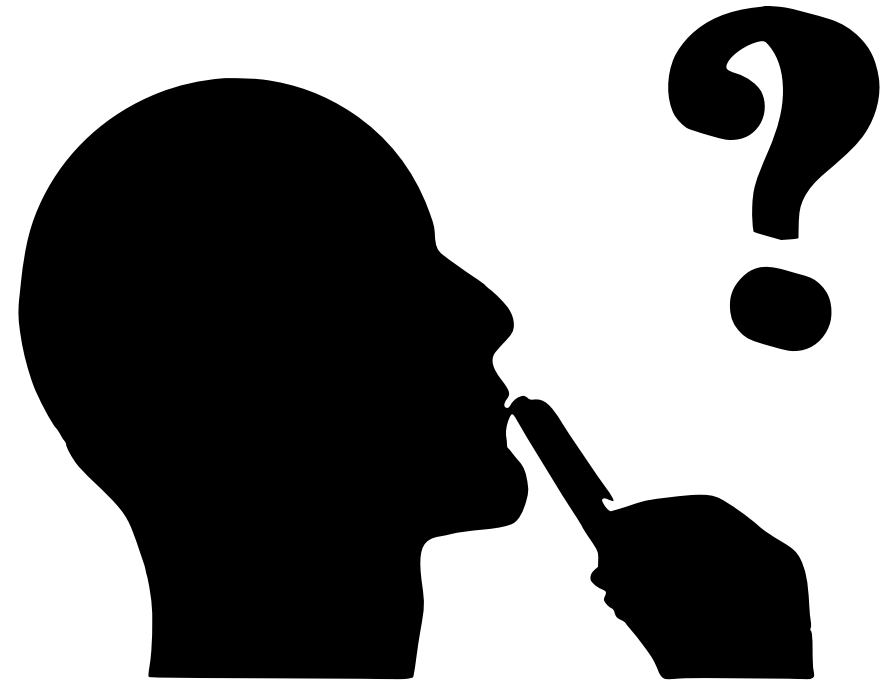
- No established guidelines
- Determine **underlying trigger**
- **Supportive care:** ACE/ARB + BP control
- IMS
 - Rituximab?

Associated Conditions (%)	Rosenstock et al. (2003)	Javaugue et al. (2013)	Payan Schober et al. (2017)	Nasr et al. (2018)	Andeen et al. (2019)	Gambella et al. (2022)
Diabetes mellitus	20.0	22.0	28.0	24.0	22.0	6.5
Positive hepatitis C serology	17.0	7.4	27.0	7.0	16.0	5.2
Monoclonal gammopathy	15.0	7.4	14.3	4.0	8.0	3.9
Auto-immune disease	—	30.0	13.0	14.0	9.0	11.7
Hematologic disorder/malignancy (excl. MG)	2.0	0.0	3.0	3.6	2.0	1.3
Solid organ cancer	5.0	3.7	12.0	6.0	5.0	3.9

Table adapted from PMID: 39084762



Final Thoughts ...



QUESTIONS & ANSWERS

