Discrepancy between clinical response and pathology result?
Questions remain after one year treatment with Pegcetacoplan in a young girl with C3 glomerulopathy

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Medical history

♀ 14 years old, referred due to:

Chronic fatigue (vitamin D + iron, little improvement)

Recurrent headaches

Hypertension

Edema lower extremities

Further systemic history negative

Family history: mother lupus nephritis

Hypertensive nephritic-nephrotic status:

Furosemide

Enalapril

Vitamin D and iron suppletion

Lab:
Creatinin 0.94 mg/dL
eGFR 78 ml/min
Albumin 27 g/L

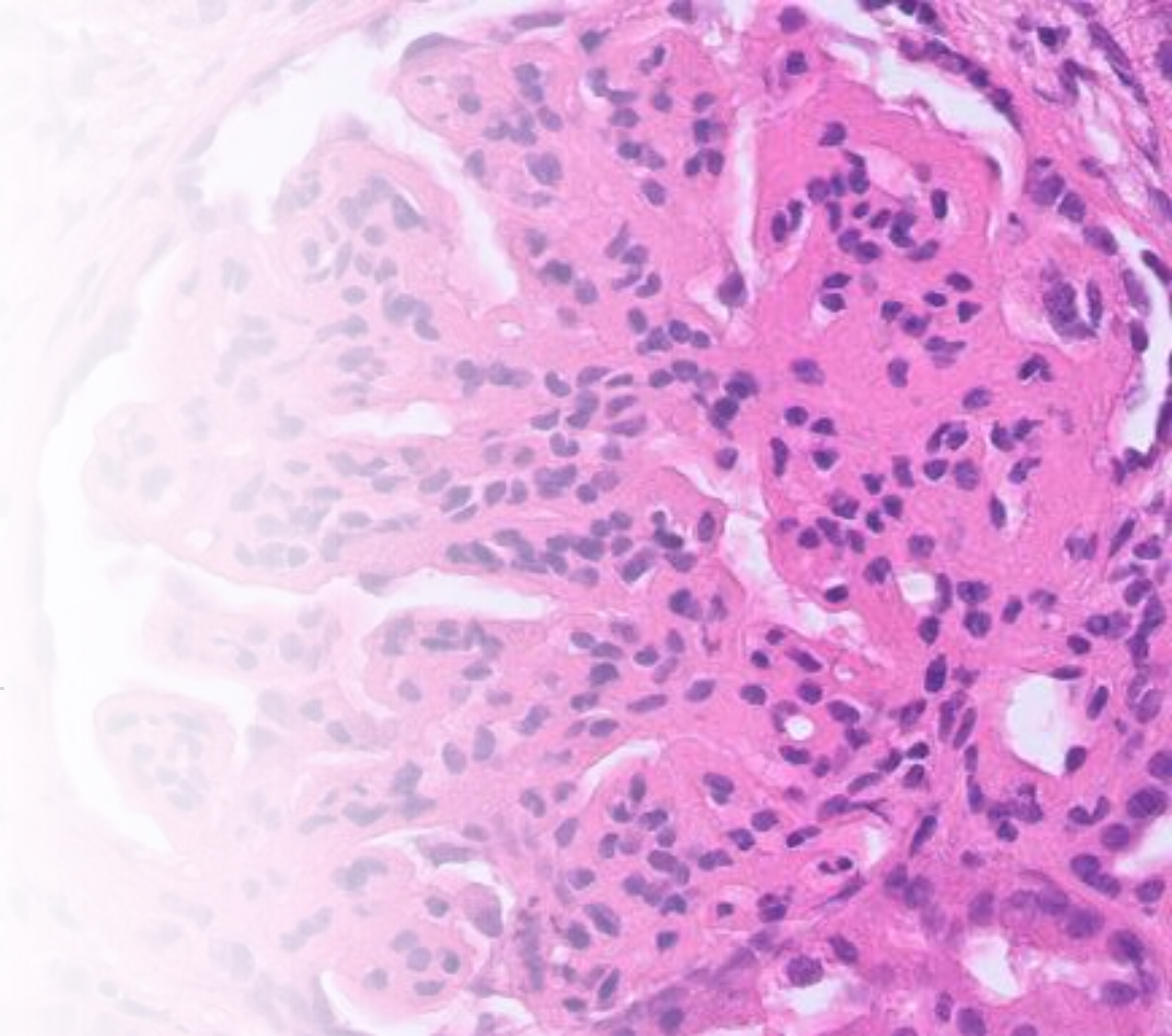
Urine

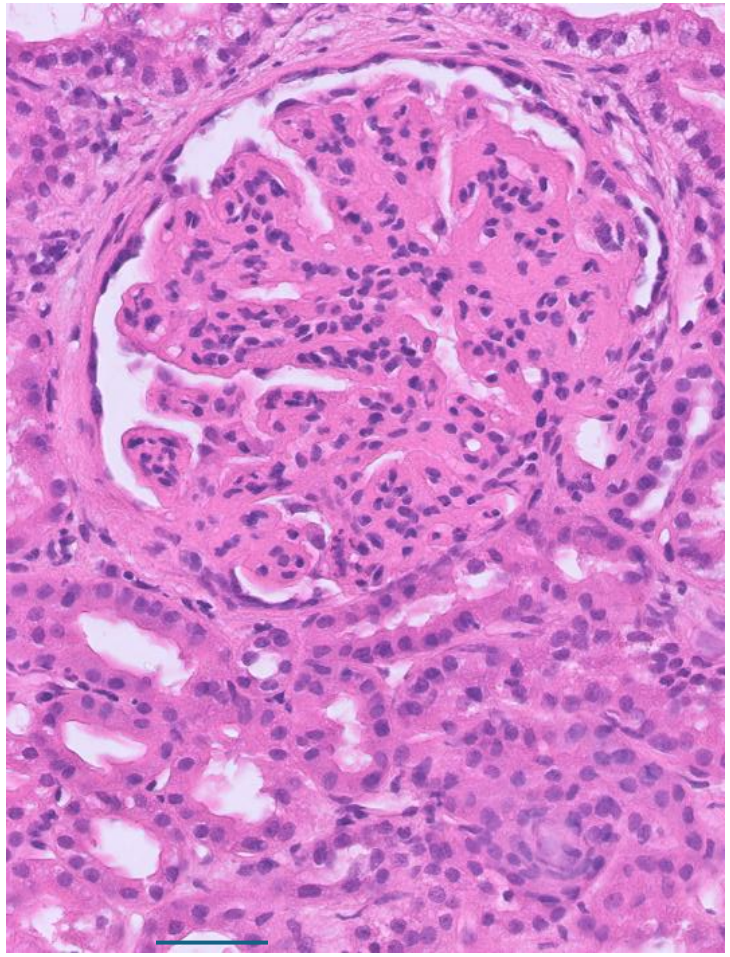
1012 RBC/mm^3,
Protein/creat : 12.7 mg/mg

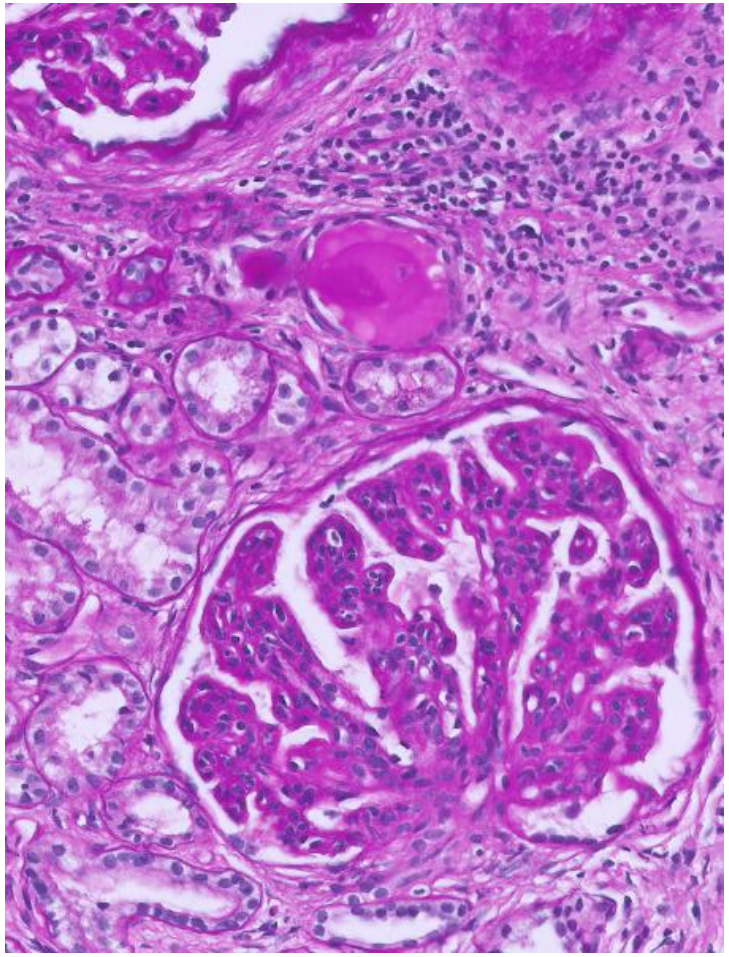
Additional lab:
C3 0.38 g/L
C3d 0.0198 g/L
C4 0.383 g/L
CH50 82%
ANA negative
ANCA negative

Renal biopsy at presentation

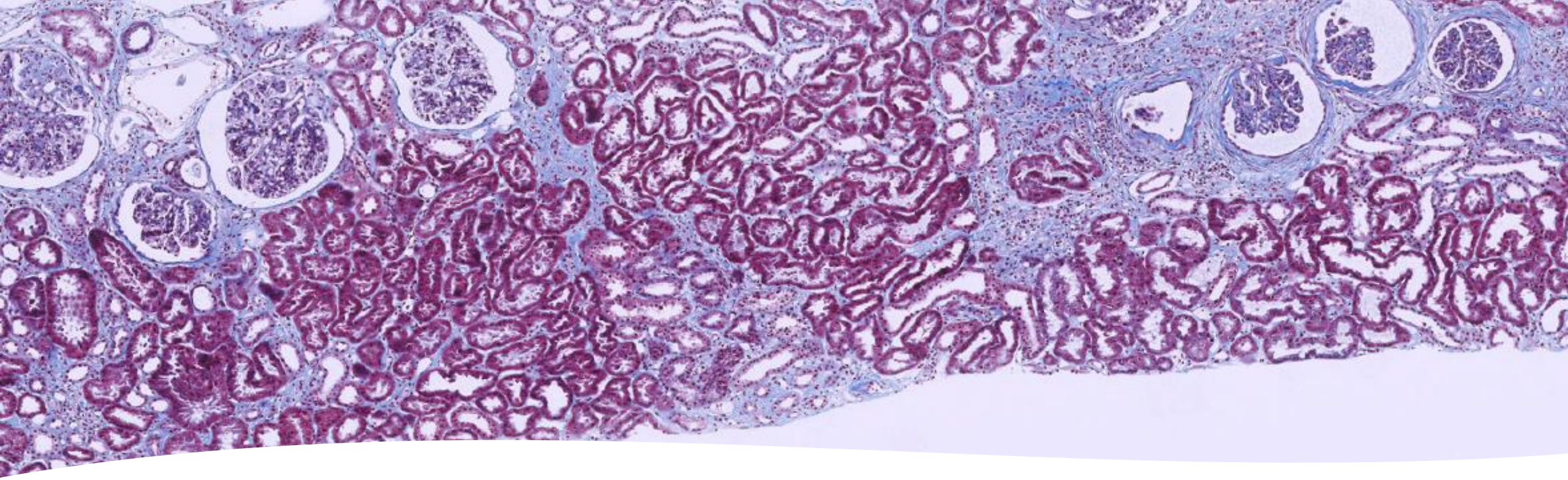
Active membranoproliferative pattern





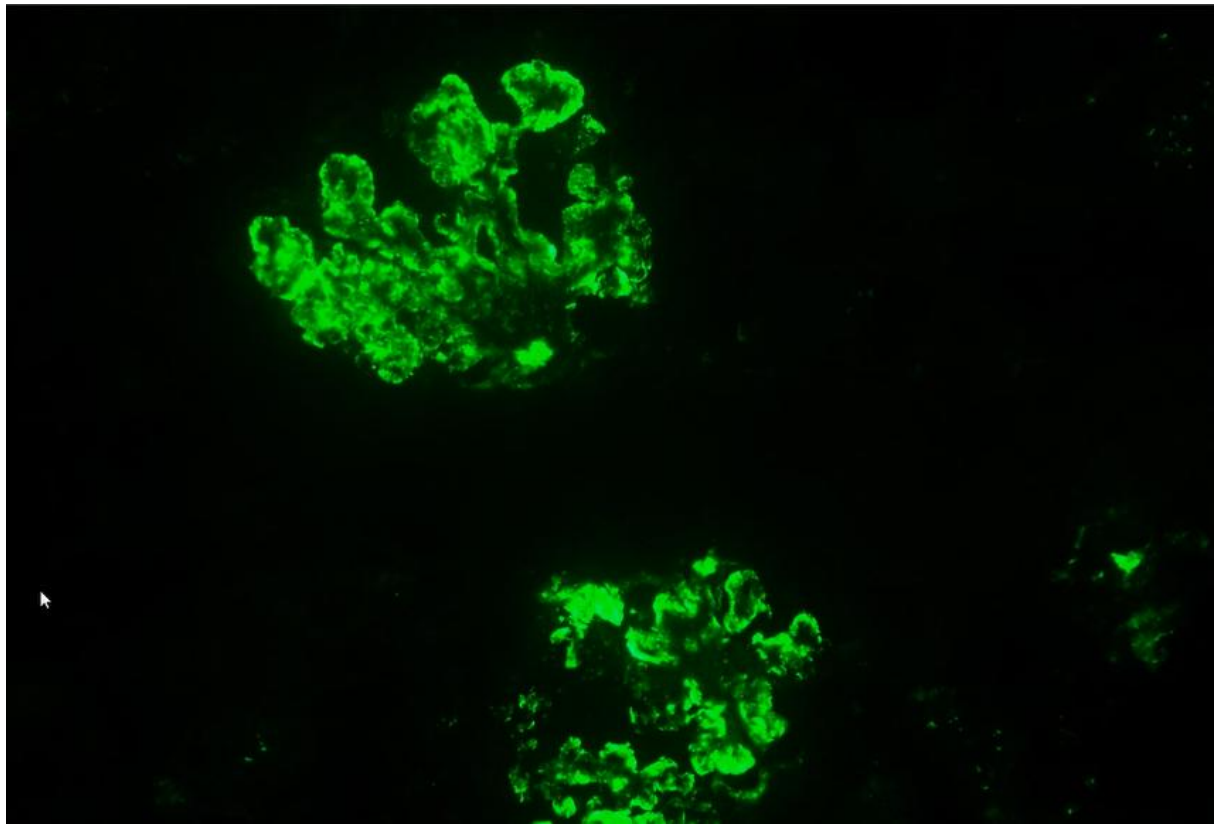


- Active membranoproliferative pattern
- with mesangial expansion,
- lobulation,
- endocapillary hypercellularity



- Moderate chronic damage
- 30 % tubulo-interstitial fibrosis
- Sethi 5/10

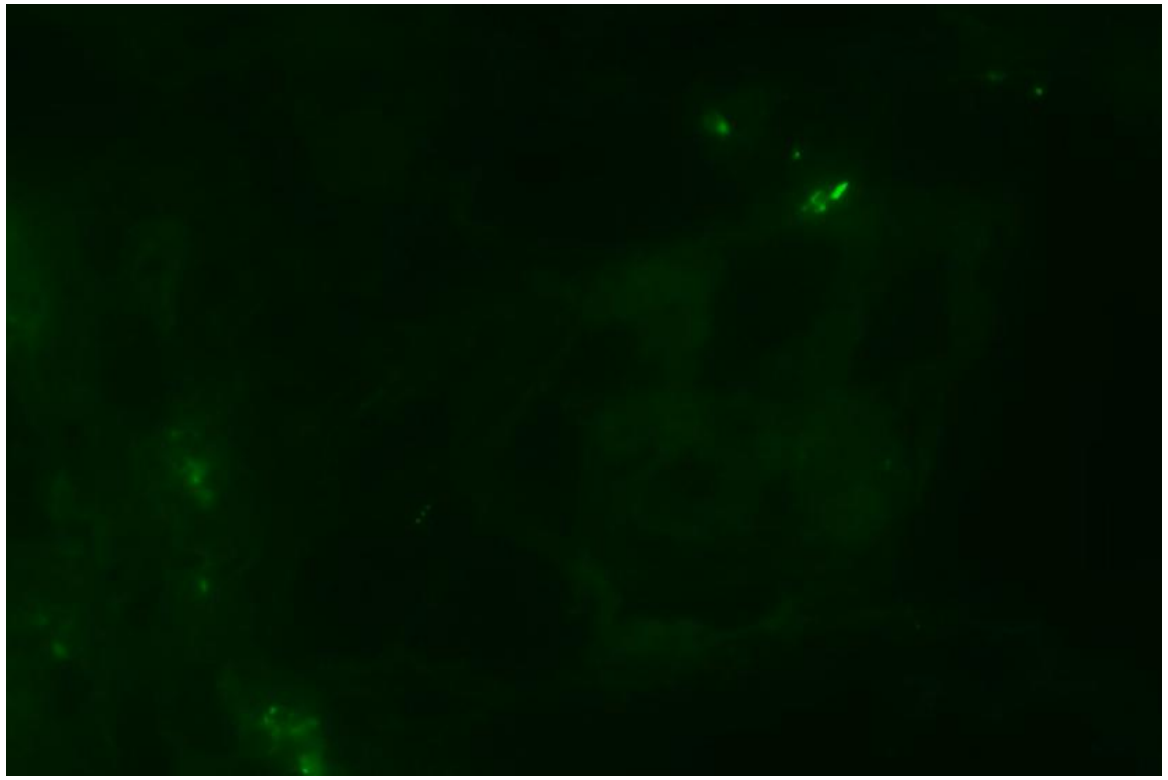
C3



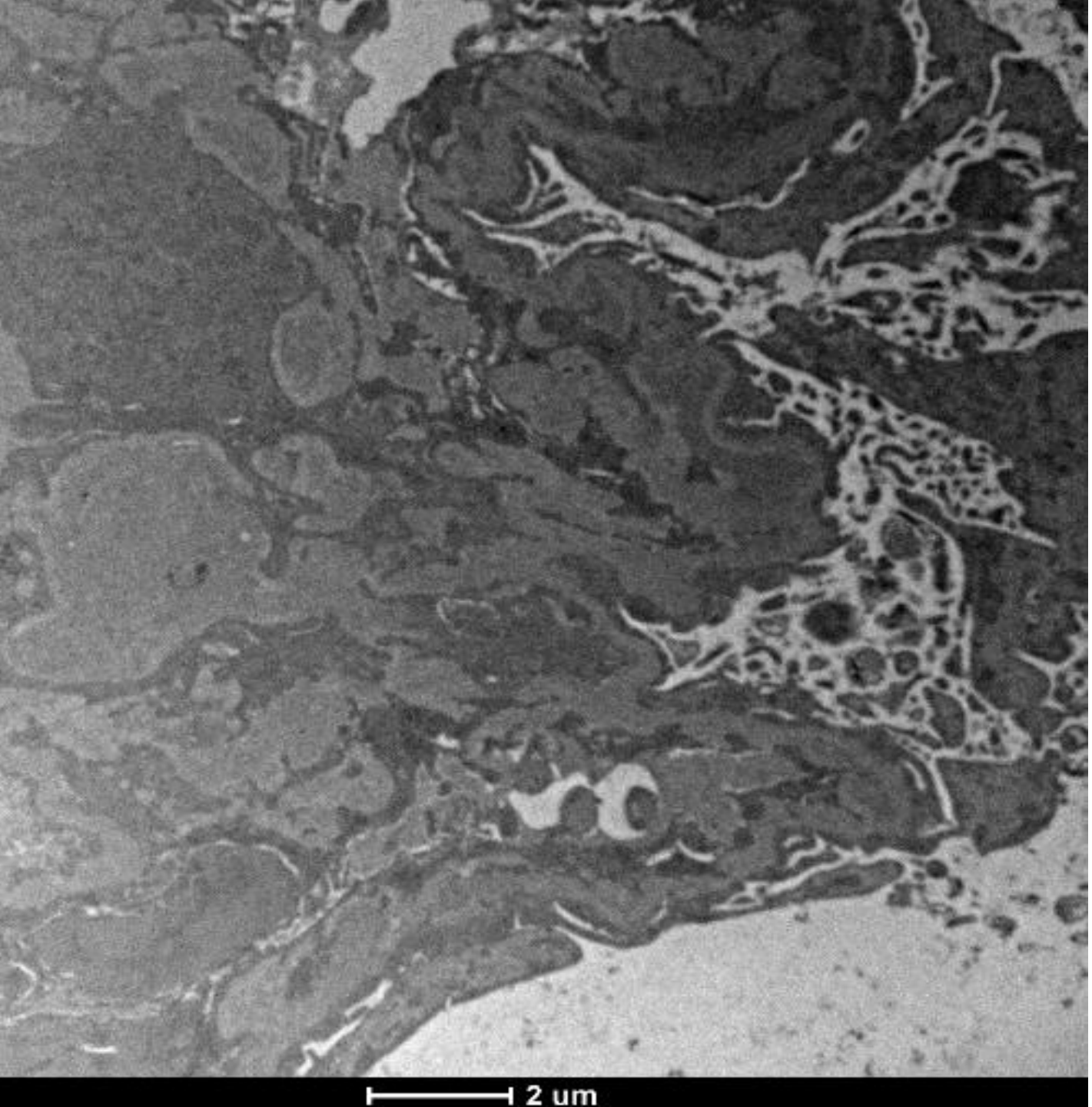
IF:
Strong C3 deposition 3+

(C3c)

IgA



IF:
No relevant
immunoglobulins
or C1q
nor light chain



- EM

- Abundant mesangial, subendothelial and intramembranous electron-dense deposits with >80% podocyte foot process effacement

Further diagnostic work-out:
no predisposition for complement disease

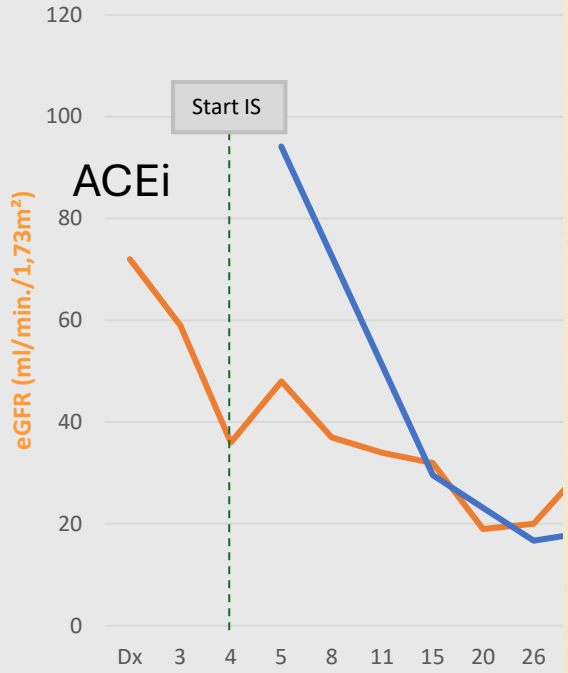
-Normal factor H and I
-factor H antibodies negative
-Very high soluble C5b-9 (thus activation of C5 convertase)
-C3 nephritic factor negative

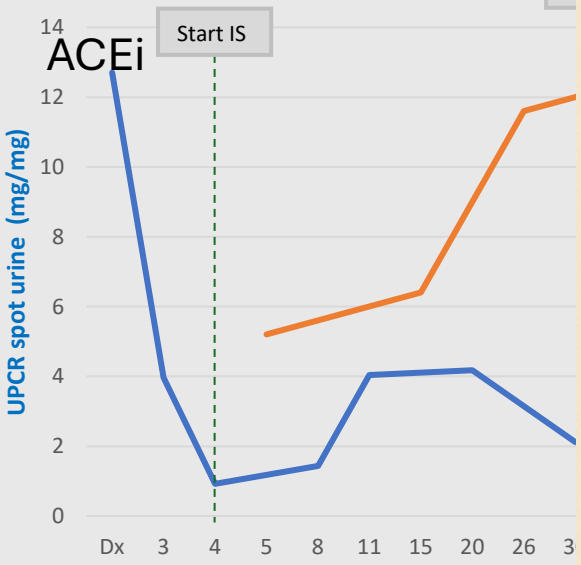
Not tested: anti-CFB and C5 nephritic factor

Genetic testing : NGS extensive gene panel (including CFH,CFI, CD46, CFB, C3, …): negative

MLPA : normal FH-FHR locus

C3 GLOMERULOPATHY: ESCAPE FROM DIALYSIS AT YOUNG AGE?



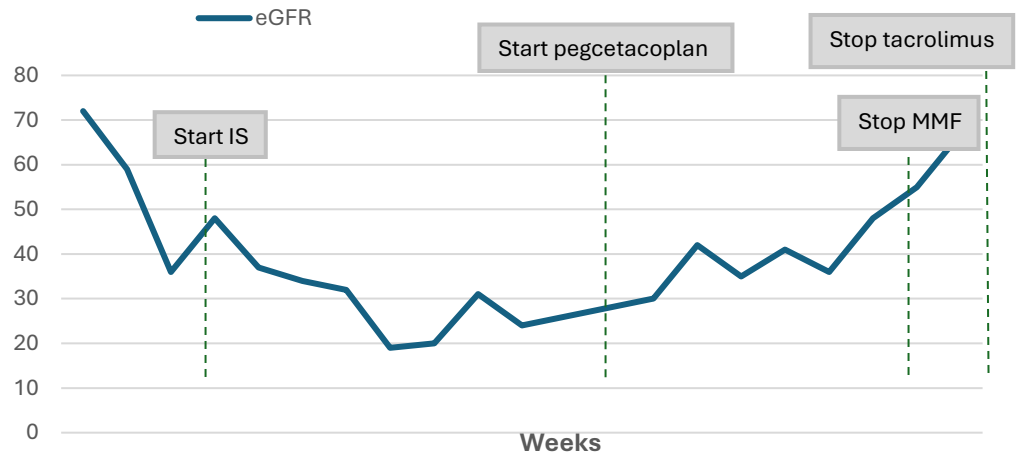


Start Pegcetacoplan
in
medical need

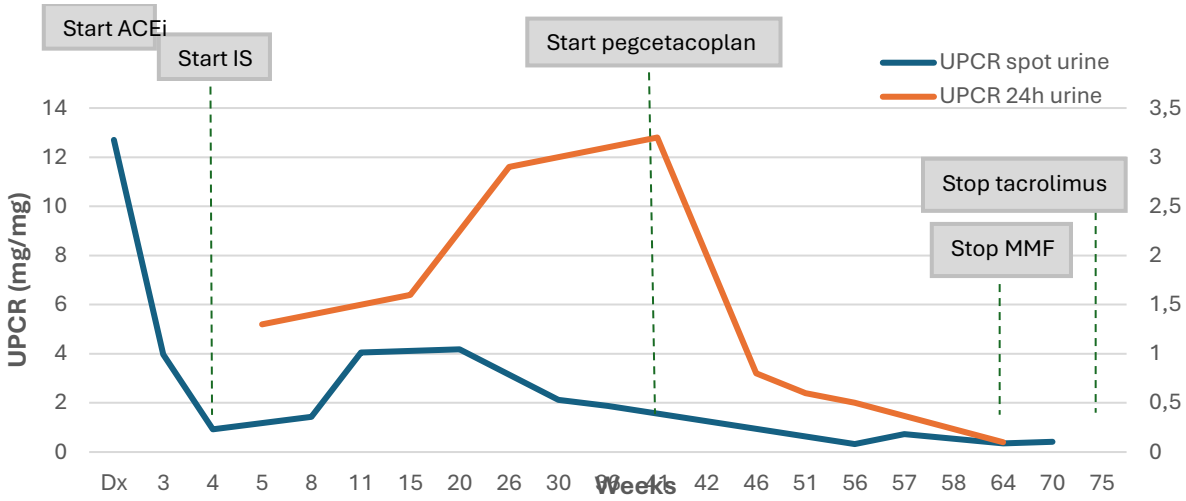
Koningin Mathilde Moeder- en kindcentrum

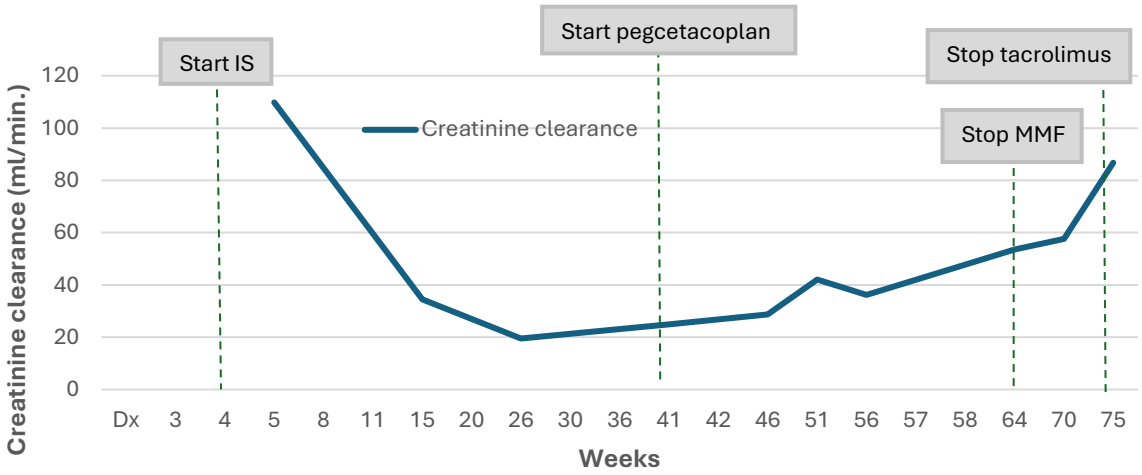
UZA

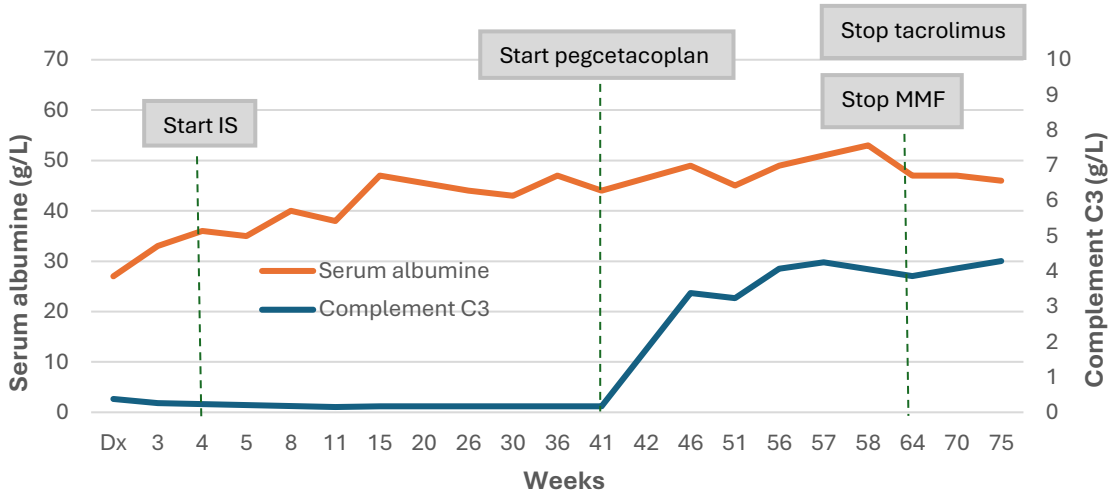
Renal function



Proteinuria

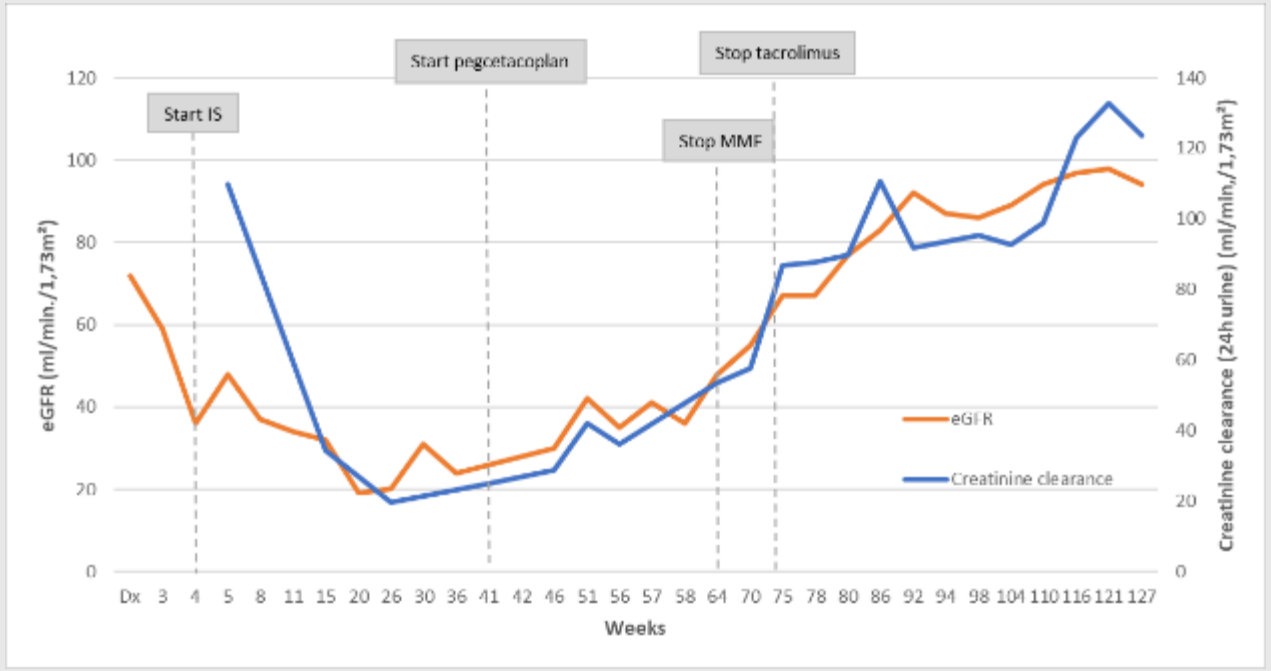




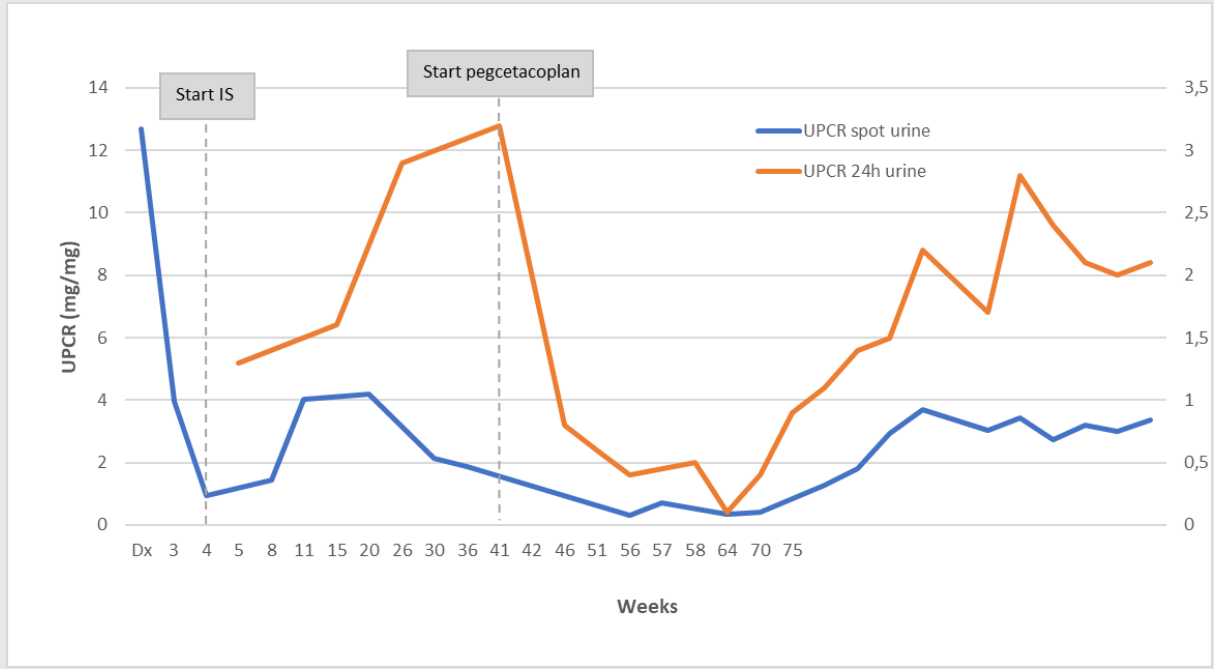


After stop MMF and tacrolimus:

further recovery of kidney function



recurrence of proteinuria

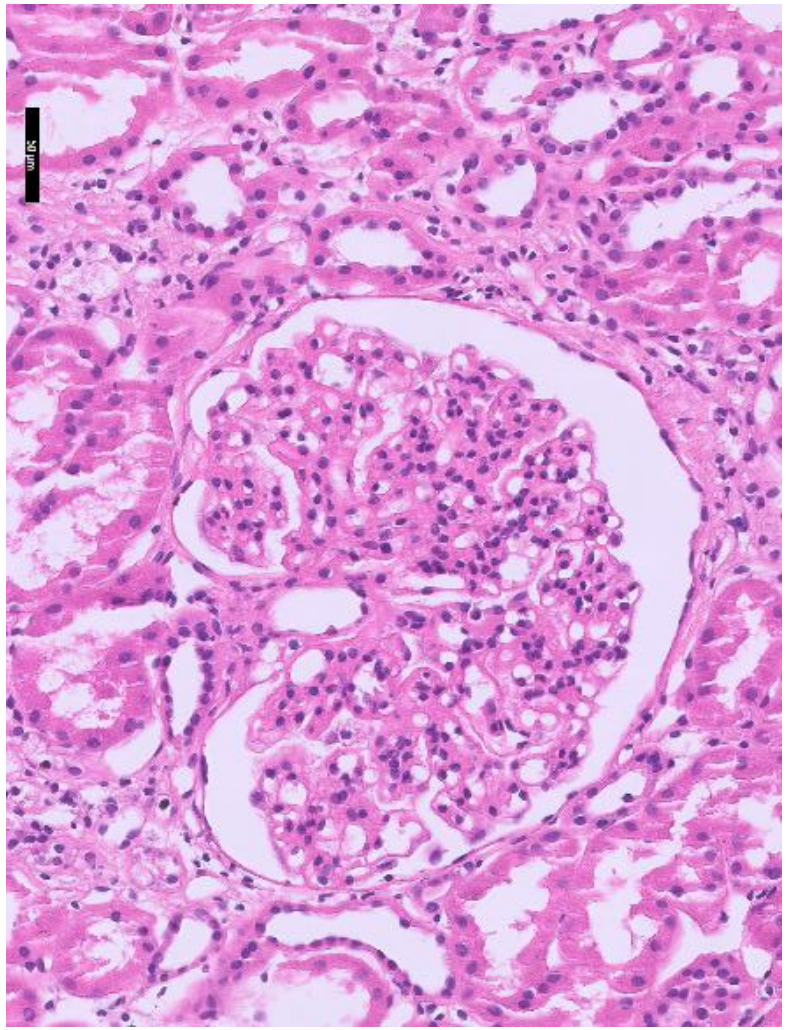


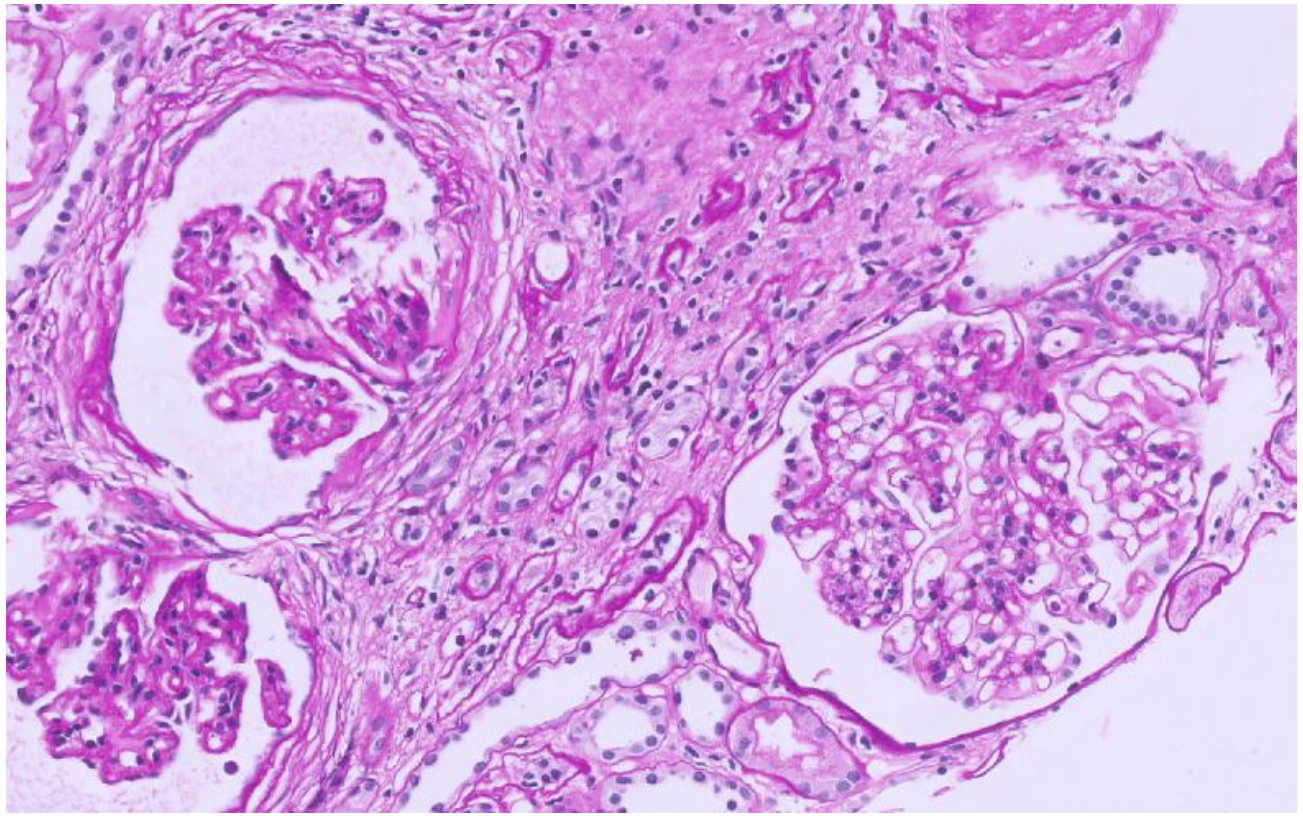
Why recurrence of proteinuria
despite
further improvement of GFR?

Second renal biopsy

90 weeks after first biopsy

53 weeks after start
Pegcetacoplan





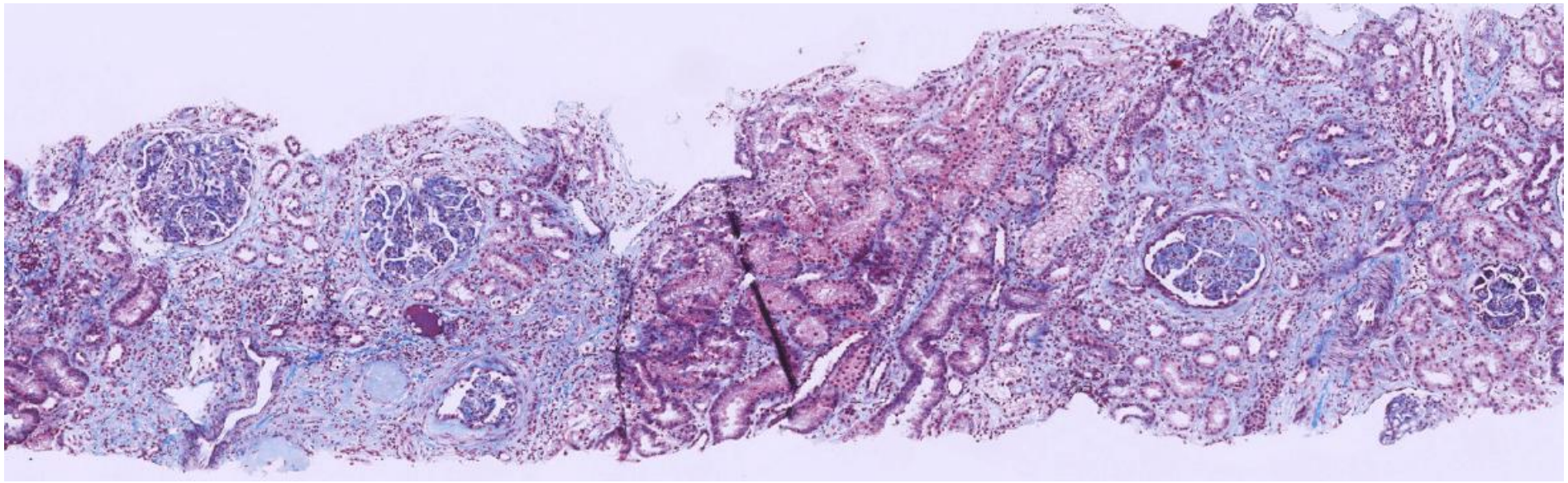
Reduced inflammatory activity

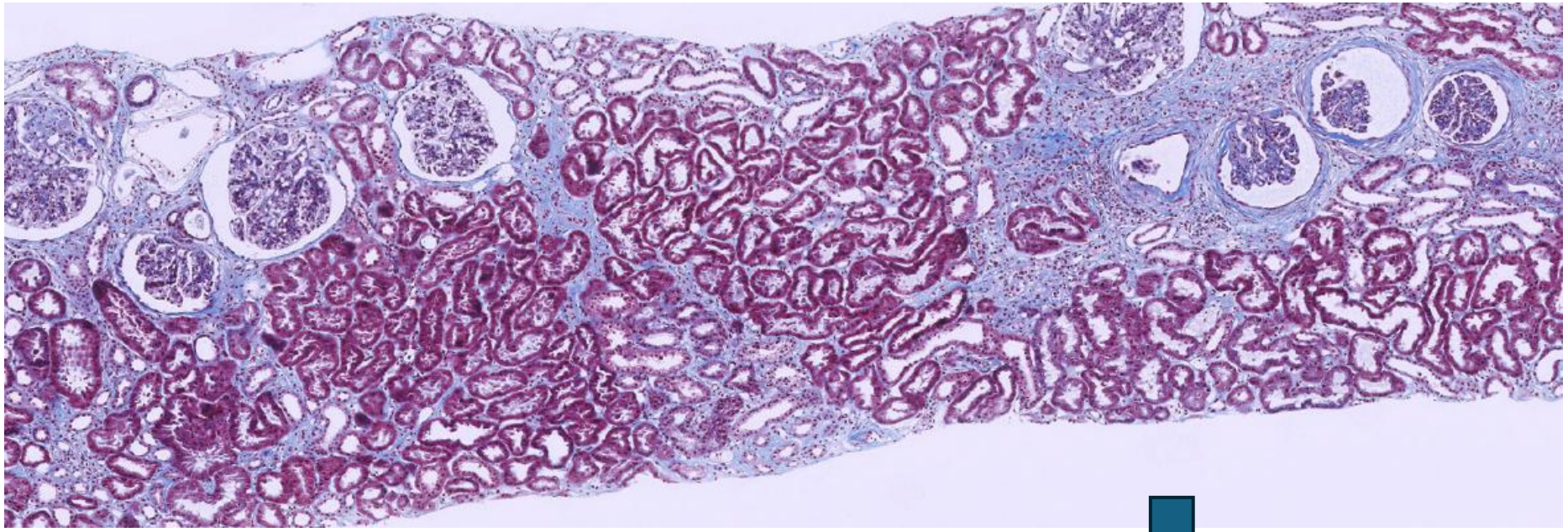
Less mesangial hypercellularity

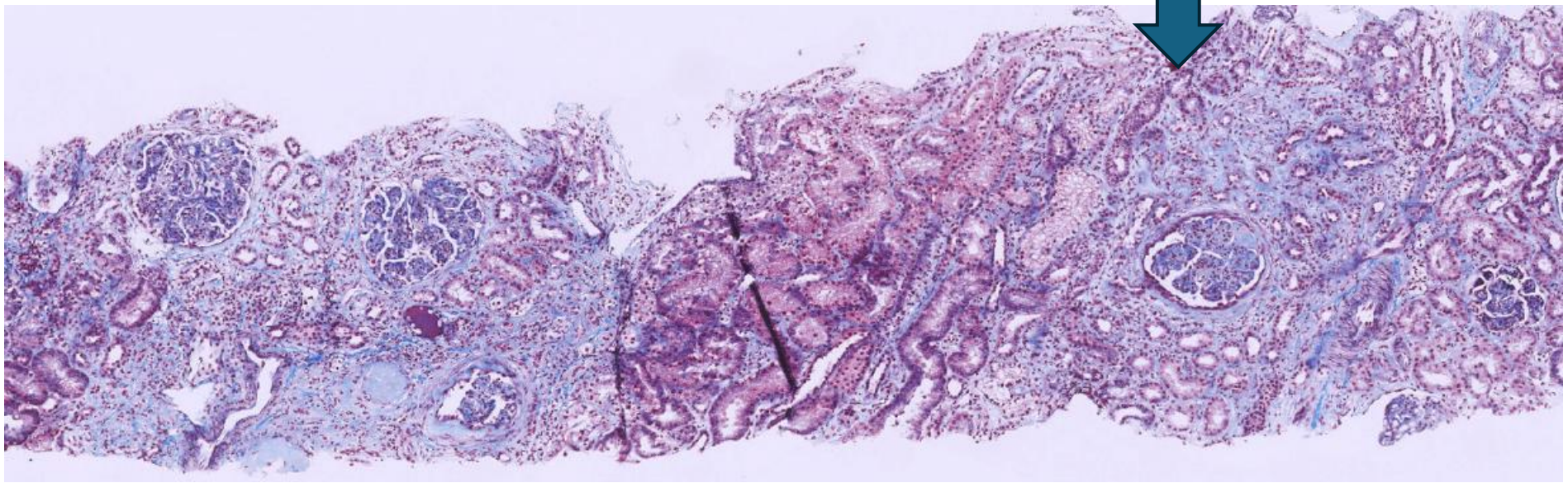
No more endocapillary hypercellularity

Progression of glomerulosclerosis, fibrosis and chronicity

Possible CNI toxicity?







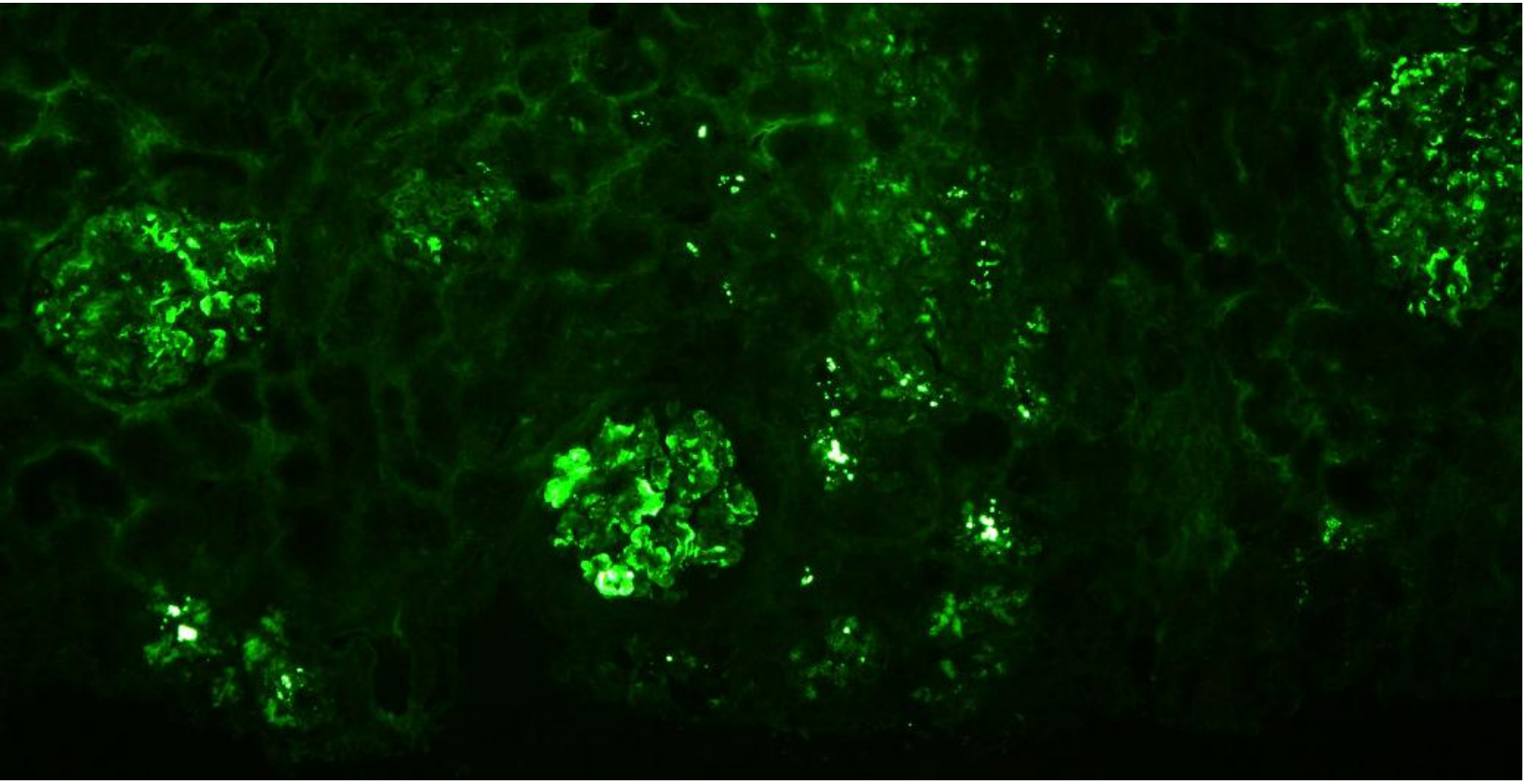
Shift to chronic scarring,

6/11 glomeruli globally sclerosed

Tubulo-IS fibrosis 50%

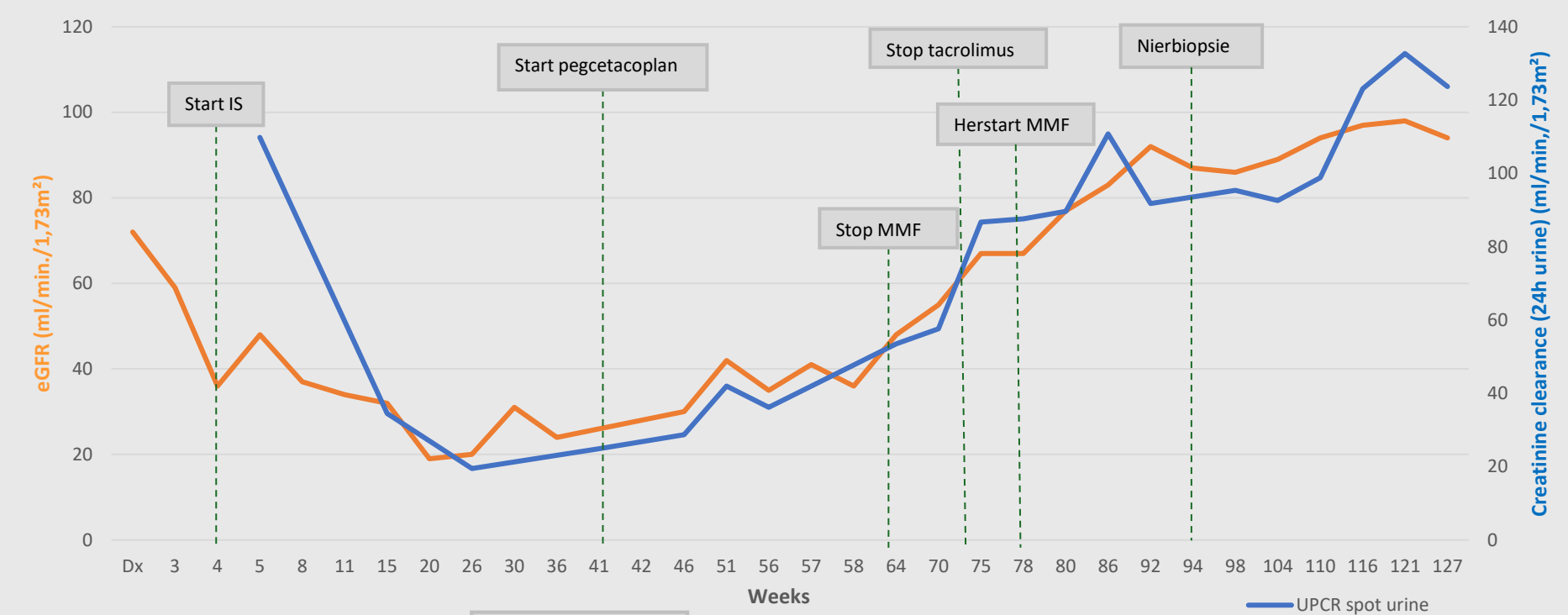
Sethi 7/10

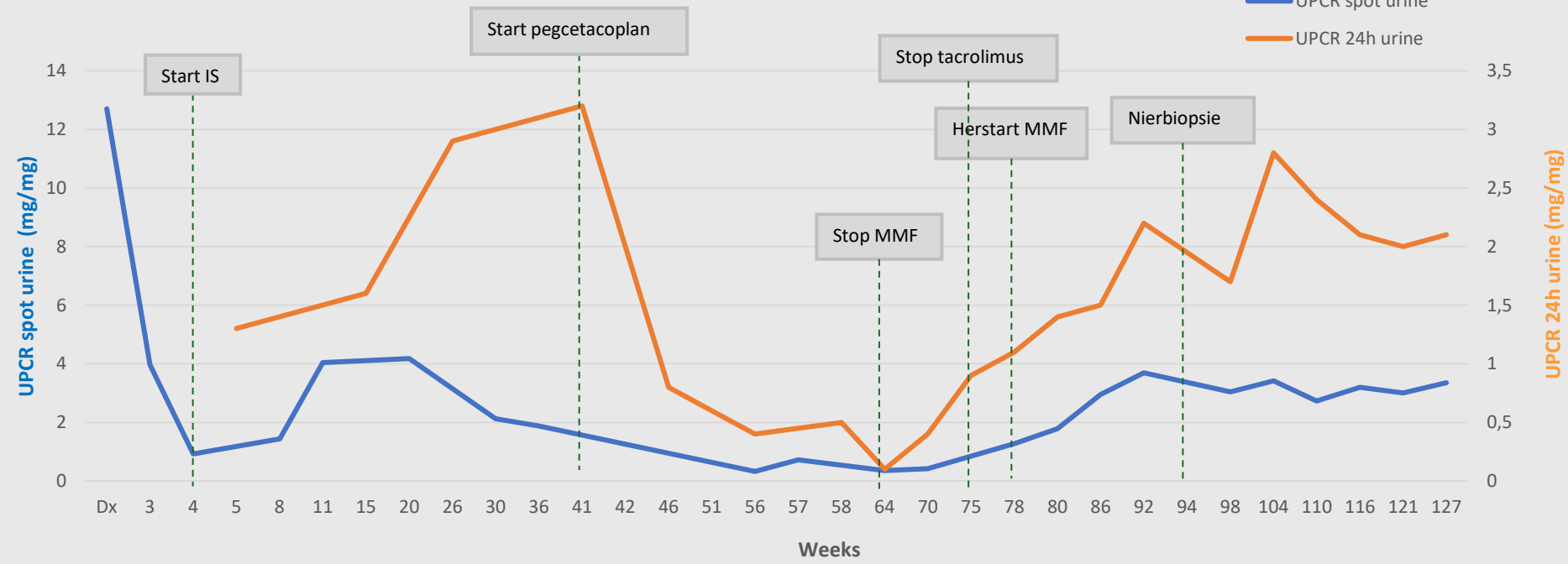
C3



IF:
Still
strongly
positive
C3

(C3c)


Start IS
Start pegcetacoplan
Stop tacrolimus
Herstart MMF
Nierbiopsie
Stop MMF
eGFR (ml/min./1,73m²)
Creatinine clearance (24h urine) (ml/min,/1,73m²)
Dx 3 4 5 8 11 15 20 26 30 36 41 42 46 51 56 57 58 64 70 75 78 80 86 92 94 98 104 110 116 121 127
Weeks


UPCR spot urine
UPCR 24h urine
Start IS
Start pegcetacoplan
Stop tacrolimus
Herstart MMF
Nierbiopsie
Stop MMF
UPCR spot urine (mg/mg)
UPCR 24h urine (mg/mg)
Dx 3 4 5 8 11 15 20 26 30 36 41 42 46 51 56 57 58 64 70 75 78 80 86 92 94 98 104 110 116 121 127
Weeks

Questions

-initial reduction in proteinuria due to ACEi or vasocontrictive effect of Tacrolimus?

-Recurrence proteinuria after stop MMF and tacro?

Due to chronic TIS damage? But no microglobulinuria

Due to hyperfiltration?

Progression of chronic fibrosis:

Biased by timing biopsies?

Tacrolimus toxicity?

-IF still strongly positive for C3c despite adult dose of Pegcetacoplan?

-Do we tolerate this proteinuria or do we restart Tacrolimus (other auto-immune ‘clone’ as cause of recurrent proteinuria after stopping Tacrolimus ?)