



**28° Congresso Nazionale  
della SOCIETÀ ITALIANA di  
NEFROLOGIA PEDIATRICA**

**24-26 Ottobre 2012**

**14.30 - 16.30**  
*Coordinatore:*  
*Moderatori:*

**CASI ANATOMO-CLINICI INTERATTIVI**  
*C. Pecoraro (Napoli)*  
*C. Pecoraro (Napoli) - A. Onetti Muda (Roma)*

## **“Visita sportiva: una proteinuria isolata....”**

**A.Pasini**

Nefrologia e Dialisi pediatrica  
S.Orsola-Malpighi, Bologna



DONA UN SORRISO PER I PICCOLI MALATI DI RENE  
*il sogno di stefano*

## **Matteo 10 anni**

Inviato dalla pediatra per riscontro occasionale di  
proteinuria isolata (30mg/dL) all'es.urine, eseguito per  
visita sportiva e confermato in 2 controlli ravvicinati

## ***1° visita ambulatoriale nefrologica***

- An. familiare: negativa
- An. pat. remota: negativa per patologie di rilievo

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A domicilio

***Es.ematici*** recenti: funzione renale n.n.(creat. 0,5mg/dL)  
**eco reni** + vie urinarie: nella norma  
**PA** dal curante sempre nella norma

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**PA** dal curante sempre nella norma

Es. obiettivo      Buone condizioni generali,  
buona crescita staturo-ponderale (h 145.5cm, kg 50.3kg)  
PA 143/75 (agitato)

**Stix urine**: PS 1015, pH 5.5, **Prot. ass., Hb ass.**

## *Esami prescritti a domicilio*

Proteinuria 24 ore

tot. **180** mg/die  
(3.8 mg/kg/die)

## *Esami eseguiti a domicilio*

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Raccolta urine	<u>orto</u> <b>190</b> mg	<u>clino</u> <b>63</b> mg	tot. <b>253</b> mg/die (5.3 mg/kg/die)
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**6 mesi dopo...**

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**6 mesi dopo...**

Raccolta urine	orto <b>1950</b> mg	PrU/CrU 3.0 mg/mg
	clino <b>950</b> mg	PrU/CrU 2.6 mg/mg
<hr/>		
<b>2900</b> mg/die		

## Ricovero

- Buone condizioni cliniche, non edemi. PA 108/60mmHg.  
h 148cm (25°-50° P), 50.800kg (75°P).

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- **Emocromo:** GB 8610, GR 4,18, Hb 11, PTL 334.000.
- **Urea** 42mg/dL, **creatinina** 0.7mg/dL,
- **Prot. Tot** 6.1g/dL, **Albumina** 3.2g/dL,
- **Col tot** 267mg/dL, **TGL** 119mg/dL.
- **IgG** 861, **IgA** 142, **IgM** 164 (mg/dL).

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- **C3** 17mg/dL (90-180), **C4** 32mg/dL(10-40),
- **AntiNucleo, AntiDNA, ENA, c-Anca, p-Anca:** neg.
- **Ricerche virali** (HAV-HBV-HCV-CMV-EBV-Adeno-Entero): neg.

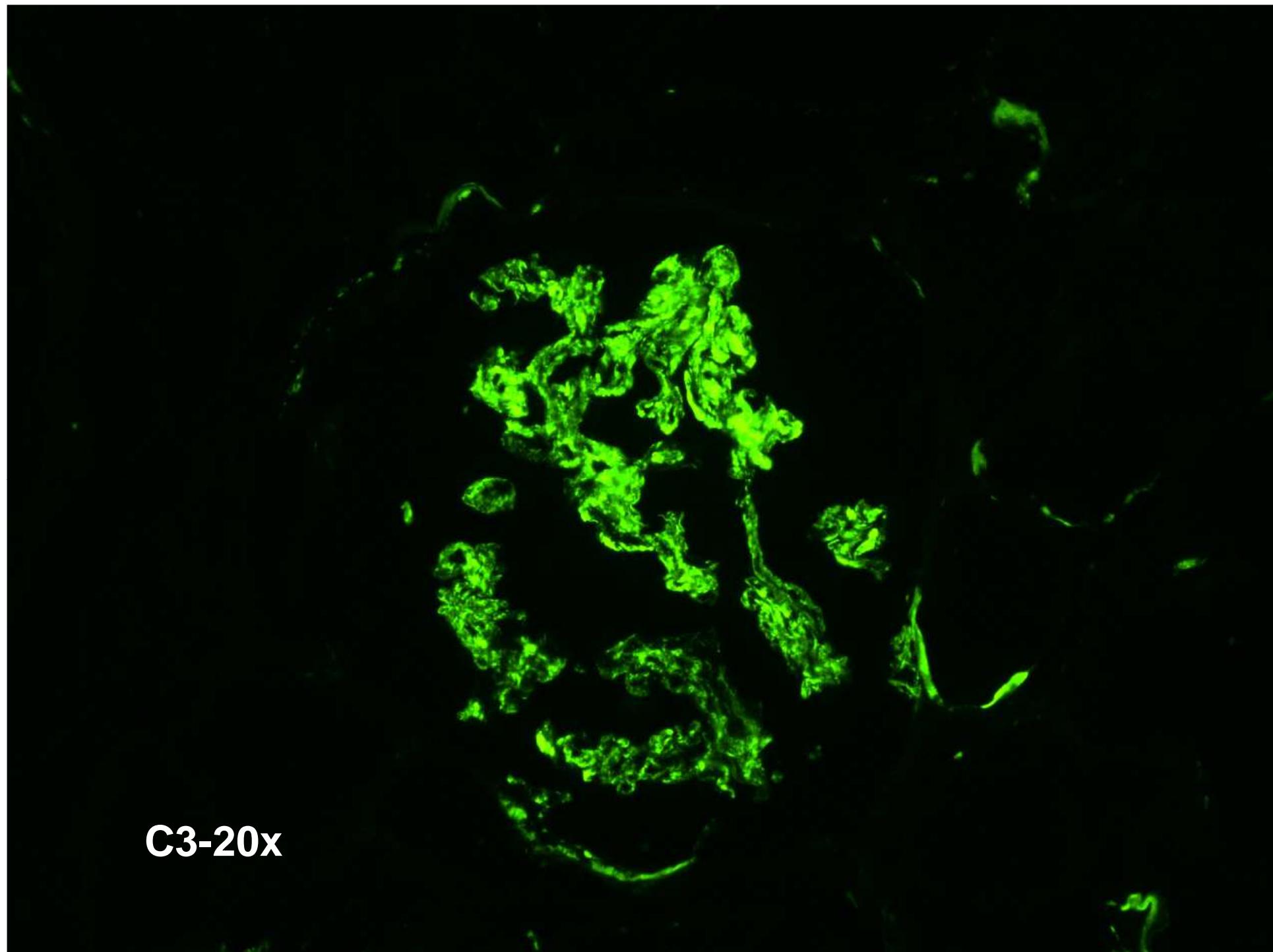
# Ricovero

- Buone condizioni cliniche, non edemi. PA 108/60mmHg.  
h 140cm (25° P), 30.800kg (> 25°P).
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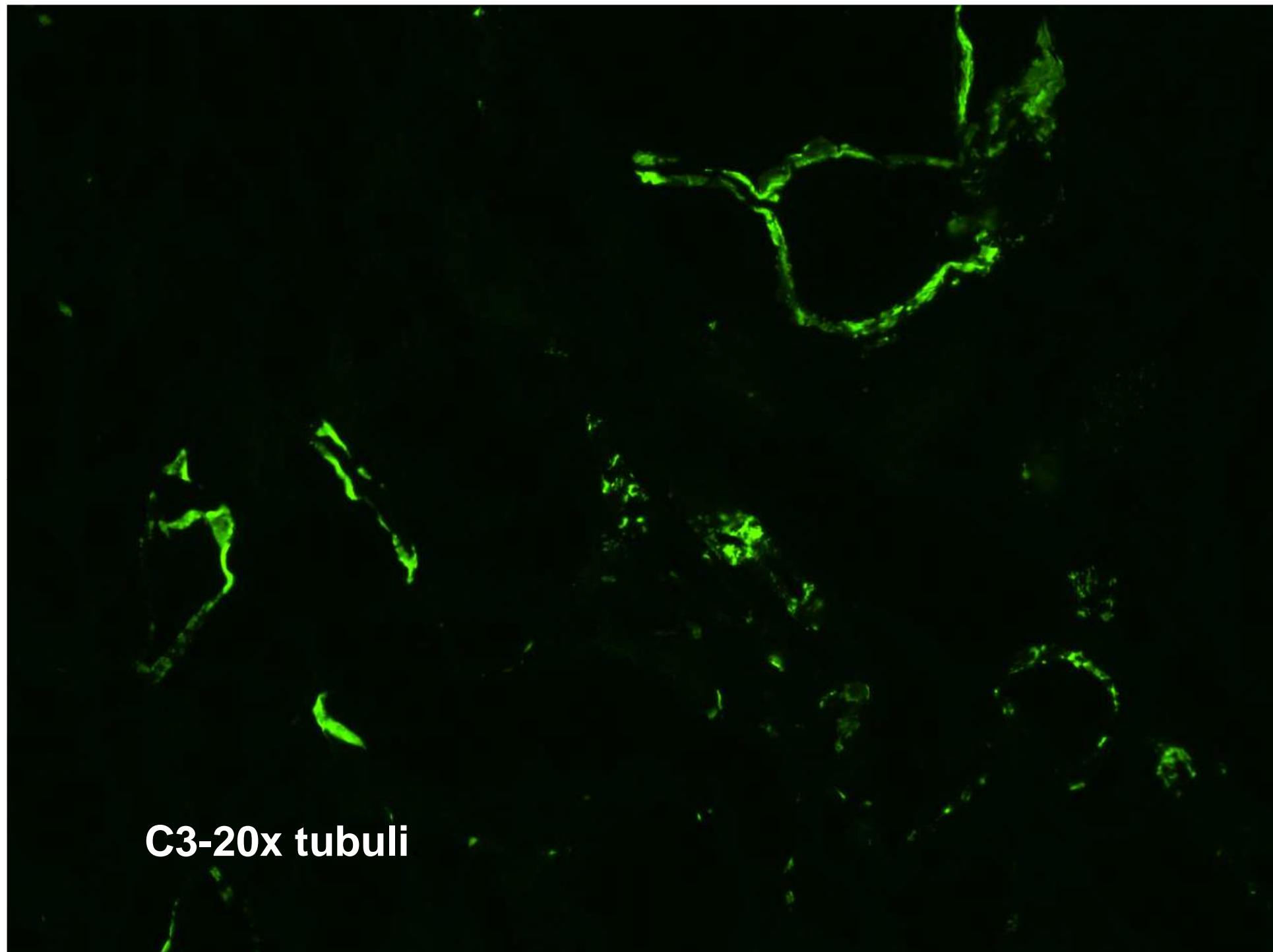
- **Proteinuria 4026 mg/die, PrU/CrU = 3.4mg/mg**
- **Es.urine:** PS 1016, pH6, **Alb 300mg/dL, Hb >0.6mg/dL**

# **Biopsia renale**

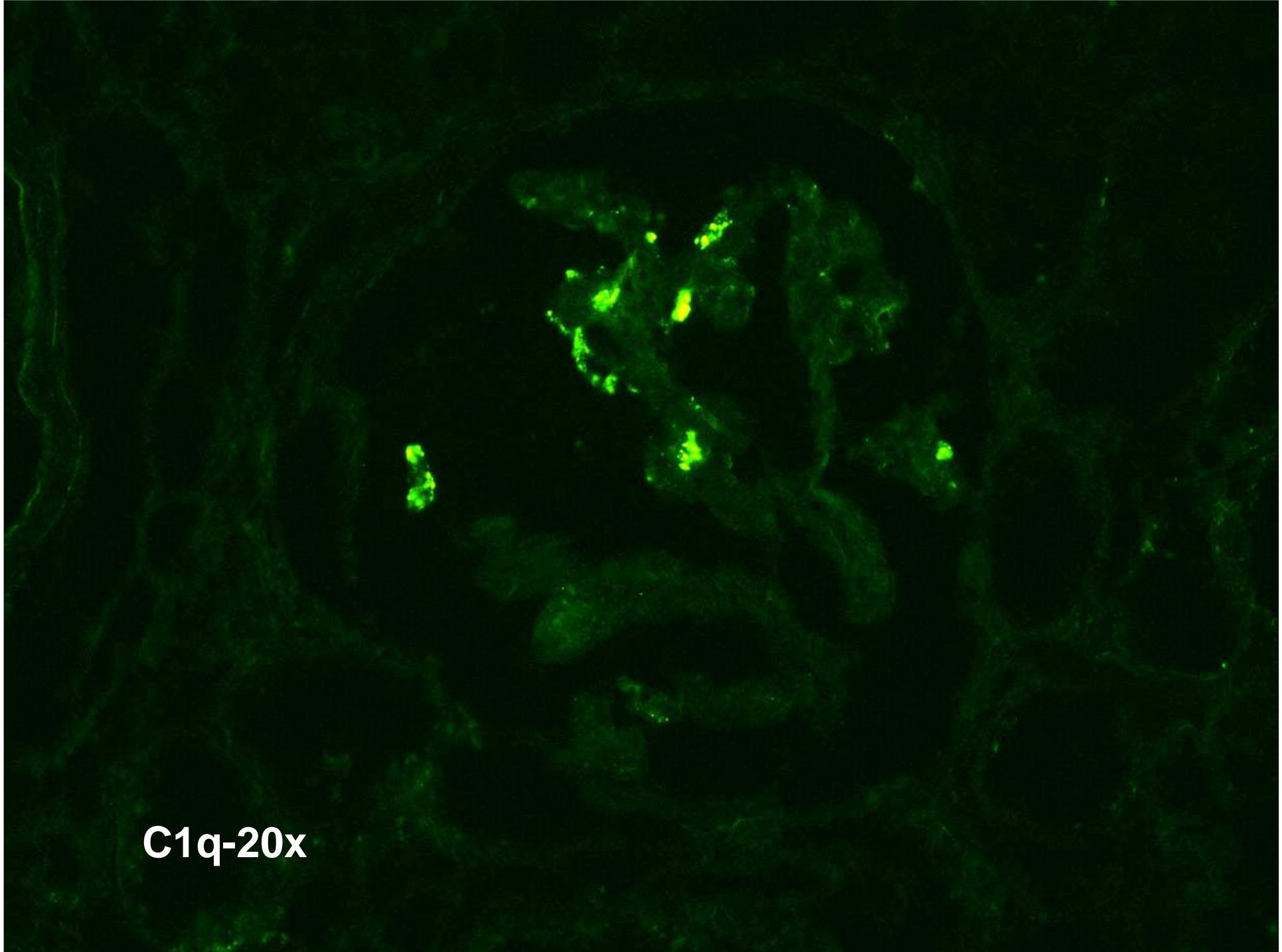
## **Immunofluorescenza**



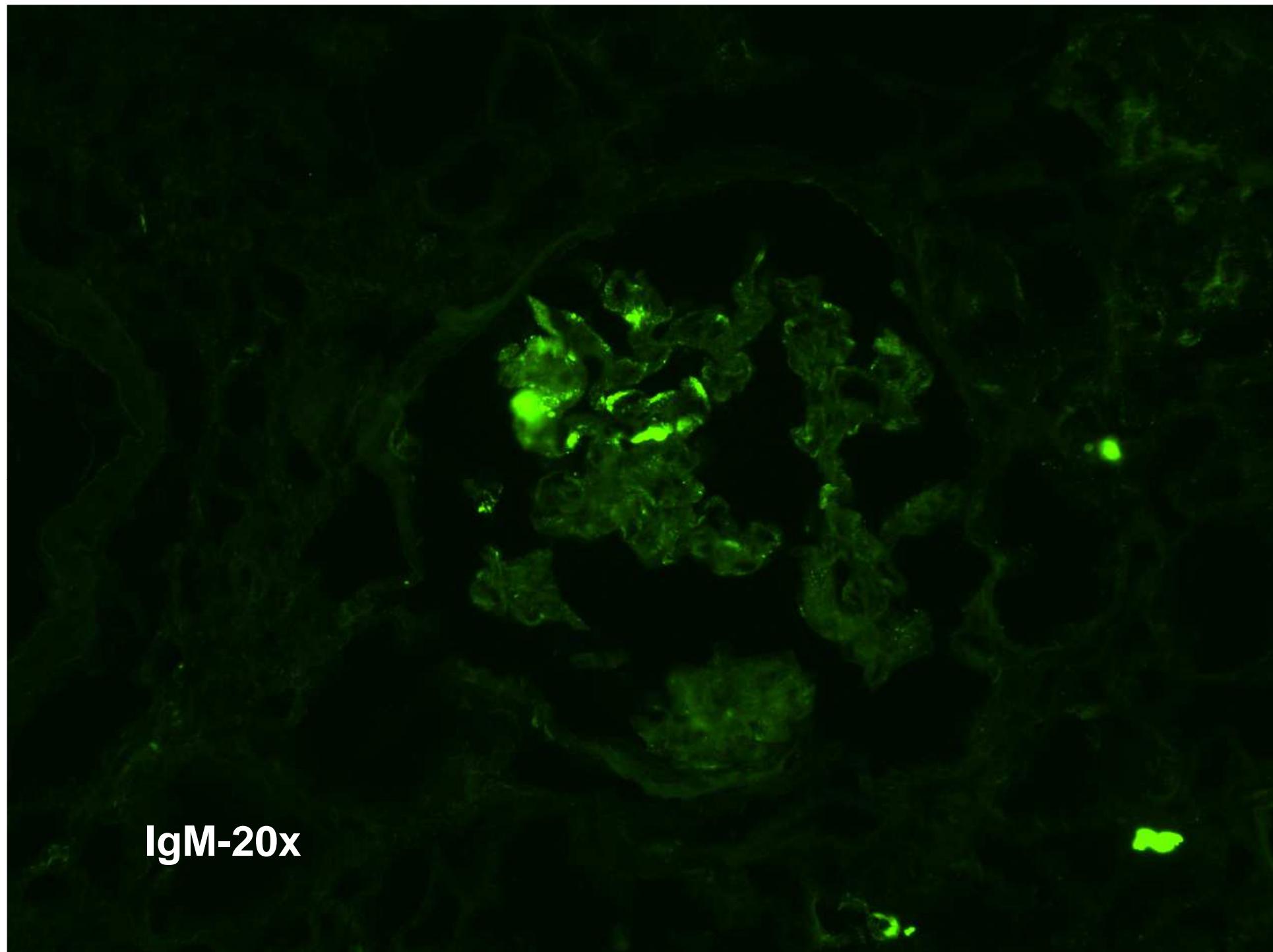
**C3-20x**



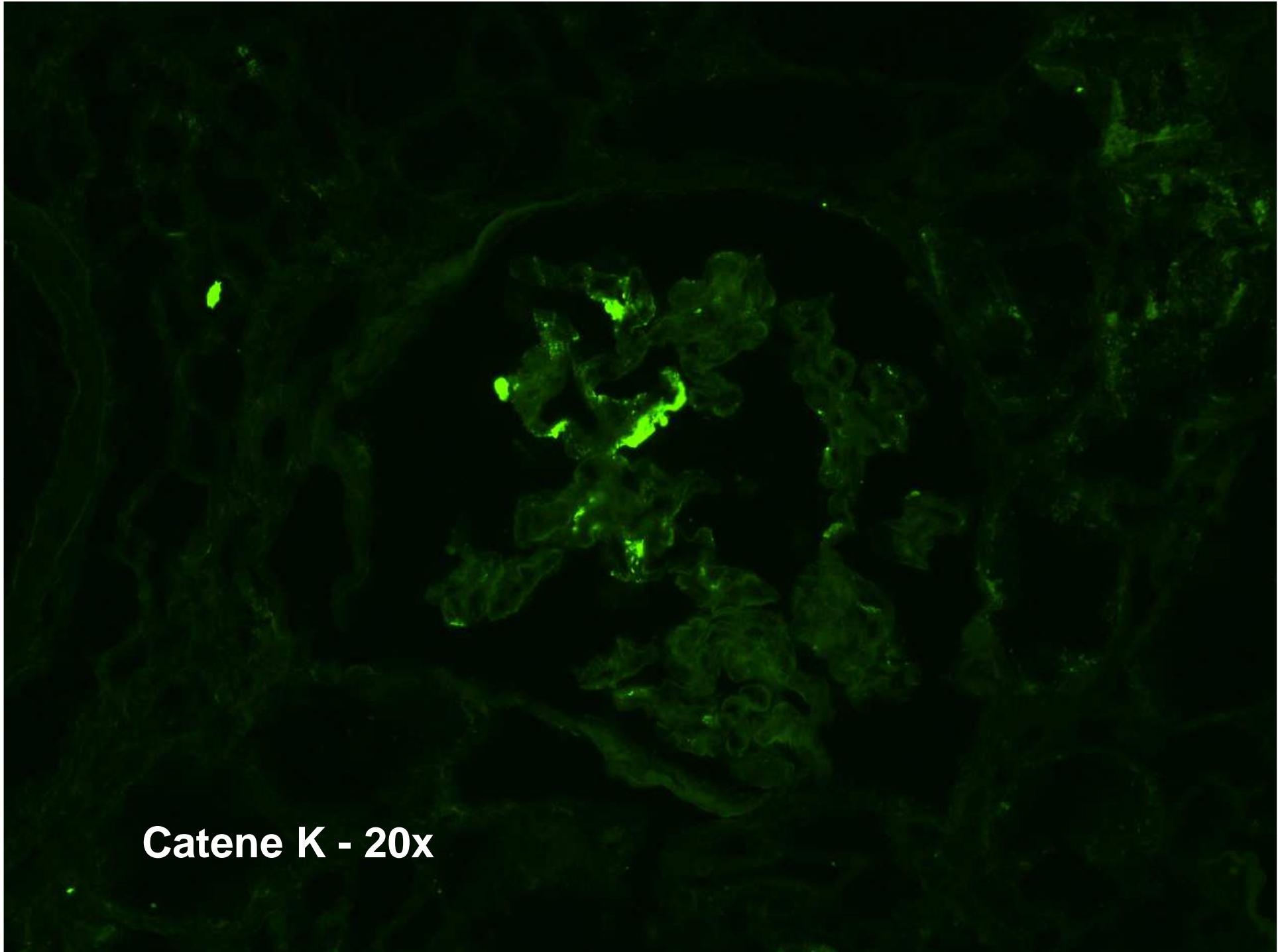
C3-20x tubuli



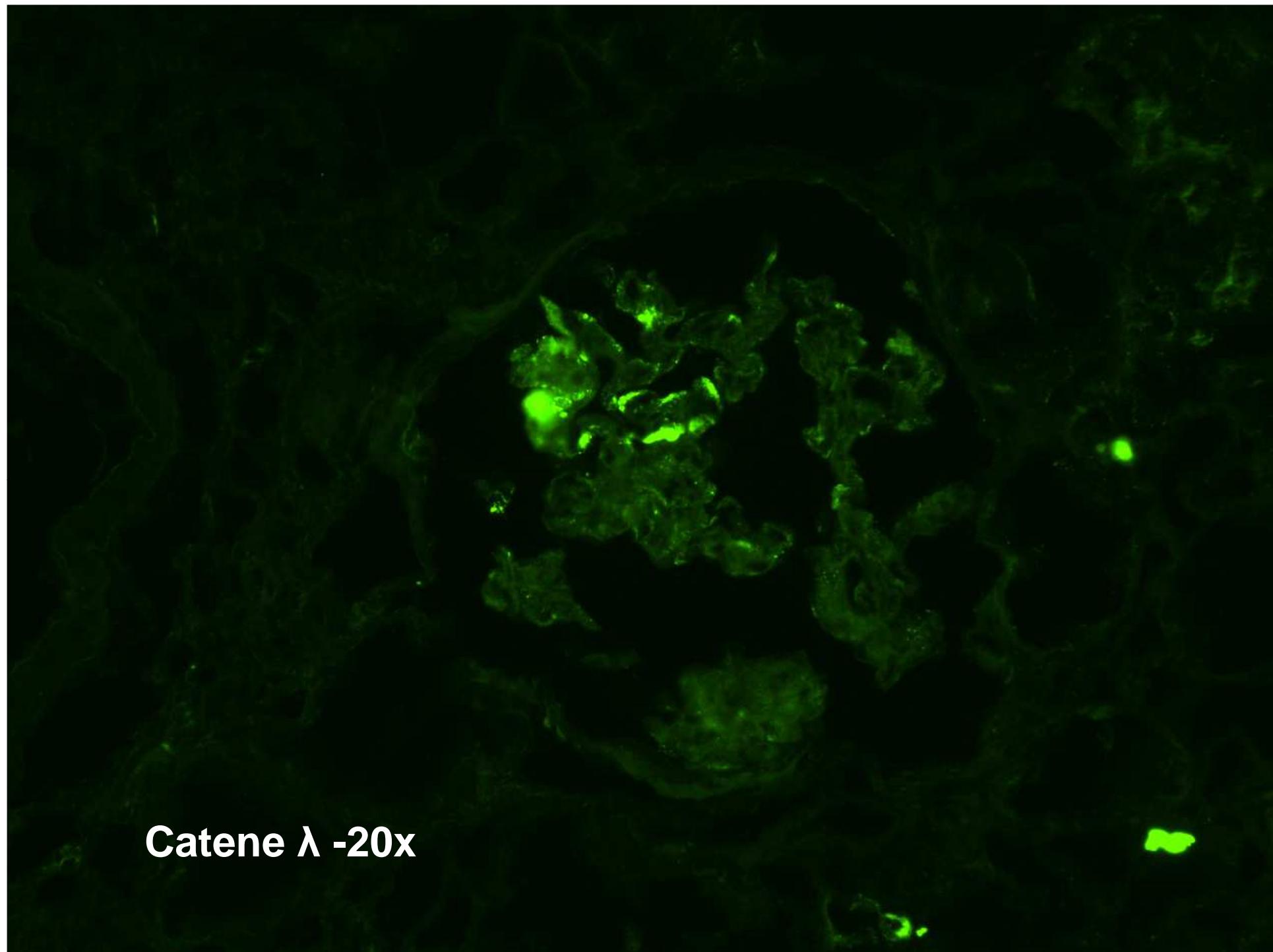
C1q-20x



IgM-20x



**Catene K - 20x**

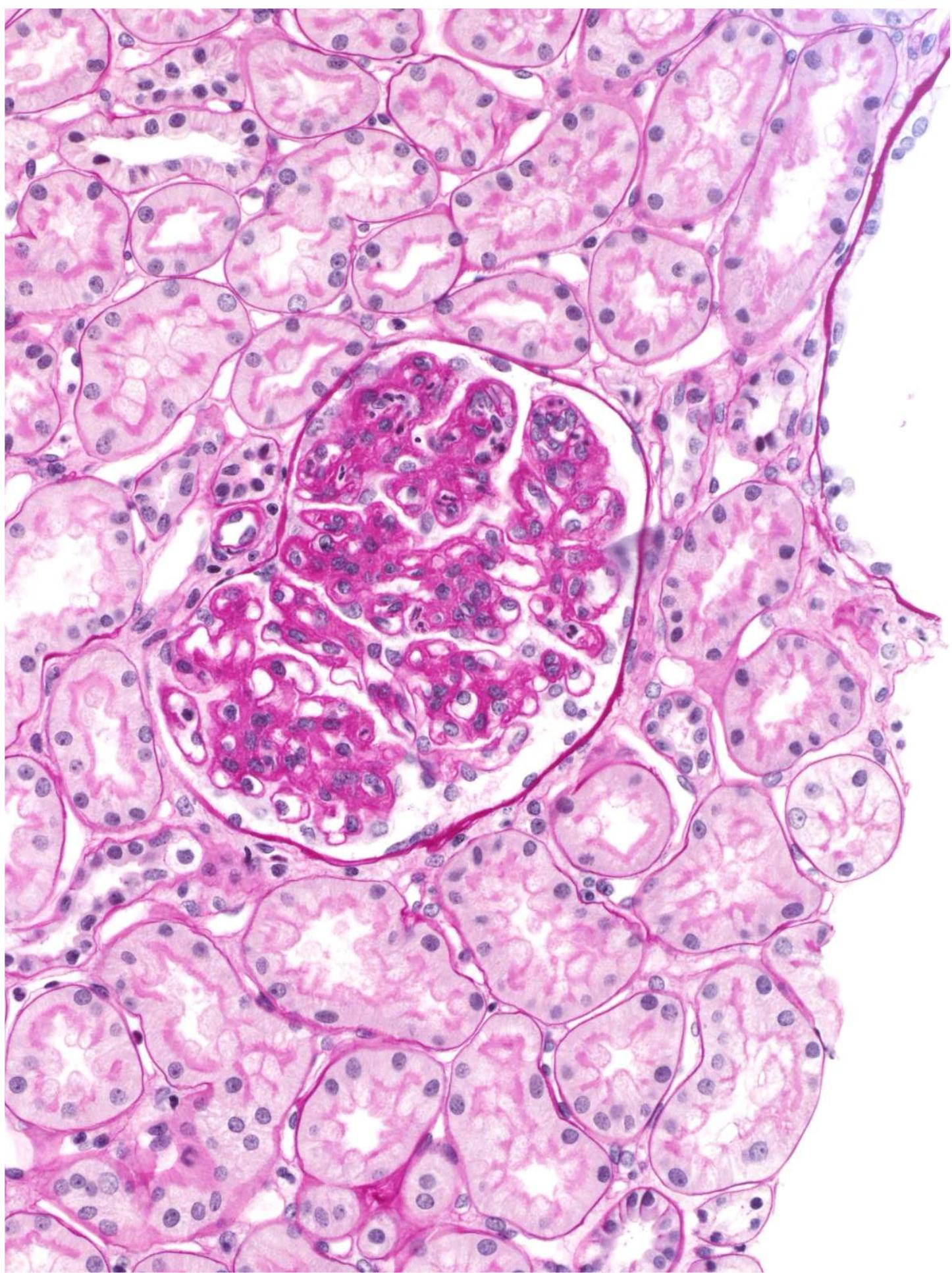


**Catene  $\lambda$  -20x**

# **Biopsia renale**

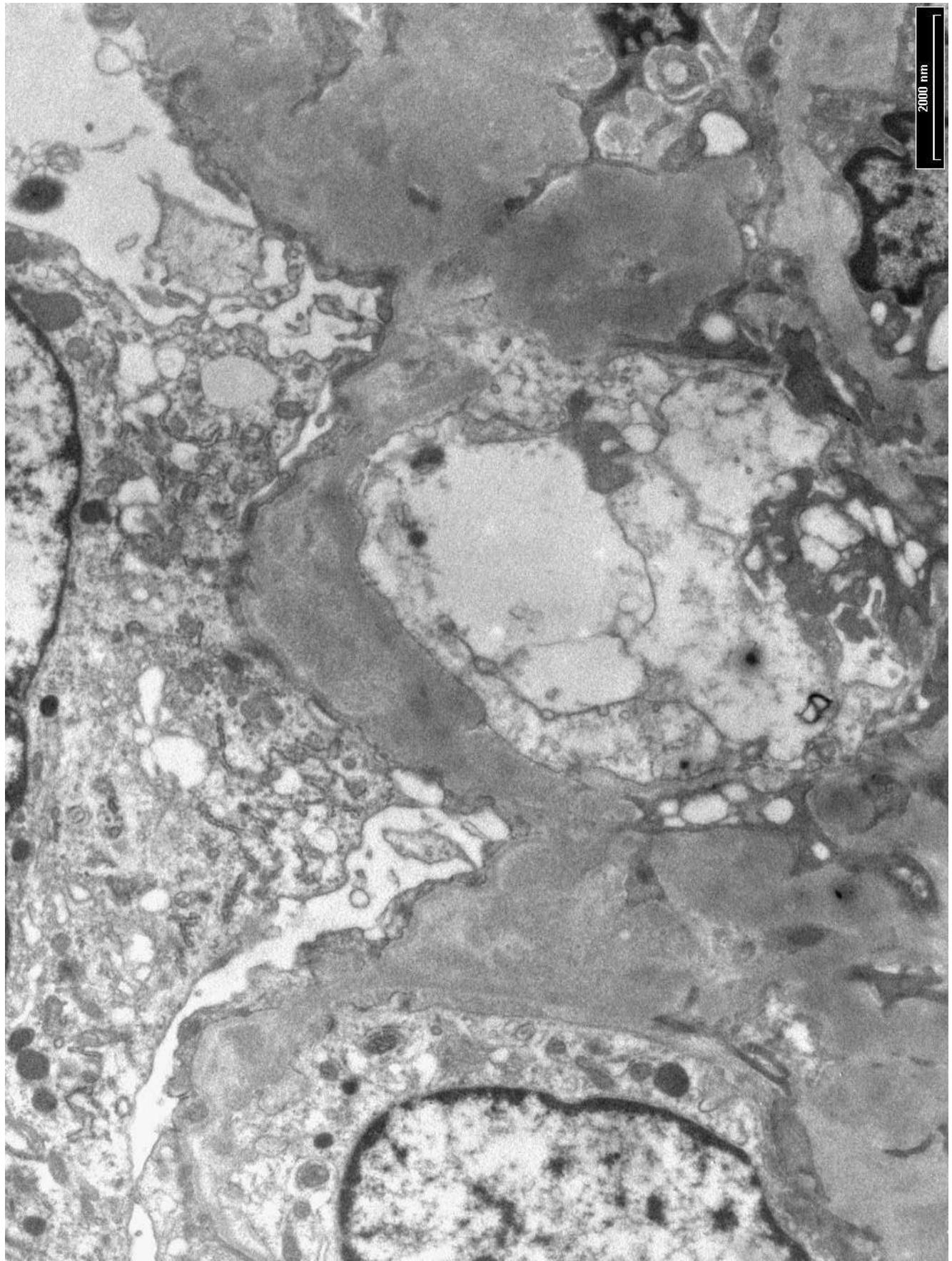
## **Microscopia Ottica**

**(13 glomeruli)**



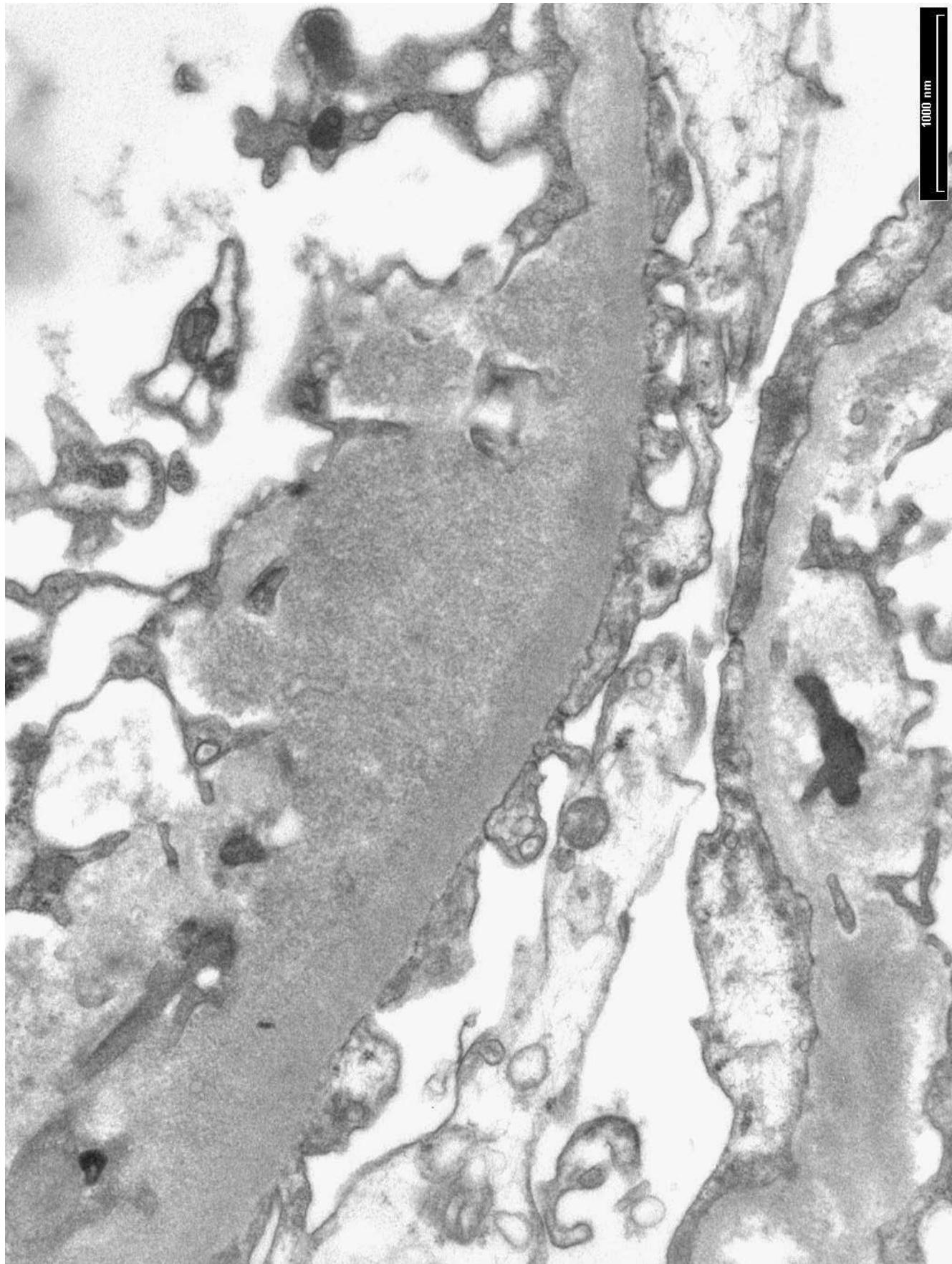
**Biopsia renale**

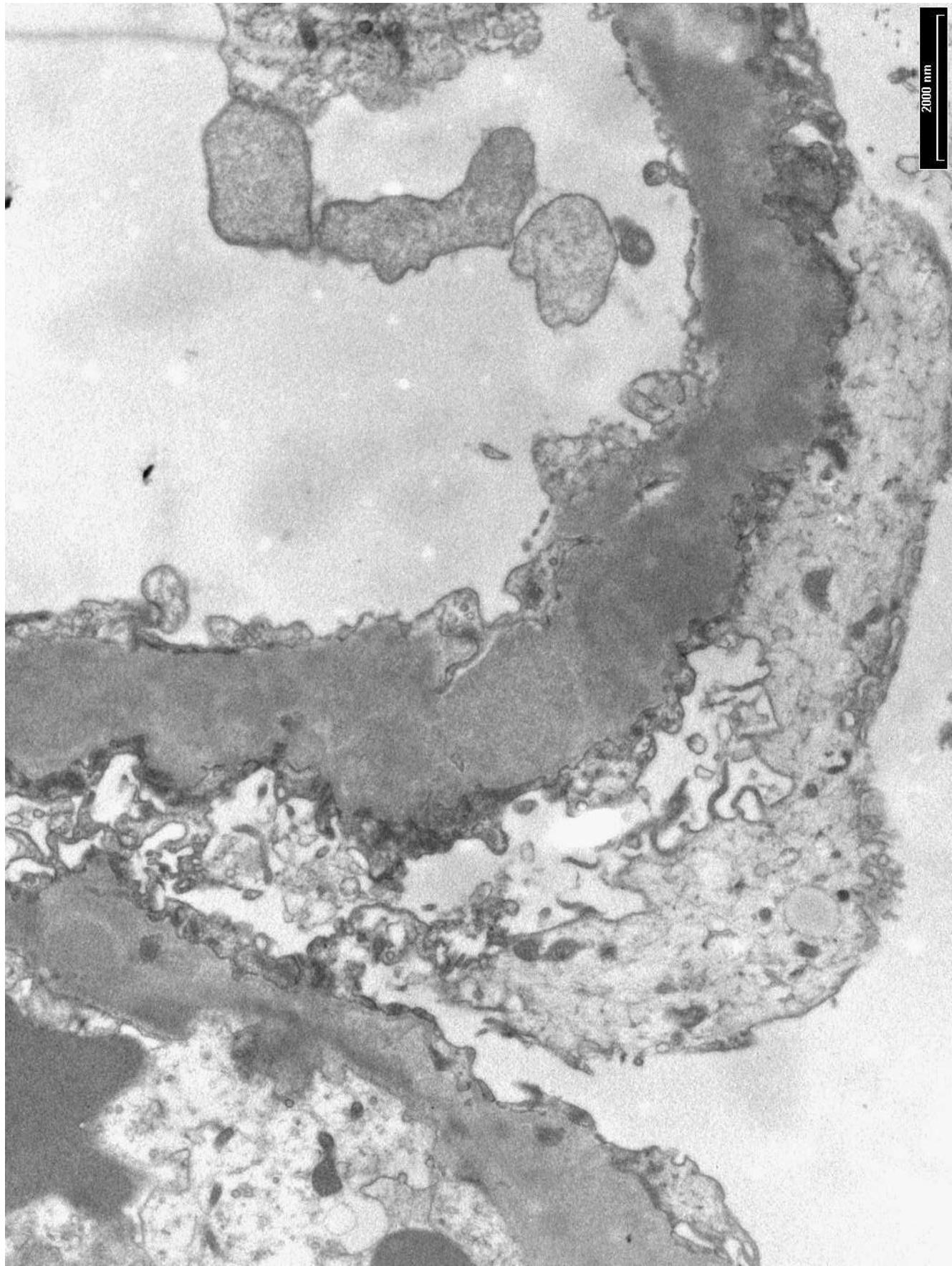
**Microscopia Elettronica**





1000 nm





## Terapia e follow-up

Matteo esegue un prelievo per lo studio delle anomalie del complemento

**Foo ed OCT** (Ocular Coherence Tomography): n.n.

Nel frattempo inizia terapia con ACE-inibitore (ramipril), ed esegue controlli quindicinali delle urine:

**PrU/CrU= 4,2 - 2,8 - 2,25 - 1,6 - 2,9 mg/mg,**  
che non mostrano un significativo miglioramento

# Studio delle anomalie del complemento

<u>Mutazioni genetiche/varianti alleliche</u>		<u>Autoanticorpi</u>	
C3	= in corso/	C3Nef	= in corso
Factor H	= neg (esone 22 in corso)	Anti Factor H	= /
Factor I	= in corso	Anti Factor I	= /
Factor B	= in corso	Anti Factor B	= /
MCP/CD46	= in corso		
CR1	= /		
CFHR3-1	= /		
CFHR5	= /		

# Studio delle anomalie del complemento

## Mutazioni genetiche/varianti alleliche Autoanticorpi

C3	= in corso/	C3Nef	= in corso
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MCP/CD46	= in corso		
CR1	= /		
CFHR3-1	= /		
CFHR5	= /		

Paziente	Data di nascita	Diagnosi	sC5-b9 ng/ml	Valori Normali ng/ml
----- <b>MATTEO</b>	<b>07/11/1999</b>	<b>GNMP</b>	<b>3523</b>	<b>127-303</b>

## C3GN\DDD: quale terapia?

- ACE-inibitori, ARB
- Plasmaferesi, plasma exchange
- Anticoagulanti: Eparina, warfarin, aspirina + dipiridamolo, sulodexide
- PDN, Metilprednisolone
- Immunosoppressori: CsA, Tc, MMF, CPM, Aza
- Anticorpi monoclonali
  - Rituximab
  - Eculizumab
  - Celldex (CDX-1135)

# Terapia DDD

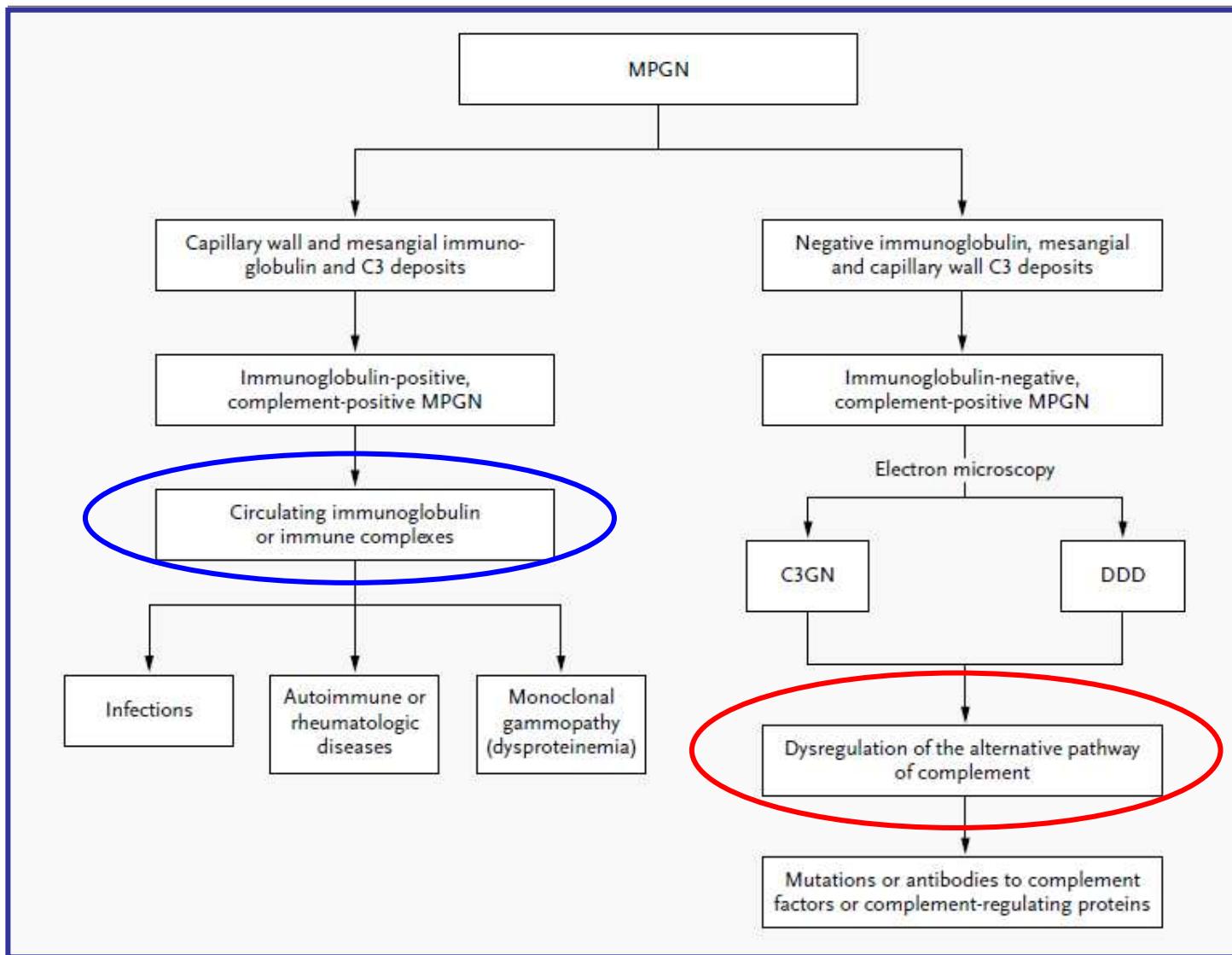
Medication	n	Percentage
Antihypertensives		
ACE Inhibitors	76	77.6
ARB/CCB	6	6.1
Non-ACE Inhibitors (excluding ARB/CCB)	13	13.3
Steroids		
Oral prednisone ( alternate day)	54	55.1
Oral prednisone (every day)	35	35.7
Methylprednisolone	9	9.2
IV steroids	8	8.2
Diuretics	47	48.0
Anticoagulants		
Heparin	9	9.2
Aspirin	7	7.1
Plasma therapy		
Plasmapheresis	4	4.1
Plasma infusion	3	3.1
Immunosuppressives		
Mycophenolate mofetil (MMF)	4	4.1
Cyclosporin	3	3.1
Tacrolimus	3	3.1
Cyclophosphamide	4	4.1
Rituximab	1	1.0
Total	98	100.0

**Clinical features and outcomes  
of 98 children and adults with DDD**

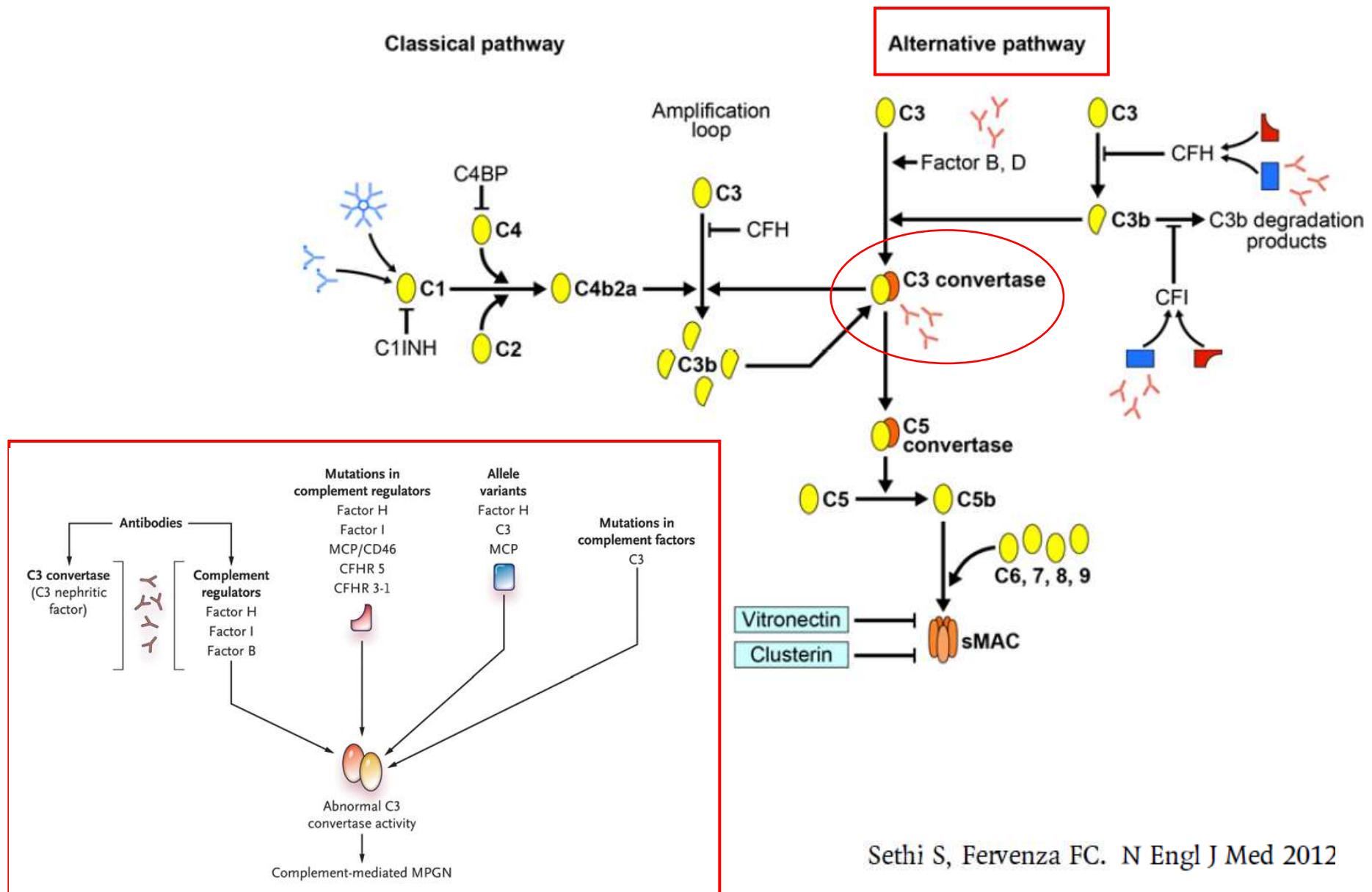
**Lu, Ped Neph 2011**

# Membranoproliferative Glomerulonephritis

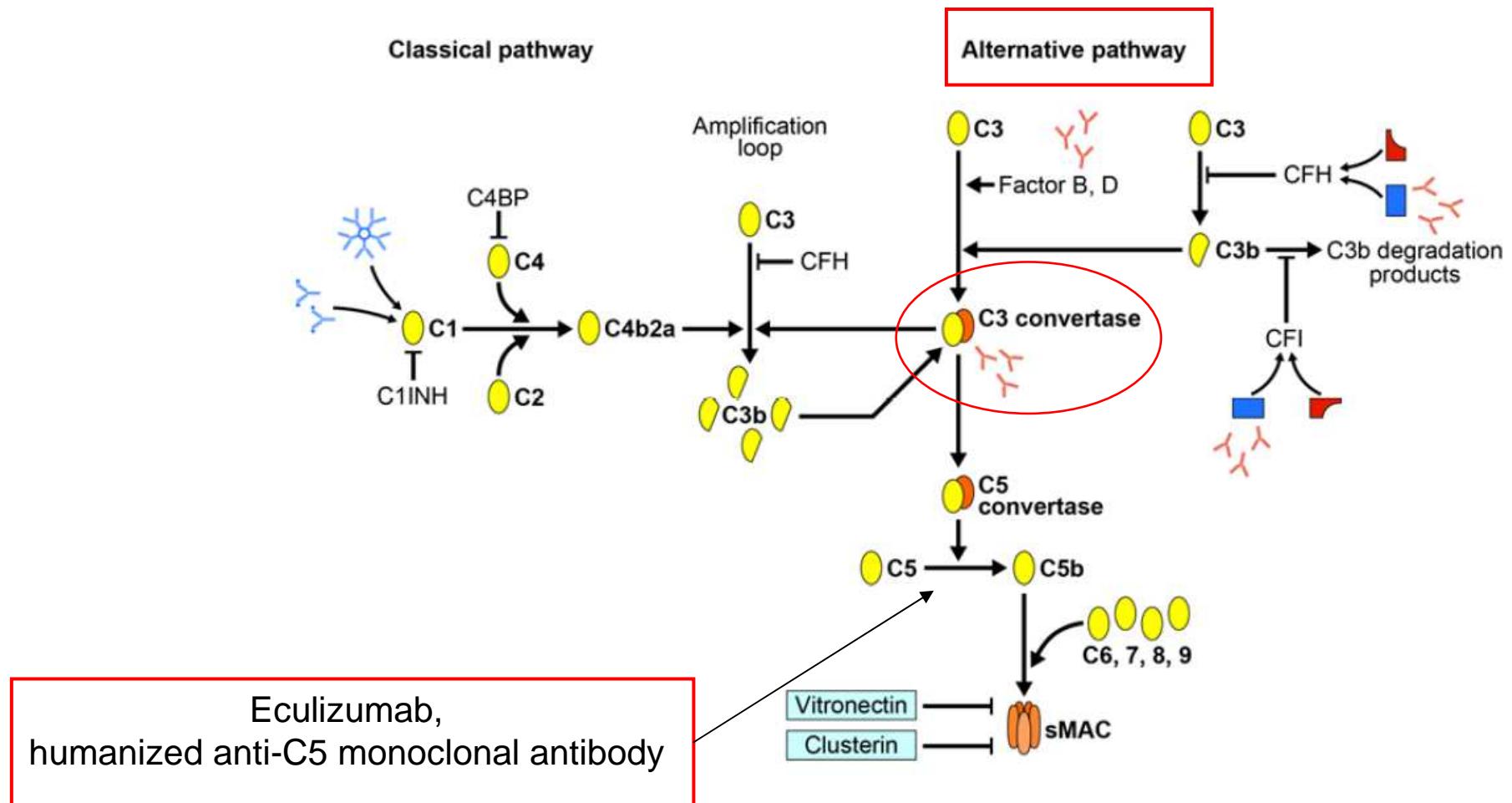
## A New Look at an Old Entity



# Complement pathway



# Complement pathway

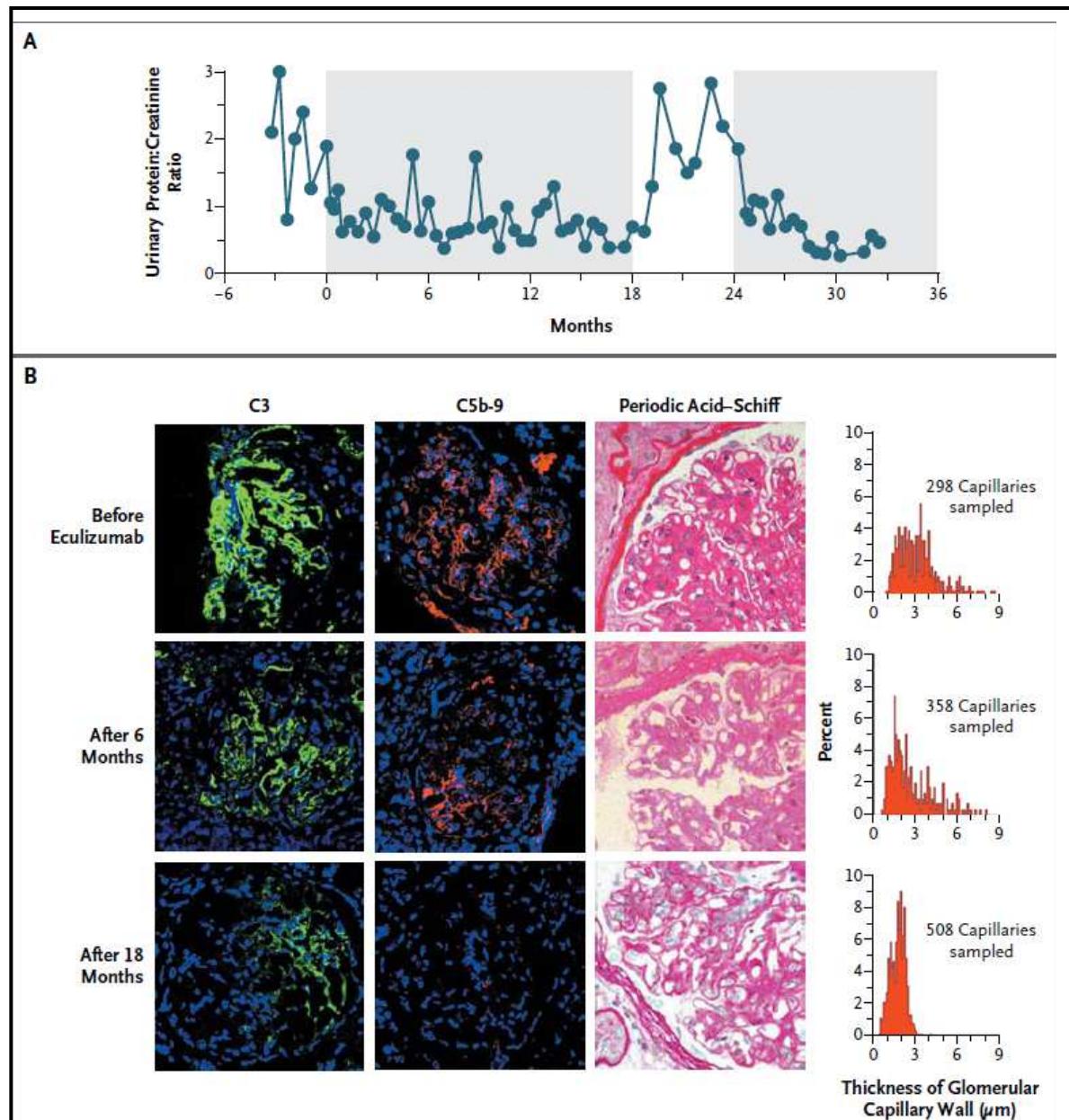


Sethi S, Fervenza FC. N Engl J Med 2012

# Eculizumab in DDD/C3GN. CASI PUBBLICATI

Pts	Reference		Risposta	Biopsia	Nativo/ Tx	sex	Età (anni)	C5b9
1	Vivarelli et al.	NEJM 2012	Yes	DDD	Native	M	17	elevated
2	Daina et al.	NEJM 2012	Yes	DDD	Native	F	22	elevated
3	Radakrishnan et al.	NEJM 2012	Yes	MPGN 1	Native	F	16	elevated
4	McCaughan et al.	AJT 2012	Yes	DDD	Tx	F	29	n.d.
5	Bomback et al.	CJASN 2012	Yes	DDD	Native	M	22	elevated
6	Bomback et al.	CJASN 2012	Yes	DDD	Tx	M	42	n.d.
7	Bomback et al.	CJASN 2012	Yes	C3GN	Tx	M	22	elevated
8	Bomback et al.	CJASN 2012	Yes	C3GN	Tx	M	20	borderline
9	Bomback et al.	CJASN 2012	No	DDD	Native	M	32	normal
10	Bomback et al.	CJASN 2012	No	C3GN	Native	M	25	normal

# Eculizumab for the Treatment of Dense-Deposit Disease



M. Vivarelli, A. Pasini, F. Emma

NEJM, 2012

# ClinicalTrials

## A) Eculizumab Therapy for DDD and C3 Nephropathy

This study is ongoing, but not recruiting participants.

**Sponsor:** Columbia University

**Collaborator:** Alexion Pharmaceuticals

**Start Date ICMJE** August 2010

**Estimated Primary Completion Date** August 2012

## B) A Pilot, Open-label Multicenter Clinical Trial of CDX-1135 in Pediatric and Adult Patients with DDD.

University of Iowa.

**CDX-1135 (by Celldex)** is a soluble, recombinant human Complement Receptor Type 1 (sCR1) that inhibits the classical, lectin and alternative complement pathways, both at the early (C3) and late (C5) activation steps in these pathways.

## A Pilot, Open-label Multicenter Clinical Trial of CDX-1135 in Pediatric and Adult Patients with DDD

### Inclusion criteria

- 4 years of age or older
- DDD as confirmed by renal biopsy **<6 months** of enrollment
- C3 serum <50% of the lower limit of normal.
- Signs of alternative pathway dysregulation (C3 breakdown products or C3Nef)

### Primary outcomes (at the end of the 26-week treatment period)

- 1 proteinuria dropped by at least 50% or to a level of <2 g/day
- 2 Serum creatinine improved by 25% or more.