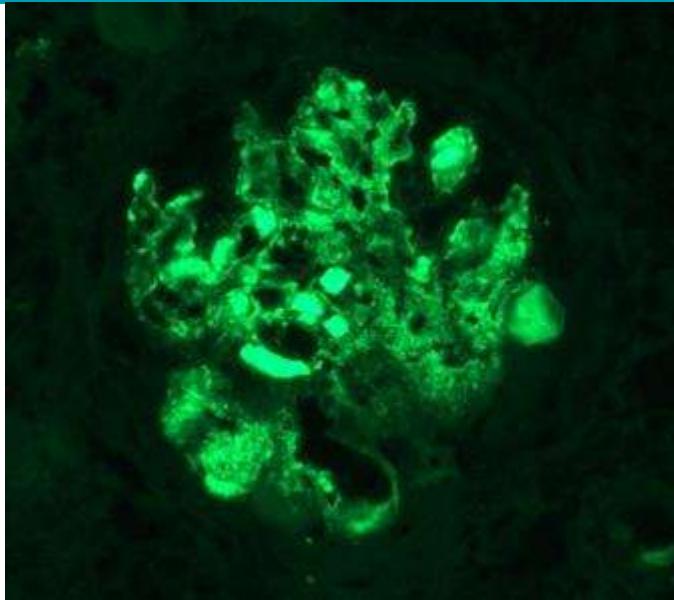


# Klinisch-pathologische conferentie Papendal 2022



Joris Roelofs, nefropatholoog  
Marc Vervloet, internist-nefroloog



# Disclosures MV

- Pharmaceutical industry
  - Lecture fees (all to institution), scientific support and advisor for: VFMCRP and Vifor, Shire, Bayer, Kissei, Cablon Medical; all companies involved in marketing or developing phosphate-lowering drugs
  - Scientific support from: Amgen, NedMag (all to institution) and FMC
  - Advisory board of: Otsuka, Astra-Zeneca, Vifor, Unicycive, Inozyme (fees to institution)
- Member of
  - KDIGO committee on CKD-MBD



# Disclosures JR

- Pharmaceutical industry
  - Lecture fees: Sanofi Genzyme
  - Consultant: Novartis, Alveron pharma



# Patient

- Geboren in 1990
- Presentatie in 2017 vanwege recidiverende episodes met rode urine (sinds 2005!), na BLWI's.
- Hypertensie bij een medische keuring, en toen bleek tevens ernstig nierfalen, kreat circa 400  $\mu\text{mol/l}$
- Gewichtstoename van 7 kg in een jaar, maar geen oedeem
- Had in afgelopen jaar soms rode puntjes op de huid distaal aan acra, die ook spontaan weer verdwenen
- Verder geen bijzonderheden bij anamnese of lichamelijk onderzoek. Bloeddruk onder behandeling 119/64

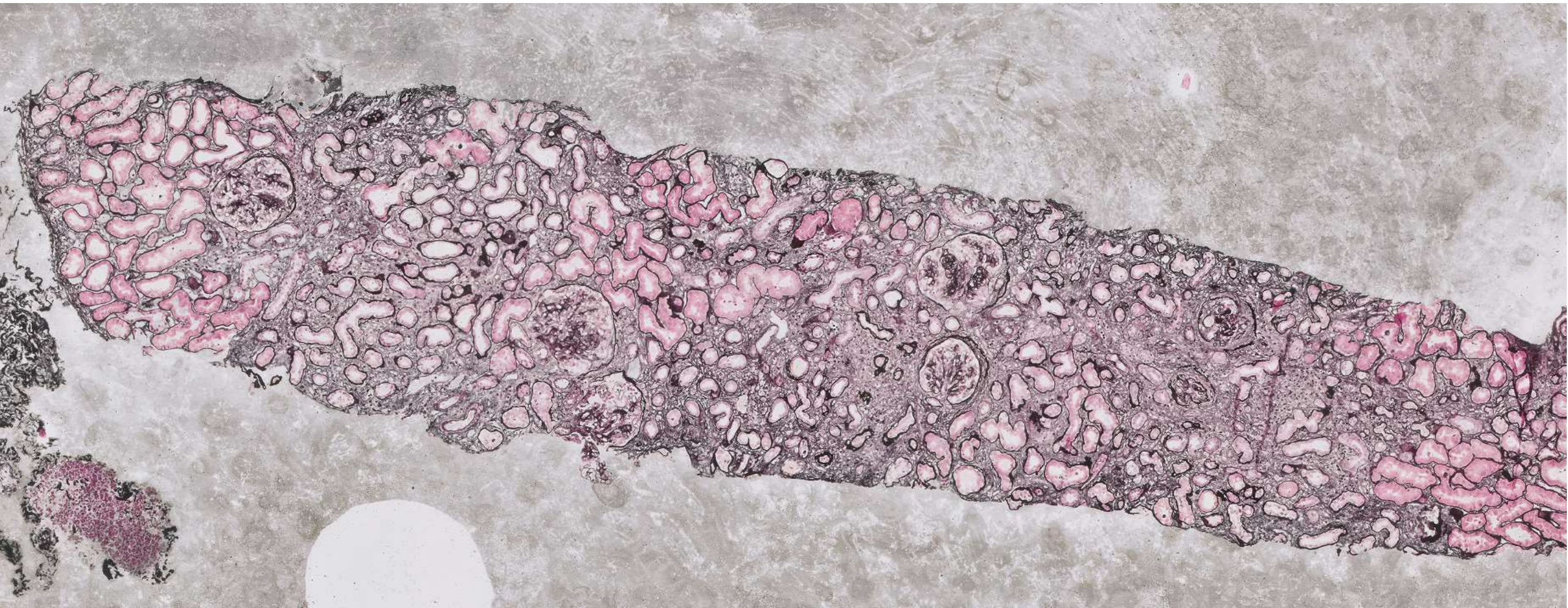


## Gegevens uit 2017

- Lab: albumine 32 g/l, kreat 500  $\mu$ mol/l, eiwitspectrum normaal
- ANA/ANCA/hepB-C/HIV/anti PLA2R ab's → negatief
- Urine: ery's 5-10 pgv, dysmorfie niet bekend, eiwit: 8.5gr/24h. Geen celcilinders gezien
- TG 11
- Echo nieren: normale grootte, geen hydronefrose
- Hij startte direct met ACE remmer en CS (MPNS waarna 60 mg prednisolon p.o.)

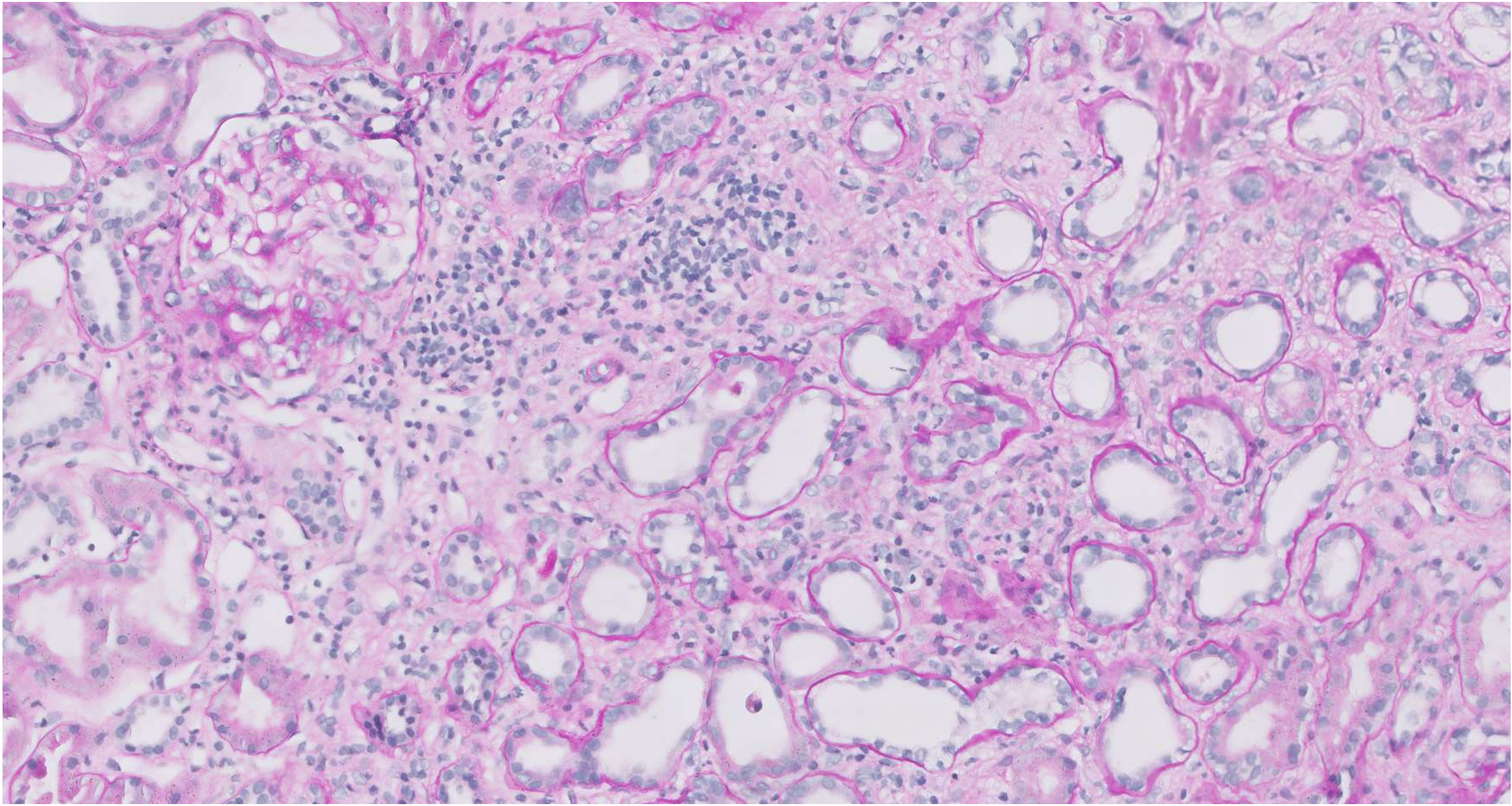


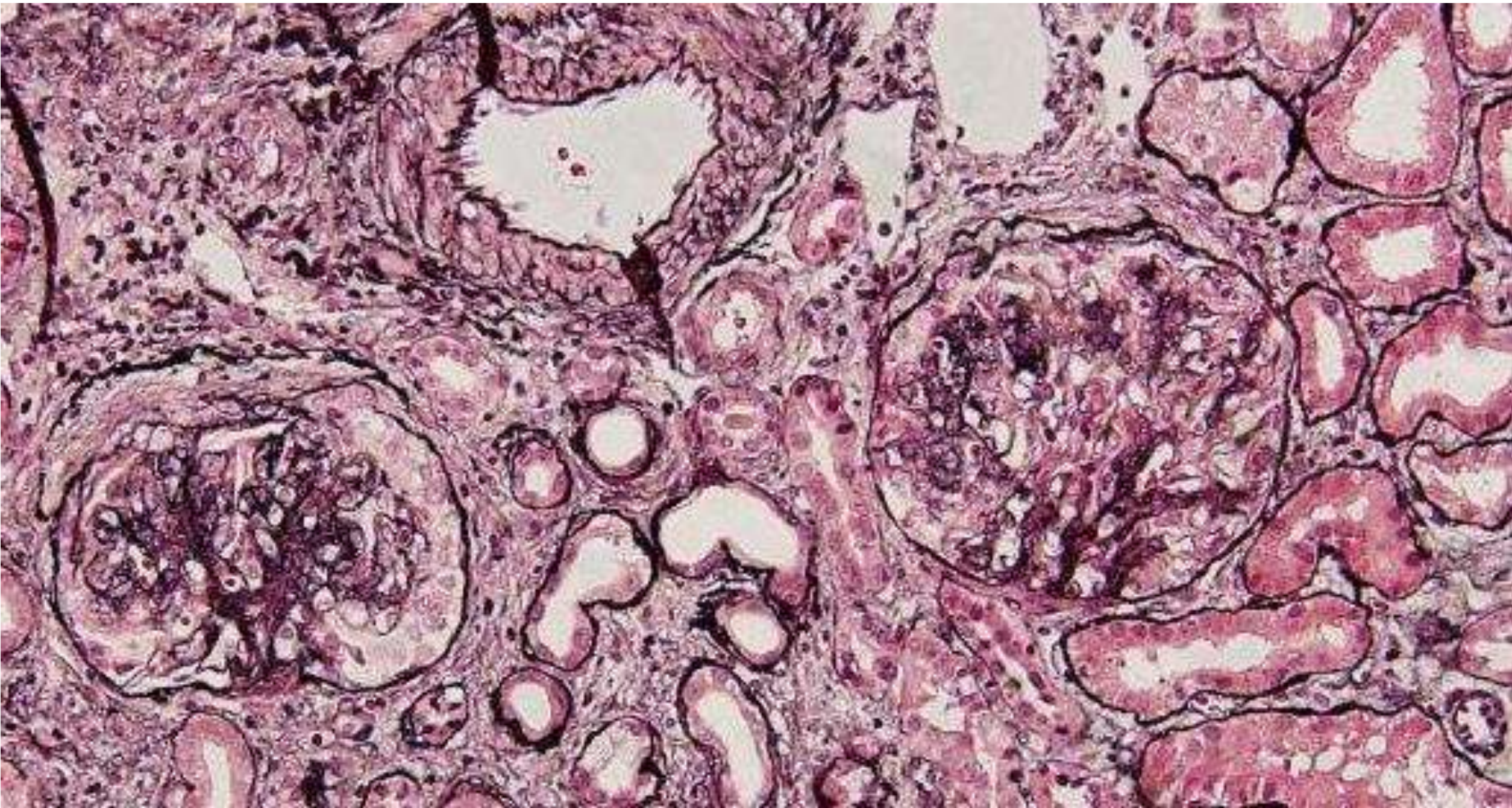
Wat is uw differentiaal diagnose nu?

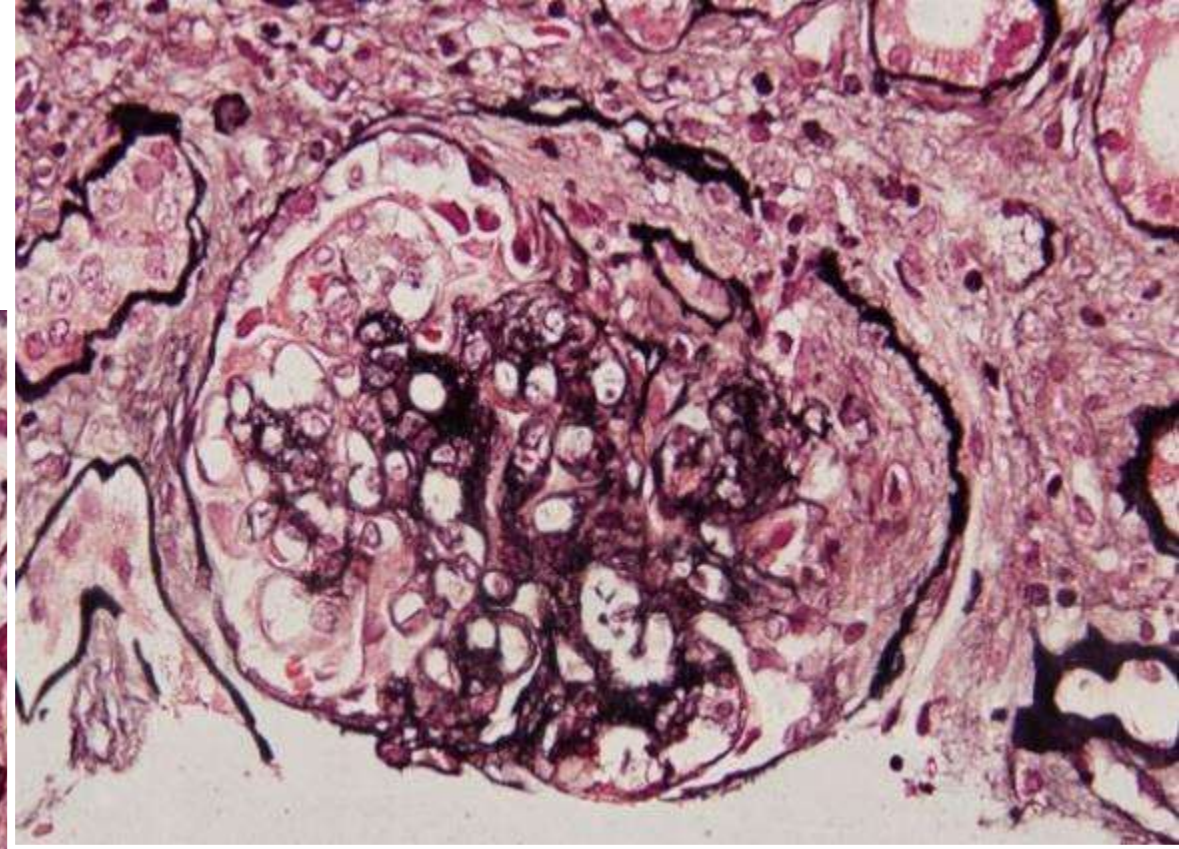
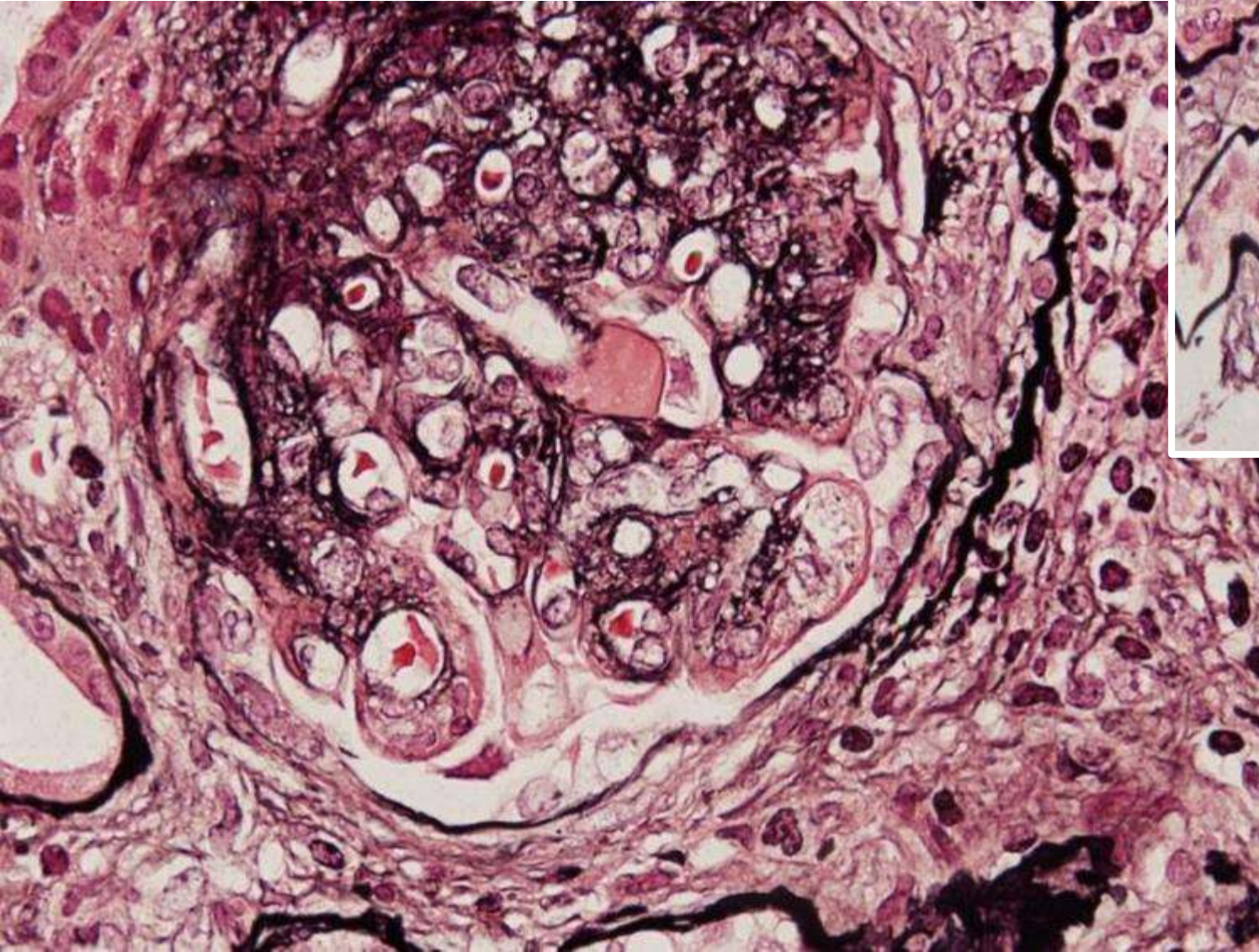


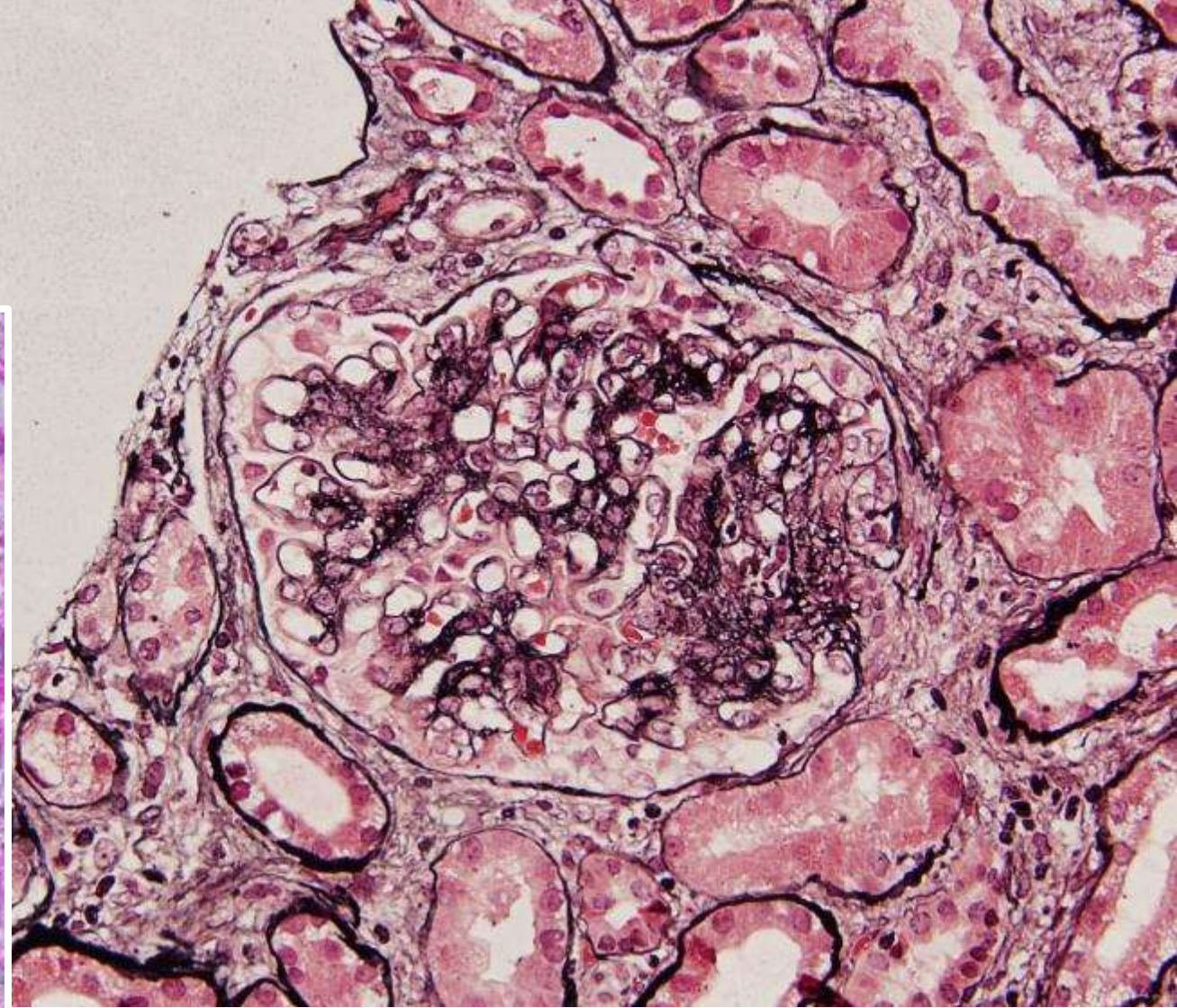
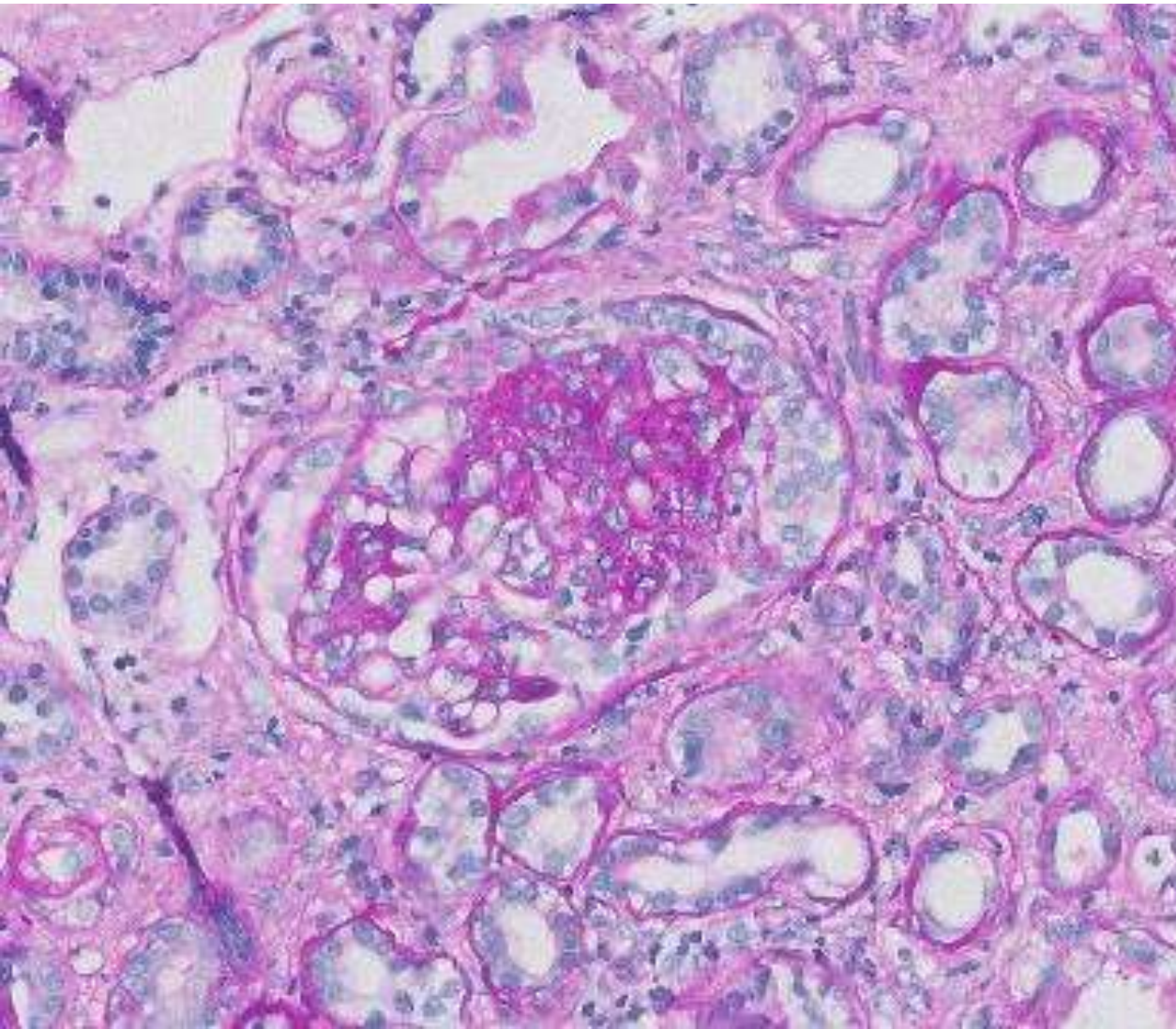
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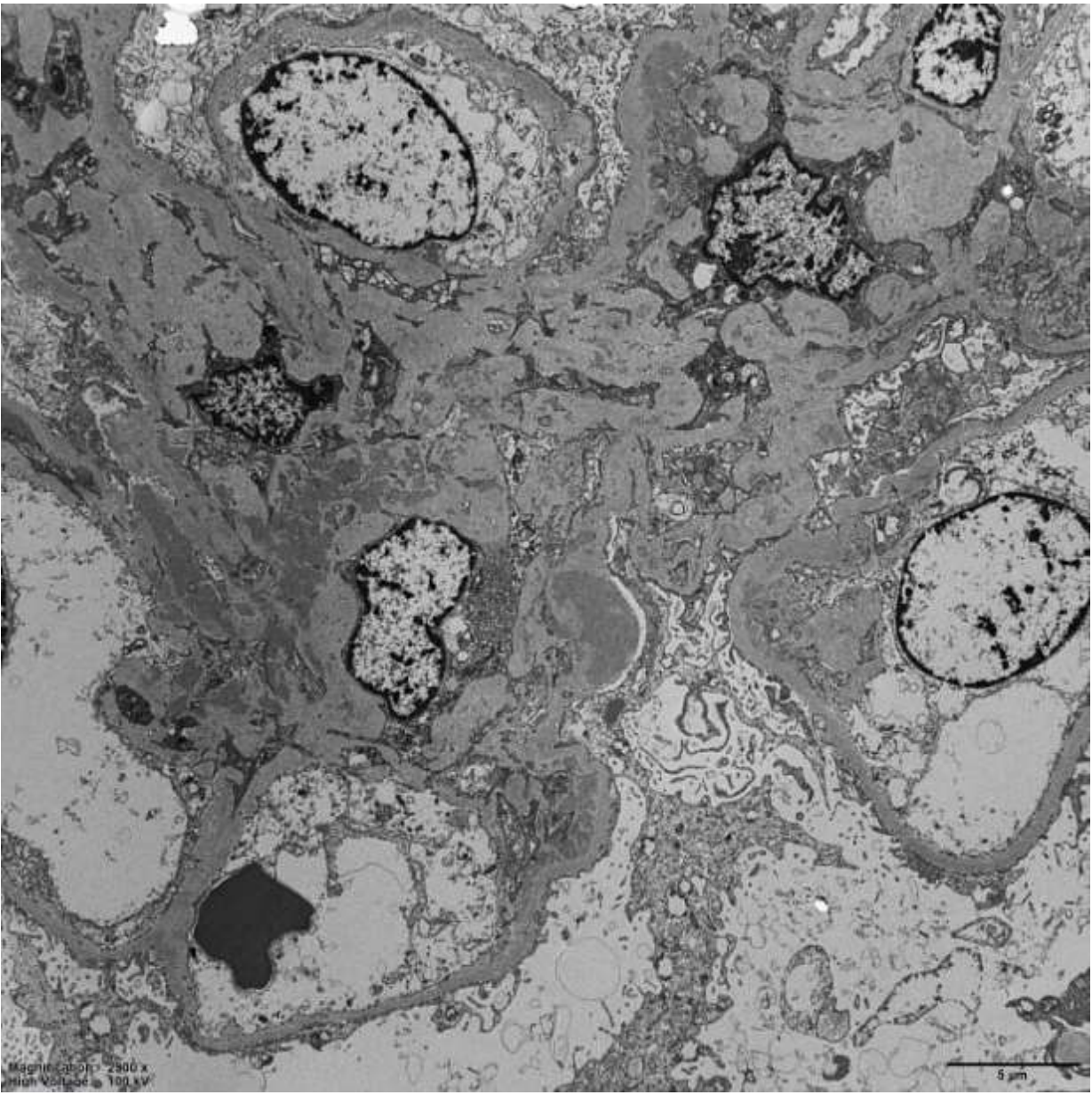
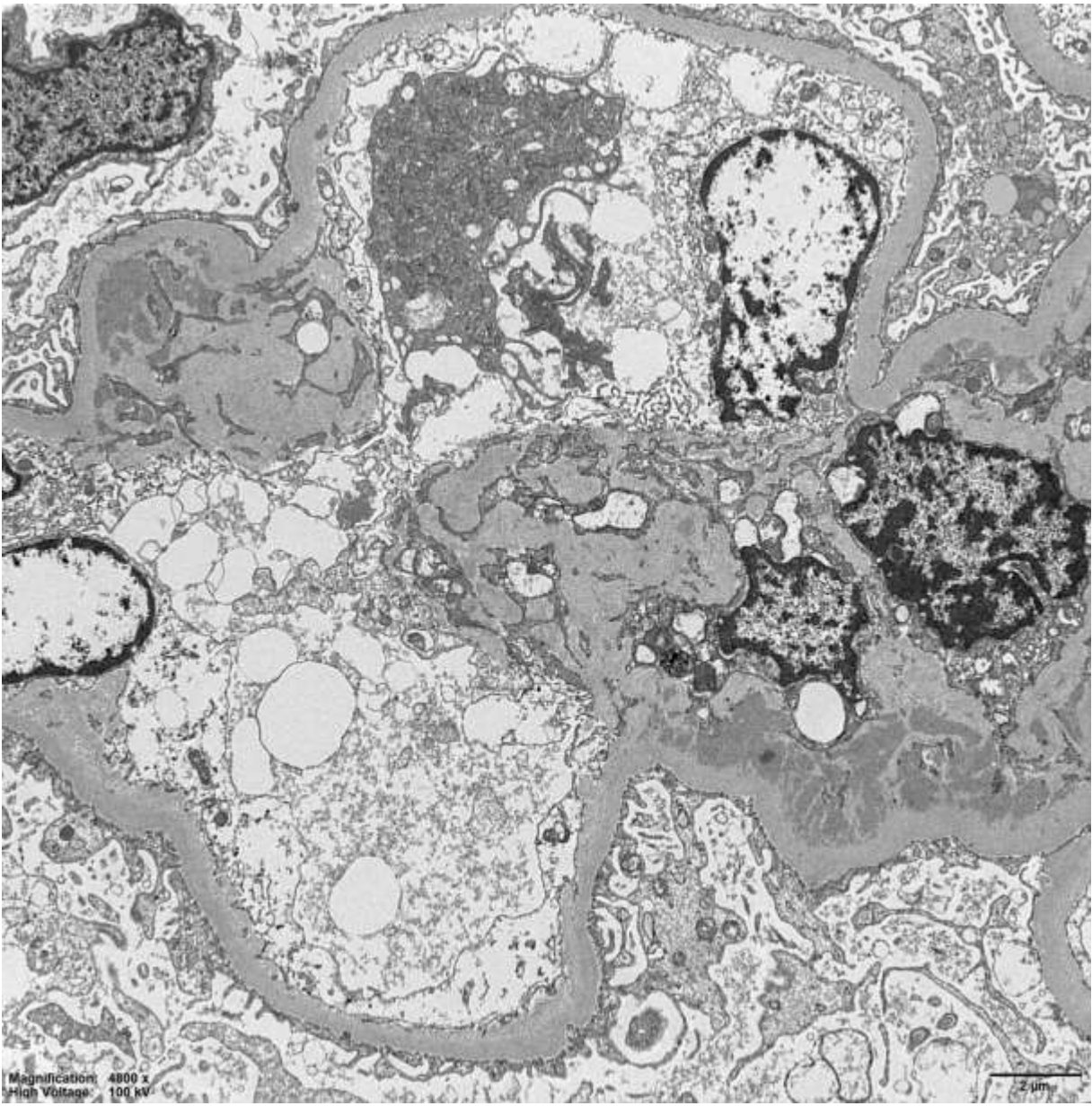
11/2/60

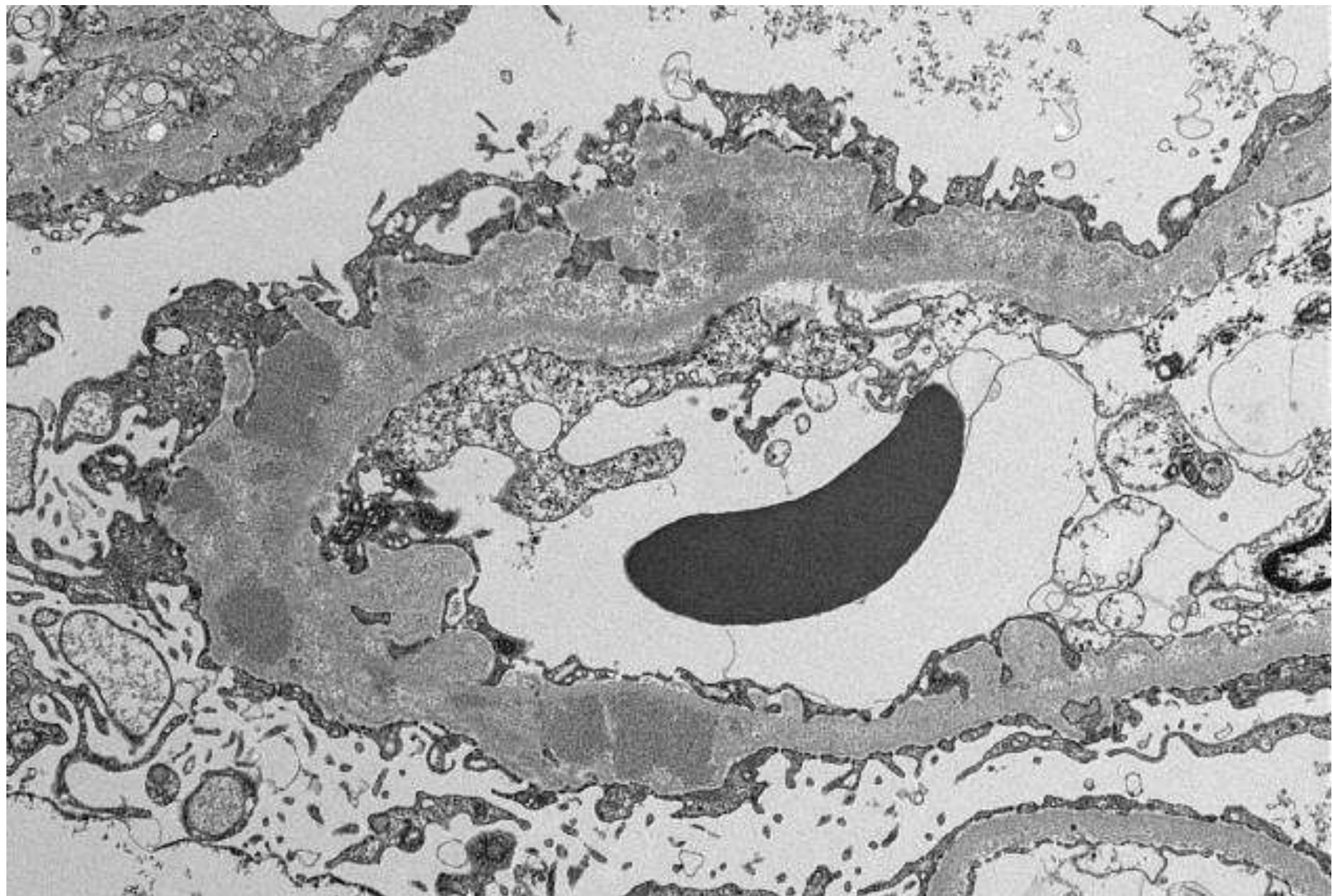


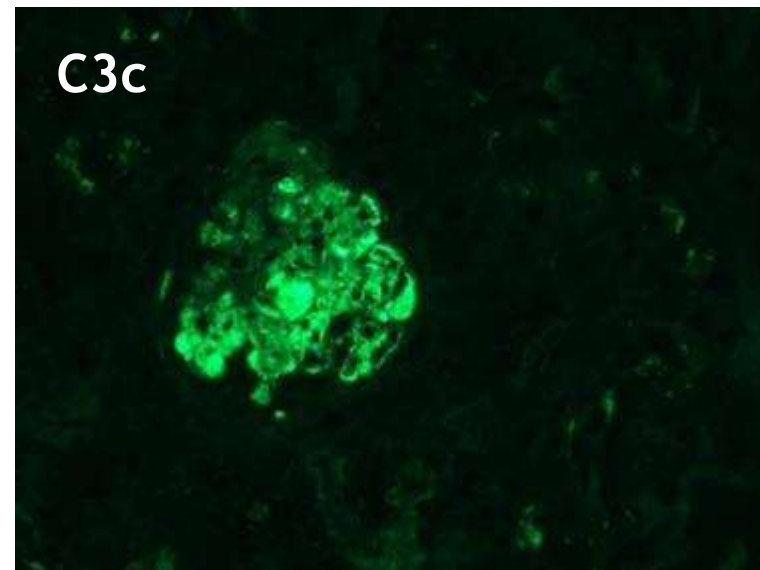
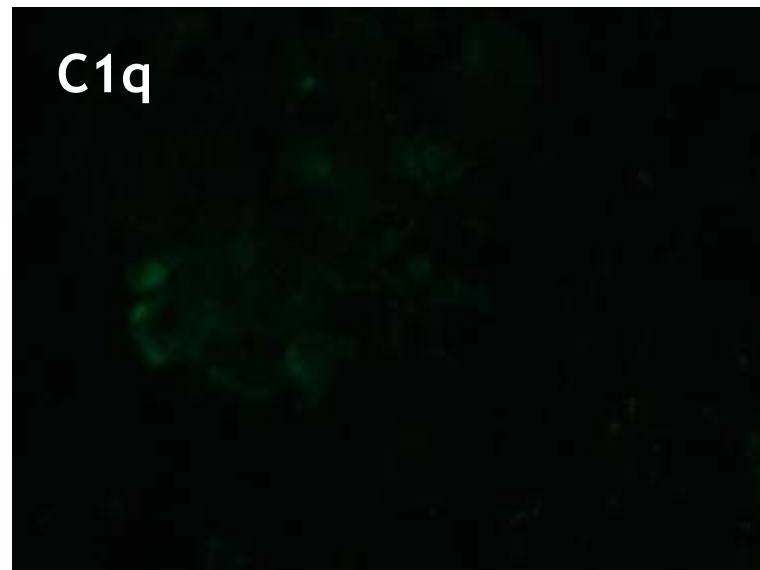
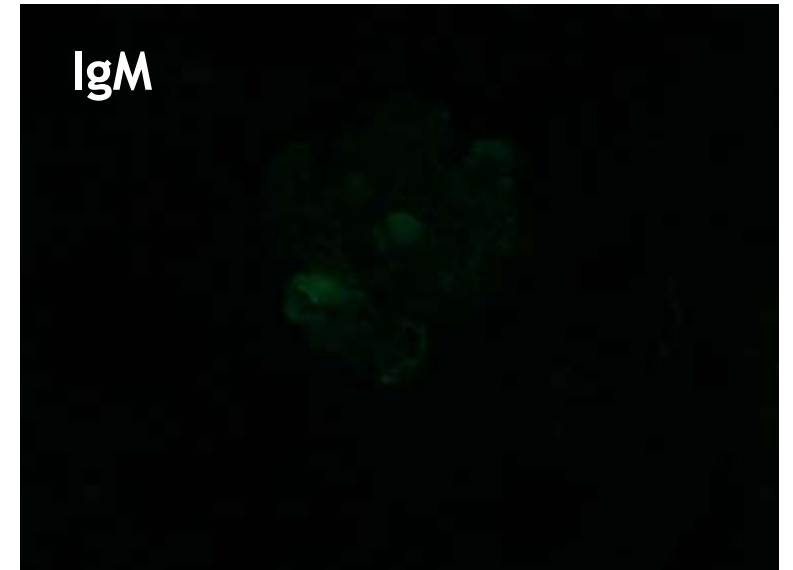
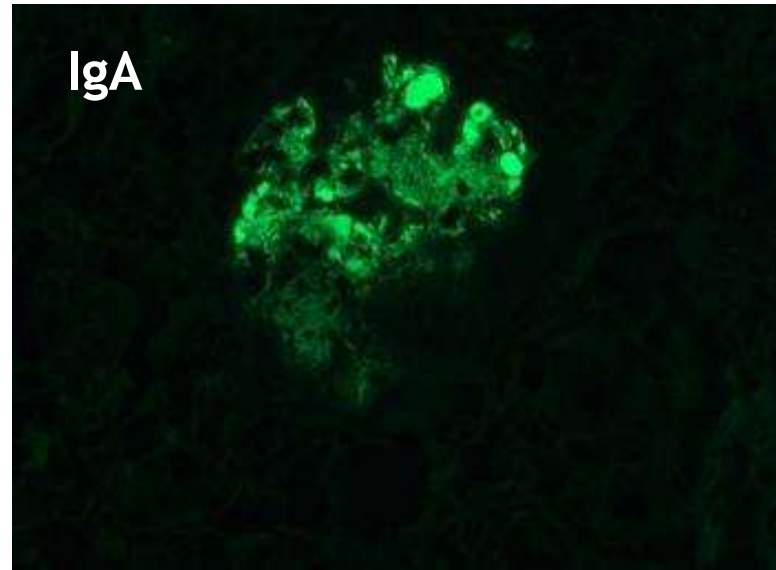
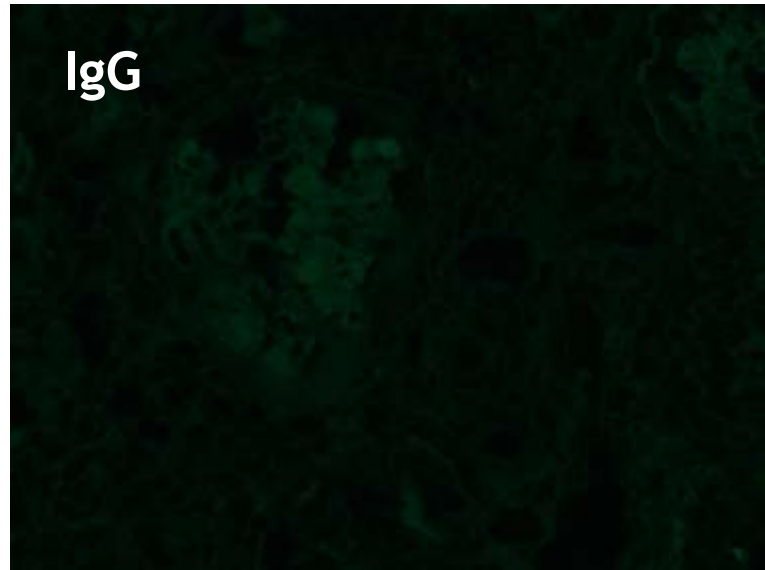










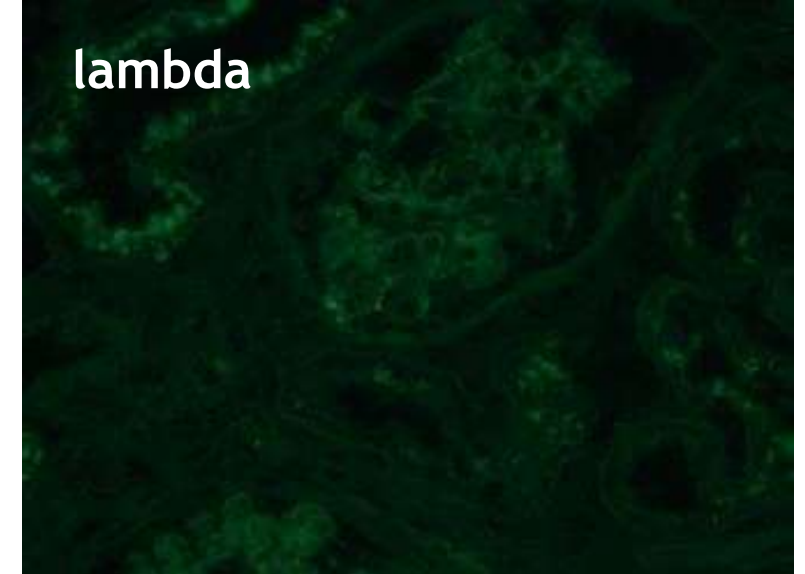
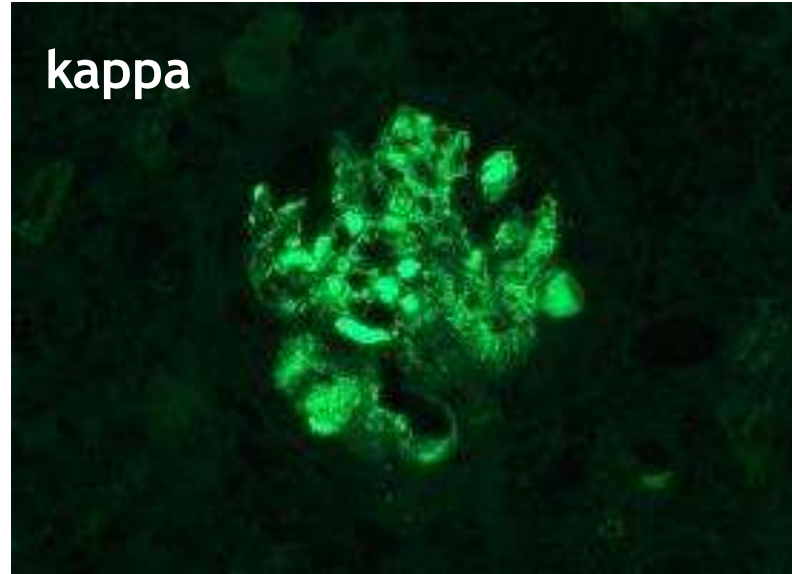
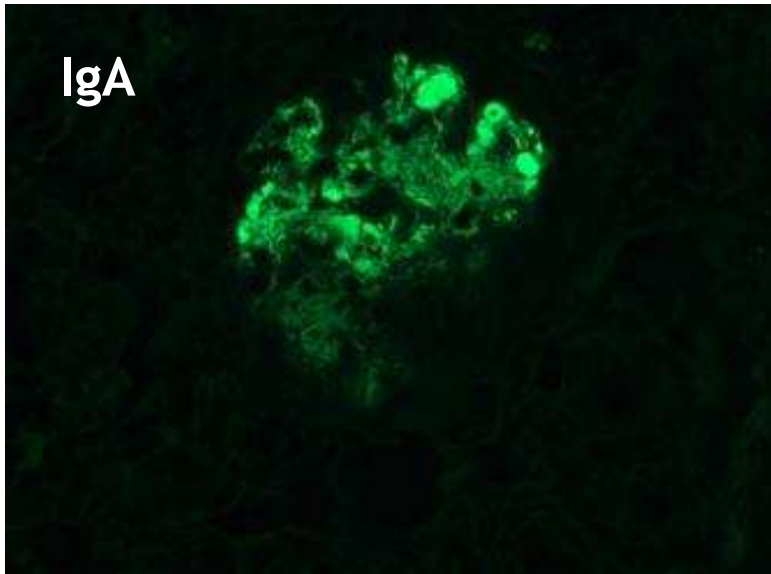




IgA nefropathie?

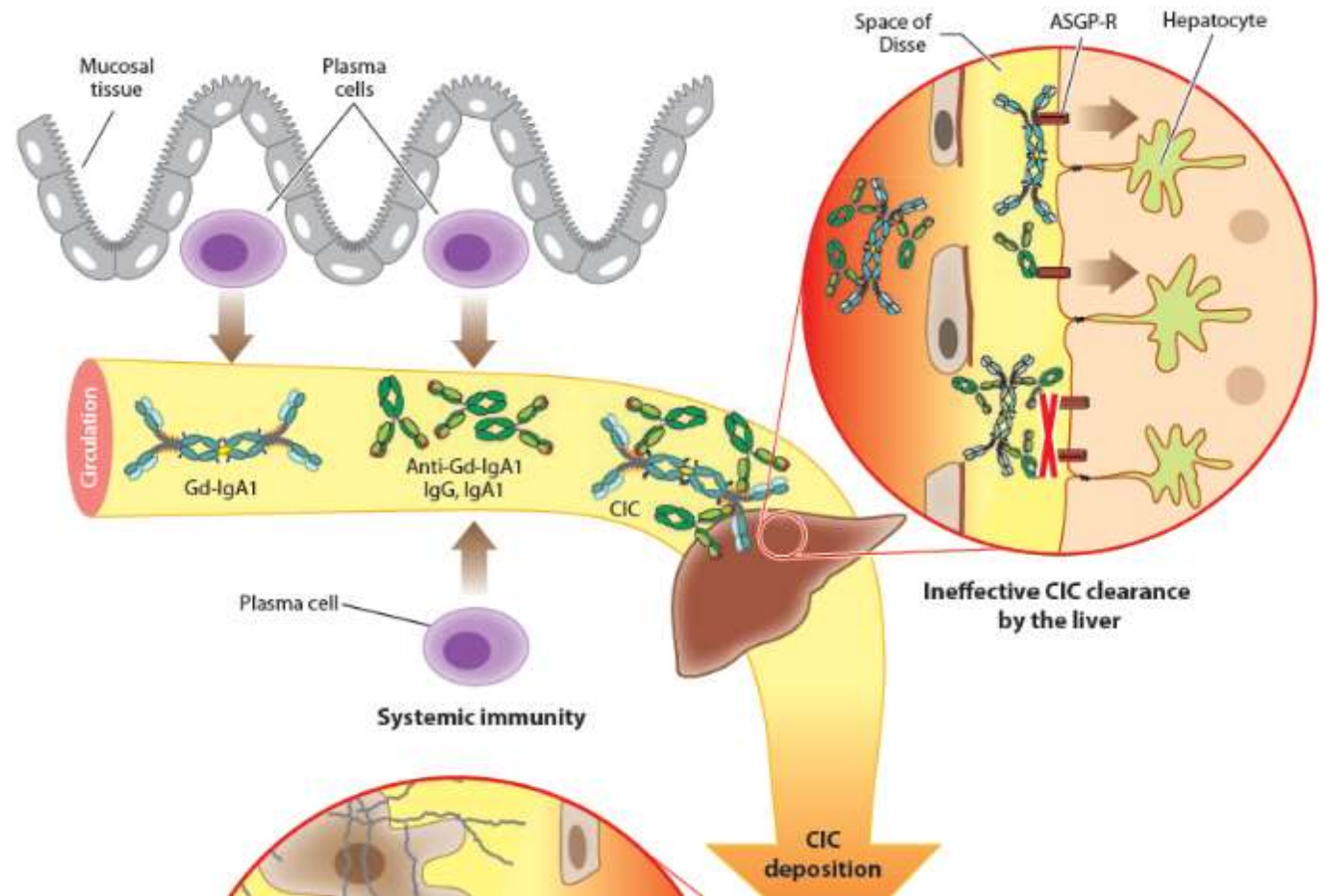
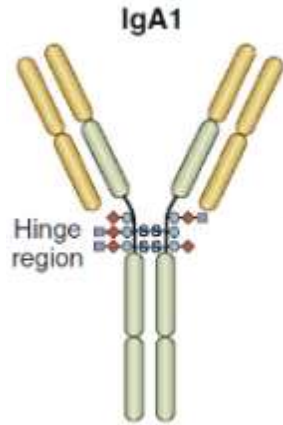


# IgA nefropathie?

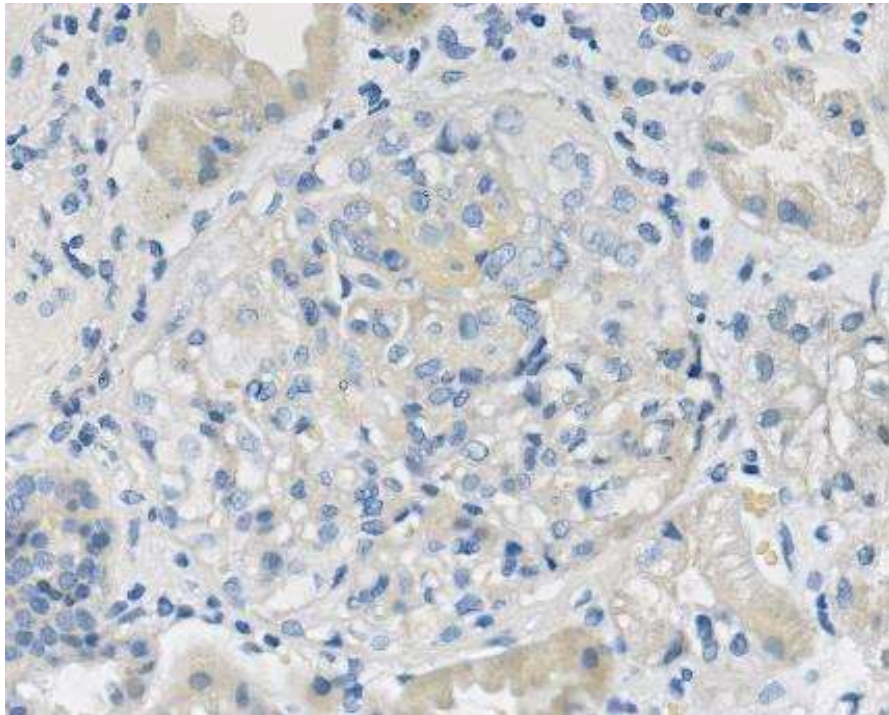
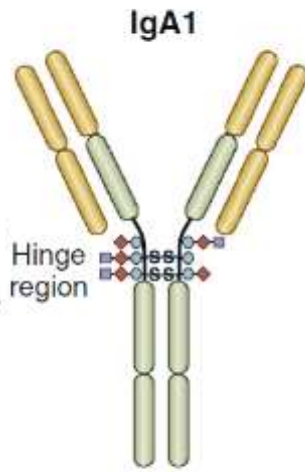
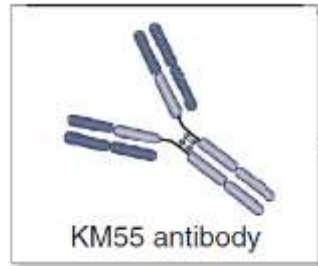




# Pathogenesis IgA nephropathy

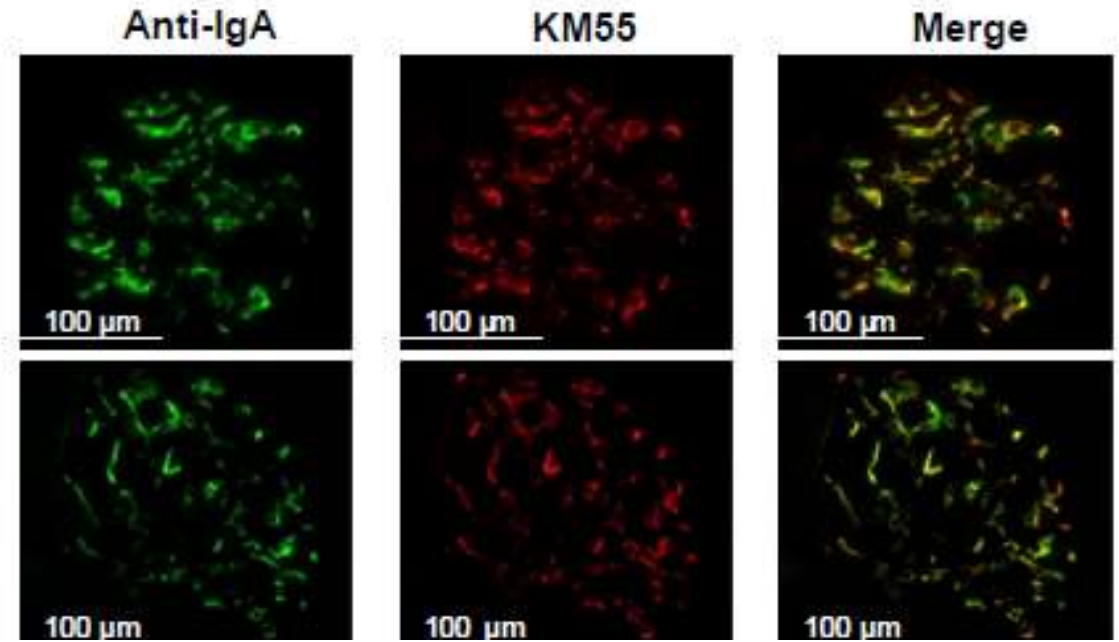


|       |                                                                      |
|-------|----------------------------------------------------------------------|
| Hit 1 | Increased galactose-deficient IgA1                                   |
| Hit 2 | Production of unique antiglycan antibodies                           |
| Hit 3 | Formation of pathogenic IgA1-containing circulating immune complexes |
| Hit 4 | Glomerular injury                                                    |



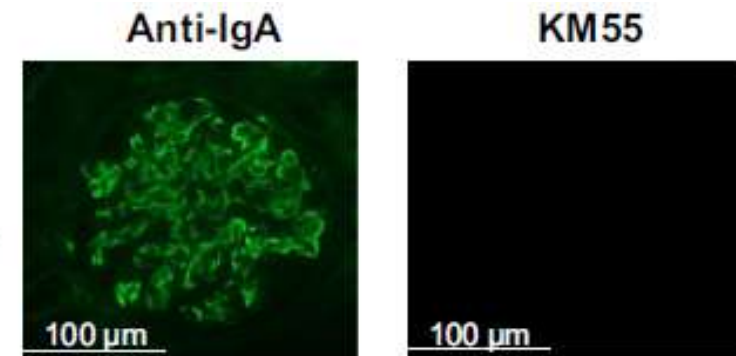
KM55

IgAN  
case 1



b

Lupus  
nephritis  
case 1





→ PGNMID op basis van monotypische IgA deposits (kappa)

clinical investigation

www.kidney-international.org

## The clinicopathologic characteristics of kidney diseases related to monotypic IgA deposits



Marguerite Vignon<sup>1</sup>, Camille Cohen<sup>1,14</sup>, Stanislas Faguer<sup>2,14</sup>, Laure-Hélène Noel<sup>3</sup>, Celine Guilbeau<sup>4</sup>, Marion Rabant<sup>3</sup>, Sarah Higgins<sup>3</sup>, Aurélie Hummel<sup>1</sup>, Alexandre Hertig<sup>5</sup>, Hélène Francois<sup>6</sup>, Moglie Lequintrec<sup>7</sup>, Eve Vilaine<sup>8</sup>, Bertrand Knebelmann<sup>1</sup>, Jacques Pourrat<sup>9</sup>, Dominique Chauveau<sup>2</sup>, Jean-Michel Goujon<sup>10</sup>, Vincent Javaugue<sup>11</sup>, Guy Touchard<sup>10,11</sup>, Khalil El Karoui<sup>12,15</sup> and Frank Bridoux<sup>11,13,15</sup>



→ 5 gevallen van  $\alpha$ -Heavy Chain Deposition Disease (HCDD)

→ 14 gevallen van IgA-PGNMID

**Table 1 | Pathological characteristics in patients with GN-mIgA**

| LM pattern | Diagnosis (yr) | Glomeruli (n) | Globally sclerosed glomeruli (%) | Extracapillary proliferation (%) | Fibrinoid necrosis | Endocapillary proliferation | Tubulointerstitial fibrosis | Interstitial inflammation | Arteriosclerosis | Arteriolar hyalinosis | Distribution of deposits | Light chain | C3 | Ultrastructural organization      |
|------------|----------------|---------------|----------------------------------|----------------------------------|--------------------|-----------------------------|-----------------------------|---------------------------|------------------|-----------------------|--------------------------|-------------|----|-----------------------------------|
| Mes GN     | 2012           | 20            | 65                               | 40                               | 0                  | Mild                        | T2                          | Moderate                  | Severe           | Y                     | P                        | Kappa       | Y  | None                              |
| Mes GN     | 2011           | 11            | 36                               | 0                                | 0                  | None                        | T0                          | Moderate                  | Moderate         | Y                     | P                        | Lambda      | N  | NA                                |
| Mes GN     | 2000           | 20            | 20                               | 40                               | 1                  | None                        | T1                          | Severe                    | Severe           | Y                     | M+P                      | Lambda      | Y  | NA                                |
| Mes GN     | 2013           | 17            | 6                                | 29                               | 0                  | None                        | T0                          | Mild                      | None             | N                     | M                        | Lambda      | N  | None                              |
| Mes GN     | 2012           | 17            | 53                               | 0                                | 0                  | None                        | T2                          | Mild                      | Severe           | Y                     | M                        | Lambda      | Y  | None                              |
| Mes GN     | 2015           | 14            | 0                                | 29                               | 0                  | None                        | T1                          | Mild                      | None             | N                     | M                        | Lambda      | Y  | None                              |
| Mes GN     | 2000           | 17            | 6                                | 6                                | 0                  | Mild                        | T1                          | None                      | Mild             | N                     | M+P                      | Kappa       | Y  | NA                                |
| MPGN       | 2012           | 11            | 27                               | 18                               | 0                  | Mild                        | T1                          | Severe                    | None             | N                     | M                        | Kappa       | Y  | None                              |
| MPGN       | 2013           | 10            | 30                               | 0                                | 0                  | Moderate                    | T2                          | Mild                      | None             | N                     | M                        | Kappa       | Y  | None                              |
| MPGN       | 2014           | 7             | 18                               | 14                               | 0                  | None                        | T2                          | None                      | Mild             | Y                     | M                        | Lambda      | Y  | None                              |
| MPGN       | 2000           | 17            | 6                                | 6                                | 1                  | Moderate                    | T0                          | Mild                      | Moderate         | Y                     | M+P                      | Kappa       | Y  | NA                                |
| MPGN       | 2006           | 12            | 33                               | 8                                | 0                  | Mild                        | T0                          | Mild                      | Nc               | N                     | M+P                      | Kappa       | Y  | None                              |
| MPGN       | 2006           | 6             | 0                                | 17                               | 0                  | Moderate                    | T2                          | Mild                      | None             | N                     | P                        | Lambda      | N  | Yes, paracrystalline organization |
| MN         | 2015           | 40            | 38                               | 0                                | 0                  | None                        | T0                          | None                      | None             | N                     | M+P                      | Kappa       | Y  | None                              |

GN-mIgA, glomerulonephritis with monotypic IgA deposits; LM, light microscopy; M, mesangial; Mes GN, mesangial glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NA, not available; P, parietal; TBM, tubular basement membrane.

Tubulointerstitial fibrosis: T0 <25%, T1 25%–50%, T2 >50%.



# Aanvullend lab Amsterdam

| Hematologie       | Chemie           | Endocrinologie   | Bloedgas | Stoll |
|-------------------|------------------|------------------|----------|-------|
| 15:54             | 25-8-17<br>14:00 | 25-8-17<br>14:24 |          |       |
| ⏮ ⏪ ⏩ ⏭           |                  |                  |          |       |
| BSE               |                  |                  |          |       |
| BSE gedef.        |                  |                  |          |       |
| CRP               |                  | <2.5             |          |       |
| Hb(mmol/l)        |                  | ↓ 6.6            |          |       |
| Ht(l/l)           |                  | ↓ 0.31           |          |       |
| Ery's             |                  | ↓ 3.7            |          |       |
| Reticulo's (%)    |                  |                  |          |       |
| Reticulo(abs)     |                  |                  |          |       |
| MCV               |                  | 84               |          |       |
| MCH               |                  | 1793             |          |       |
| MCHC              |                  | 21.3             |          |       |
| Trombocyten       | voldoende        | 195              |          |       |
| Eo's              |                  |                  |          |       |
| Leukocyten(x10... | ↑ 10.4           | ↑ 10.4           |          |       |
| Vraagstelling     | Diff bij merg    |                  |          |       |

|                       |  |  |        |
|-----------------------|--|--|--------|
| Vrije K/L ratio       |  |  |        |
| Vrij-Kappa (Pro...    |  |  | ↑ 36.1 |
| Vrij-Lambda (Pr...    |  |  | 25.3   |
| Vrije K/L ratio (...) |  |  | 1.43   |
| C4                    |  |  | 0.26   |
| C3                    |  |  | ↓ 0.87 |



| 15:57            | 25-8-17<br>14:24 | 28-8-17<br>10:27 | 28-8-17<br>13:47 | 30-8-17<br>12:53 | 1-9-17<br>7:55 | 6-9-17<br>8:28 | 11-9-17<br>11:28 | 20-9-17<br>11:45 |
|------------------|------------------|------------------|------------------|------------------|----------------|----------------|------------------|------------------|
| ⏮ ⏪ ⏩ ⏭          |                  |                  |                  |                  |                |                |                  |                  |
| Natrium          | ↓ 135            |                  |                  |                  |                | 138            |                  | 142              |
| Kalium(mmol/l)   | ↑ 5.2            | 4.4              |                  | 4.0              |                | ↓ 3.5          | 4.0              | 4.6              |
| Chloor           | 104              |                  |                  |                  |                |                |                  |                  |
| Calcium          | 2.43             | 2.36             |                  |                  |                | ↓ 2.17         |                  | 2.37             |
| Ca-ion           |                  |                  |                  |                  |                |                |                  |                  |
| Ca-corr_alb      |                  |                  |                  |                  |                | 2.36           |                  | 2.54             |
| Magnesium        | 0.97             |                  |                  |                  |                |                |                  |                  |
| Fosfaat          |                  | ↑ 1.62           |                  | 1.18             |                | 1.38           |                  | 1.21             |
| Glucose          | 6.4              |                  |                  | 5.0              | 4.8            | 4.5            |                  | 4.7              |
| Totaal eiwit     |                  |                  | 63               |                  |                |                |                  |                  |
| Albumine         | 36               |                  |                  |                  |                | ↓ 30           |                  | ↓ 32             |
| Creatinine       | ↑ 495            | ↑ 303            |                  | ↑ 217            |                | ↑ 181          | ↑ 168            | ↑ 172            |
| Cockcroft        |                  |                  |                  |                  |                |                |                  |                  |
| eGFR (CKD-EP...) | ↓ 13             | ↓ 23             |                  | ↓ 35             |                | ↓ 43           | ↓ 47             | ↓ 46             |
| MDRD man         |                  |                  |                  |                  |                |                |                  |                  |
| MDRD vrouw       |                  |                  |                  |                  |                |                |                  |                  |
| eGFR (MDRD)      |                  |                  |                  |                  |                |                |                  |                  |
| Ureum            | ↑ 43.9           | ↑ 37.5           |                  | ↑ 23.1           |                | ↑ 12.0         |                  | ↑ 10.9           |
| Urinezuur        |                  |                  |                  |                  |                |                |                  |                  |
| Bilirubine       |                  |                  |                  |                  |                |                |                  |                  |
| Gecon.Bili       |                  |                  |                  |                  |                |                |                  |                  |
| Alk.Fosf.        | 55               |                  |                  |                  |                |                |                  |                  |
| γ-GT             |                  |                  |                  |                  |                |                |                  |                  |
| ASAT             |                  |                  |                  |                  |                |                |                  |                  |
| ALAT             | 19               |                  |                  |                  |                |                |                  |                  |
| LDH              | 143              |                  |                  |                  |                |                |                  | 221              |



verder

- Hep B/C/HIV, cryoglobulines allemaal negatief
- ANCA, anti-GBM, anti-PLA2R ab negatief
- Geen M-proteïne aantoonbaar



# Beenmerg

- Totaal slechts 0,05% plasmacellen, geen klonaliteit
- PET: negatief

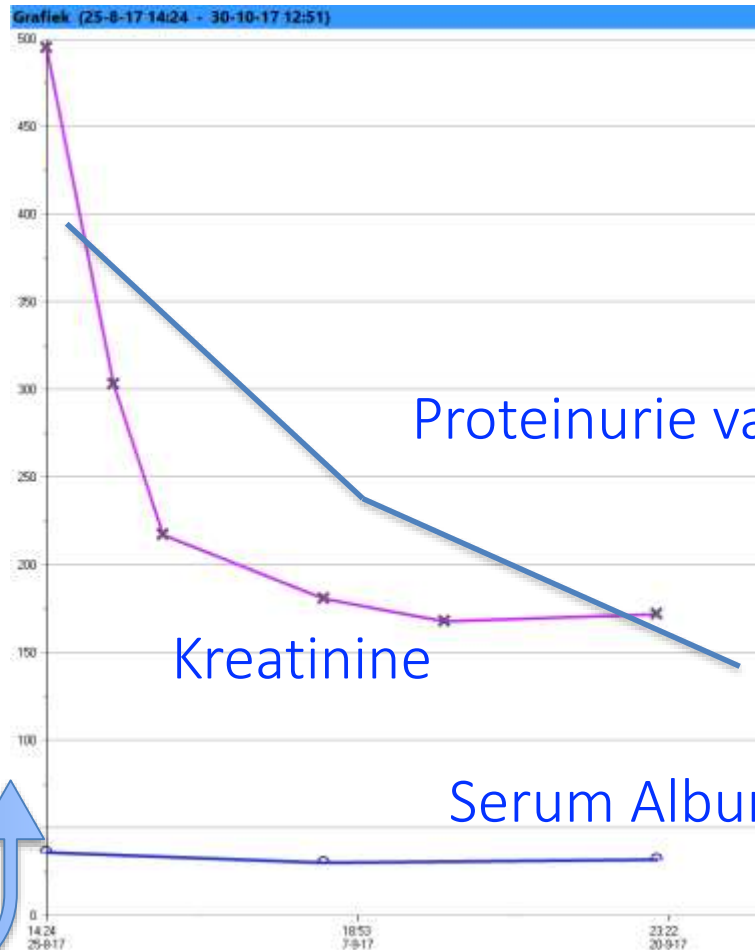


# Beloop

- Gestart met methylprednisolon 3x1000mg, vervolgens prednisolon 60mg 1dd
- Overgeplaatst voor pre-dialyse zorg en evt transplantatie
- Geen klachten, verbeterende nierfunctie → eind september start taperen prednison
- Lab voor retour: kreat 172, 24h urine: eiwit 2.44 gr
- Terug naar elders



# Beloop



Proteinurie van 8 naar 2,4 gram/2 weken

Kreatinine

Serum Albumine rond 30 g/l

MPNS start 3 dagen voor  
overplaatsing



# Brief 13-12-2022

- Maart 2018: relapse, naar hoge dosis prednison + MMF
- Remissie na drie maanden, sep 2022: kreatinine 128  $\mu\text{mol/l}$ , AKR 18 mg/mmol



# Grootste serie; n=19

**Table 2 | Baseline clinical and biological characteristics of patients with glomerulonephritis and monotypic IgA deposits**

|                                         | All patients |        | GN-mlgA (n = 14) |                     | $\alpha$ -HCDD (n = 5) |                     |
|-----------------------------------------|--------------|--------|------------------|---------------------|------------------------|---------------------|
|                                         | Median Range |        | Median Range     |                     | Median Range           |                     |
| Age (yr)                                | 58           | 33–84  | 55               | 33–75               | 69                     | 58–84               |
| Male/Female                             | 10/9         |        | 9/5              |                     | 1/4                    |                     |
| Serum creatinine ( $\mu$ mol/l)         | 148          | 71–320 | 138.5            | 71–275              | 169                    | 133–320             |
| eGFR (ml/min/m <sup>2</sup> )           | 42           | 13–81  | 52               | 22–81               | 29                     | 13–50               |
| CKD stage V (n)                         | 1            |        | 0                |                     | 1                      |                     |
| CKD stage IV (n)                        | 5            |        | 3                |                     | 2                      |                     |
| CKD stage III (n)                       | 9            |        | 7                |                     | 2                      |                     |
| GFR > 60 ml/min/1.73 m <sup>2</sup> (n) | 4            |        | 4                |                     | 0                      |                     |
| Peripheral edema                        | 7/19         | 37%    | 5                | 36%                 | 2                      | 40%                 |
| Hypertension                            | 10/19        | 50%    | 9                | 65%                 | 1                      | 20%                 |
| Microscopic hematuria                   | 18/19        | 95%    | 13               | 93%                 | 5                      | 100%                |
| Albuminemia g/l                         | 32           | 19–41  | 34               | 19–41               | 33                     | 25–36               |
| Proteinuria g/d                         | 3.5          | 0.4–9  | 4.25             | 0.4–7.8             | 3.5                    | 0.7–9               |
| Nephrotic syndrome                      | 3            | 15%    | 2                | 15%                 | 1                      | 20%                 |
| Positive cryoglobulinemia               | 0            |        | 0                |                     | 0                      |                     |
| ANCA, isotype IgA                       | 2            |        | 1                |                     | 1                      |                     |
| Extrarenal manifestations               |              |        | 2 <sup>a</sup>   | 15%                 | 3 <sup>b</sup>         | 60%                 |
| Associated comorbidities                |              |        | 1                | Chronic hepatitis C | 1                      | Digestive carcinoma |

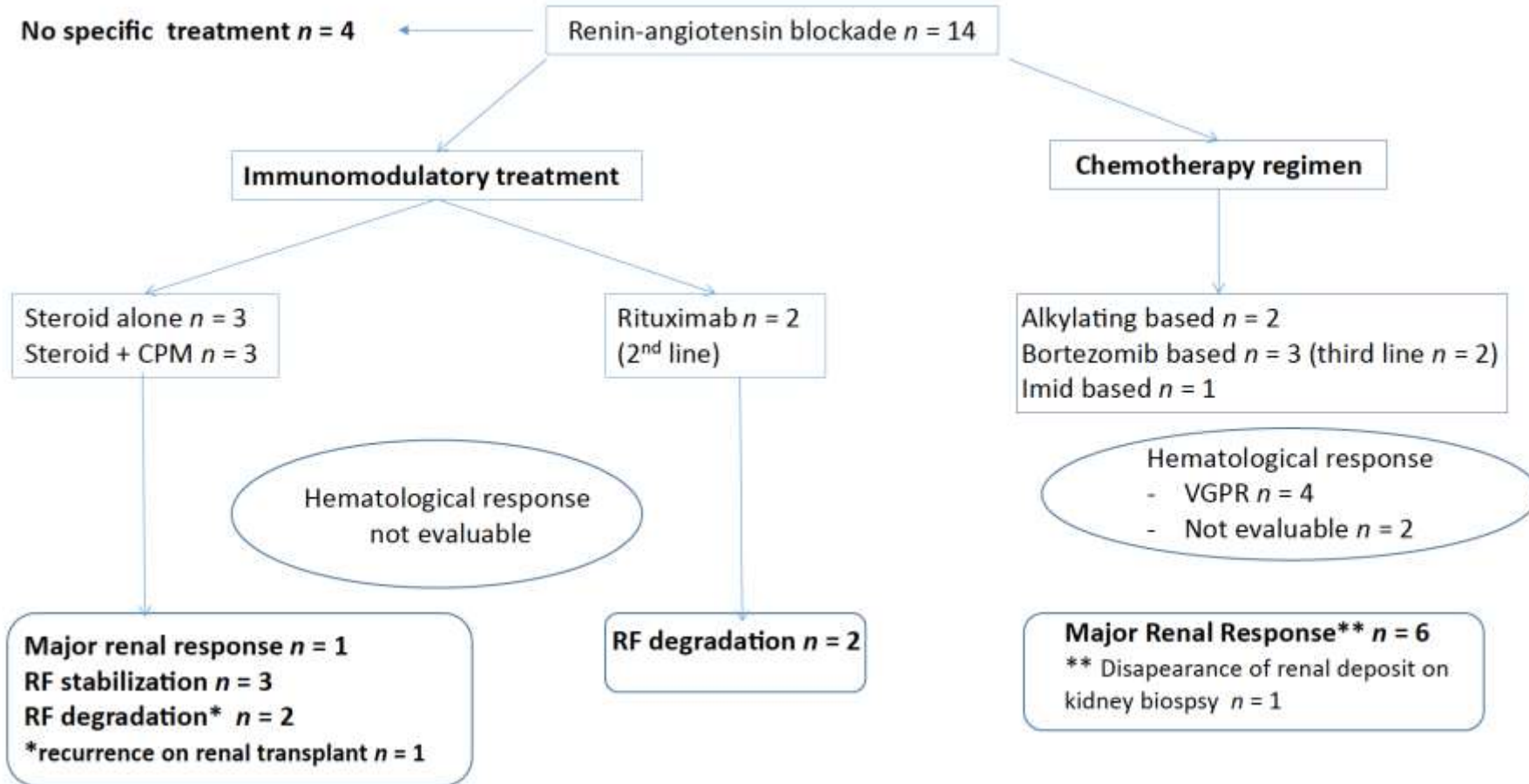
$\alpha$ -HCDD,  $\alpha$  heavy chain deposition disease; ANCA, anti-neutrophil cytoplasmic antibodies; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GN-mlgA, glomerulonephritis with monotypic IgA deposits.

<sup>a</sup>Skin purpura n = 2, including 1 with cerebral vasculitis.

<sup>b</sup>Skin purpura n = 3, including 1 with lung deposits and 1 with digestive deposits.



# Hoe werden deze 19 behandeld





# Conclusie

- PGNMID met mIgA deposits is niet IgAN
- Het is een vorm van MGRS
- Behandeling op kloon gericht lijkt logisch
- Erg zeldzaam ? Of vaak gemist?