

# “An unexpected twist...”

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**THE 47<sup>TH</sup> ANNUAL SCIENTIFIC MEETING**

of the Australasian Division of the  
International Academy of Pathology

# Disclosure of Relevant Financial Relationships

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No relevant financial relationships.

# 23 year-old male

- Previously healthy, warehouse worker
- No known family history of illness
- **Presented with:**
  - 4-week history of increased urinary frequency and worsening fatigue
  - No associated fever, flu-like symptoms
  - No bloody/frothy urine

# On examination

- Afebrile
- **BP 170/100 mm Hg**
- HR 70 bpm
- RR 18 bpm, SaO2 97%
  
- Heart sounds dual no murmur; chests clear to auscultation
- Abdomen soft non-tender, bowels sound present
- No renal angle tenderness
- Calves non-tender, no lower limb oedema
- No rashes/joint pain

# Urine dipstick of midstream urine

- **Protein +++ (>3 g/L)** [normal value <0.3 g/L]
- No casts seen in centrifuged deposit.
- Leucocytes, Erythrocytes, Squamous epithelial cells – **Normal value**
- Glucose, Nitrite – **Negative**
- Final urine MCS- No growth

# Renal function

- eGFR **34 mL/min/1.73m<sup>2</sup>** [normal value >90]
- Creatinine **234 umol/L** [normal value 60-110]
- Urea **16 mmol/L** [normal value 3.4-9.0]

# Lipid profile

- Cholesterol **13.4 mmol/L** [normal value <5.5]
- Triglyceride **2.9 mmol/L** [normal value <2.1]
- LDL **10.9 mmol/L** [normal value <3.1]
- HDL **0.8 mmol/L** [normal value >0.9]

# Within normal limits

- Blood count; Liver function; Routine chemistry

# Renal ultrasound

- Normal bilateral kidney size and appearance
- No scarring
- No mass
- No hydronephrosis

# Impression

- Acute kidney injury with nephrotic syndrome

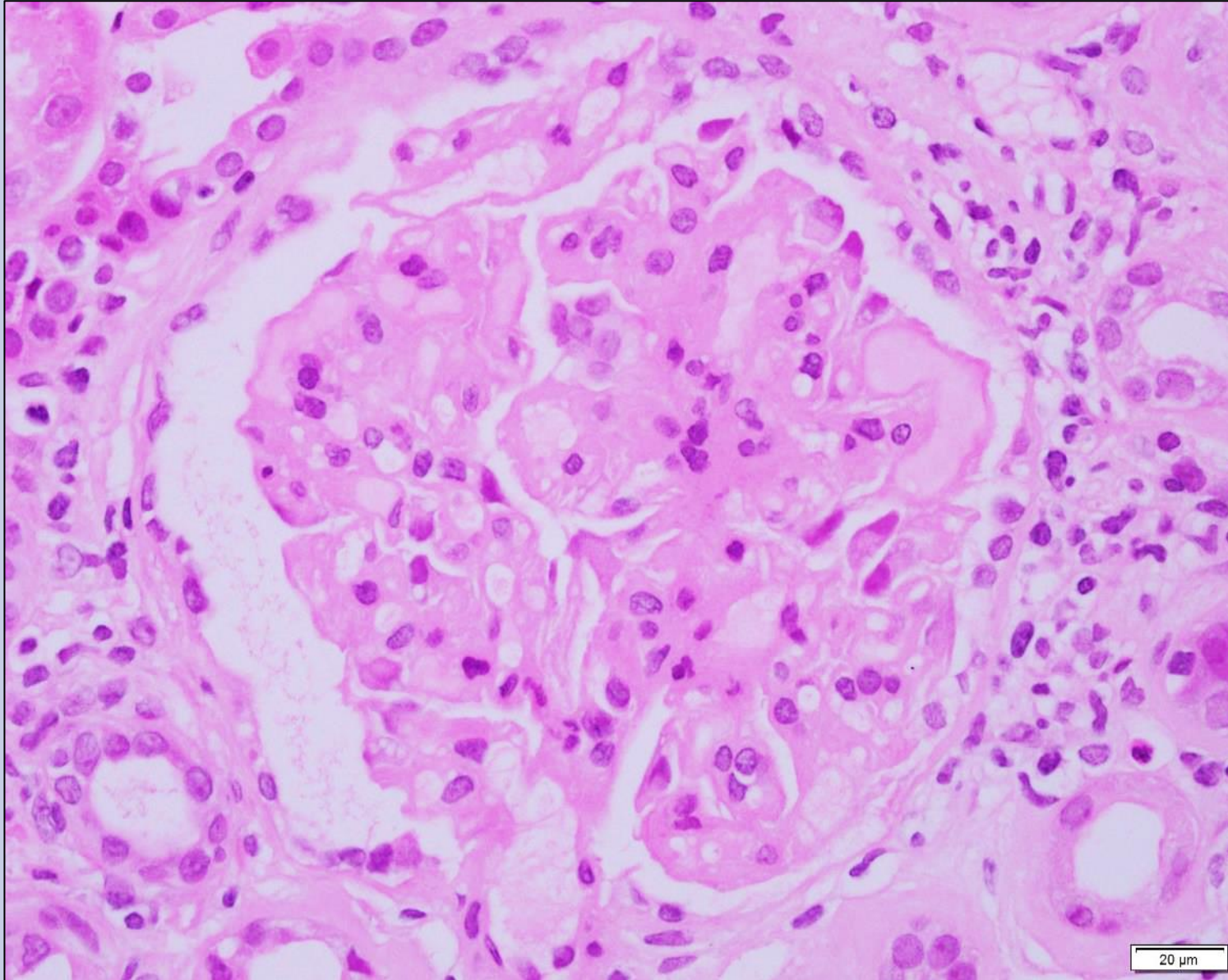
# Plan/management

- Commenced on **antihypertensives**
- **Serology tests (infectious/autoimmune/vasculitis)**
  - Streptococcal serology (Antistreptolysin-O; Strep. Ab. DNase) → negative
  - HBV (HBsAg and anti-HBc), HCV (anti-HCV), HIV → negative
  - Antinuclear antibodies and Anti-extractable nuclear antigen Ab → negative
  - Rheumatoid arthritis serology (RHF and Anti-CCP) → below reference range
  - Anti-neutrophil cytoplasmic antibodies → negative
  - Glomerular basement membrane antibodies → negative
  - Complement C3 and C4 → within normal limits
- **Renal biopsy**

# Renal biopsy

- **Diffuse global glomerular abnormality**
- Only 2 out of 18 glomeruli appear normal
- No necrotising lesions
- No neutrophilic infiltrate

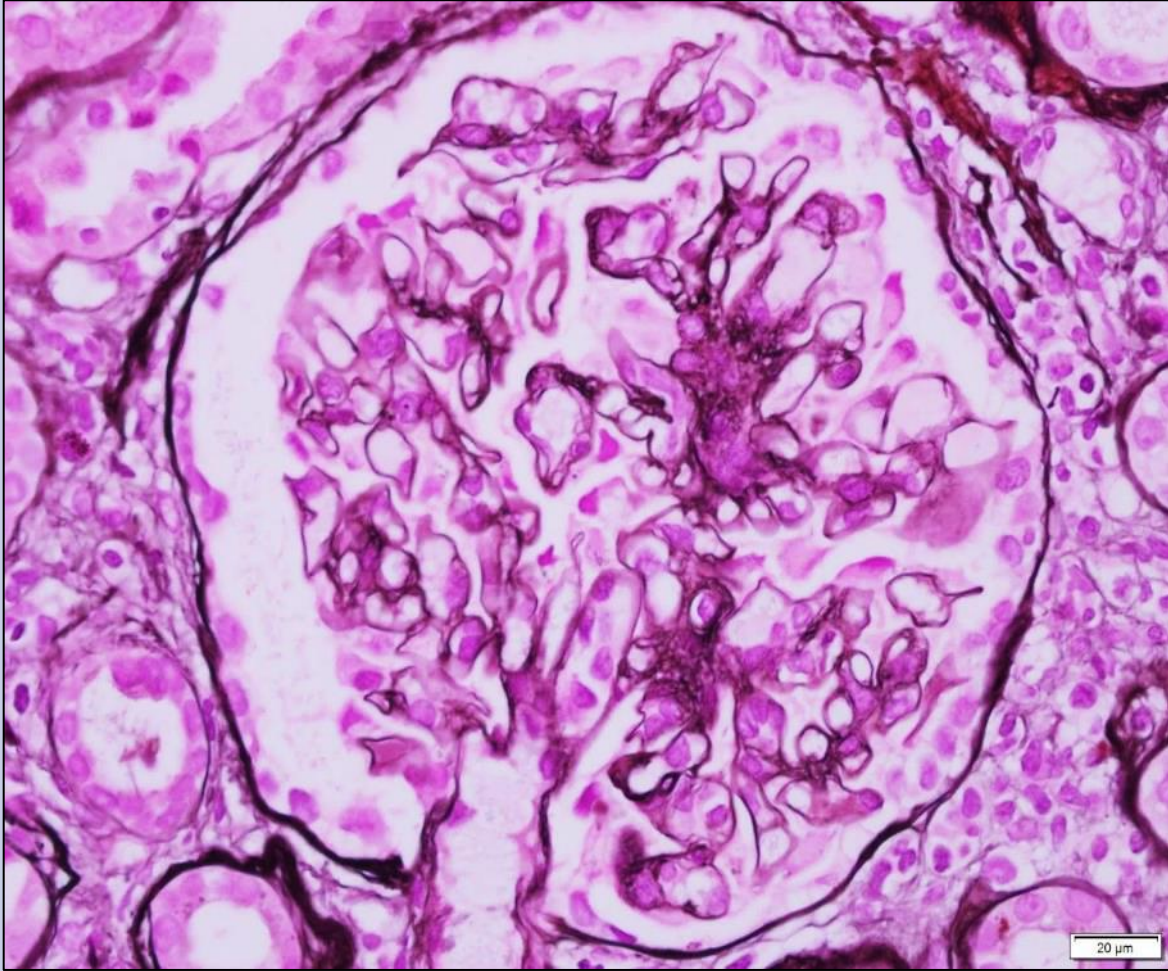
# Renal biopsy



## Glomeruli (H&E)

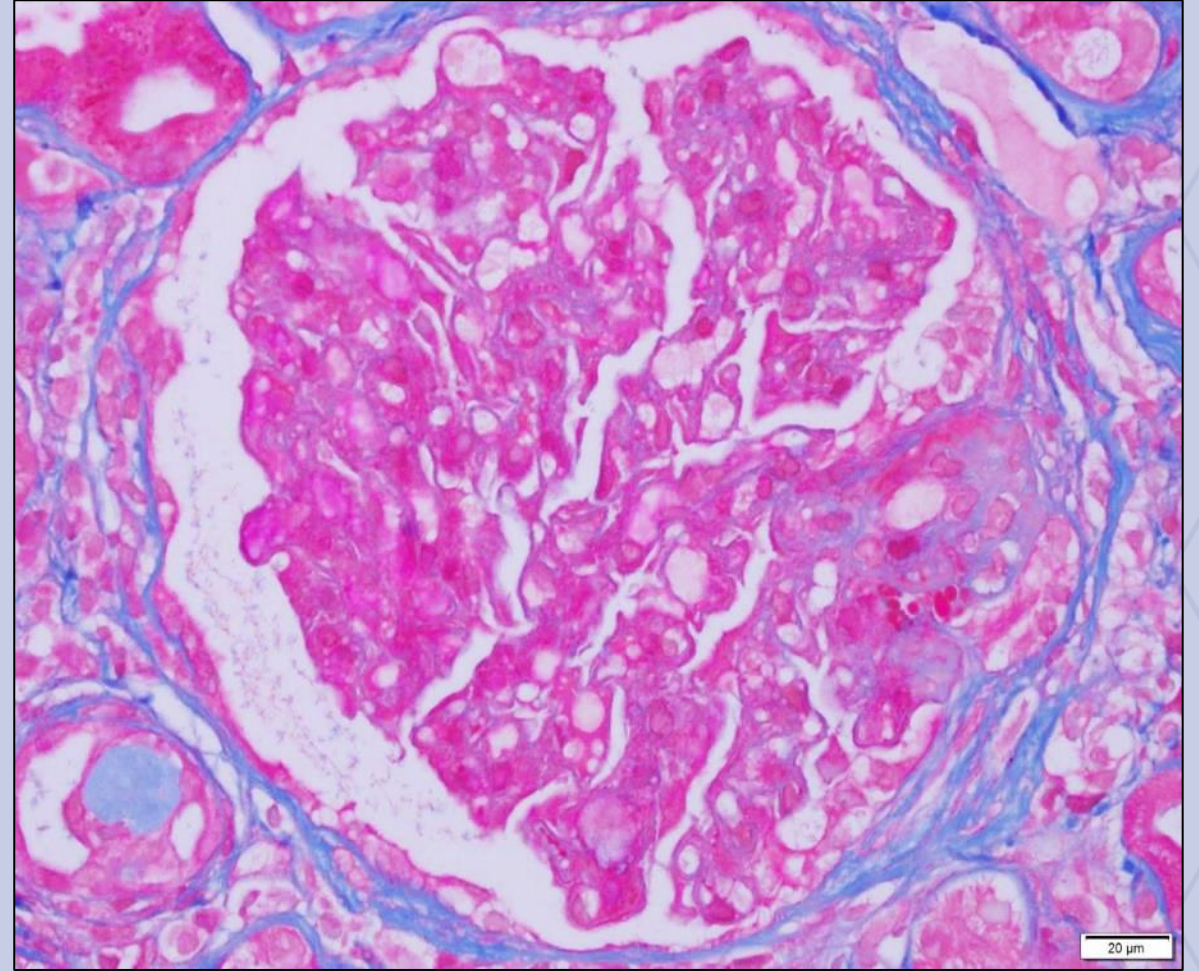
- Increased mesangial matrix and cellularity
- Accentuation of lobules

# Renal biopsy



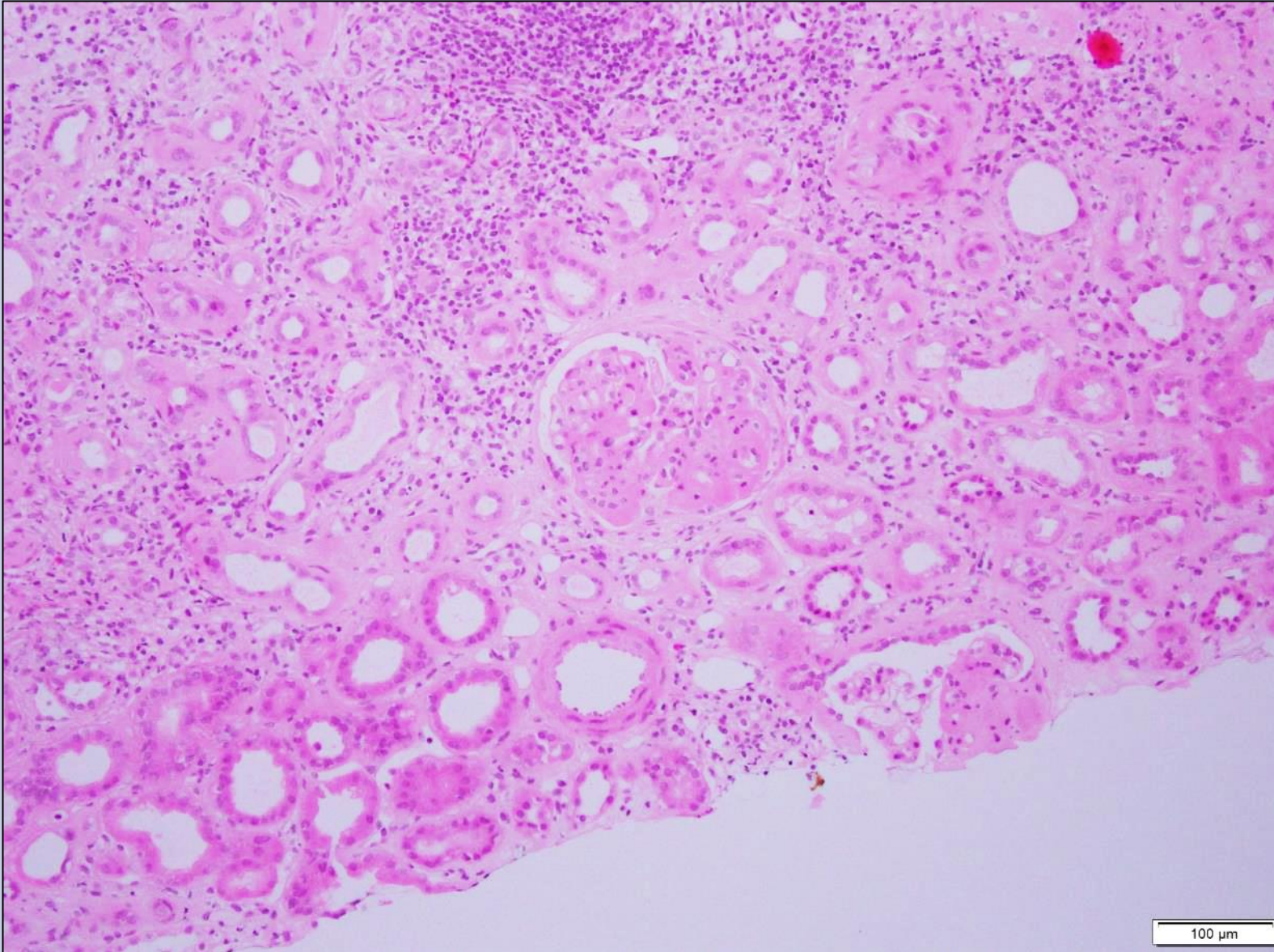
Glomeruli (silver stain)

- Extensive membrane double contouring



Glomeruli (Trichrome)

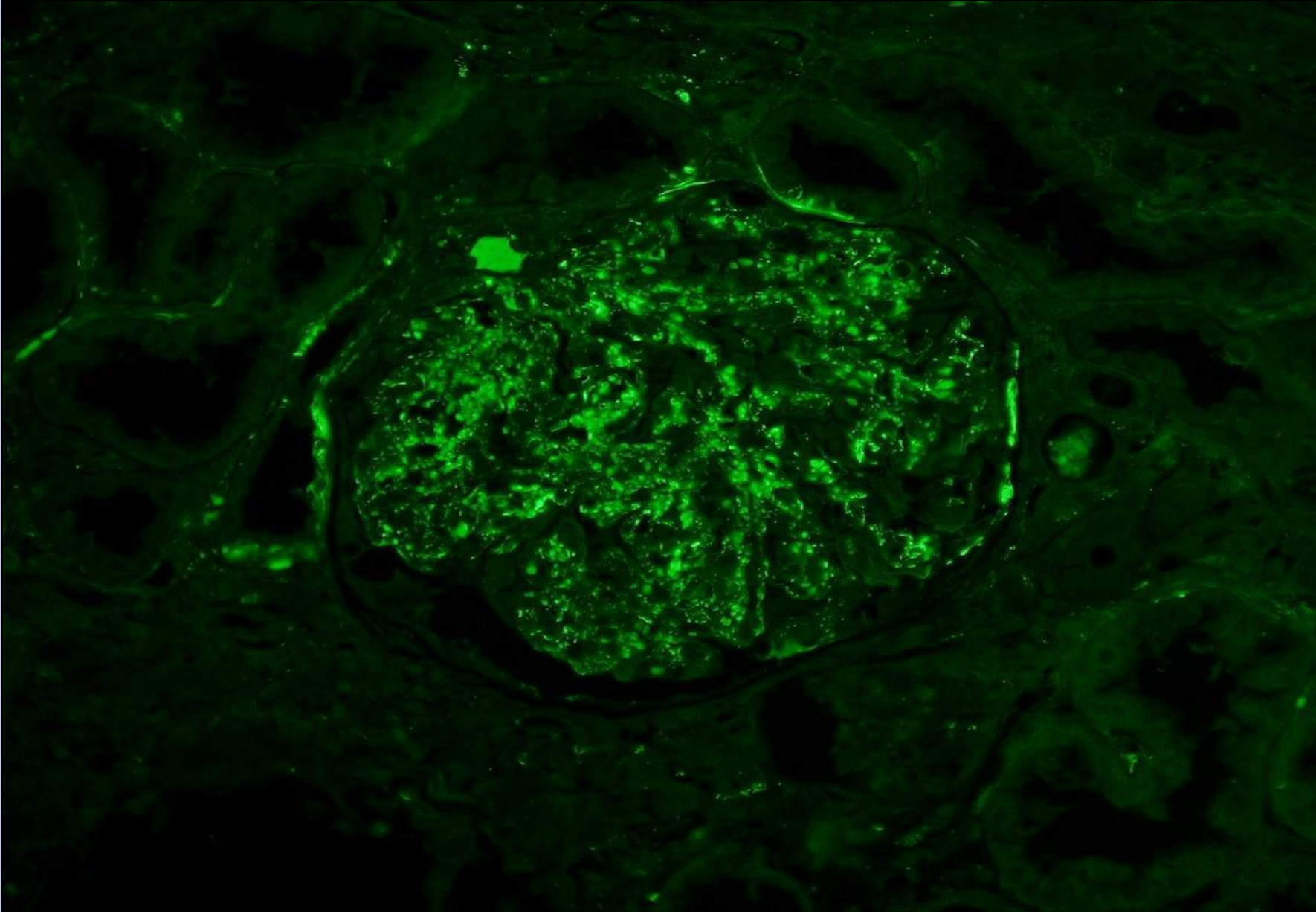
# Renal biopsy



## Tubules and interstitium

- Tubular atrophy
- Patchy moderately dense inflammation
- Mostly lymphocytes, some plasma cells
- ~50% cortical tubules involved

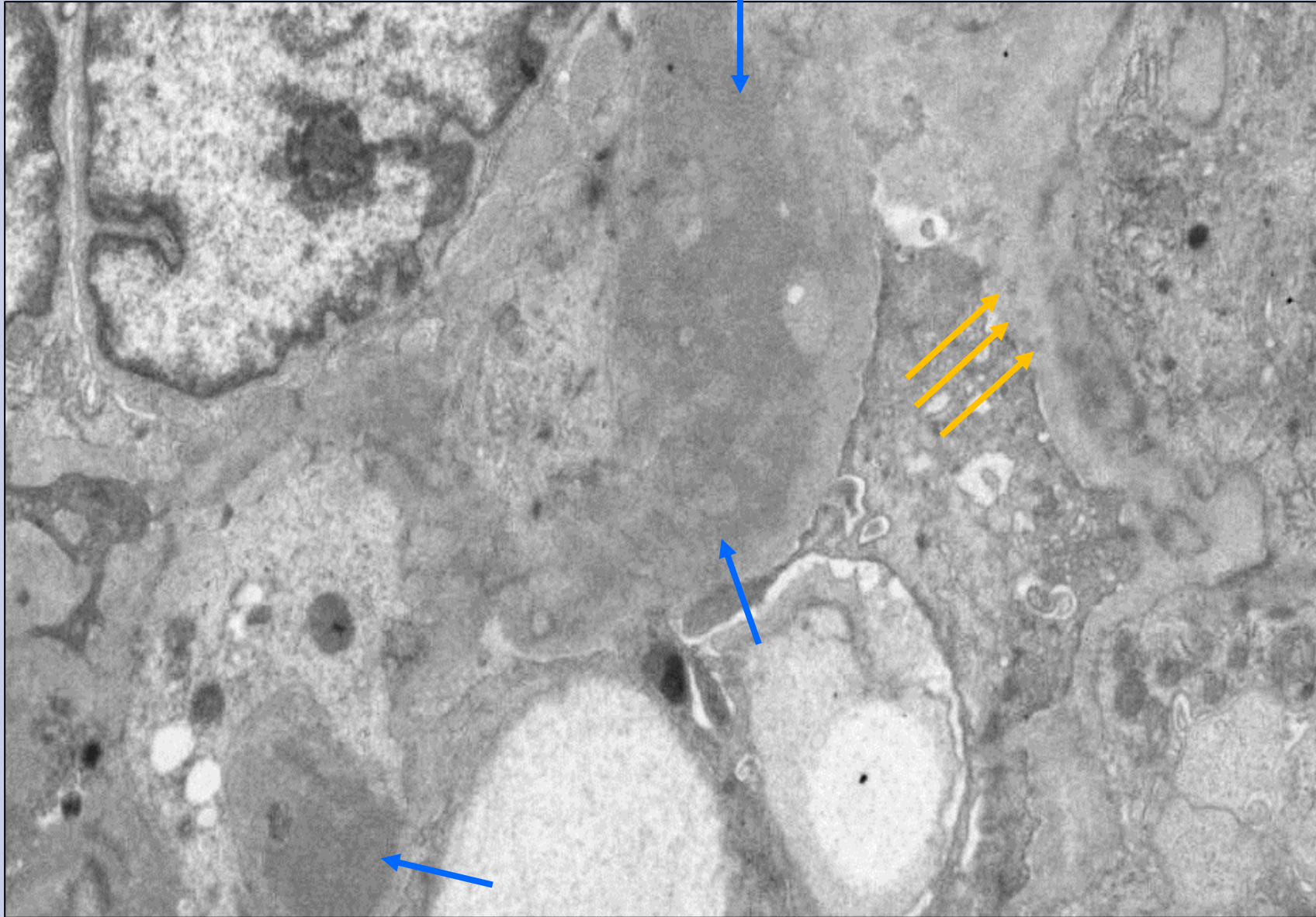
# Renal biopsy



Direct immunofluorescence

- C3 positive

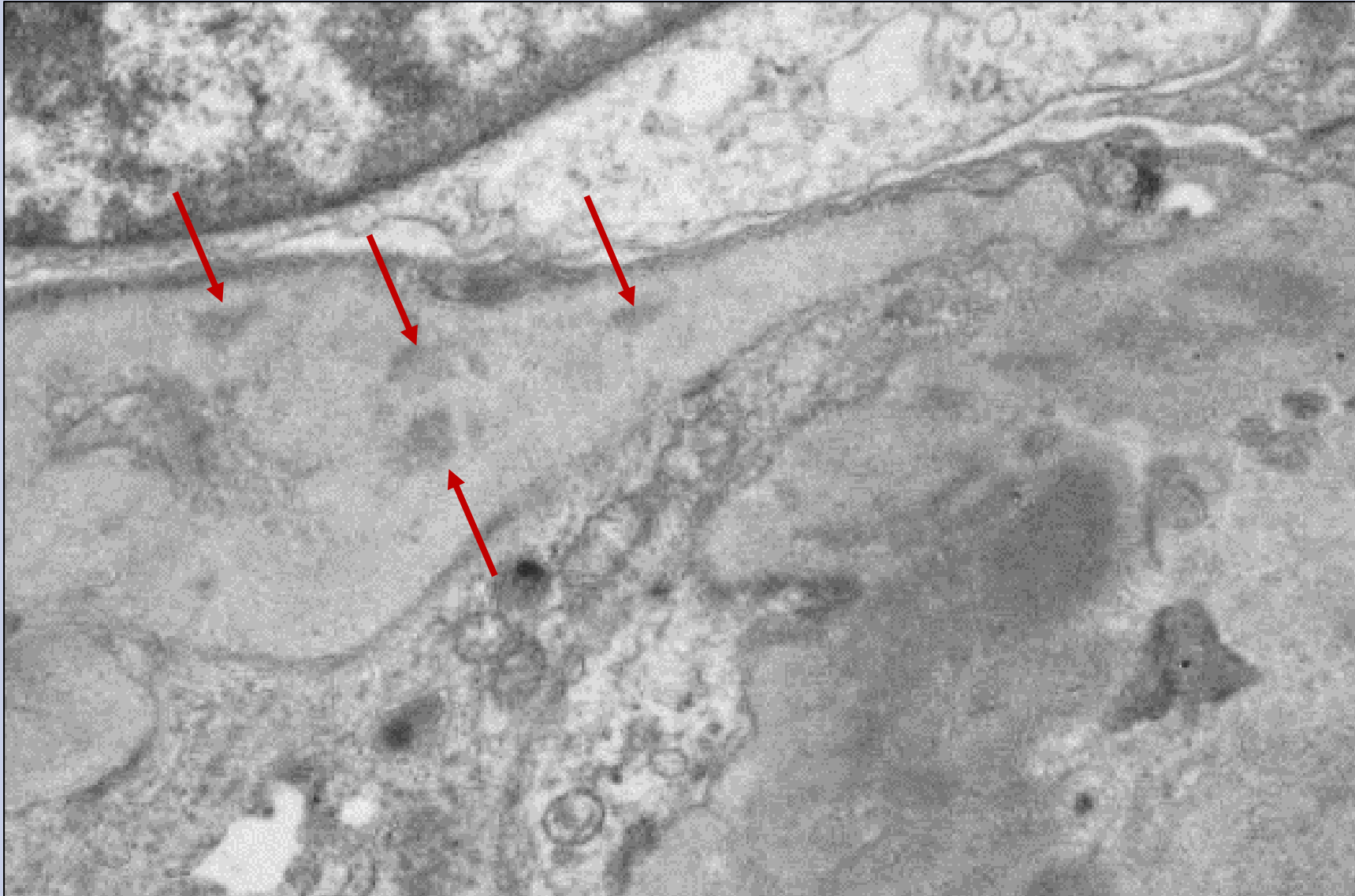
# Renal biopsy (EM) – C3 deposits !!!



## Ultrastructural studies

- Subendothelial deposits
- Trace subepithelial deposits

# Renal biopsy (EM) – C3 deposits !!!



## Ultrastructural studies

- Intramembranous deposits

# Diagnosis

## ➤ C3 Glomerulonephritis

Discharged from hospital

- Anti-hypertensives, anti-proteinuric medication and immunosuppressant

# Over the next 2 years...

Renal function continues to fluctuate

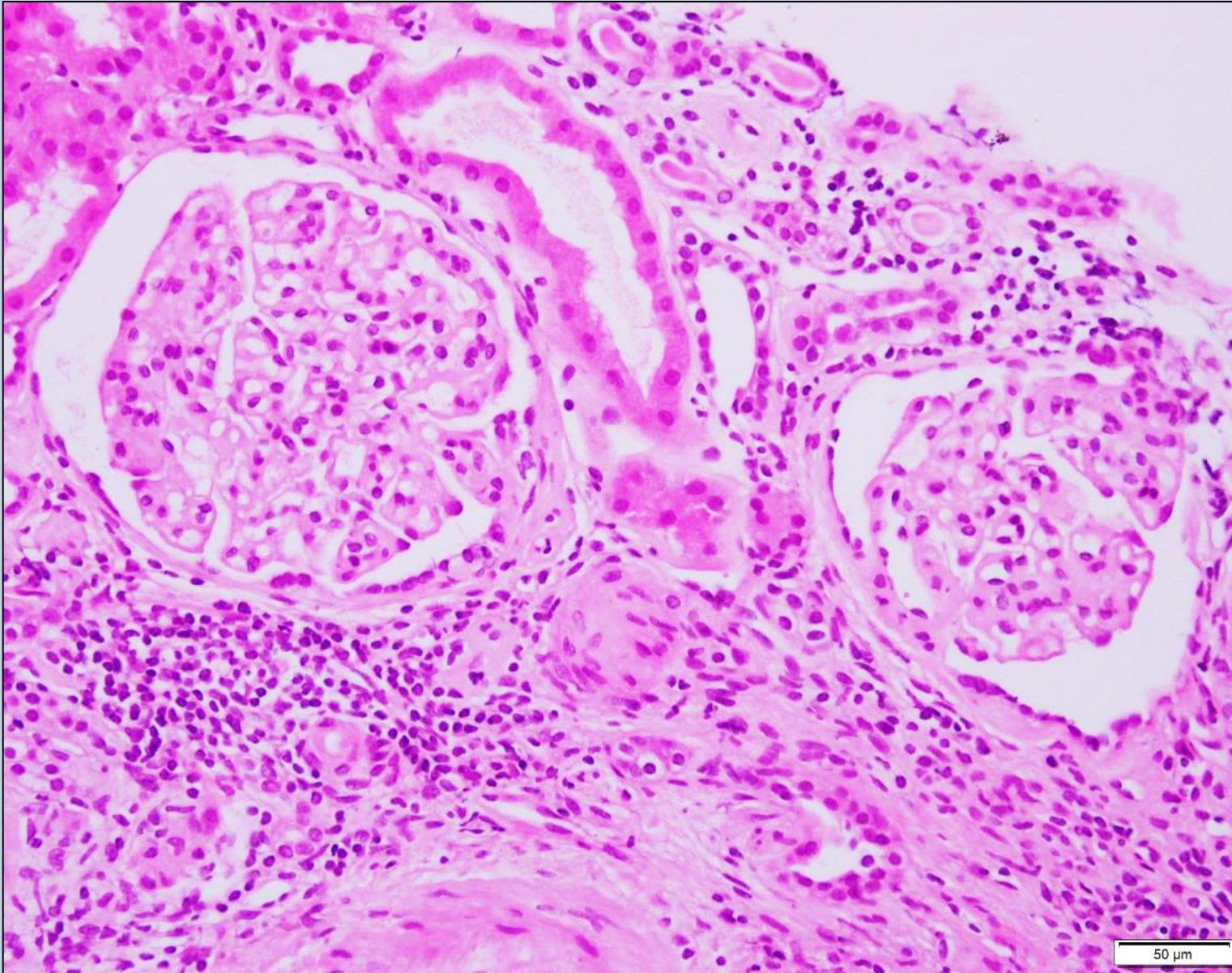
- eGFR **31 mL/min/1.73m<sup>2</sup>**
- Marked **nephrotic range proteinuria**
- BP **160/105 mm Hg**

# 2 years later...

## Repeat renal biopsy

- 18 glomerular profiles seen in sections, with 8 sclerosed glomeruli
- Diffuse global glomerular abnormality
- Direct IF: C3 positive (3+ granular capillary loops and mesangium)
- Subendothelial deposits (EM)

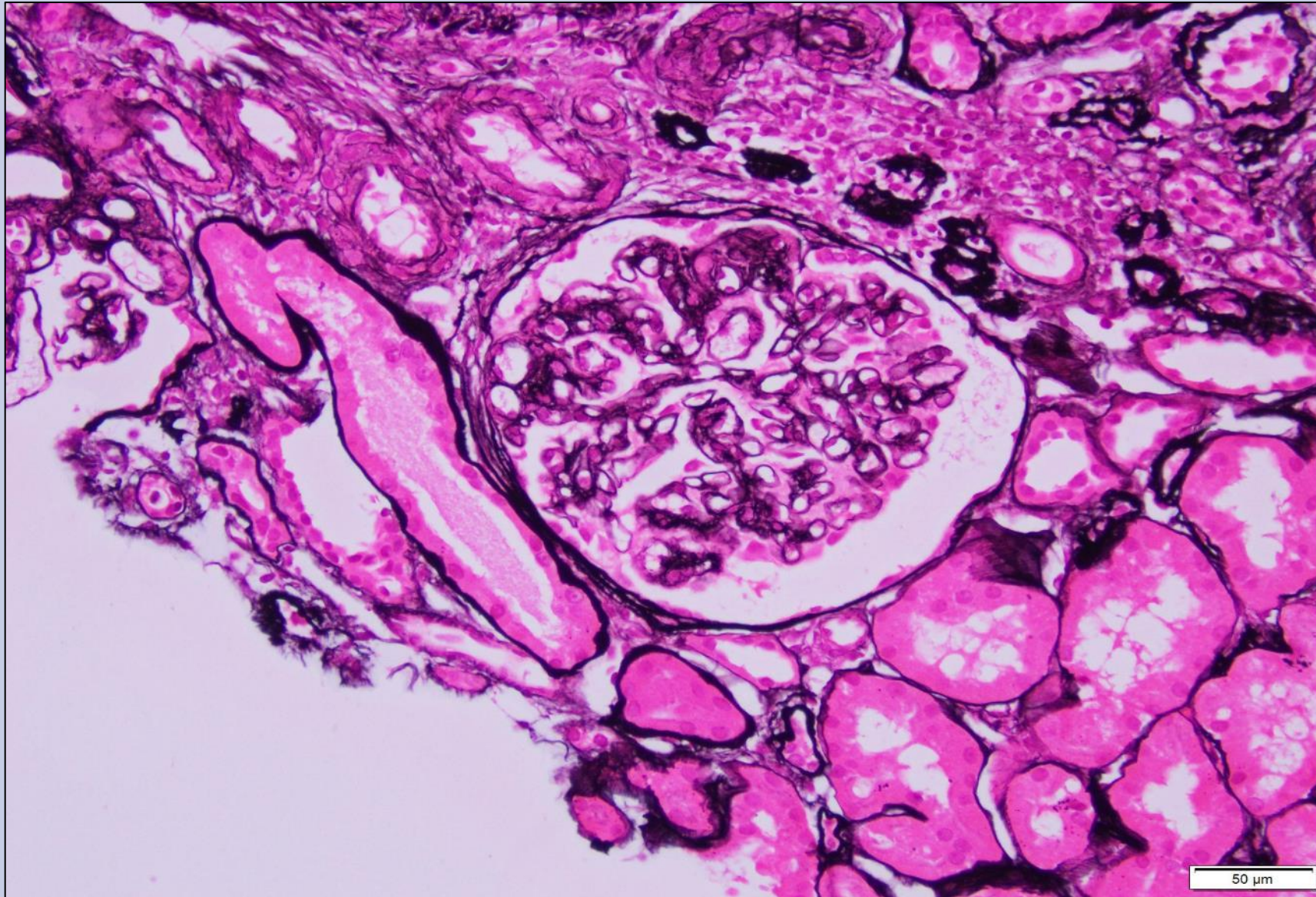
# Renal biopsy (2 years later)



Glomeruli (H&E)

- Increased mesangial matrix and cellularity
- Accentuation of lobules

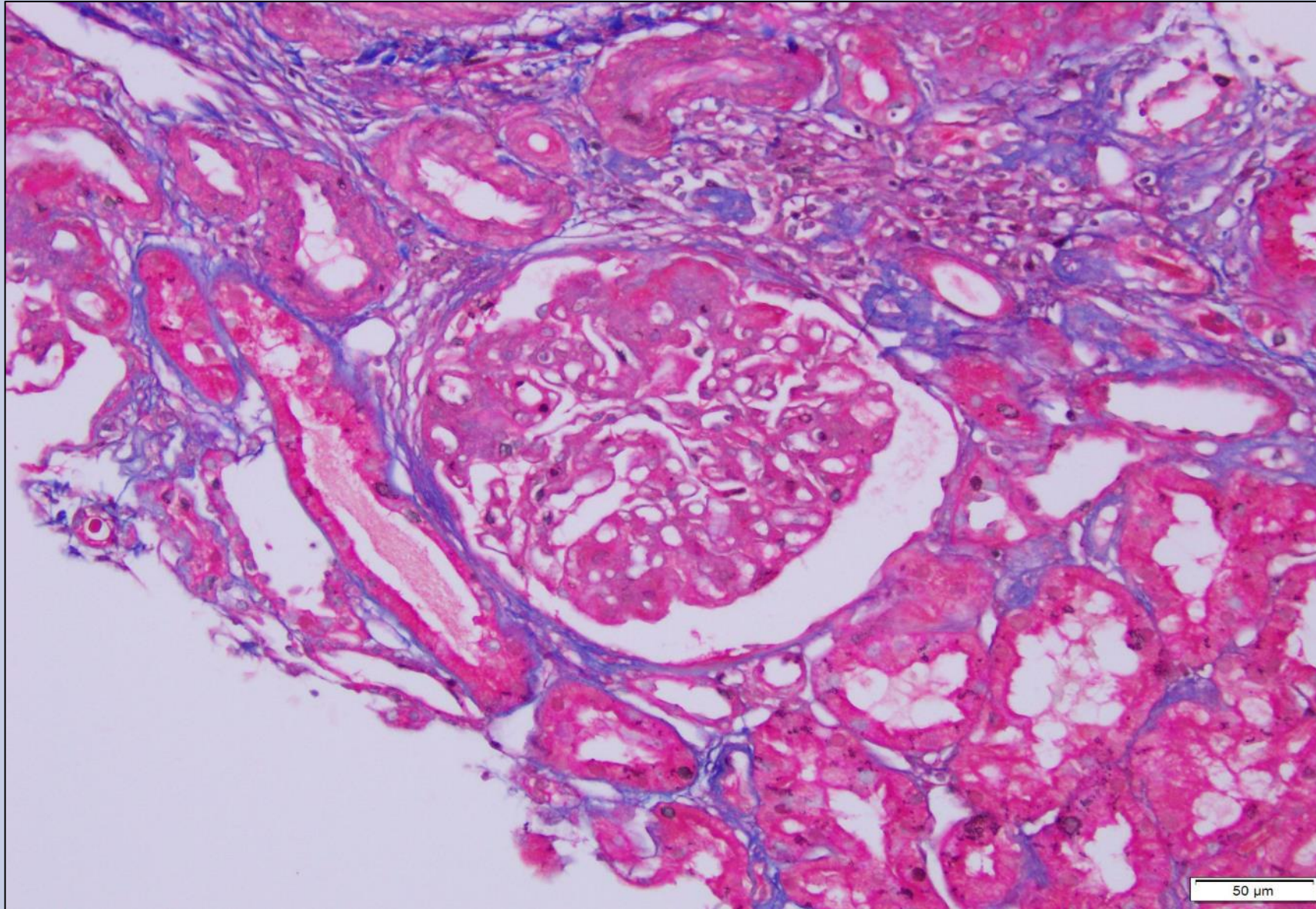
# Renal biopsy (2 years later)



Glomeruli (silver stain)

- membrane double contouring

# Renal biopsy (2 years later)



Renal parenchyma (trichrome)

- Advanced scarring/fibrosis
- Estimated up to 70%

# Diagnosis

## ➤ Recurrent C3 Glomerulonephritis

# Despite compliance...

- Progressive decline in renal function !!!
  - eGFR **25 mL/min/1.73m<sup>2</sup>**

# Whole genome sequencing

# Whole genome sequencing

A hemizygous missense variant detected in the

## COL4A5 gene

### COL4A5 gene

- Encodes alpha 5 chain of **type IV collagen**
- Integral to structure and stability of **Glomerular basement membrane !!!**

# Whole genome sequencing

A hemizygous missense variant detected in the

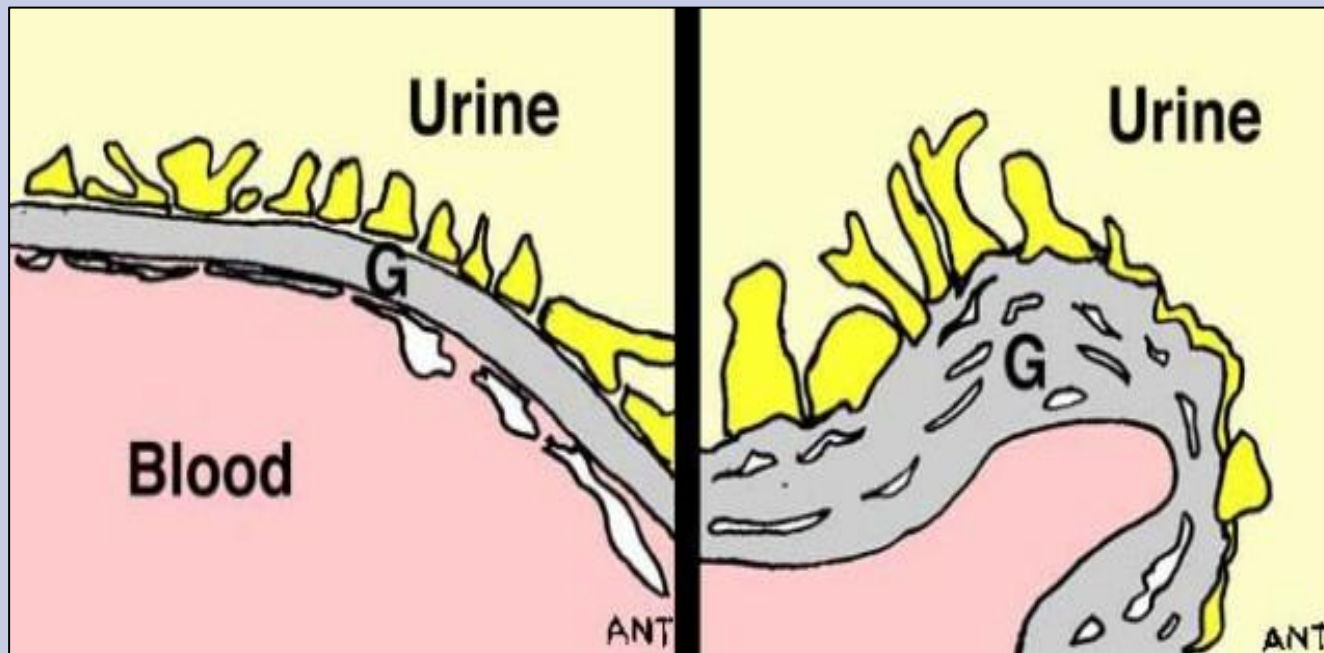
**COL4A5 gene**

supports clinical diagnosis of

**X-linked Alport Syndrome (XLAS) 1**

# X-linked Alport Syndrome 1 (XLAS)

- Early onset of **end-stage renal disease**
  - Often before age 30
- Glomerular basement membrane abnormalities
  - **Thinning, thickening, diffuse lamellations and splitting**



<https://edren.org/ren/edren-info/alport-syndrome>

# X-linked Alport Syndrome 1 (XLAS)

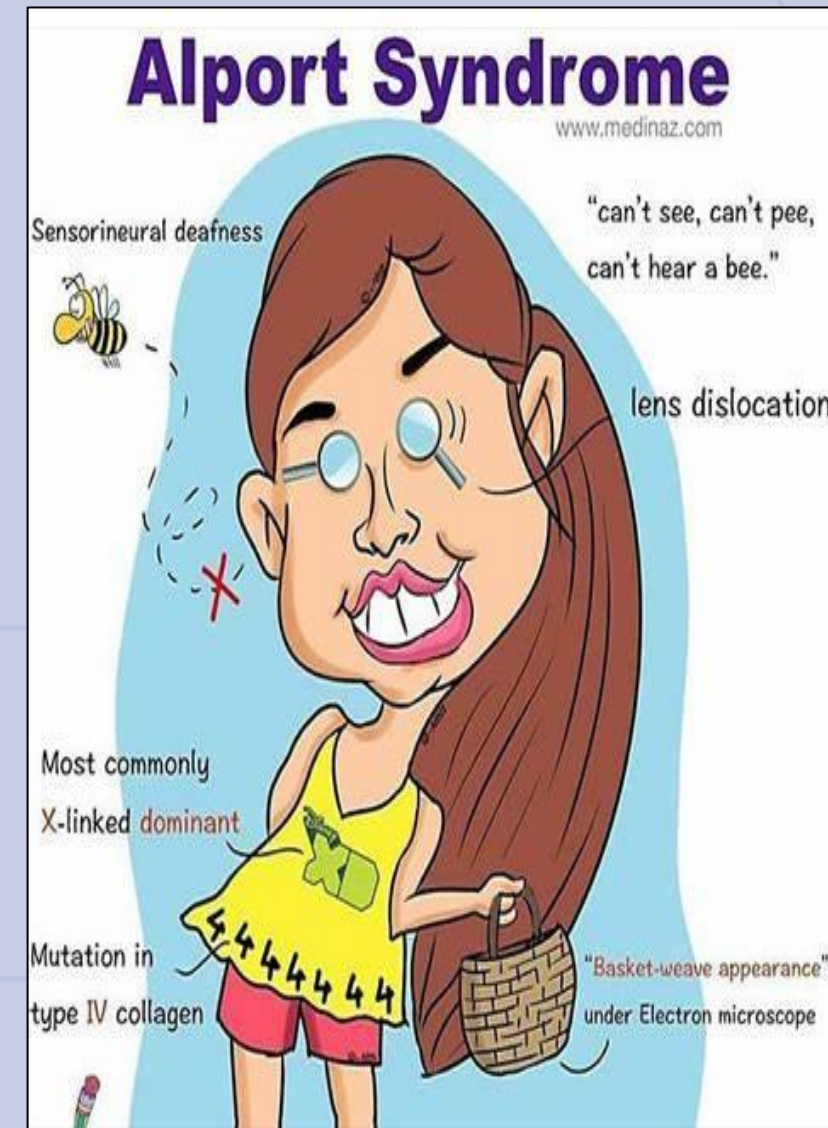
## Treatment / Recommendations ???

- ACE inhibitor or ARB
  - May **delay** the onset of **end-stage renal disease**
- Renal transplantation
  - May assist in **ameliorating** the phenotype

# X-linked Alport Syndrome 1 (XLAS)

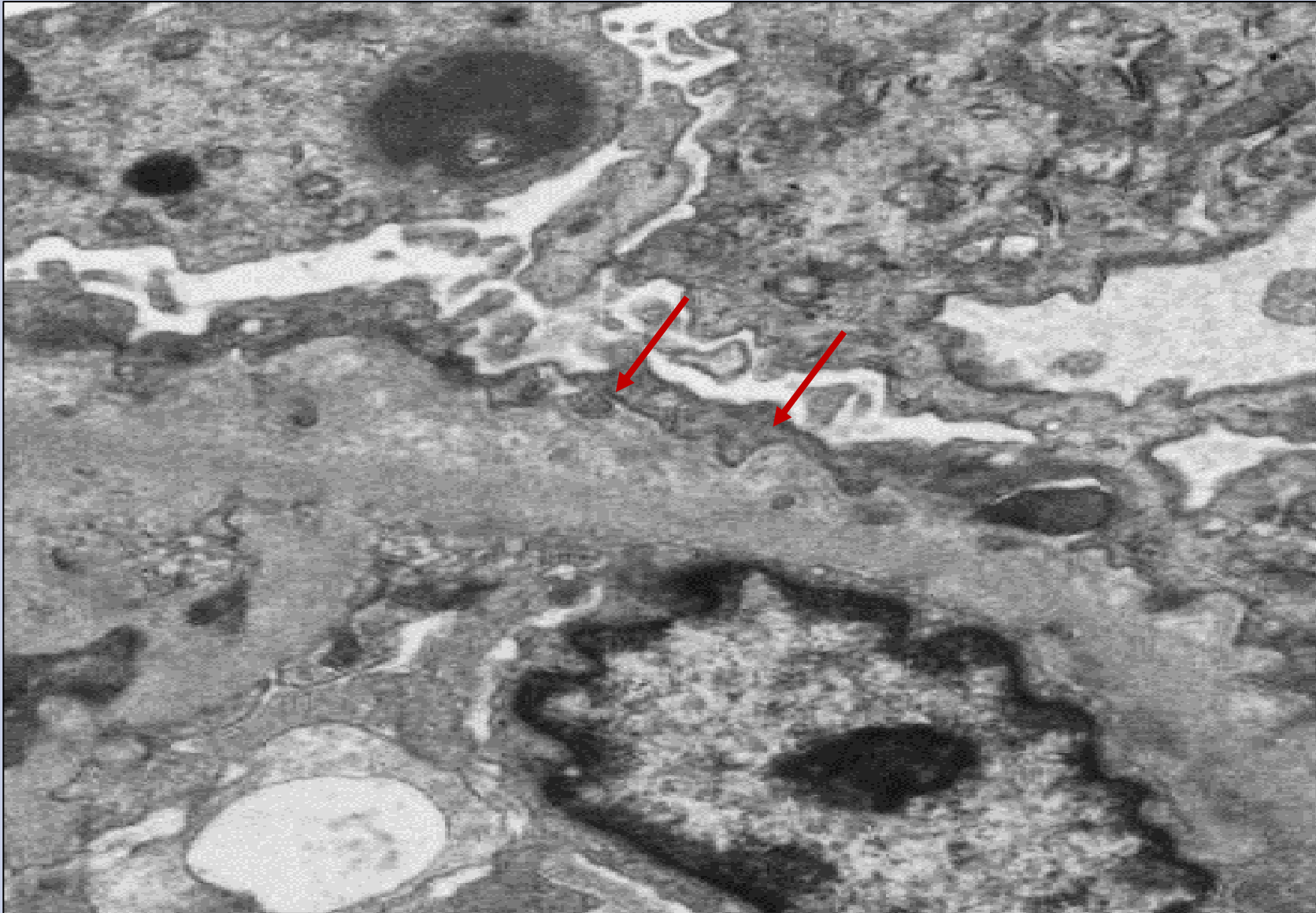
## Additionally...

- Risk of **aortic/arterial disease**
  - before age of 25-40
- Risk of **ocular anomalies**
  - corneal erosion, cataracts, anterior lenticonus
- Risk of **progressive sensorineural hearing loss**
  - by age of 30 (60% likelihood)



Medinaz - A Visual Learning Platform  
(<https://medinaz.com>)

# EM (first renal biopsy)



## Significant GBM abnormalities

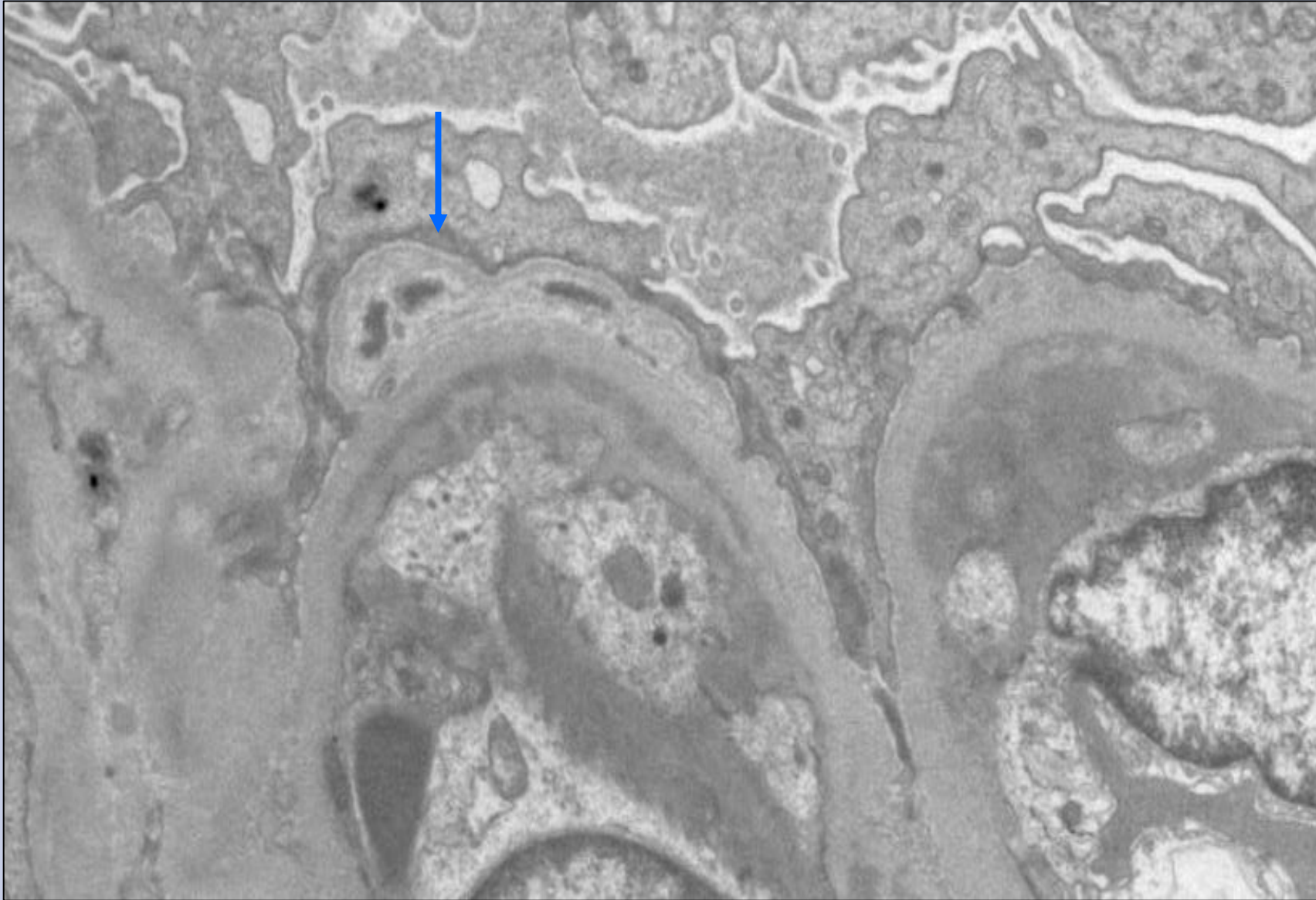
- Basketweave appearance

## Note:

### GBM in second renal biopsy

- ischaemic wrinkling and collapsed

# EM (first renal biopsy)



## Significant GBM abnormalities

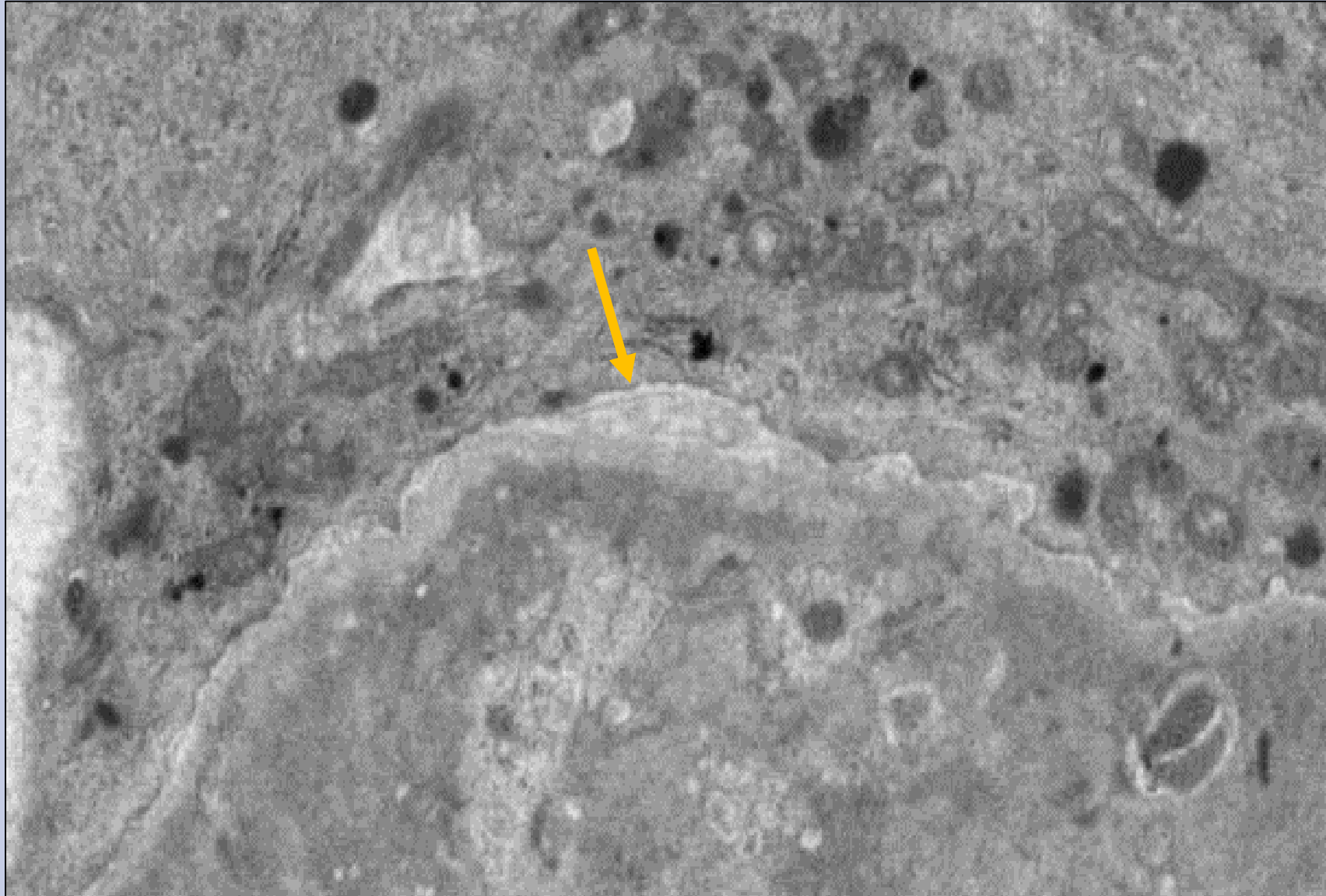
- Splits

### Note:

GBM in second renal biopsy

- ischaemic wrinkling and collapsed

# EM (first renal biopsy)



## Significant GBM abnormalities

- Laminations

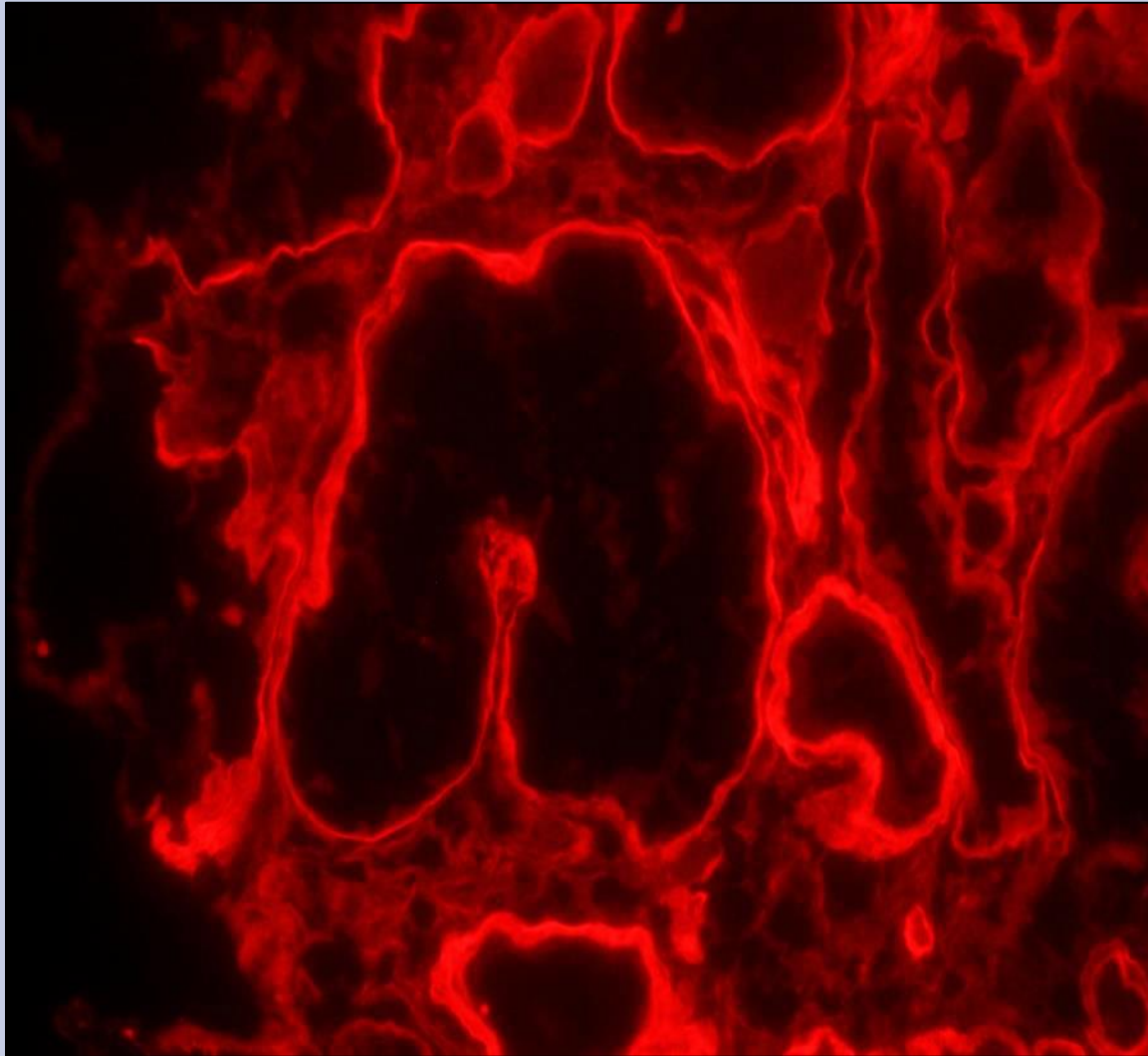
## Note:

GBM in second renal biopsy

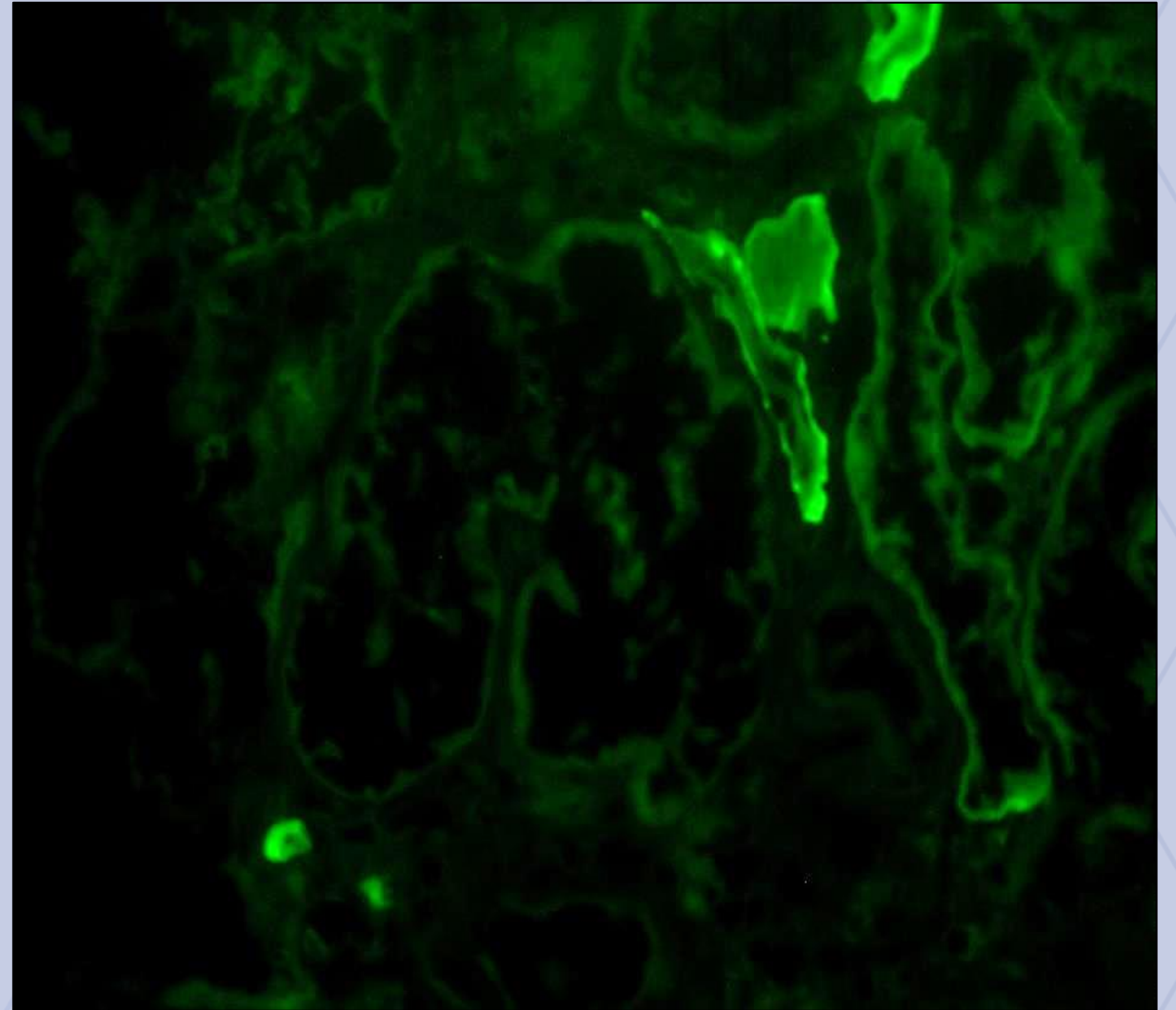
- ischaemic wrinkling and collapsed

# IF stains for COLA4 ( $\alpha 2$ and $\alpha 5$ )

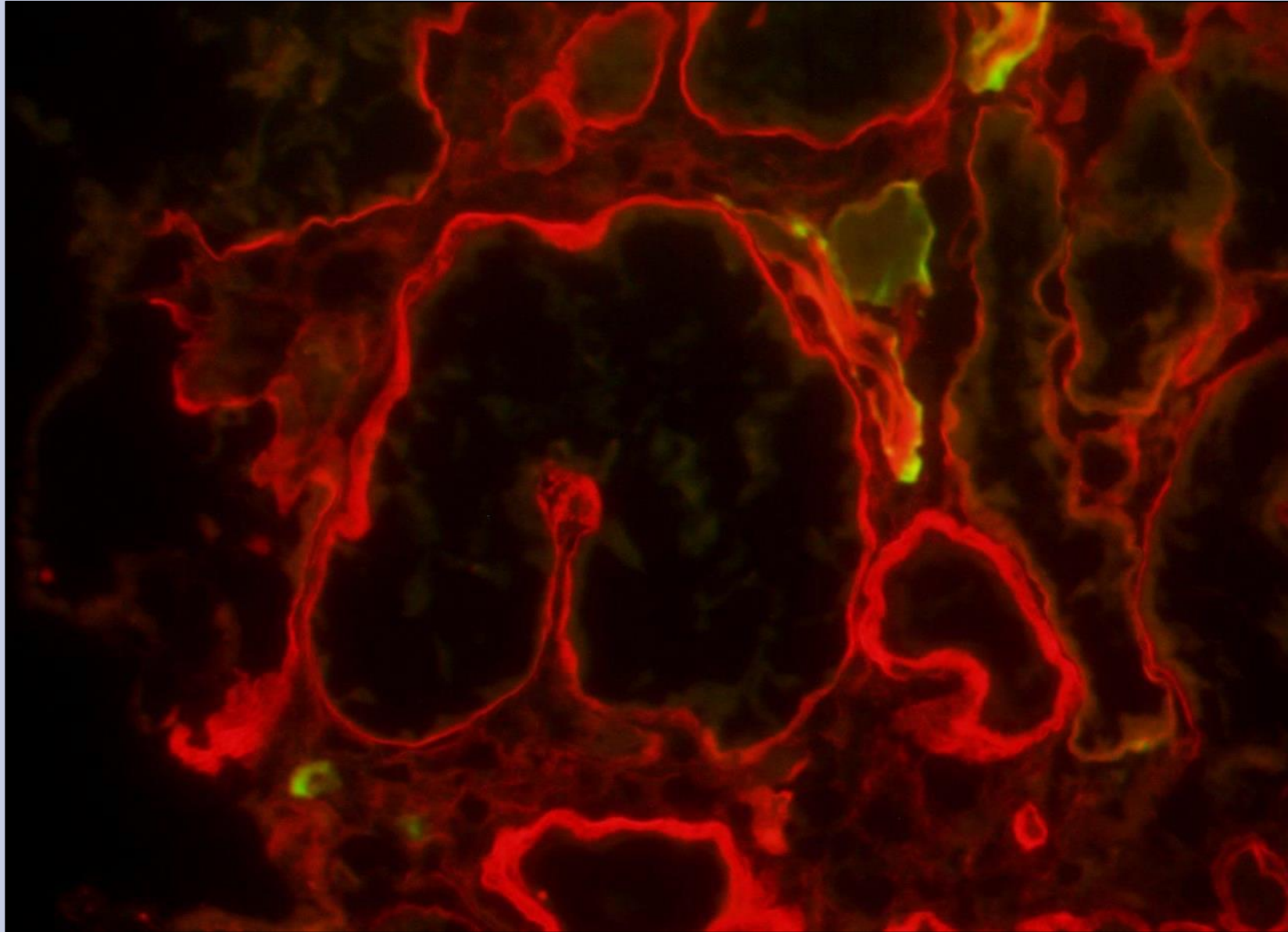
$\alpha 2$  = **red** (normal positivity retained)



$\alpha 5$  = **green** (affected in Alport syndrome!!)



# IF stains for COLA4 ( $\alpha 2$ and $\alpha 5$ )



$\alpha 2$  = red

$\alpha 5$  = green

(loss of staining !!!)

# Co-morbid **XLAS** and **C3GN**

➤ **Extremely rare !!!**

Only 1 case reported in China in 2021

# Update on patient progress...

- Treatment failure with mycophenolate
  - eGFR **19 mL/min/1.73m<sup>2</sup>**
- Commenced Eculizumab infusion
  - eGFR **24 mL/min/1.73m<sup>2</sup>**
- Awaiting fistula creation for anticipated **dialysis**
- Seeking live donor for non-dialysis pre-emptive **transplant...**

# References

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Thank you

