

ORGANIZADO POR:

Evidenze

Lo que revela el tejido: Biomarcadores en la biopsia renal

Dr. Pablo Cannata |

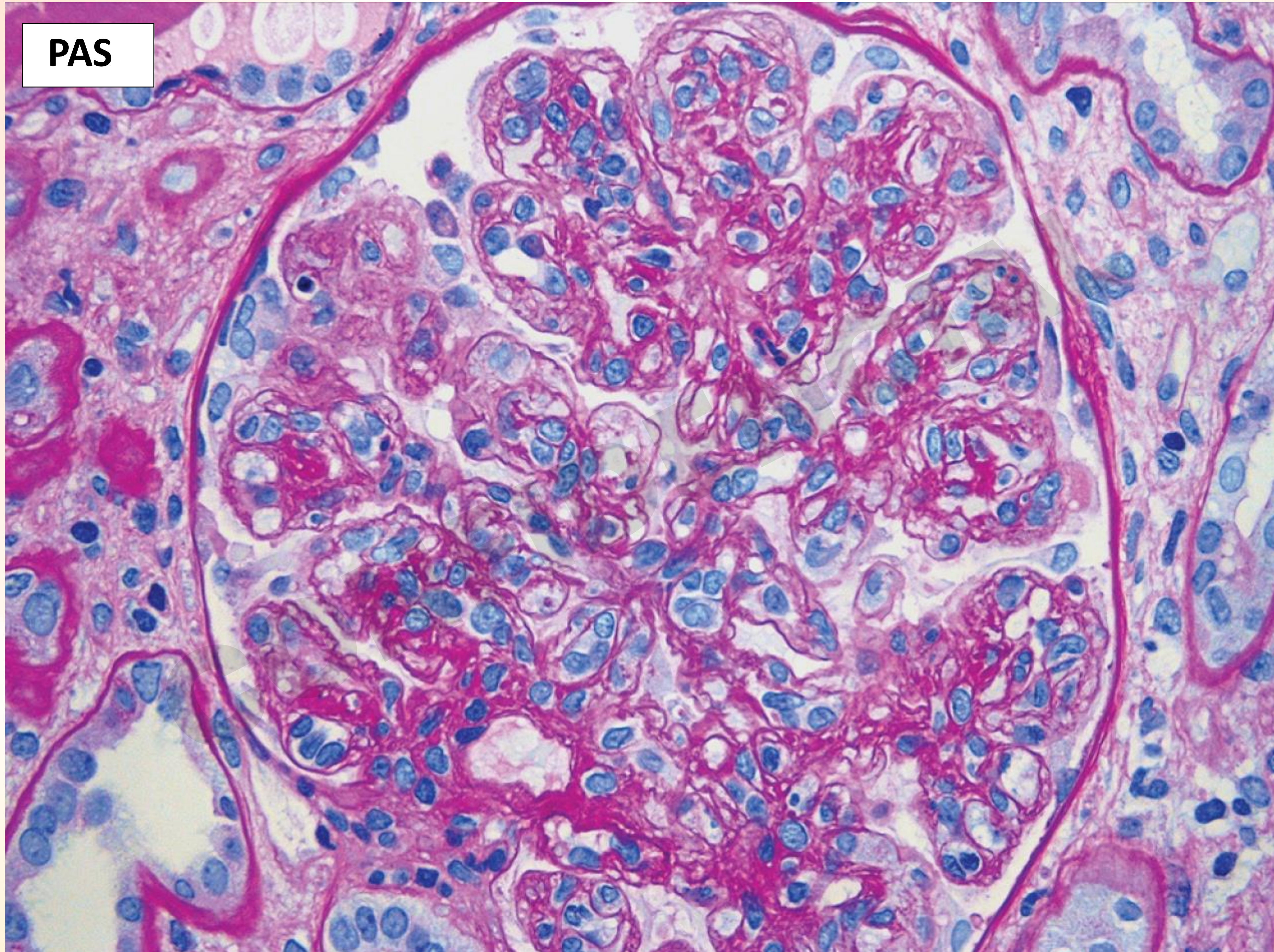
Hospital Universitario Fundación Jiménez Díaz, Madrid

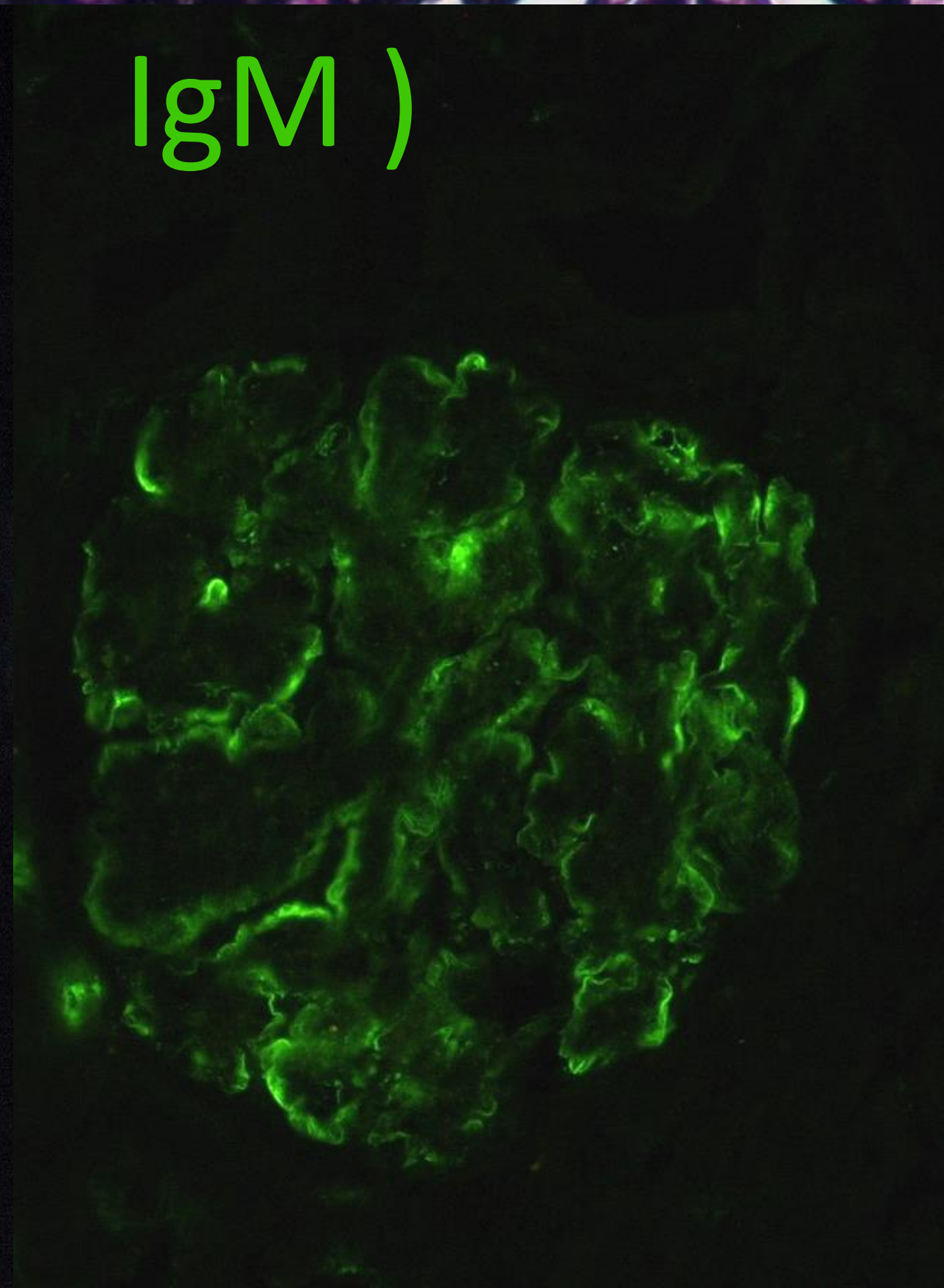
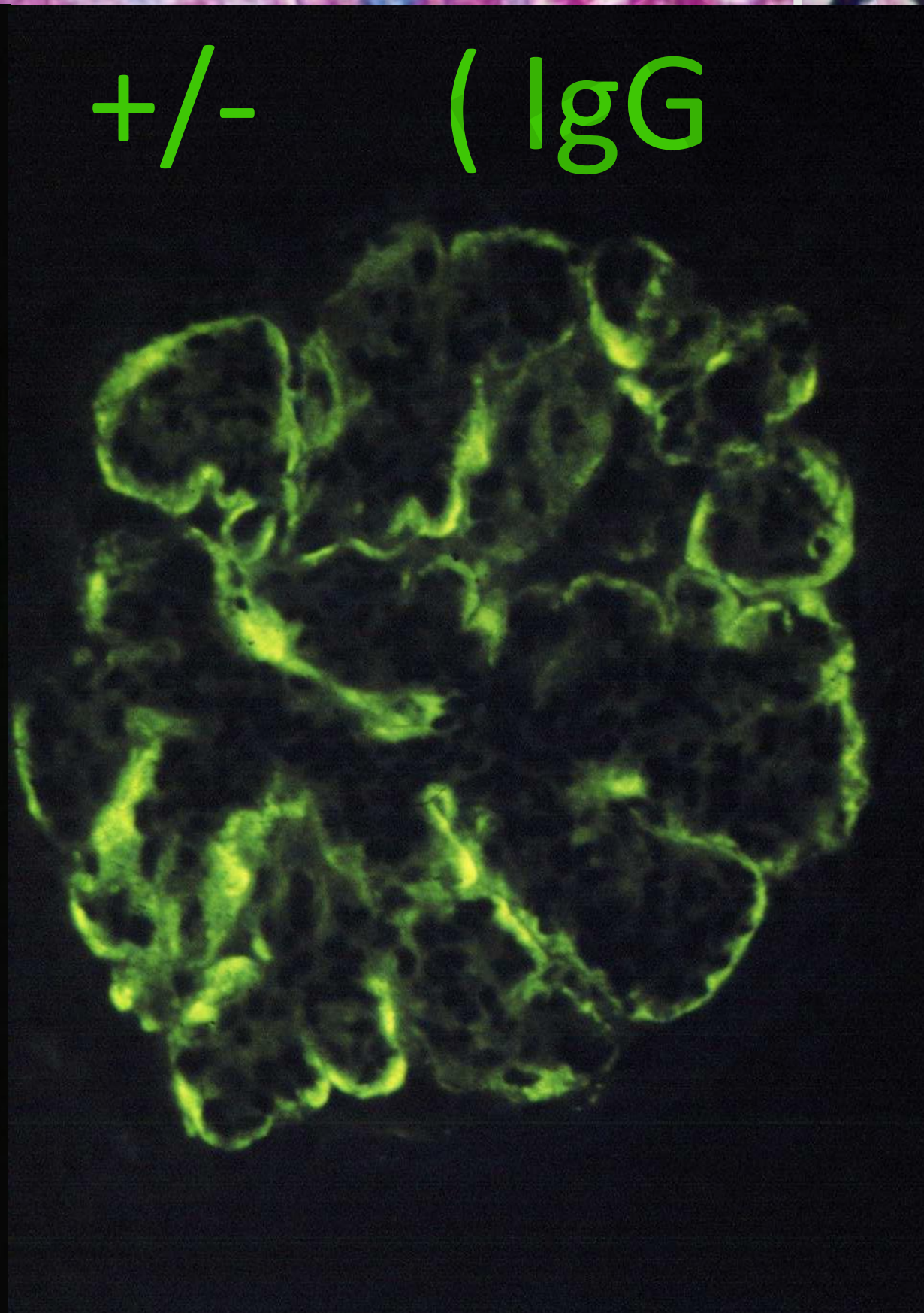
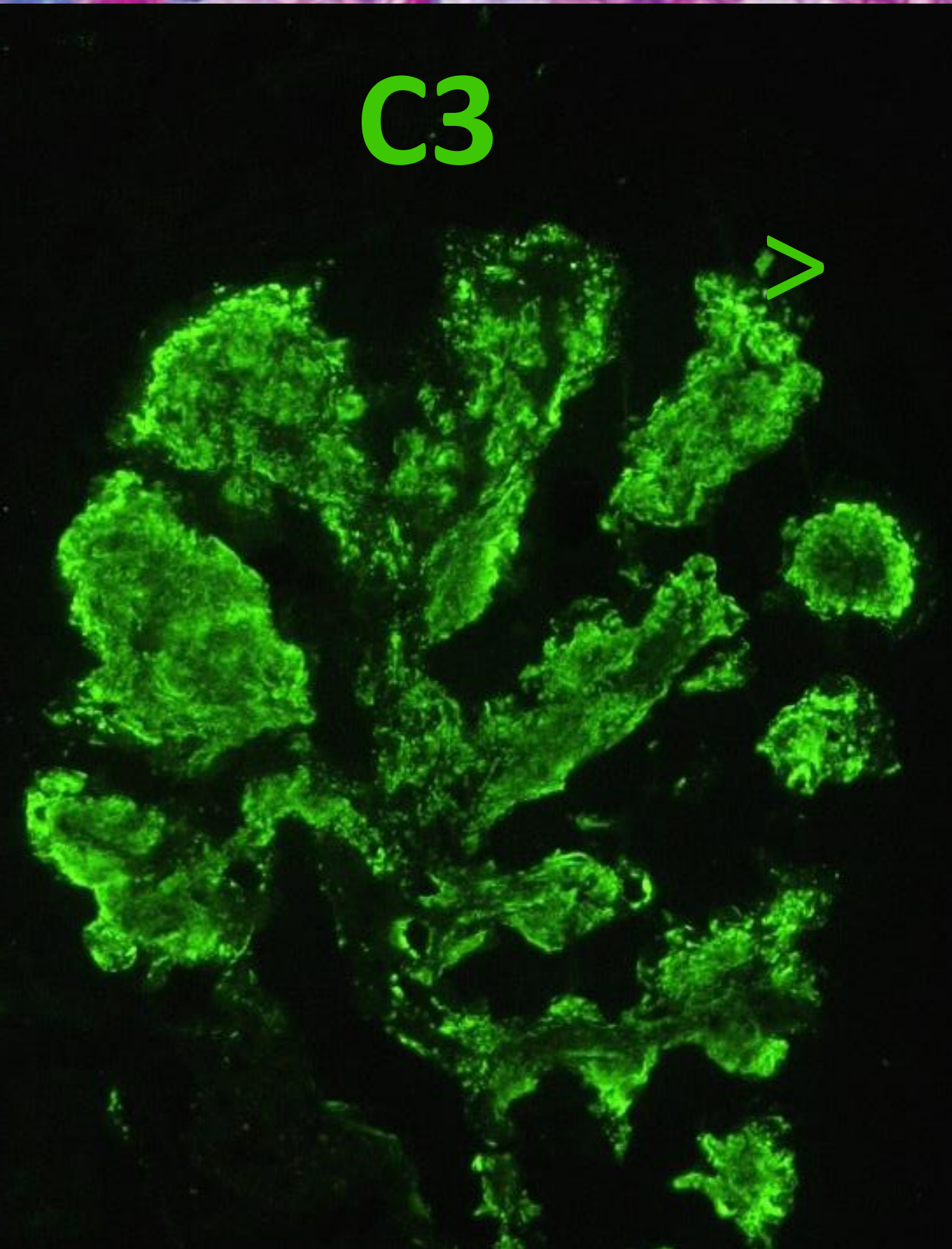
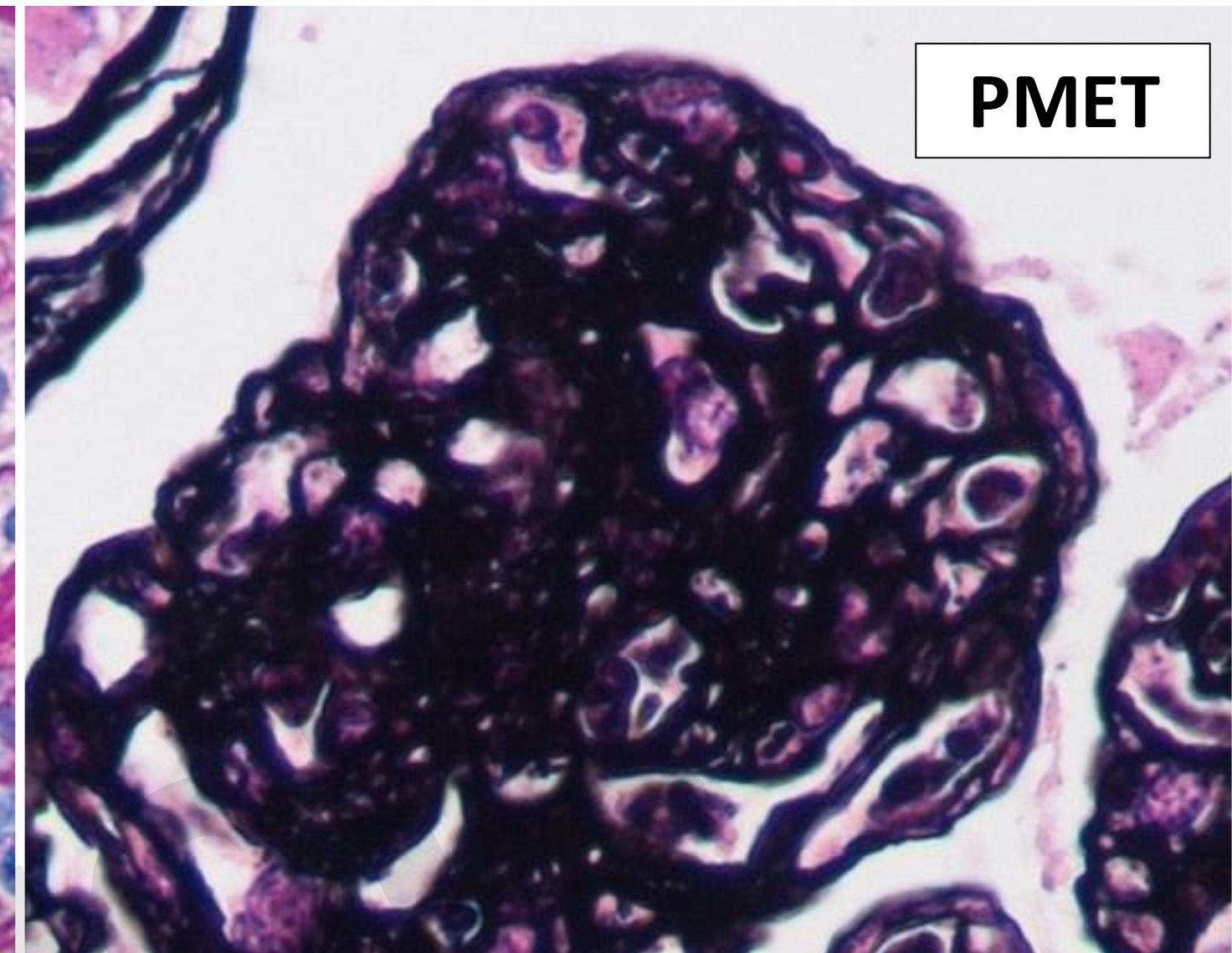
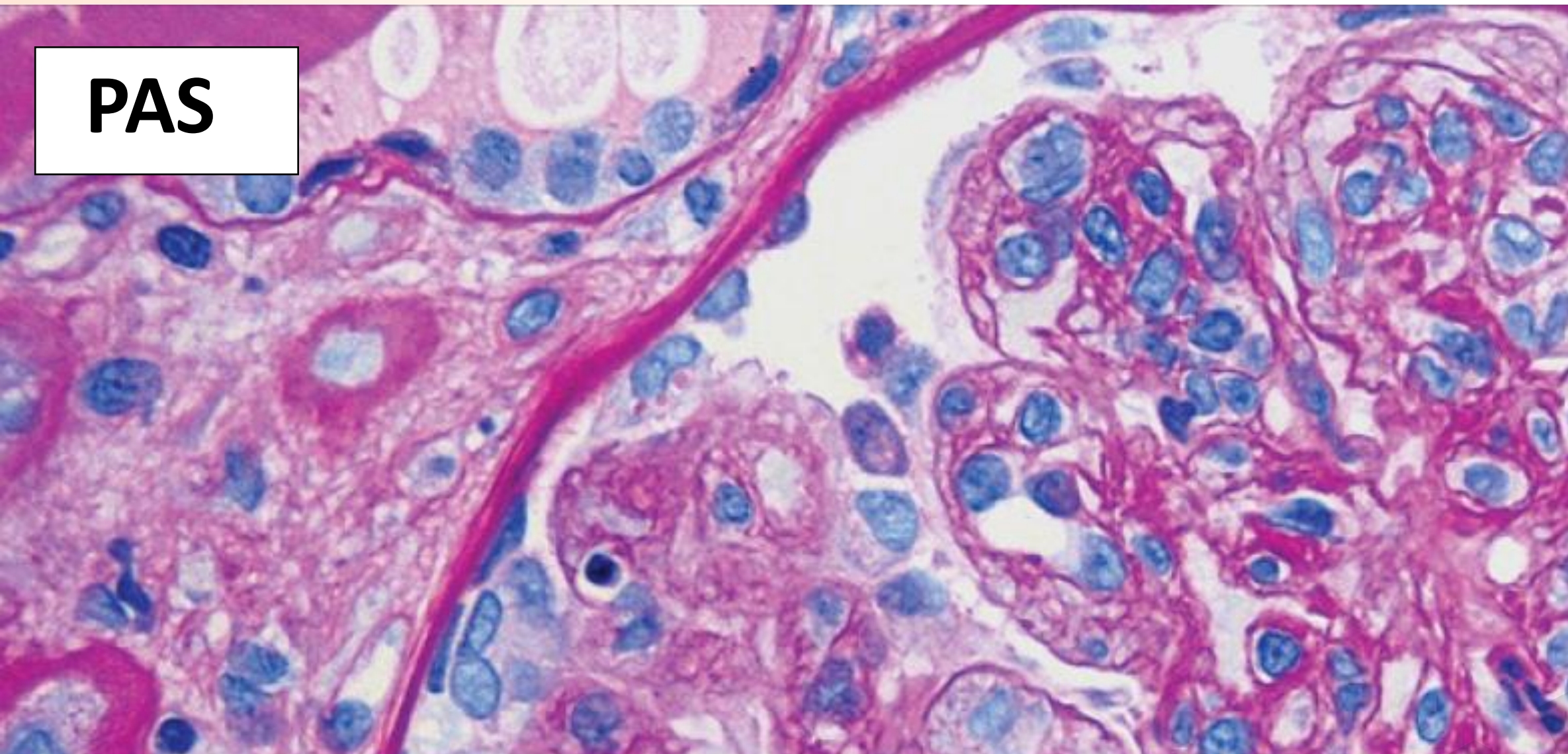


AMPLIANDO EL HORIZONTE
EN EL ABORDAJE DE LAS NEFROPATÍAS RARAS.

1. Introducción y contexto clínico-patológico

PAS





Patología del glomérulo renal

Atlas de
microscopia óptica, electrónica
e inmunofluorescencia

Horacio Oliva
Antonio Barat
Luis Hernando

Salvat

Cuadro 4-1. Clasificación de las glomerulonefritis

- I. Lesión glomerular mínima
- II. Lesiones glomerulares evidentes
 - A. Específicas
 - Microangiopatía trombótica
 - Amiloidosis
 - Glomeruloesclerosis diabética
 - Nefropatía membranosa de la malaria
 - Nefritis lúpica con cuerpos hematoxinófilos
 - B. Inespecíficas
 - 1. Difusas
 - No proliferativas
 - GN extramembranosa
 - GN membranosa
 - Esclerosis mesangial infantil
 - Proliferativas
 - GN endocapilar pura
 - GN endocapilar con semilunas focales
 - GN endocapilar con semilunas difusas
 - GN membranoproliferativa ²
 - a) Forma pura
 - b) Con patrón lobular
 - c) Con semilunas
 - 2. Focales
 - GN segmentaria y focal
 - GN esclerosante focal
 - Hialinosis segmentaria
 - Fibrosis global
- III. Lesiones glomerulares inclasificables
 - Nefritis hereditaria familiar
 - GN membranoproliferativa focal
 - GN extramembranosa con proliferación mesangial
 - GN muy evolucionadas

Según R. Habib.

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Patología del glomérulo renal

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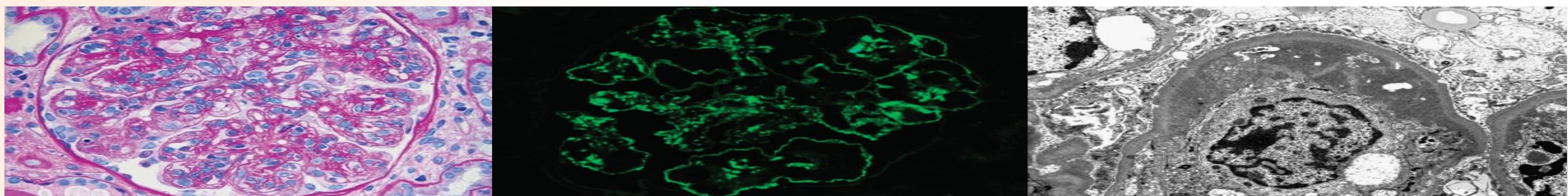
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Clasificación de la GNMP



Tipo I	Proliferación mesangial difusa y uniforme, interposición mesangial, dobles contornos.	IgG+C3 / C3 +/- IgM, IgA, C1 msg y subendot.	Mesangial, subendot.
Tipo II (EDD)	Prolif. mesangial moderada, engrosam. mb basal.	C3 en pared capilar (lineal), anillos msg.	Depósitos densos intramb y msg nodular.
Tipo III Burkholder	Proliferación mesangial difusa y uniforme, interposición msg, dobles contornos, púas.	IgG+C3 / C3 +/- IgM, IgA, C1 msg, subendot y subepitelial.	Mesangial subendotelial y subepitelial.
Tipo III Strife-Anders	Proliferación mesangial difusa y uniforme, engrosam. marcado mb b, interposición msg y dobles contornos variable.	IgG+C3 / C3 +/- IgM, IgA, C1 msg y transmb.	Mesangial intramb +/- subendotelial +/- subepitelial.

GNMP secundaria

Infecciones

Hepatitis C
Hepatitis B
Endocarditis
Abscesos viscerales
Shunts V-A infectados
Malaria
Esquistosomiasis
Mycoplasma
Virus Epstein-Barr
VIH

Enfermedades Autoinmunes

Lupus eritematoso sistémico
Síndrome anti-fosfolípido
Enfermedad mixta del tejido conectivo
Artritis reumatoide
Síndrome de Sjögren

Disproteinemias

Crioglobulinemia (tipos I y II)
Enf. depósito de cadenas ligeras
Enf. depósito de cadenas pesadas
Macroglobulinemia de Waldenström
GN fibrilar
GN inmunotactoide

Enf. malignas

Leucemias y linfomas

Enf. hepáticas crónicas

Cirrosis
Déficit de alfa1-antitripsina

Microangiopatías trombóticas

Síndrome urémico hemolítico
Púrpura trombótica trombocitopénica

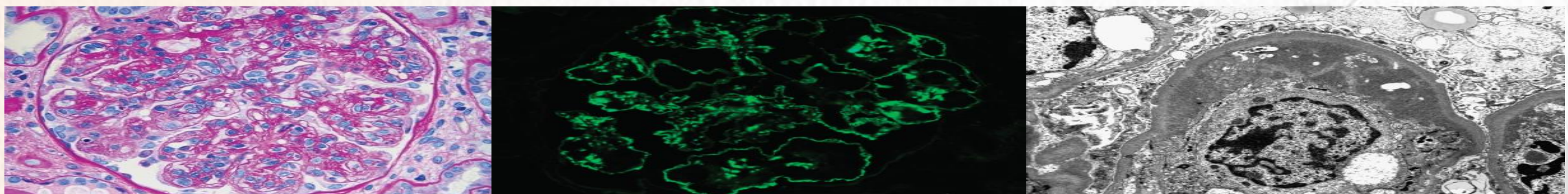
Anemia falciforme

Nefritis por radiación

Glomerulopatía del trasplante

Esclerosis sistémica

GNMP primaria

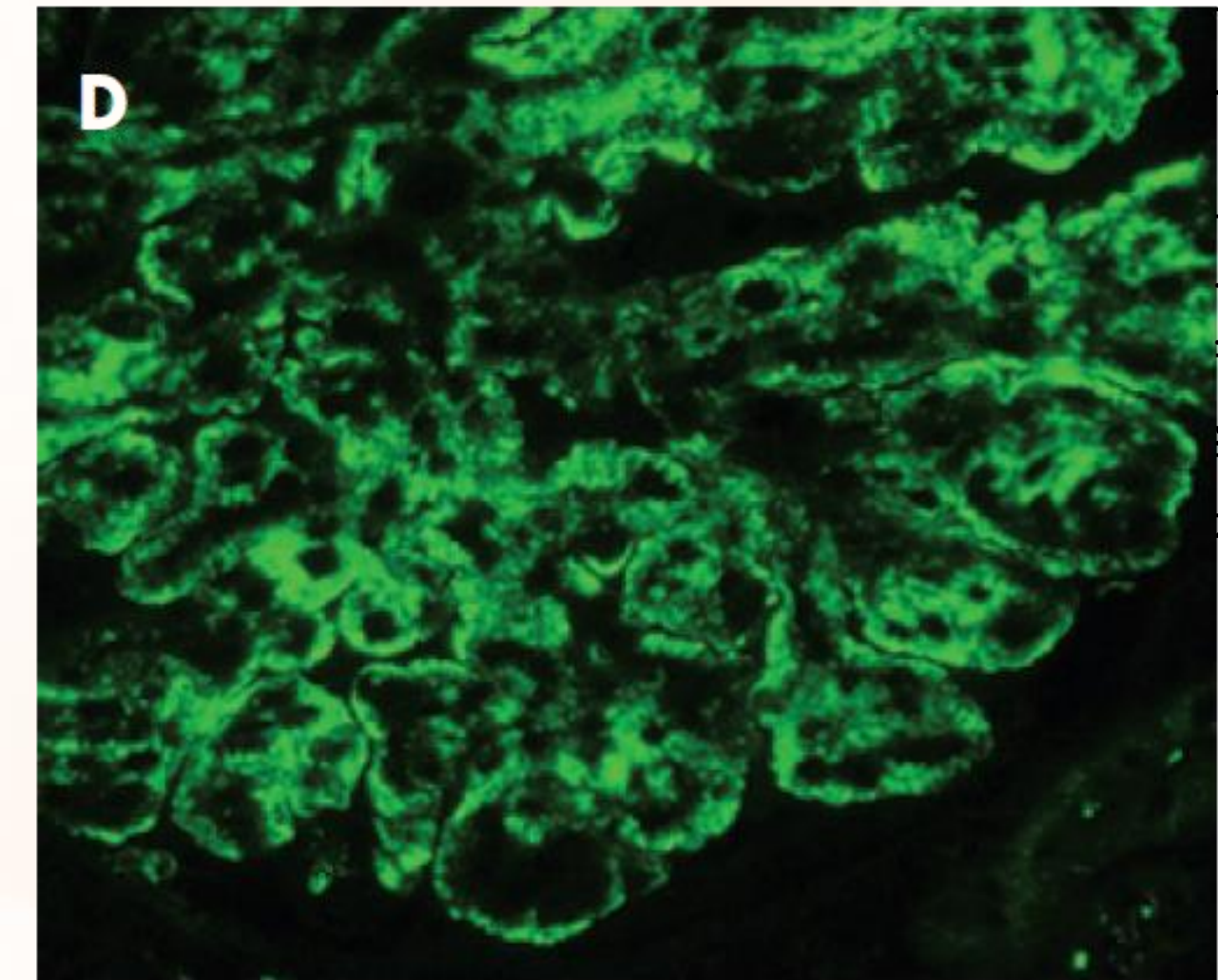
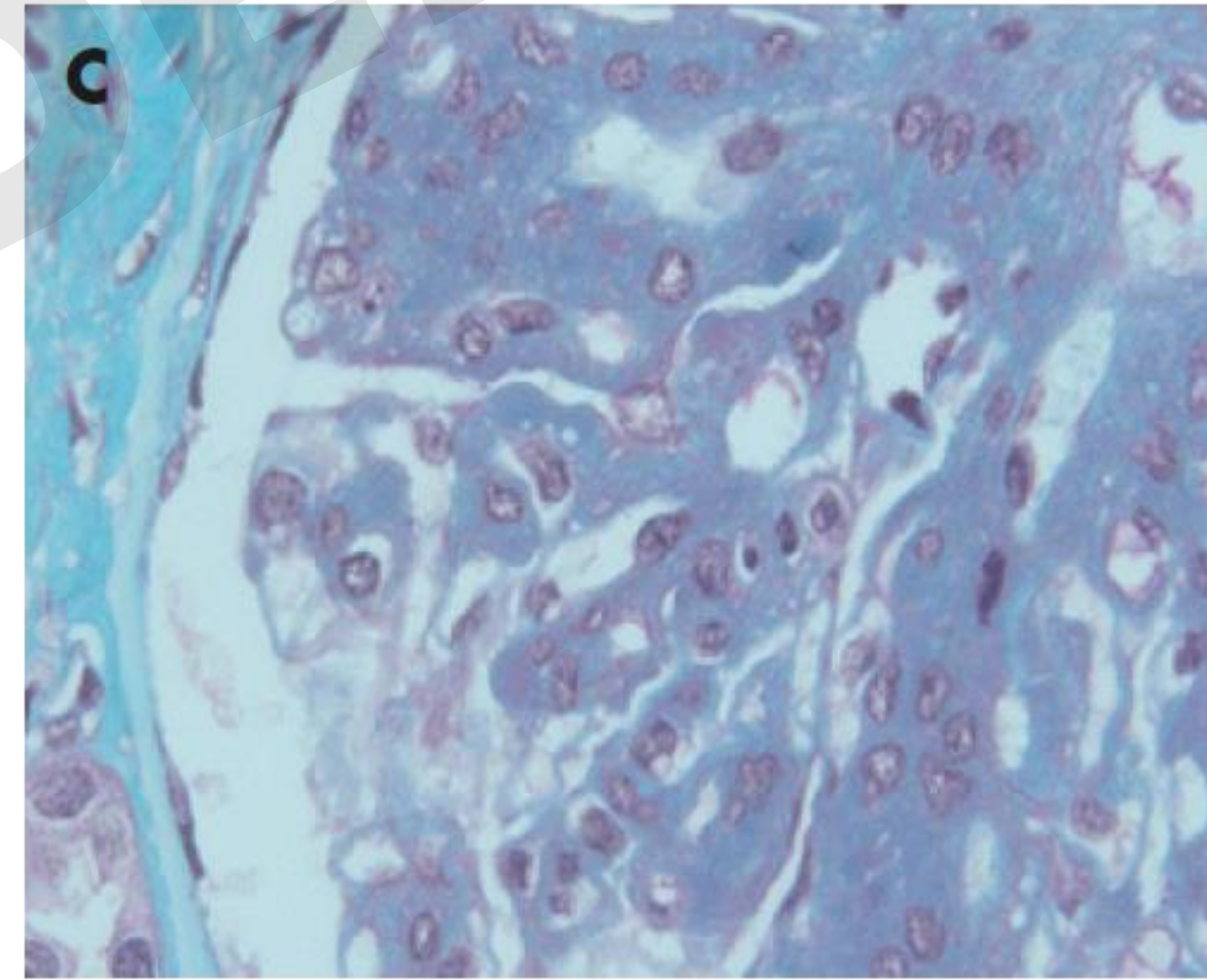
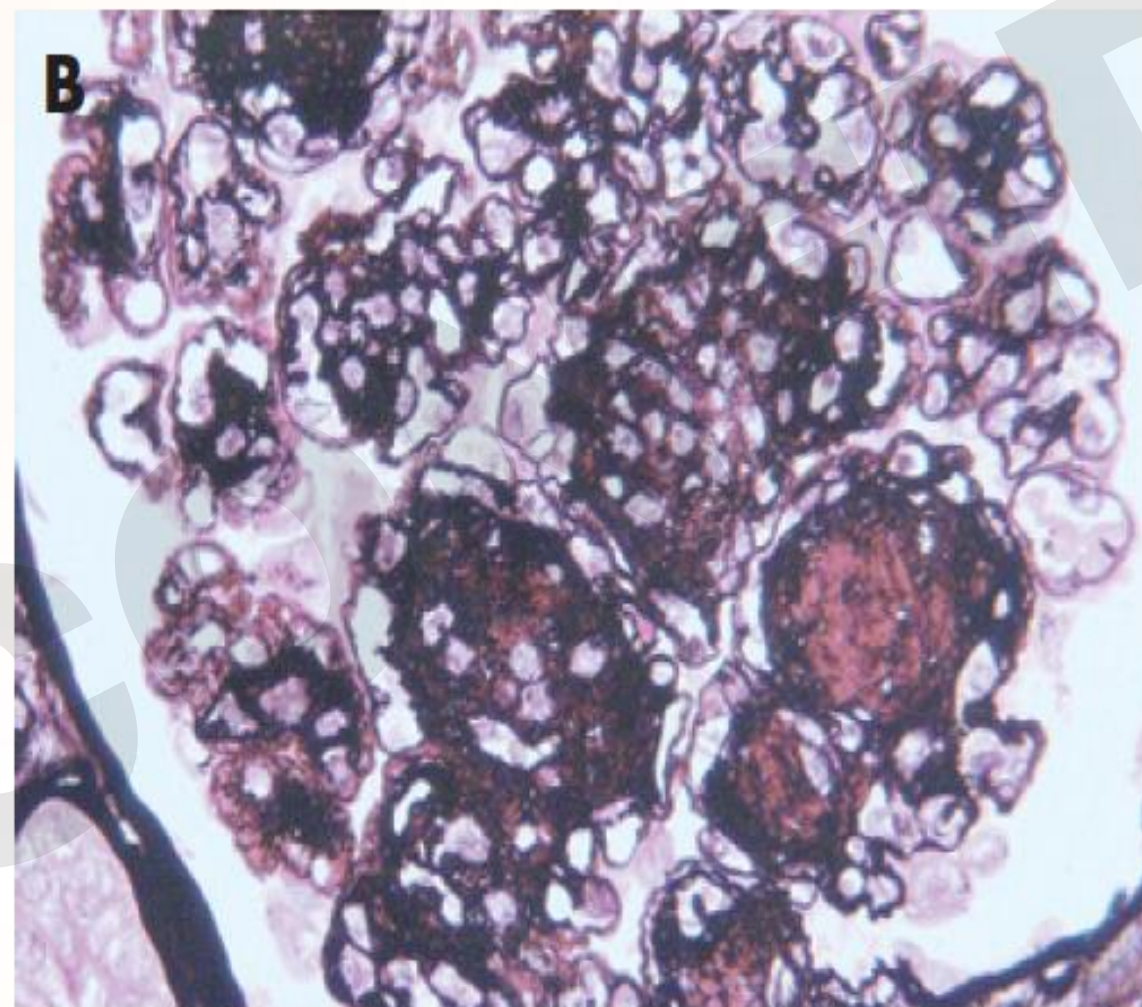
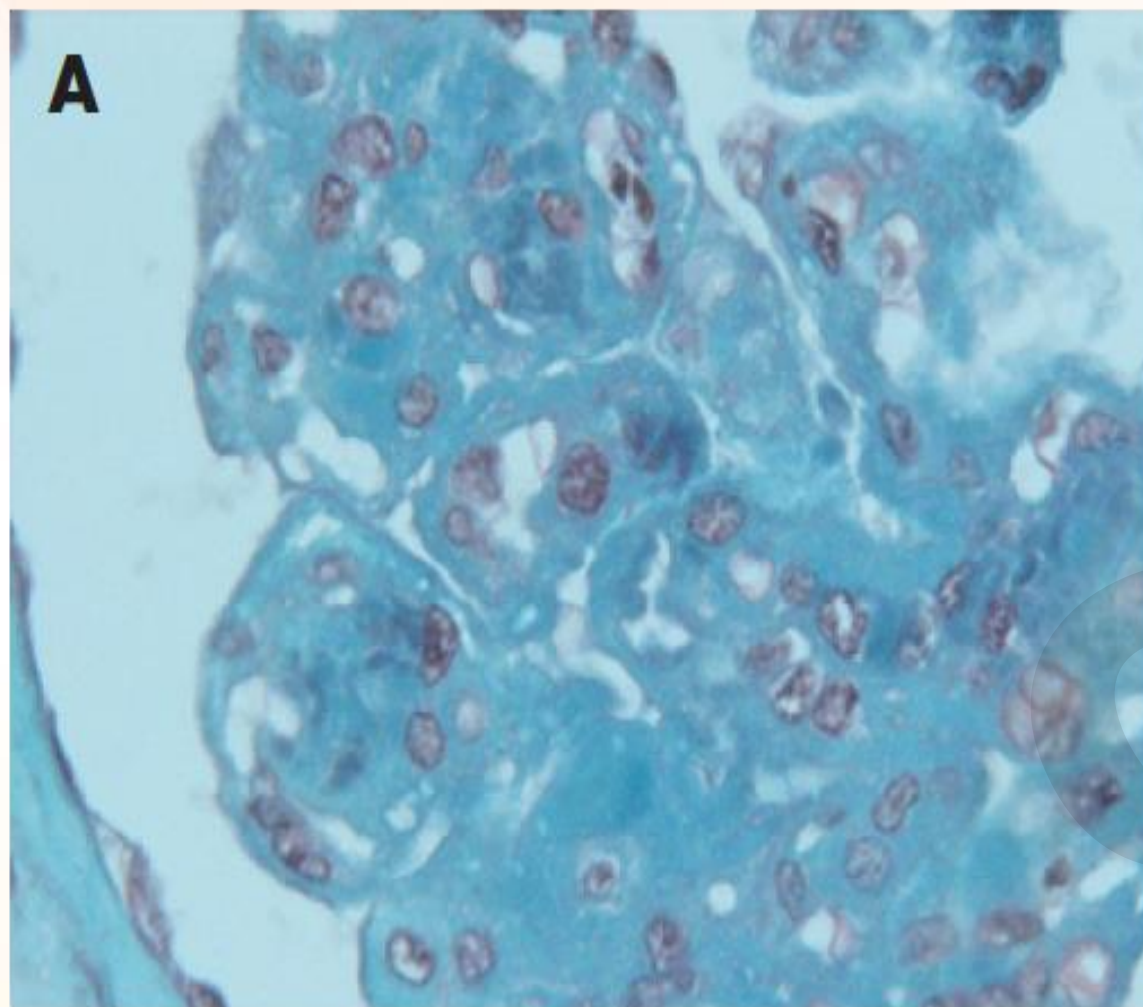


Tipo I	Proliferación mesangial difusa y uniforme, interposición mesangial, dobles contornos.	IgG+C3 / C3 +/- IgM, IgA, C1 msg y subendot.	Mesangial, subendot.
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ORIGINAL ARTICLE

Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome

Aude Servais, Véronique Frémeaux-Bacchi, Moglie Lequintrec, Rémi Salomon, Jacques Blouin, Bertrand Knebelmann, Jean-Pierre Grünfeld, Philippe Lesavre, Laure-Hélène Noël, Fadi Fakhouri



PERSPECTIVES

OPINION

C3 glomerulopathy: a new classification

Fadi Fakhouri, Véronique Frémeaux-Bacchi, Laure-Hélène Noël, H. Terence Cook and Matthew C. Pickering

Box 2 | C3 glomerulopathy

Inclusion criteria

- Glomerular deposition of complement C3
- Absence (or only scanty deposition) of immunoglobulin within glomeruli

Examples

- Dense deposit disease
- Idiopathic C3 glomerulonephritis¹
- Membranoproliferative glomerulonephritis type I with isolated subendothelial deposition of complement C3⁵
- Familial membranoproliferative glomerulonephritis type III^{22,23}
- CFHR5 nephropathy (familial C3 glomerulonephritis associated with heterozygous mutation in *CFHR5*)²⁴

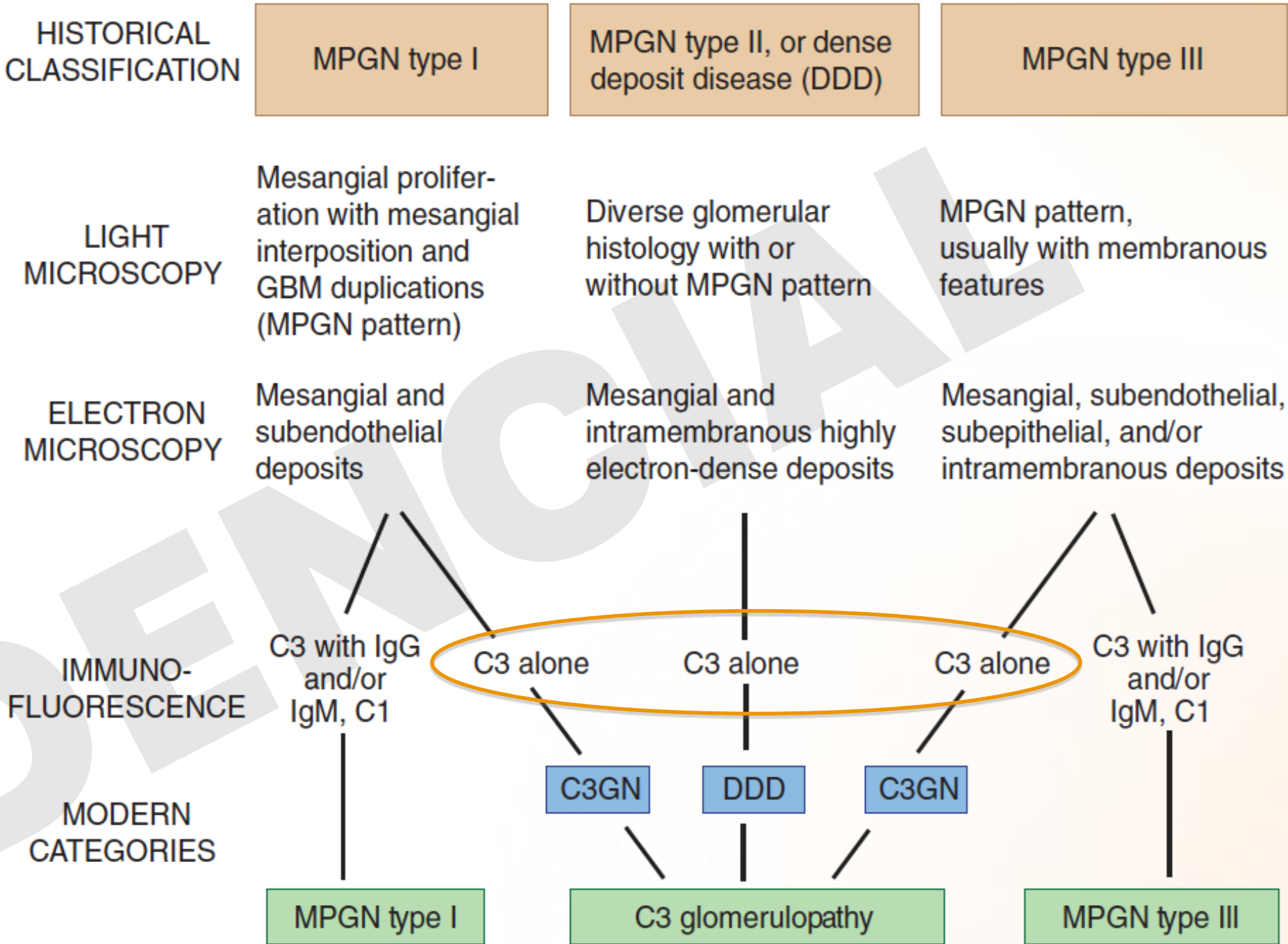
Table 1 | Pathological features of idiopathic MPGN1, DDD, and C3GN^{1–5}

	Idiopathic MPGN1	DDD	C3GN
Defining features	Membranoproliferative inflammation on light microscopy Subendothelial electron-dense GBM deposits Absence of a recognized etiology, e.g. systemic lupus erythematosus	Dense osmiophilic intramembranous GBM deposits Glomerular C3 staining with little or no immunoglobulin staining	Subendothelial and/or mesangial electron-dense deposits Isolated glomerular C3 staining (no immunoglobulin or C1q staining)
Other features	Glomerular C3* and IgG staining	Variable glomerular inflammation	Variable glomerular inflammation

*MPGN1 has been reported in individuals with C3 deficiency demonstrating that MPGN pathology can develop in the absence of C3 activation. Abbreviations: C3, complement C3; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; GBM, glomerular basement membrane; MPGN, membranoproliferative glomerulonephritis.

C3 glomerulopathy: what's in a name?

Vivette D. D'Agati¹ and Andrew S. Bomback²



2012. Kidney International

C3 glomerulopathy: what's in a name?

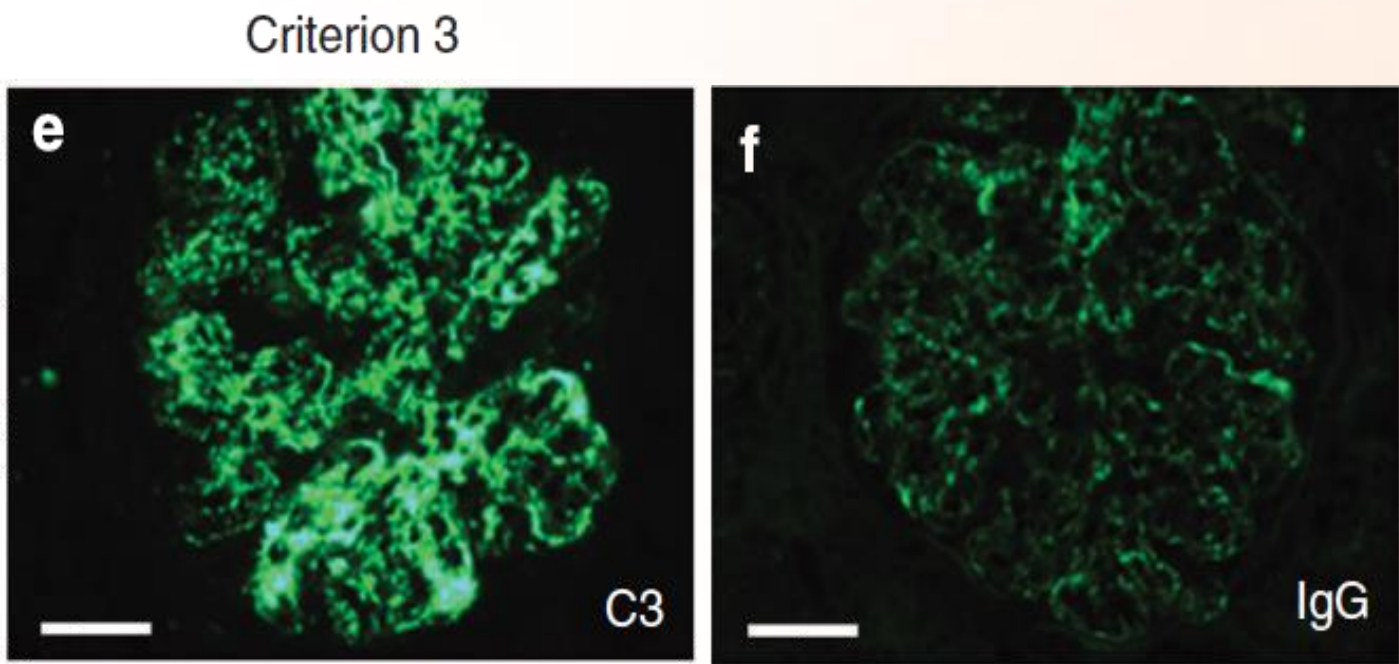
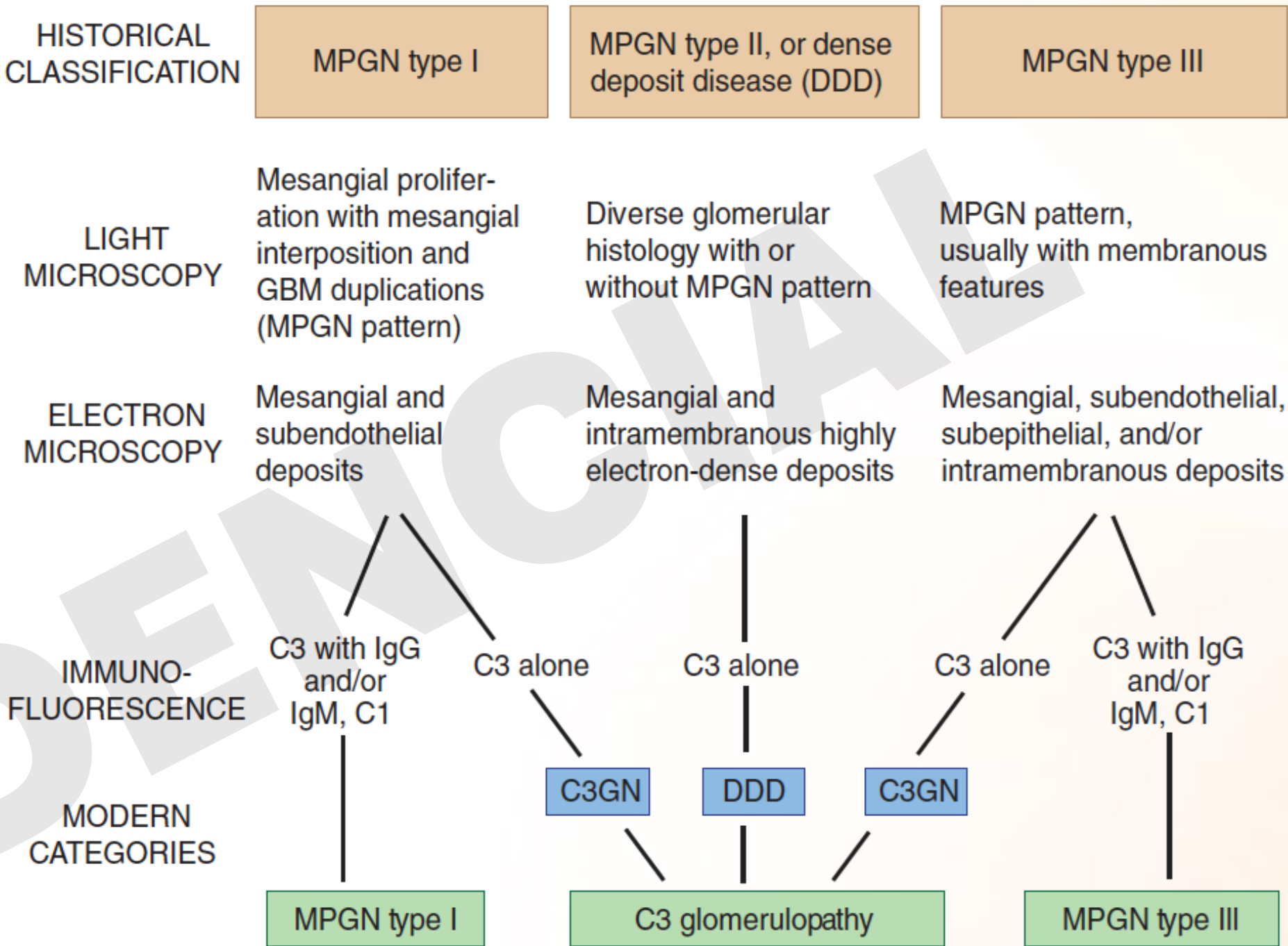
Vivette D. D'Agati¹ and Andrew S. Bomback²

2013. Kidney International

Toward a working definition of C3 glomerulopathy by immunofluorescence

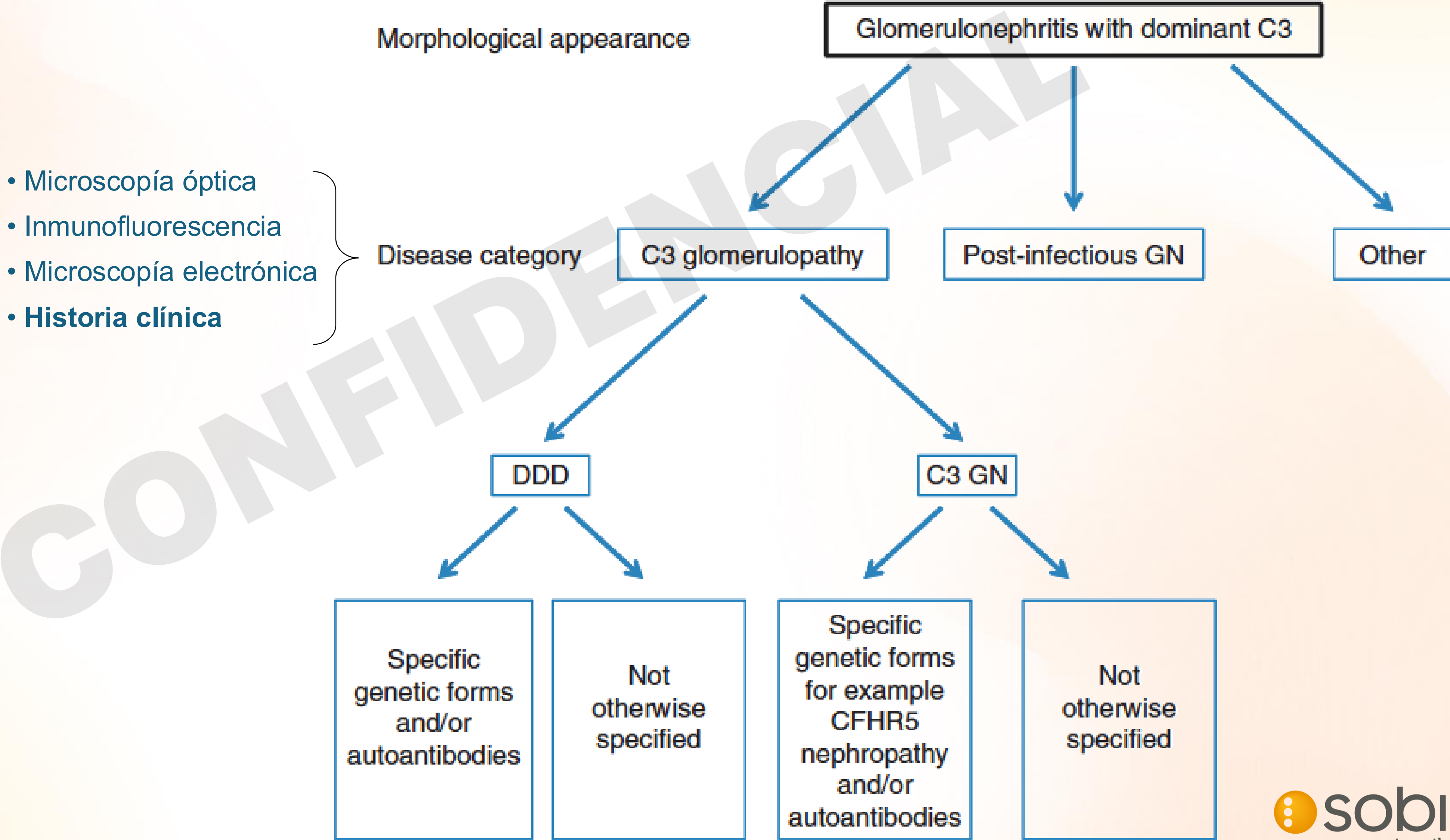
Jean Hou¹, Glen S. Markowitz¹, Andrew S. Bomback², Gerald B. Appel², Leal C. Herlitz¹, M. Barry Stokes¹ and Vivette D. D'Agati¹

Thus, 'C3 only' is an impractical definition of C3 glomerulopathy, and we propose a definition of C3 dominant and at least two orders of magnitude more intense than any other immune reactant, which requires validation by alternative pathway evaluation. These criteria provide a framework for identifying patients most likely to benefit from investigations of alternative complement pathway dysregulation.



OPEN

C3 glomerulopathy: consensus report



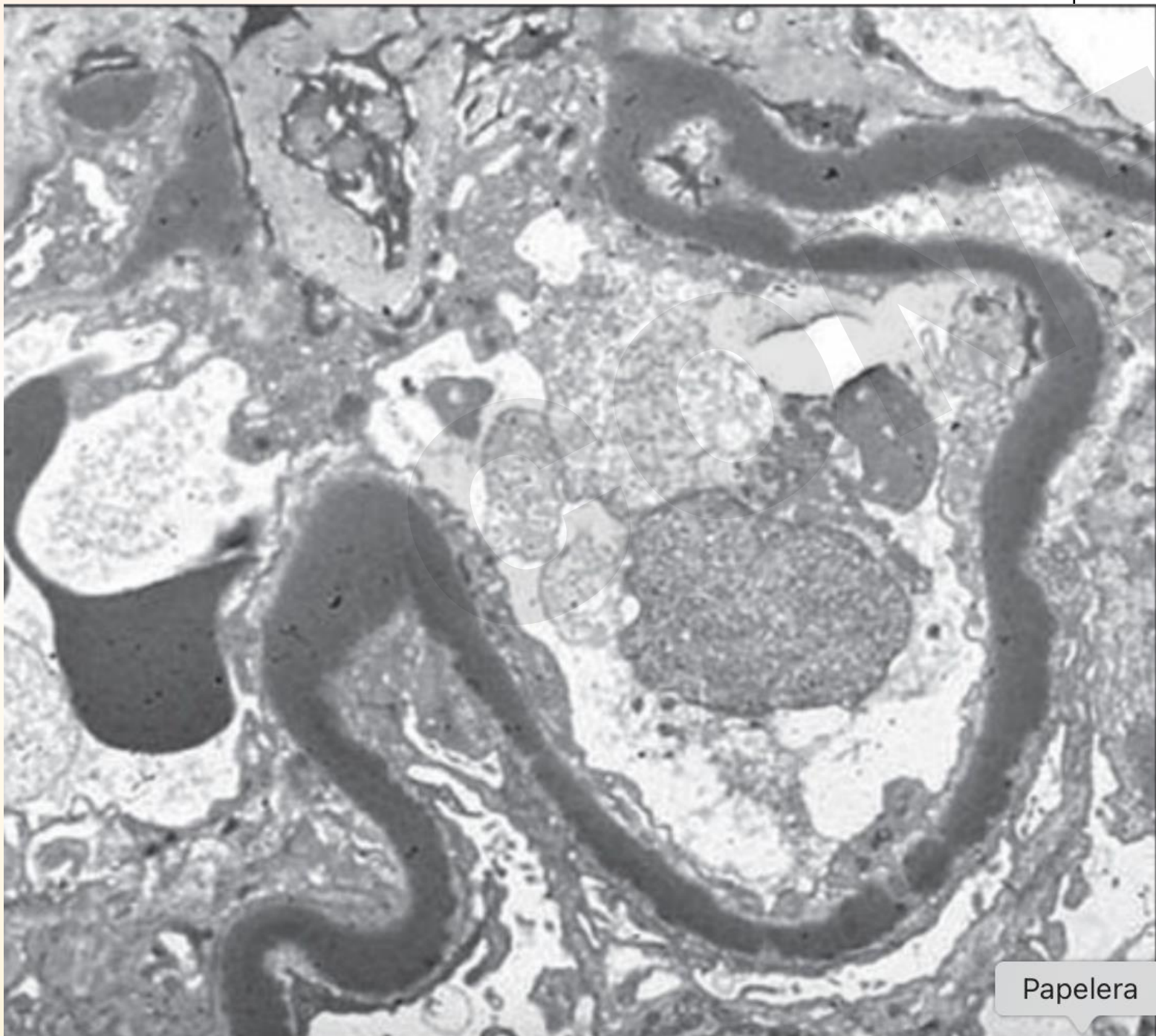
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OPEN

C3 glomerulopathy: consensus report

- Microscopía óptica
- Inmunofluorescencia
- **Microscopía electrónica**



Papelera

Morphological appearance

Glo

Disease category

C3 glomerulopathy

DDD

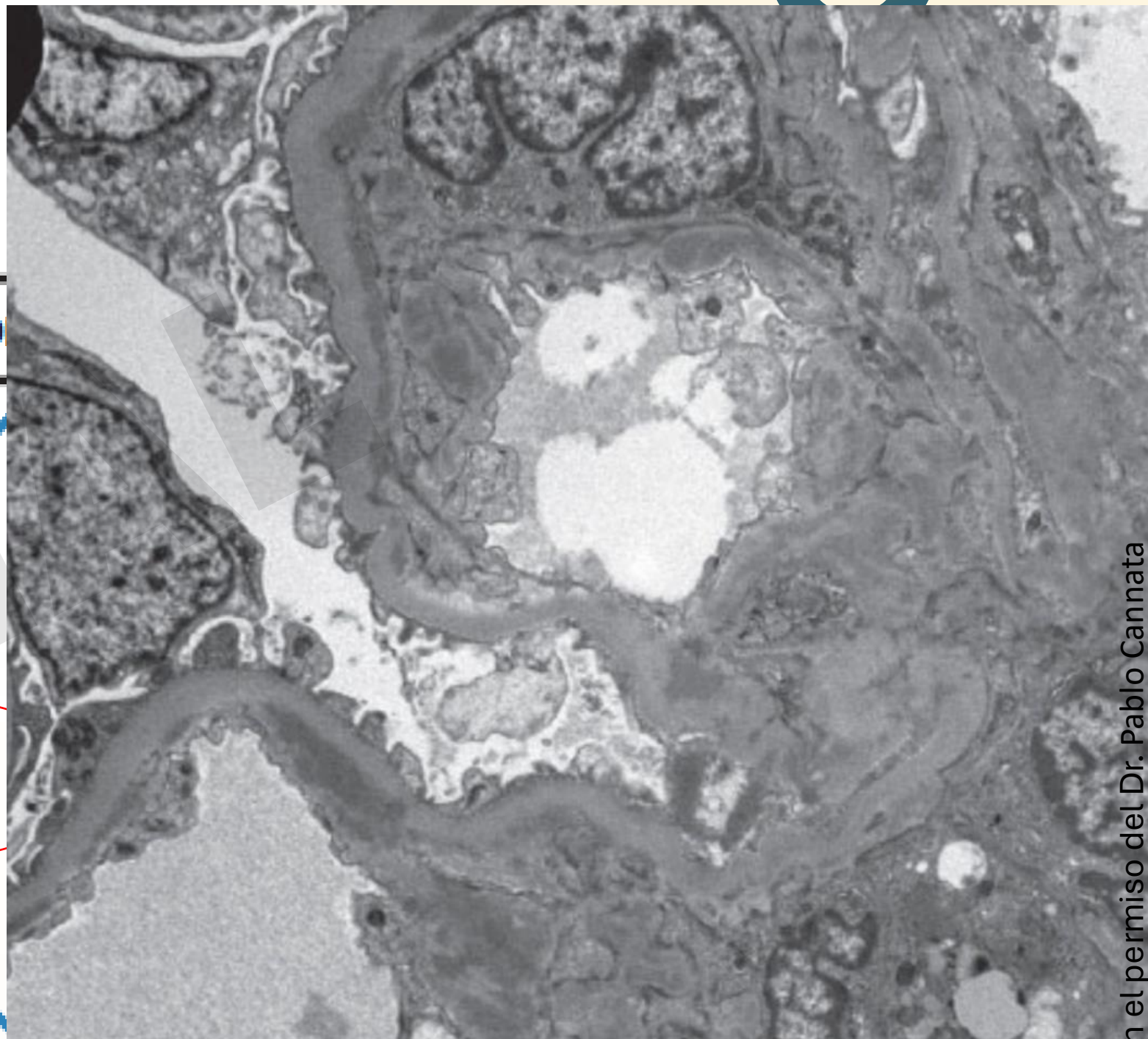
C3 GN

Specific
genetic forms
and/or
autoantibodies

Not
otherwise
specified

Specific
genetic forms
for example
CFHR5
nephropathy
and/or
autoantibodies

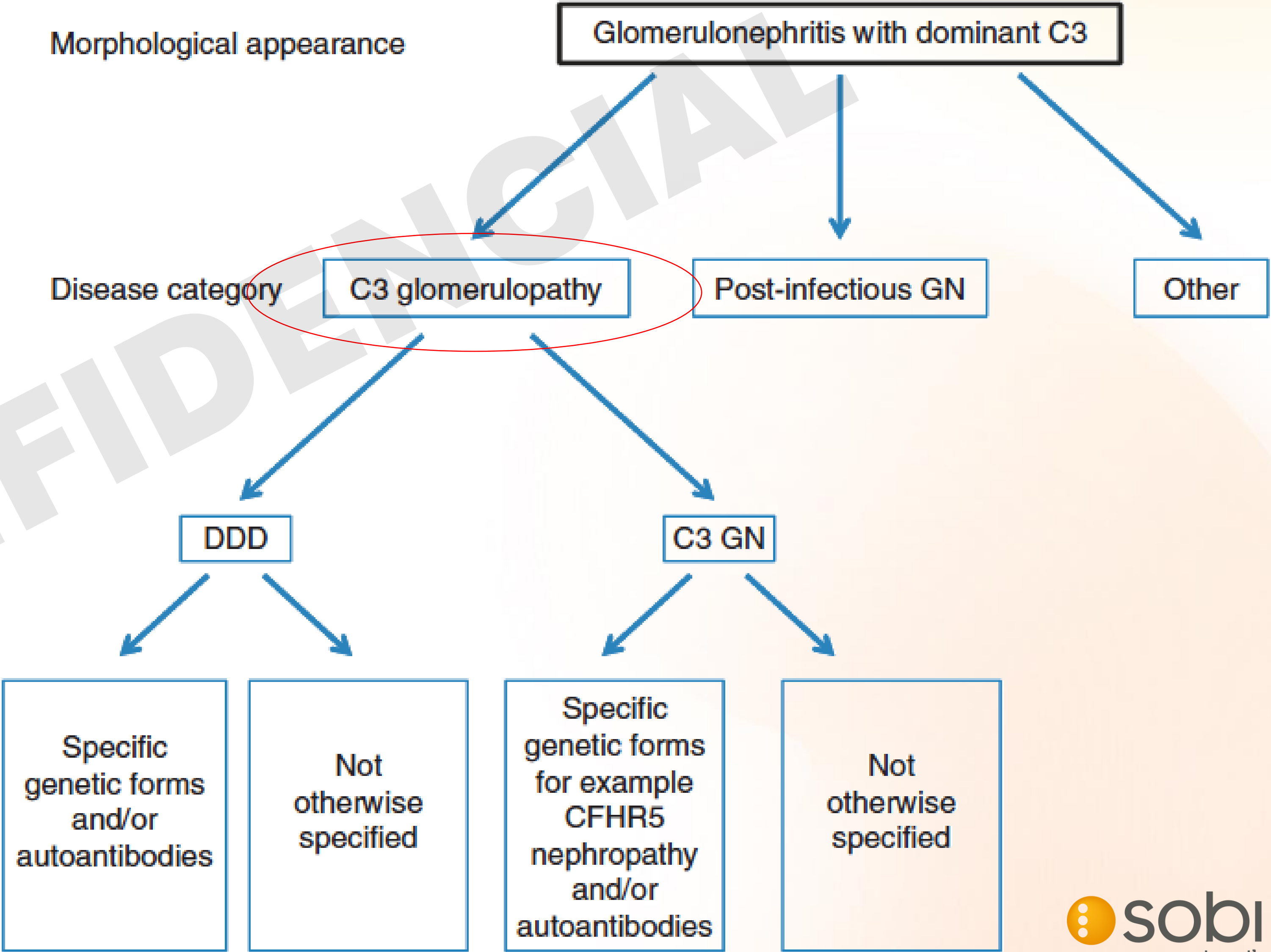
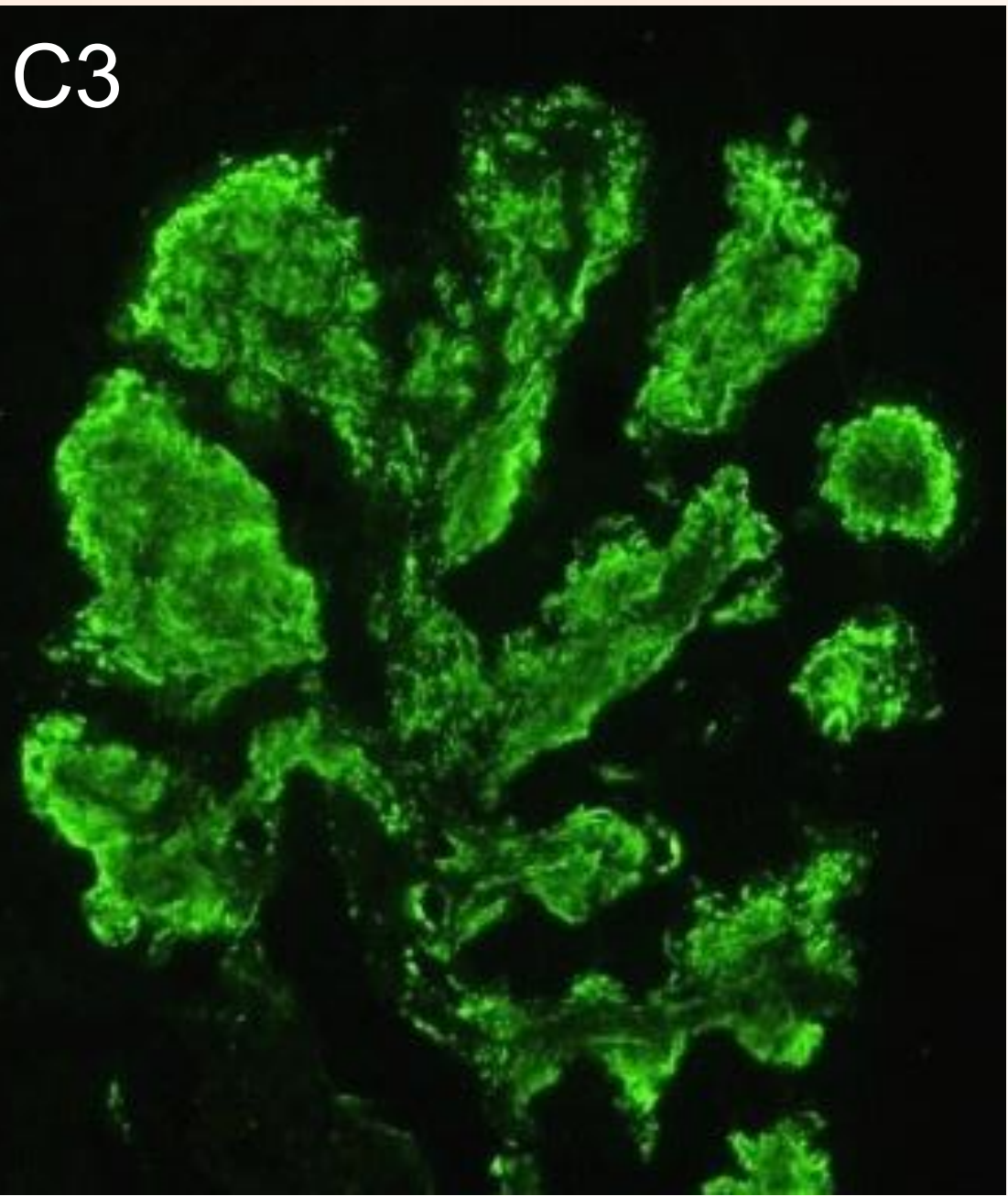
Not
otherwise
specified



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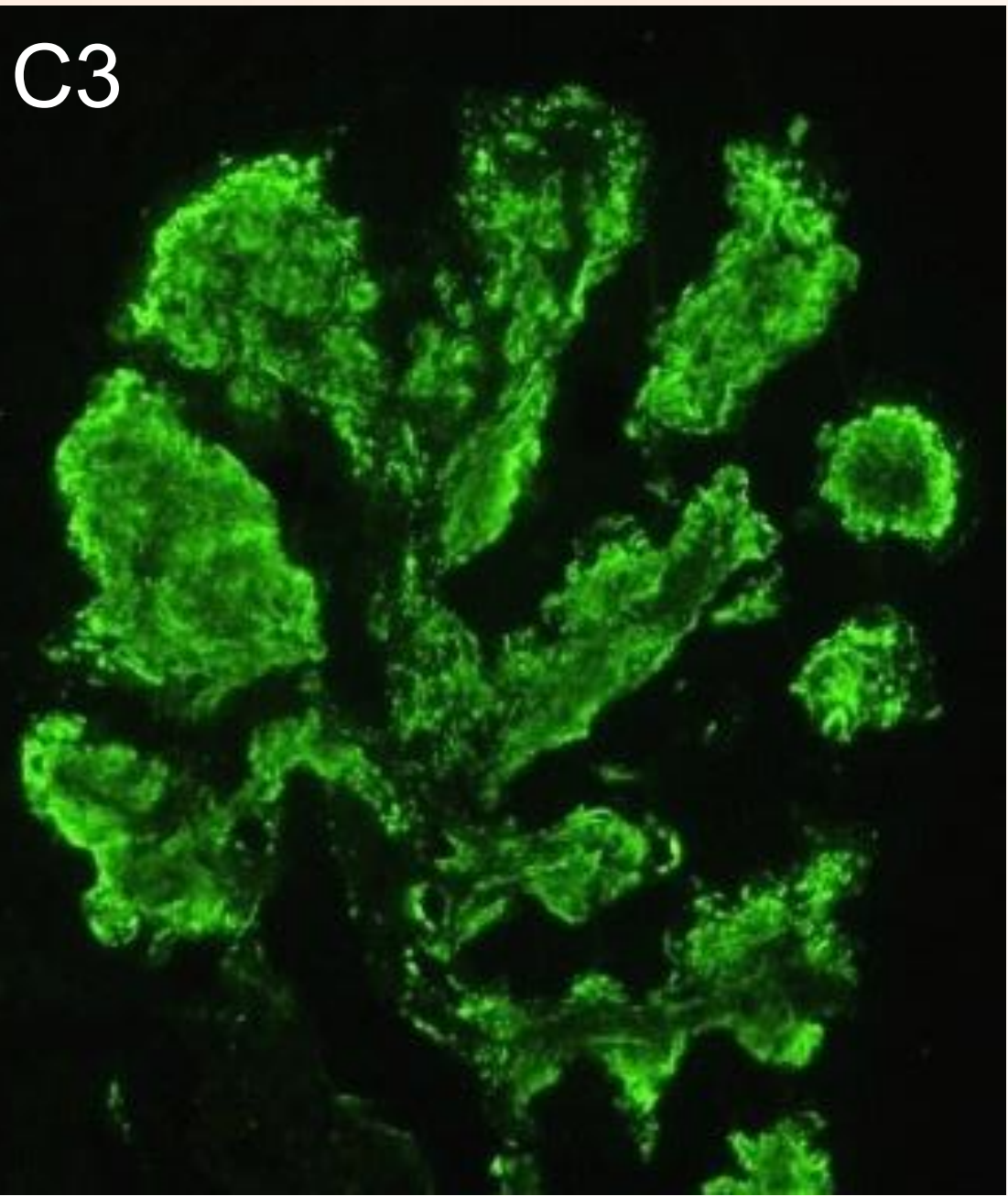
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C3 glomerulopathy: consensus report



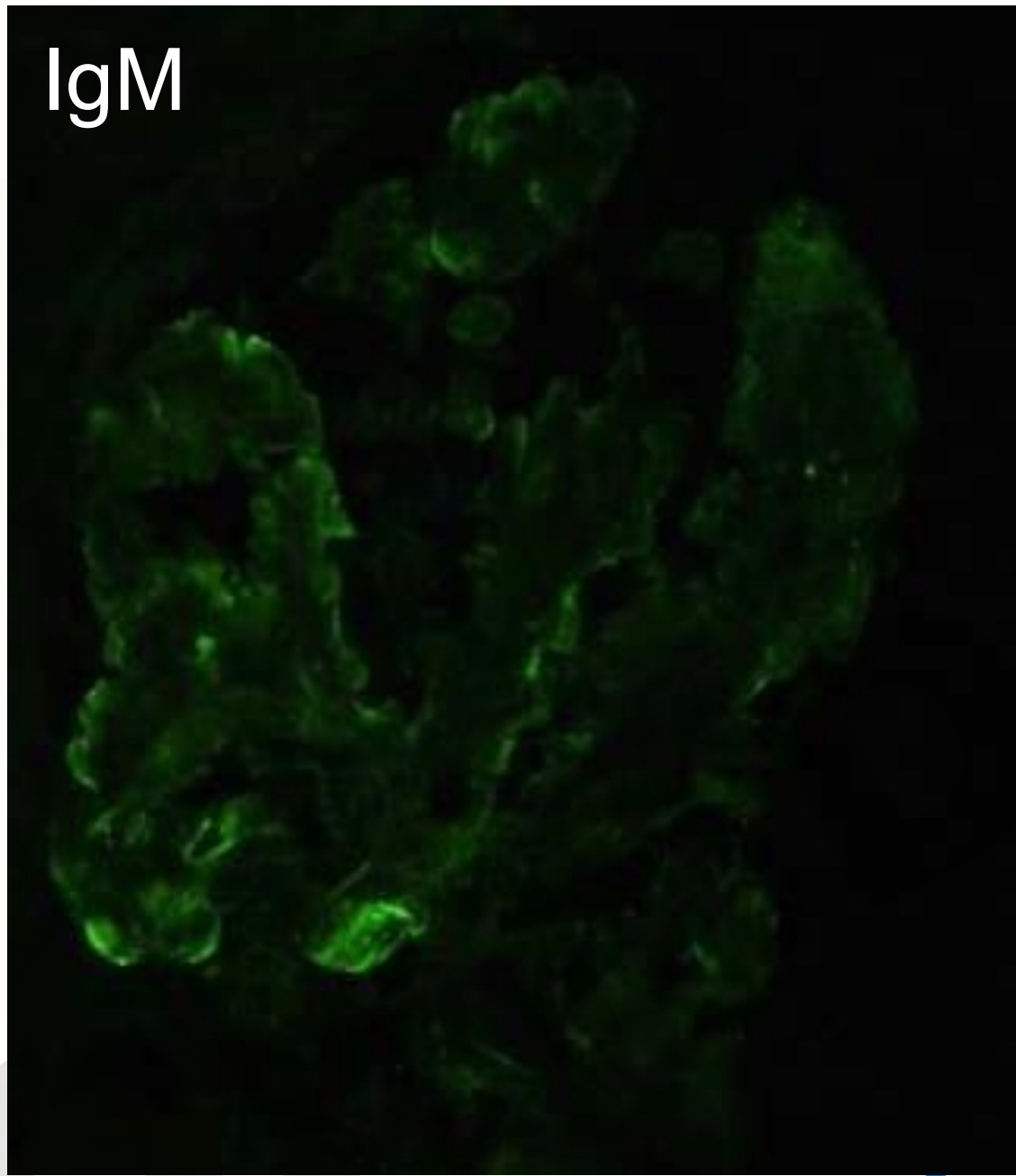
OPEN

C3 glomerulopathy: consensus report

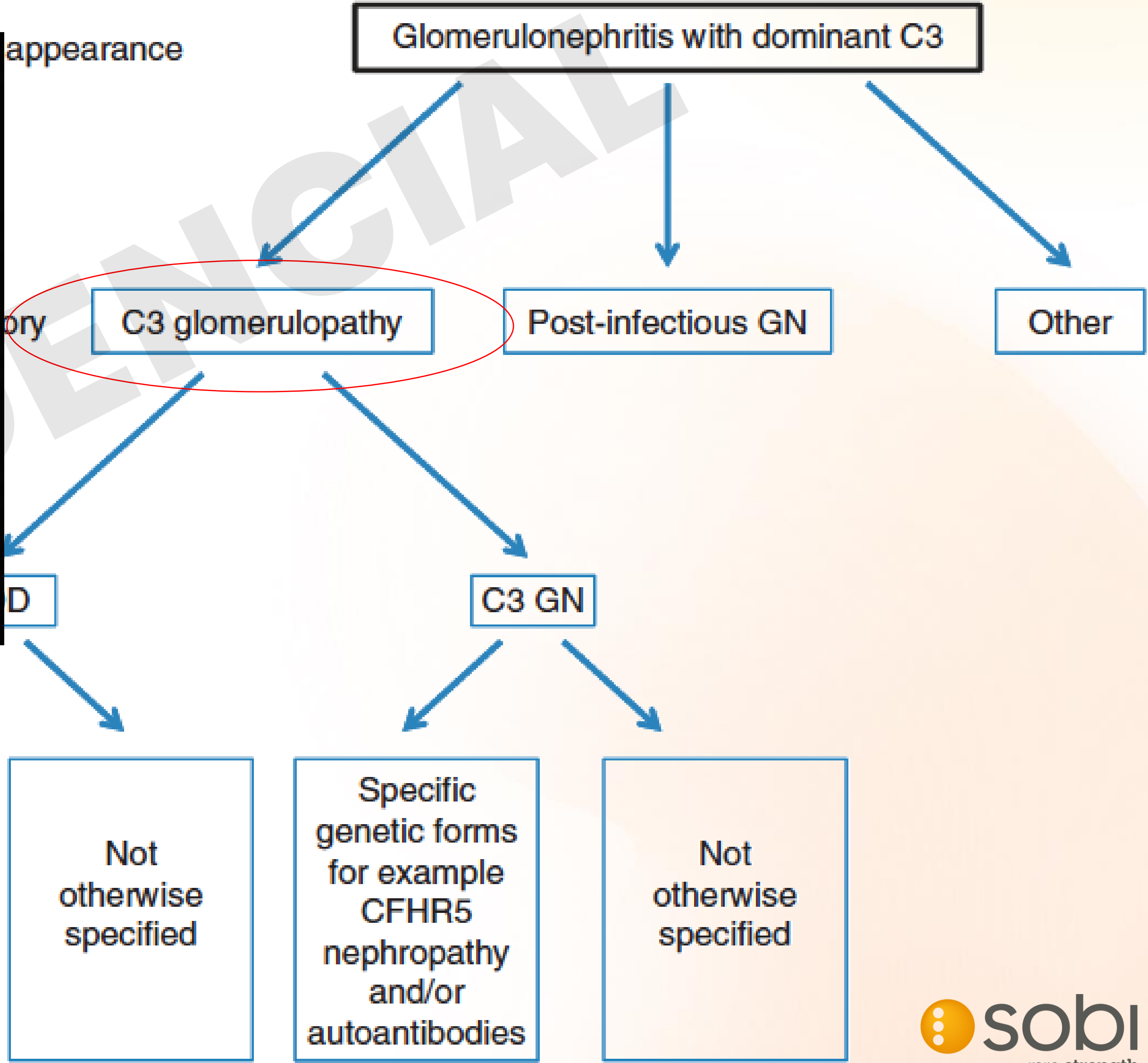


C3 (3+)

>>



Ig (1+)



2. Punto de partida: biomarcadores de rutina en la biopsia renal

2. Punto de partida: biomarcadores de rutina en la biopsia renal

La inmunofluorescencia

Inmunofluorescencia

- **Técnica de elección** (más sensible y específica) para el diagnóstico de **nefropatías mediadas por mecanismos inmunológicos**.

CONFIDENCIAL

Inmunofluorescencia

- **Técnica de elección** (más sensible y específica) para el diagnóstico de **nefropatías mediadas por mecanismos inmunológicos**.
- Se realiza **rutinariamente en todas las biopsias renales en tejido fresco congelado**.
(* Se puede realizar con limitaciones sobre tejido fijado: IF-P).

CONFIDENCIAL

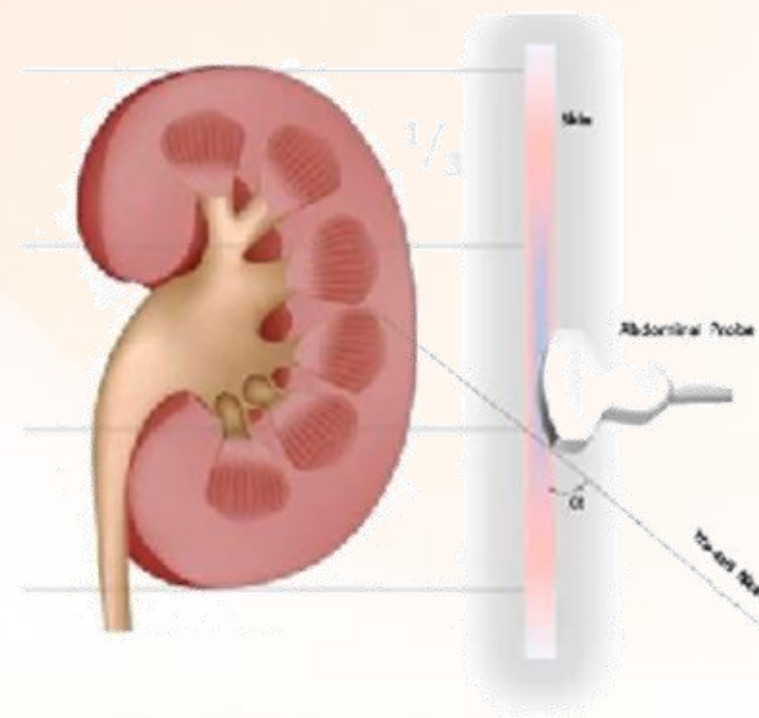
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(C5b-9, C4d, albúmina, fibrinógeno).

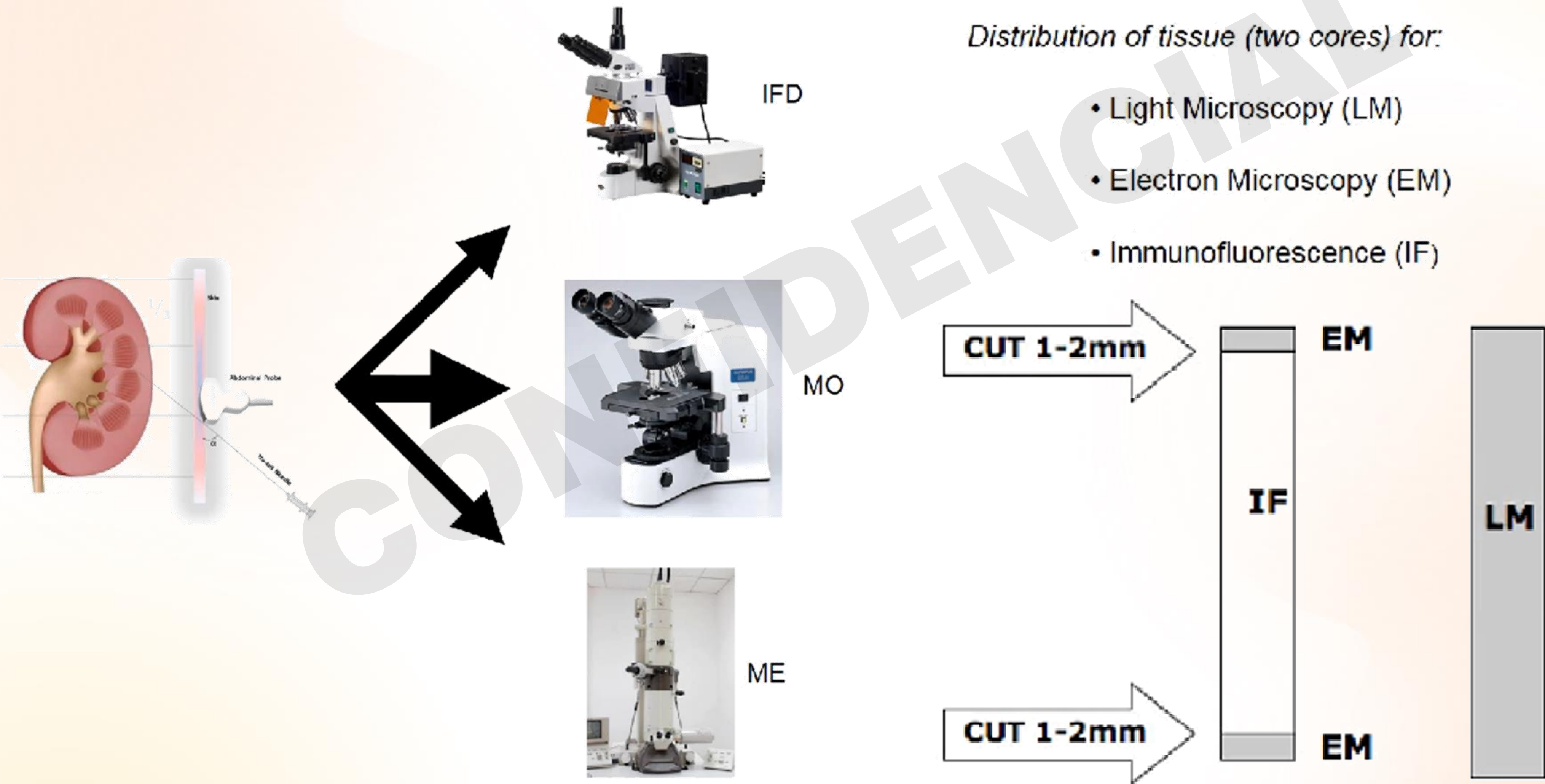
Inmunofluorescencia

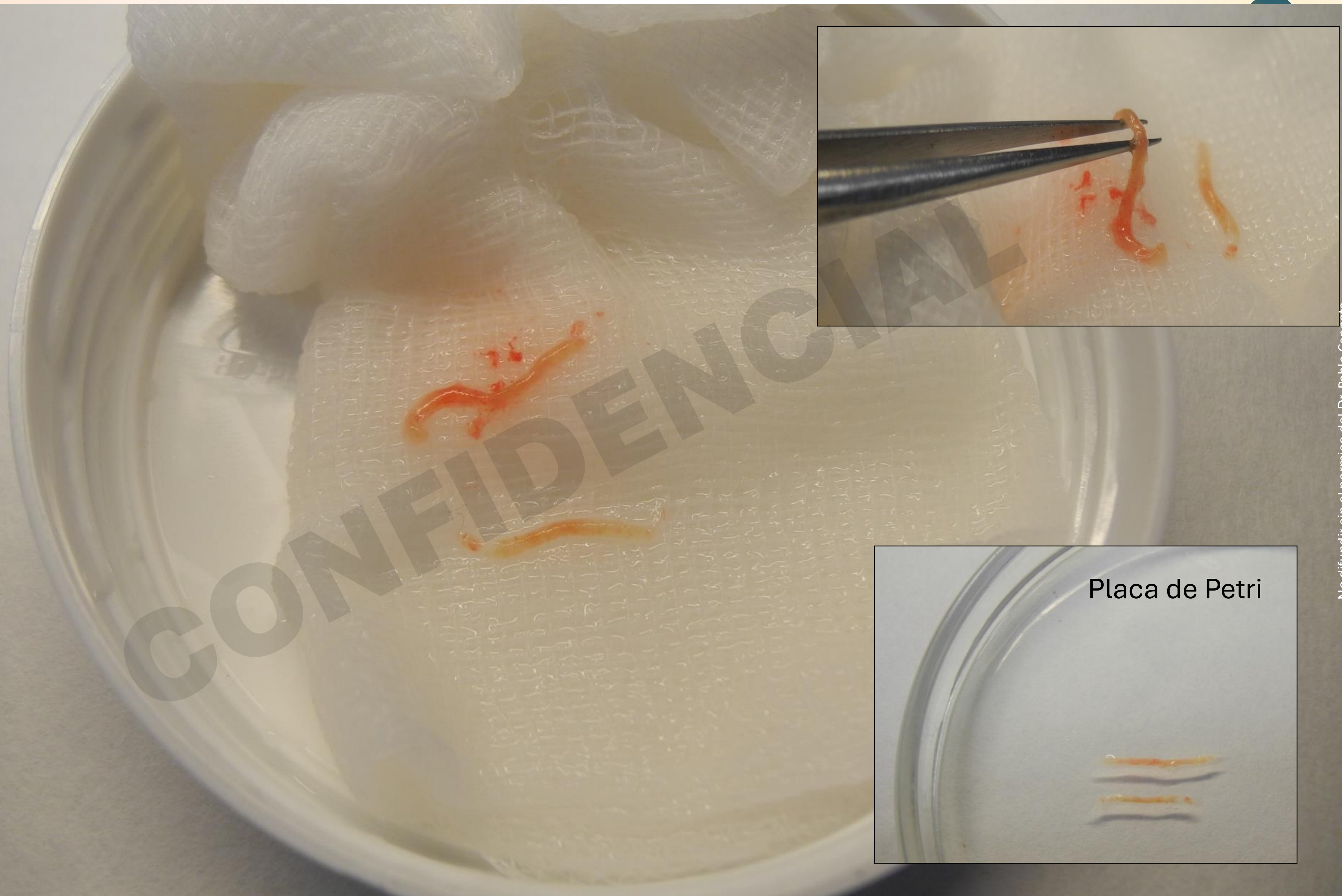
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- Anticuerpos utilizados: **IgG IgA, IgM, C3, C1q**, kappa lambda.
(C5b-9, C4d, albúmina, fibrinógeno).
- Se valora:
 - Anticuerpo/s positivo/s.
 - Intensidad de tinción: **0 / 1+ / 2+ / 3+**.
 - Patrón de positividad: granular, lineal, borroso (smudgy).
 - Distribución de la tinción: difusa; global; segmentaria; focal.
 - Topografía de la tinción: mesangial, subendotelial, subepitelial...

Importancia de la fase preanalítica: selección de fragmentos para cada técnica



Importancia de la fase preanalítica: selección de fragmentos para cada técnica





CONFIDENCIAL

Placa de Petri



Formulario de solicitud de biopsia renal

NHC: _____ Sexo: _____ Nombre y apellidos _____ Edad: _____
 Fecha de la biopsia _____ Hora _____ Número de cilindros remitidos _____
 Indicación de la biopsia: _____
☐ Síndrome nefrótico ☐ Síndrome nefrítico

Antecedentes personales

¿Tiene bx renal previa? ☐ NO / ☐ SÍ, diagnóstico: _____
☐ Diabetes ☐ HTA ☐ Obesidad ☐ Fumador ☐ GMSR ☐ AINES ☐ Tóxicos _____
☐ Otros _____

Breve resumen de historia clínica: _____

Trasplante:

CsA/Tacrolimus _____ Nefropatía nativa _____
 DSA _____ Fecha del trasplante _____ Datos donante _____

Serología y laboratorio:

CrS _____	Proteinuria 24h _____	Hb _____	Hematuria _____	FGR _____
Prot/Cr _____	Albuminuria _____	LDH _____	Otros _____	
ANA _____	ANCA _____	Anti-DNA _____	AntiMBG _____	
ssa/ssb _____	VHA _____	VHB _____	VIH _____	Sars-Cov 2 _____
FR _____	C3 _____	C4 _____	PLA2R _____	Crioglob. _____
SCL-70 _____	Kappa (suero) _____	Lambda (suero) _____	Ratio K/L (suero) _____	
Kappa (orina) _____	Lambda (orina) _____	Ratio K/L (orina) _____	Otros _____	

Juicio clínico: _____

Fecha y firma: _____

Formulario de solicitud de biopsia renal

NHC: _____ Sexo: _____ Nombre y apellidos _____ Edad: _____
 Fecha de la biopsia _____ Hora _____ Número de cilindros remitidos _____
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☐ Otros _____

Breve resumen de historia clínica: _____

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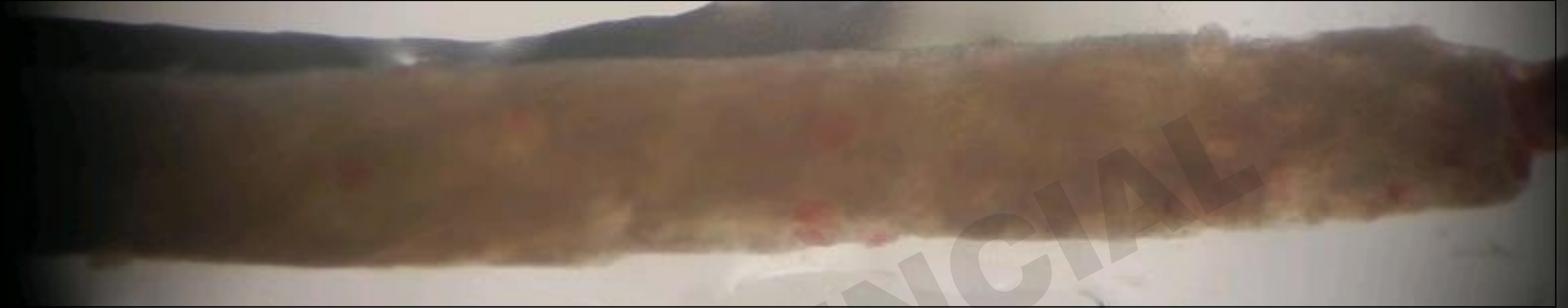
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CrS _____	Proteinuria 24h _____	Hb _____	Hematuria _____	FGR _____
Prot/Cr _____	Albuminuria _____	LDH _____	Otros _____	
ANA _____	ANCA _____	Anti-DNA _____	AntiMBG _____	
ssa/ssb _____	VHA _____	VHB _____	VIH _____	Sars-Cov 2 _____
FR _____	C3 _____	C4 _____	PLA2R _____	Crioglob. _____
SCL-70 _____	Kappa (suero) _____	Lambda (suero) _____	Ratio K/L (suero) _____	
Kappa (orina) _____	Lambda (orina) _____	Ratio K/L (orina) _____	Otros _____	

Juicio clínico: _____

Fecha y firma: _____

MO



MO



IFD



ME



Selección del tejido para técnicas de MO, IFD y ME



ME (1-2 mm; 2-3 glomérulos)

IFD (5-10 glom.)

**Congelar
tejido**

↑Artefacto de congelación

Directamente en el **criostato**

Inmersión en **nitrógeno líquido**

Selección del tejido para técnicas de MO, IFD y ME



ME (1-2 mm; 2-3 glomérulos)

IFD (5-10 glom.)

**Congelar
tejido**

↑Artefacto de congelación

Directamente en el **criostato**

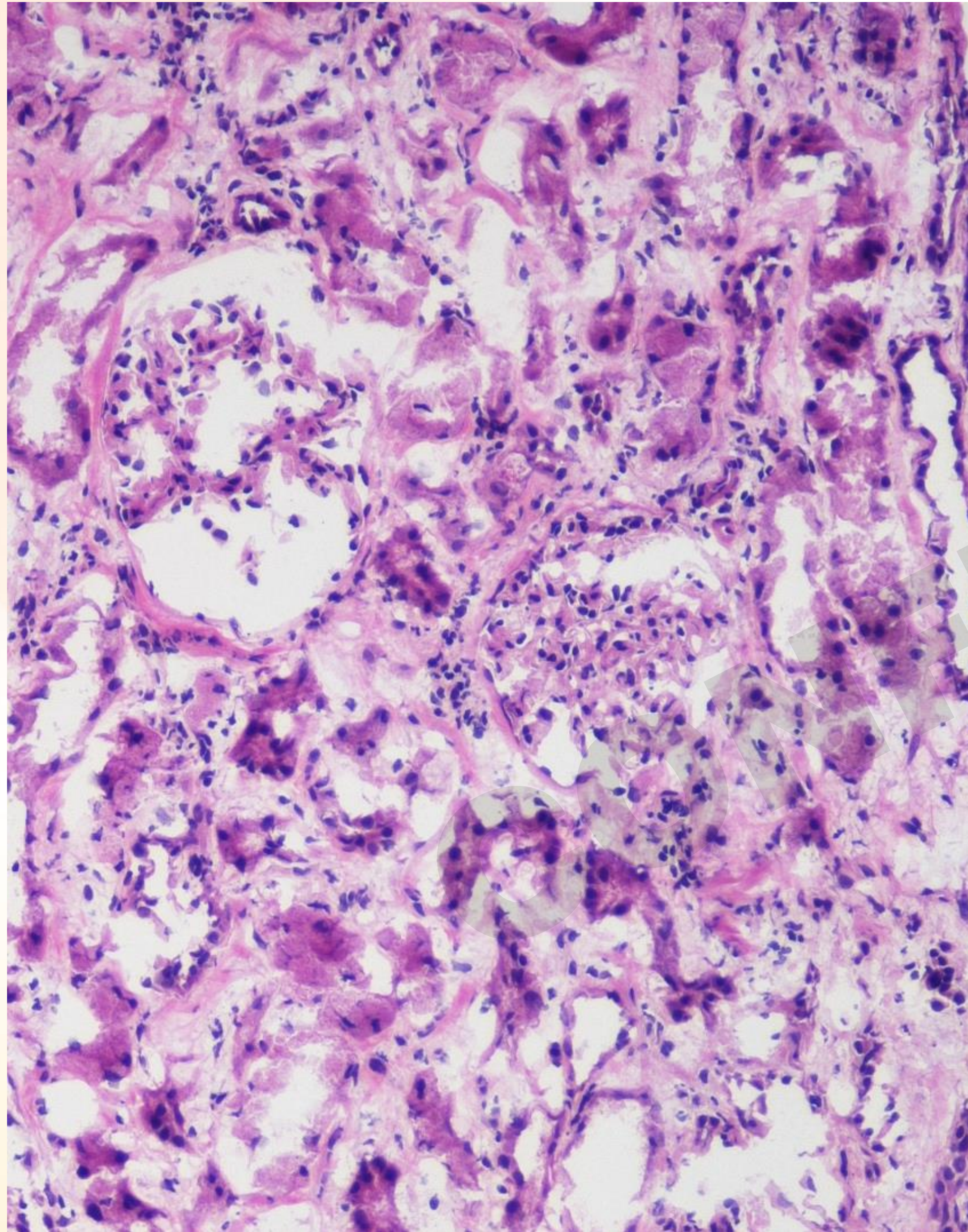
Inmersión en **nitrógeno líquido**

Inmersión en **isopentano/metilbutano**
a baja temp.

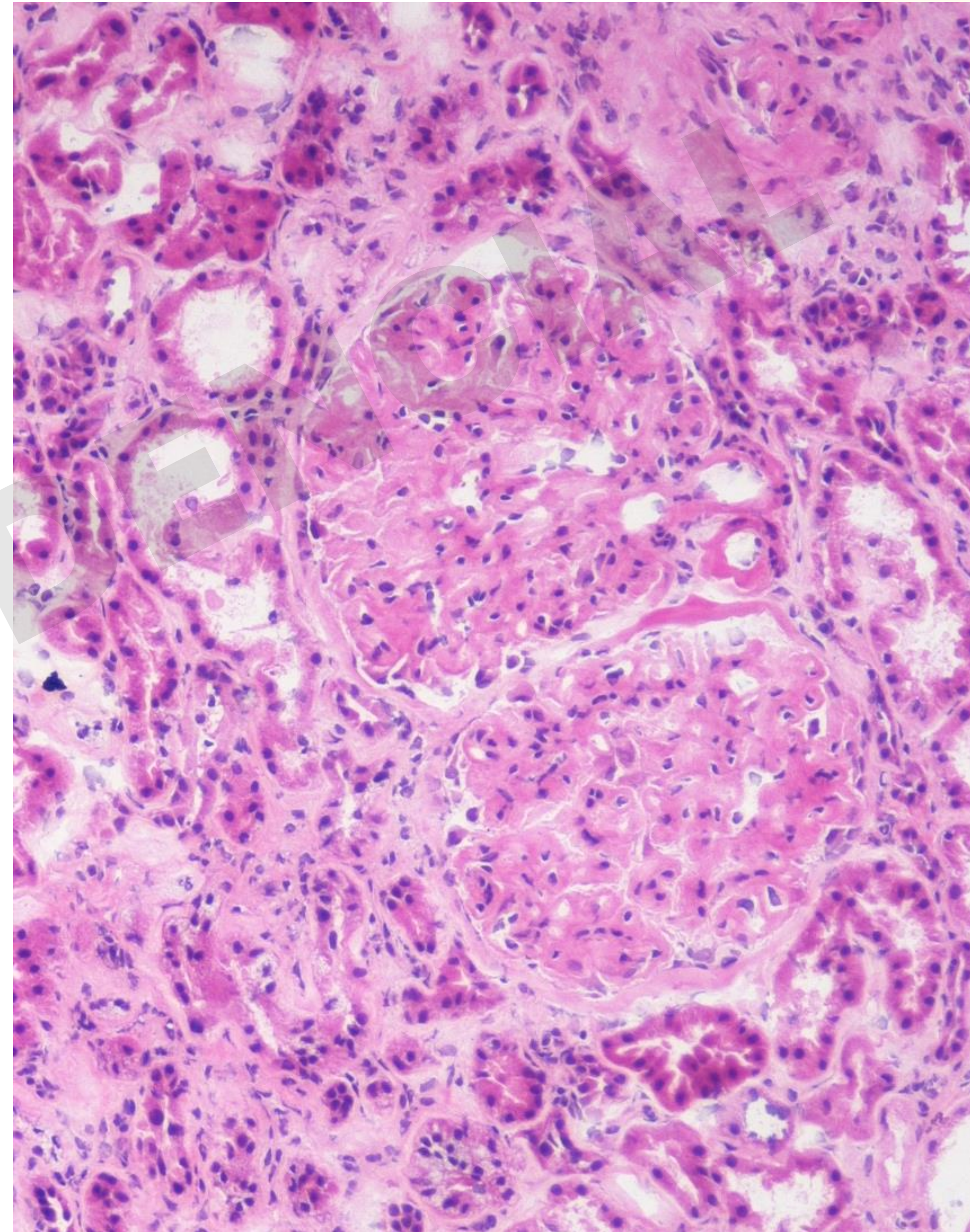
Criogenización rápida
(*PrestoChill*)

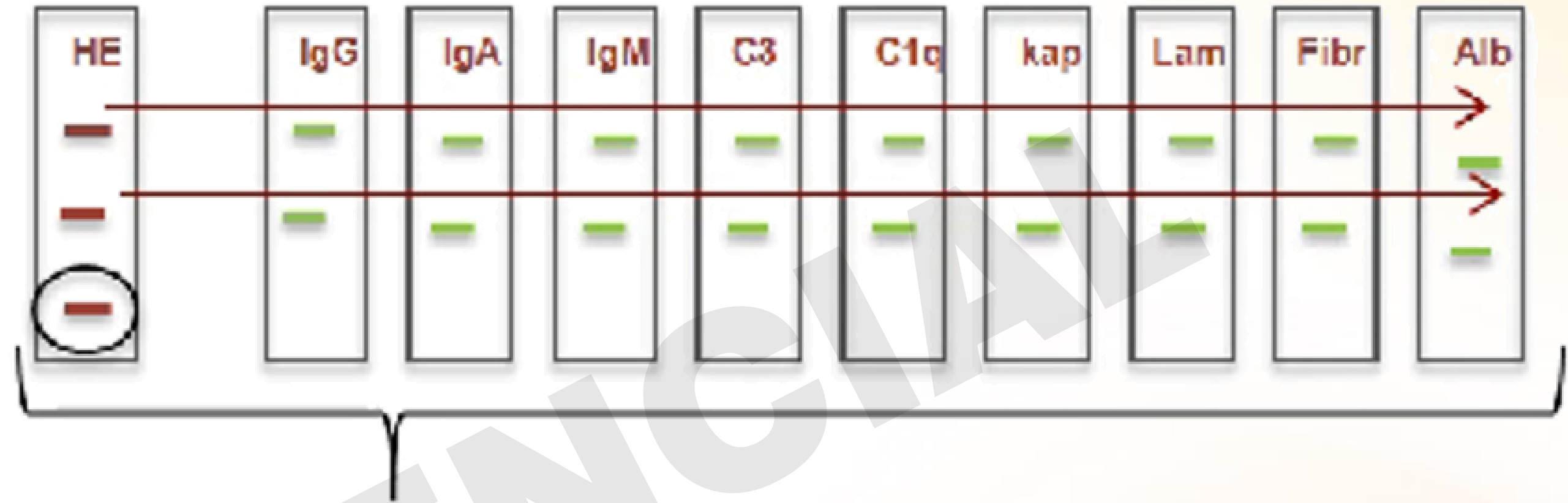


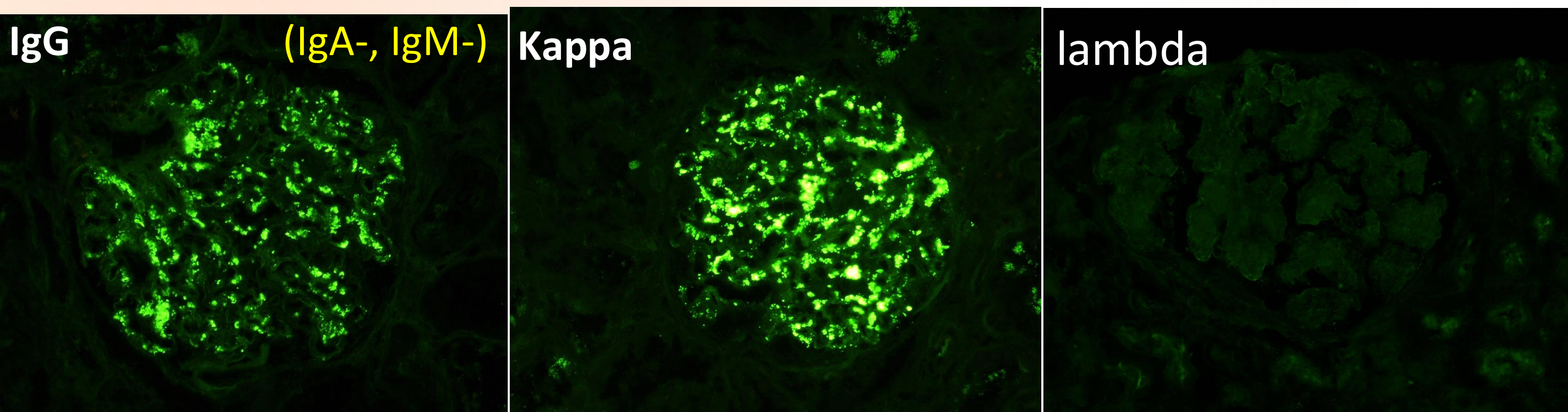
Congelado en **criostato**



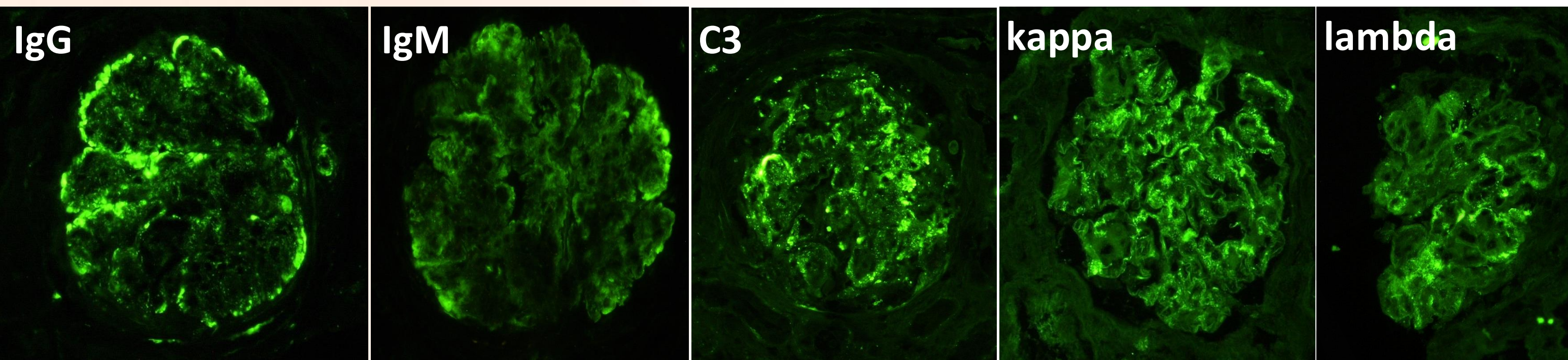
Congelado en **metilbutano**



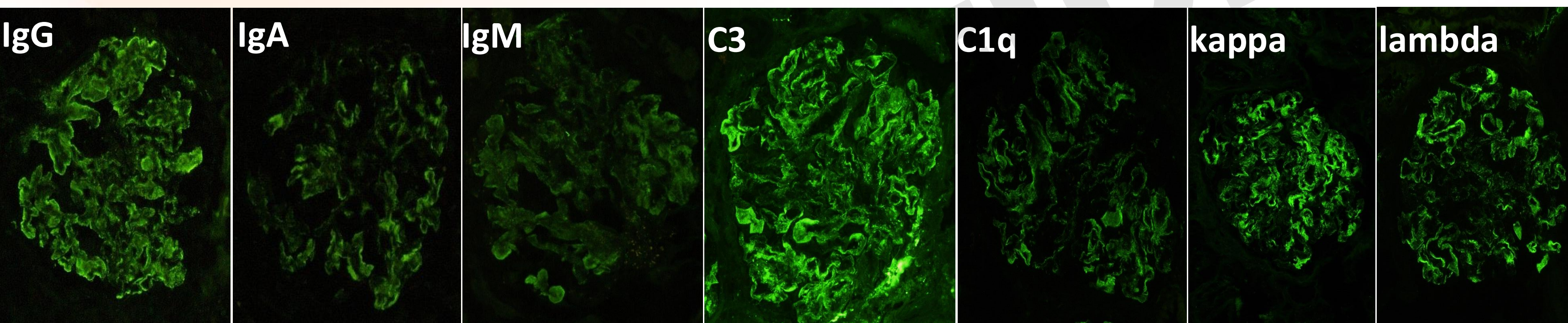




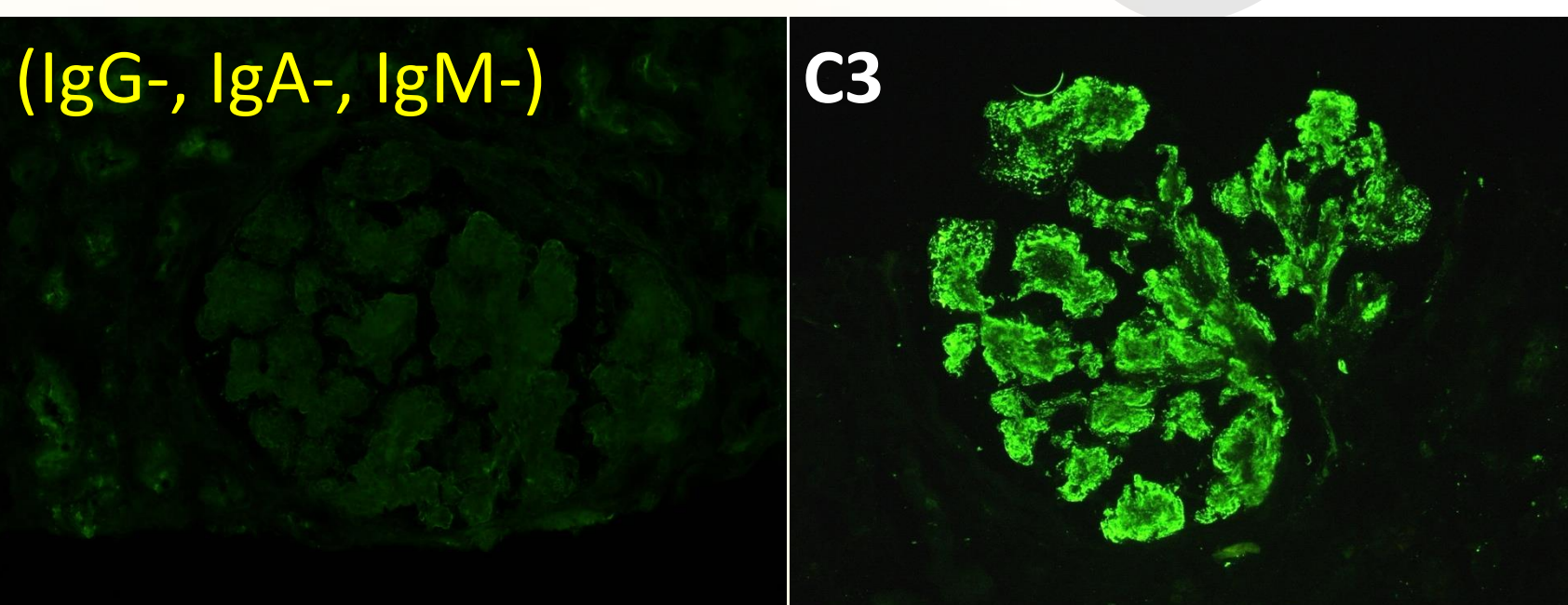
→ Monotypic disease



→ Infection associated MPGN

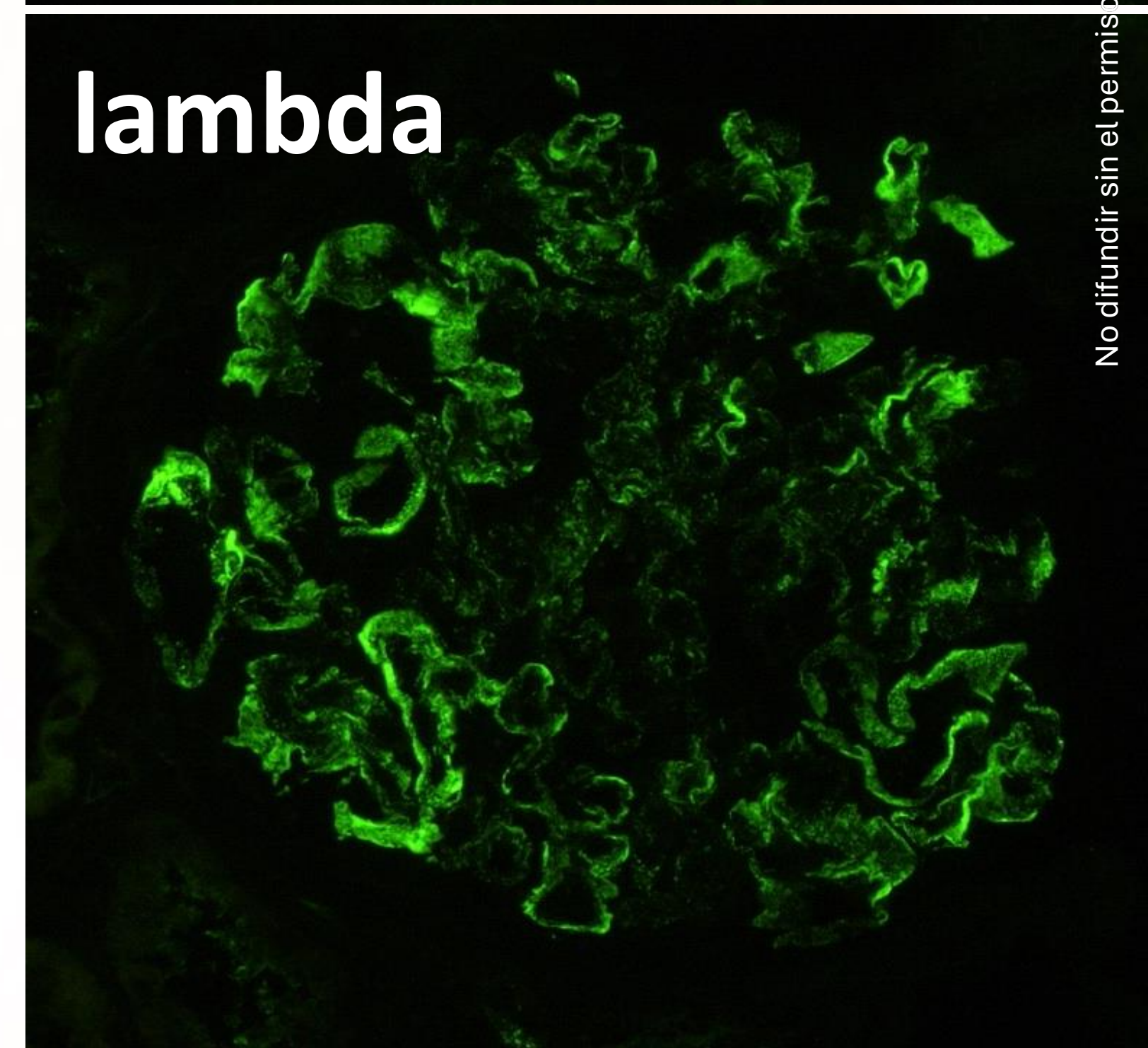
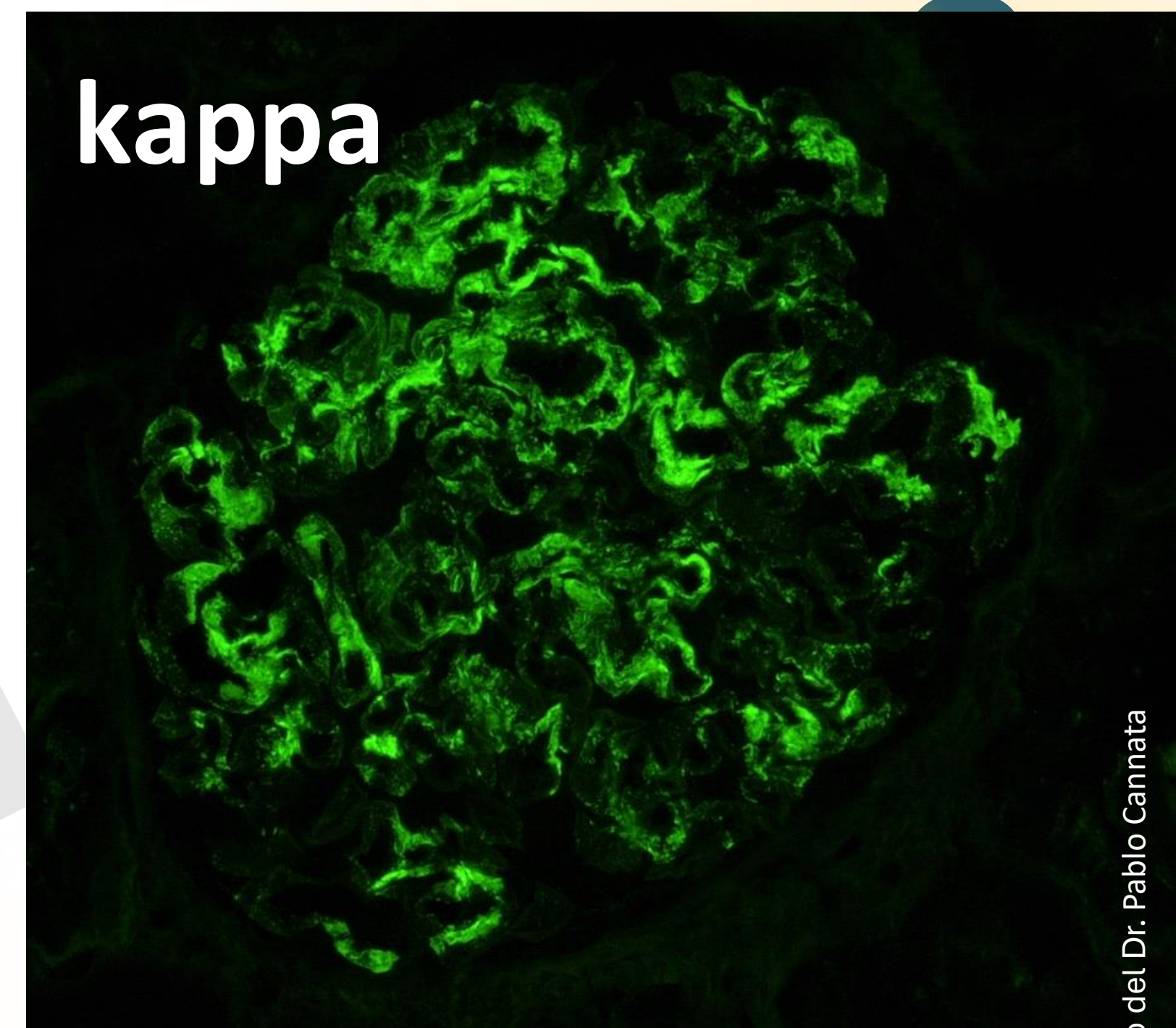
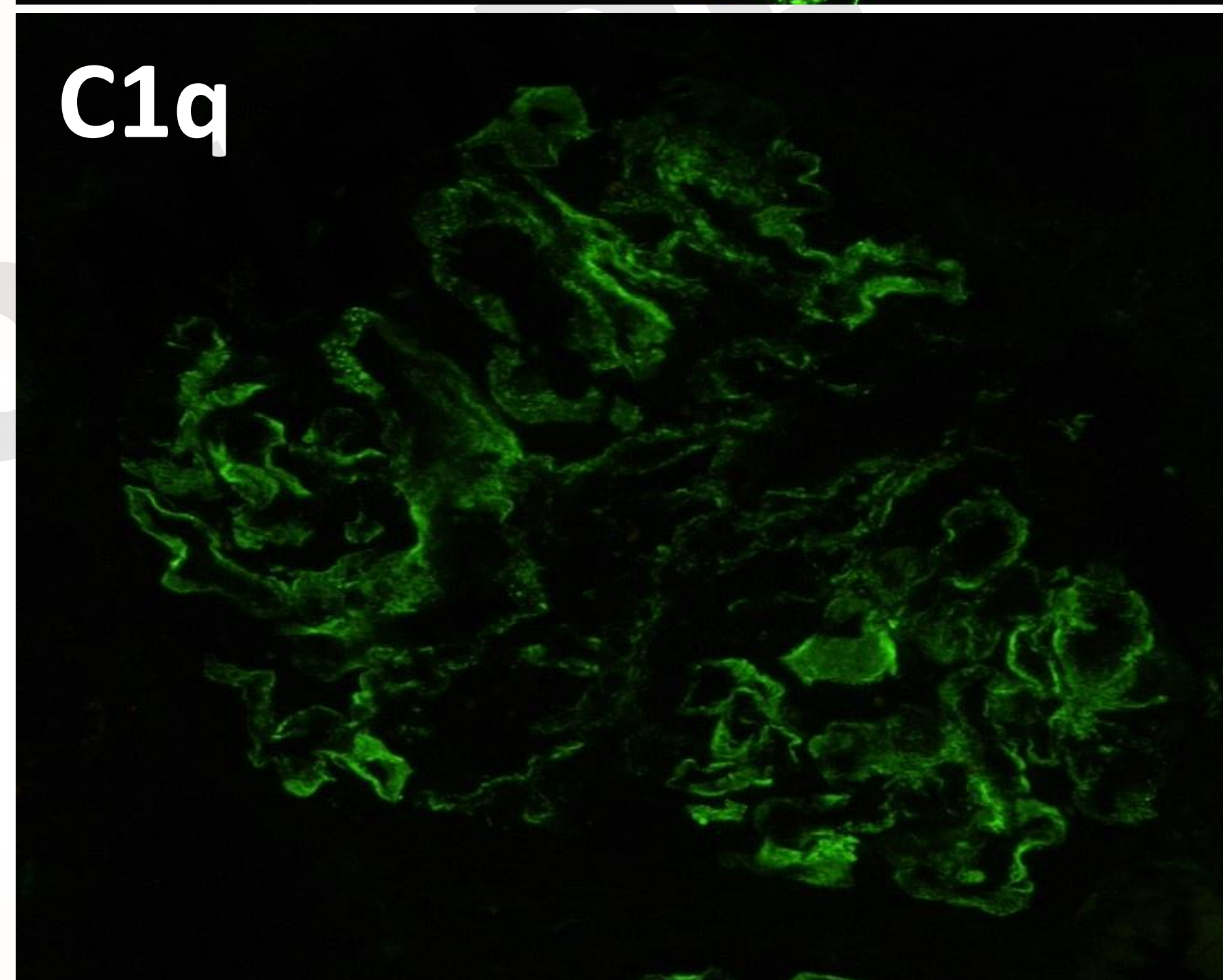
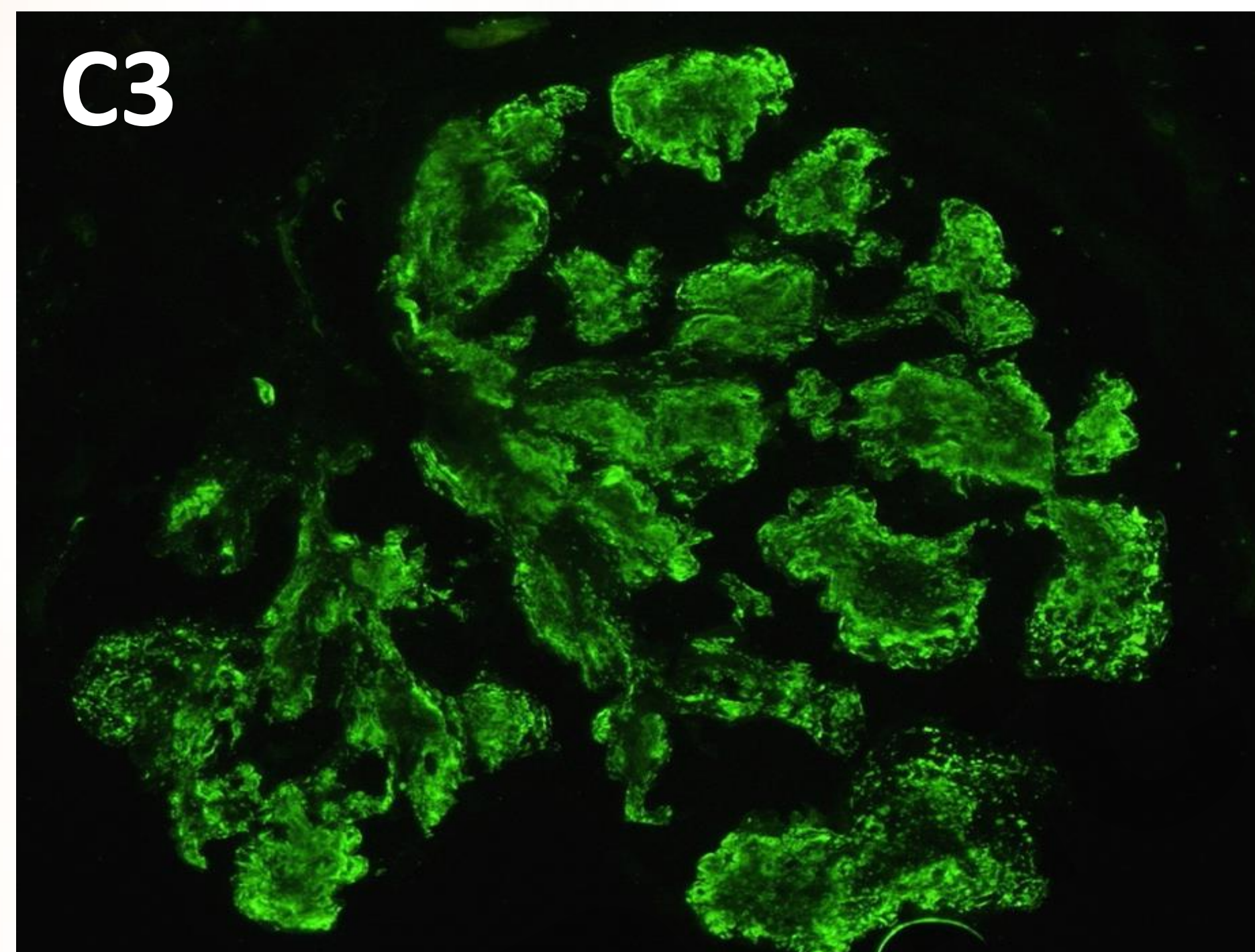
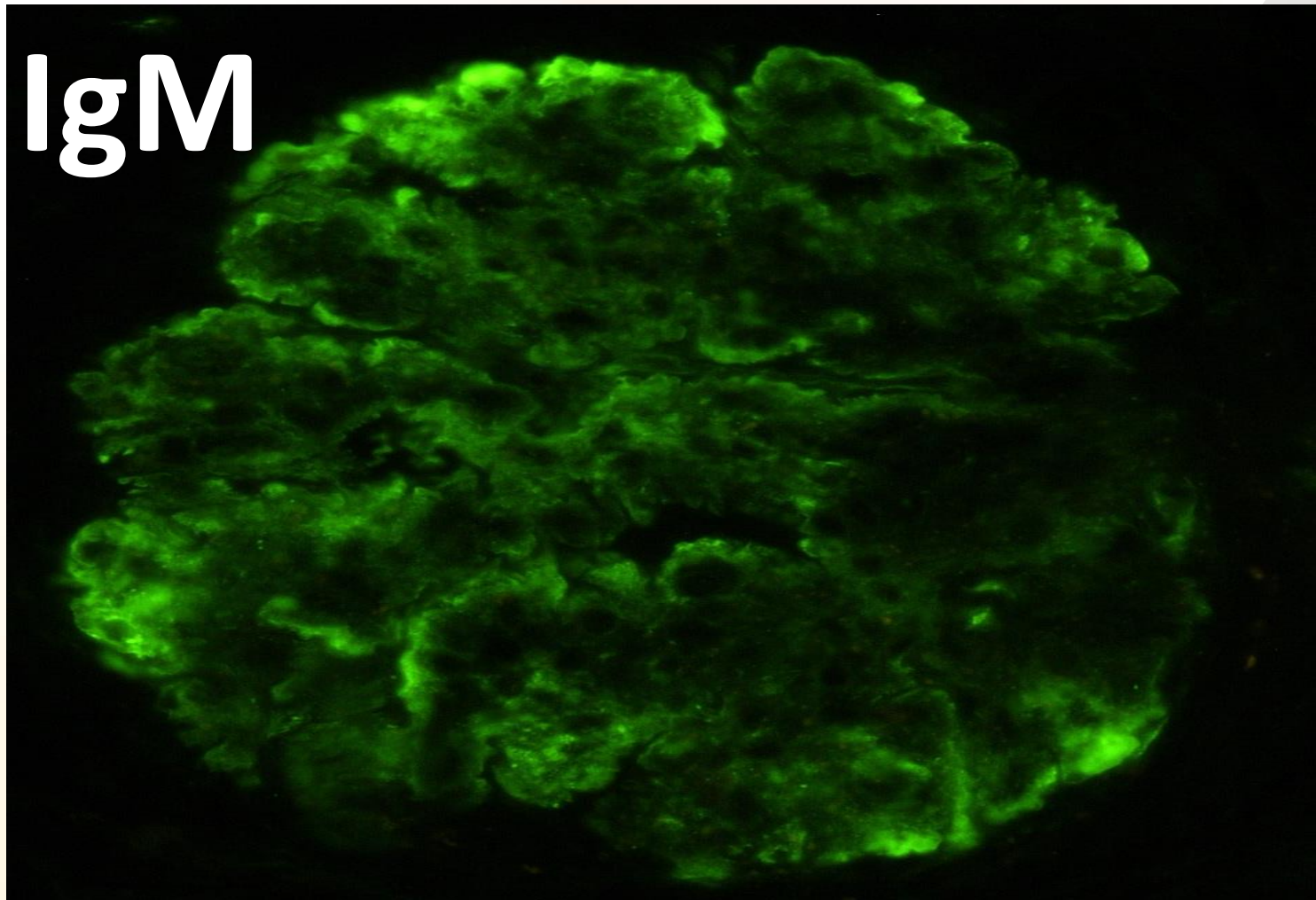
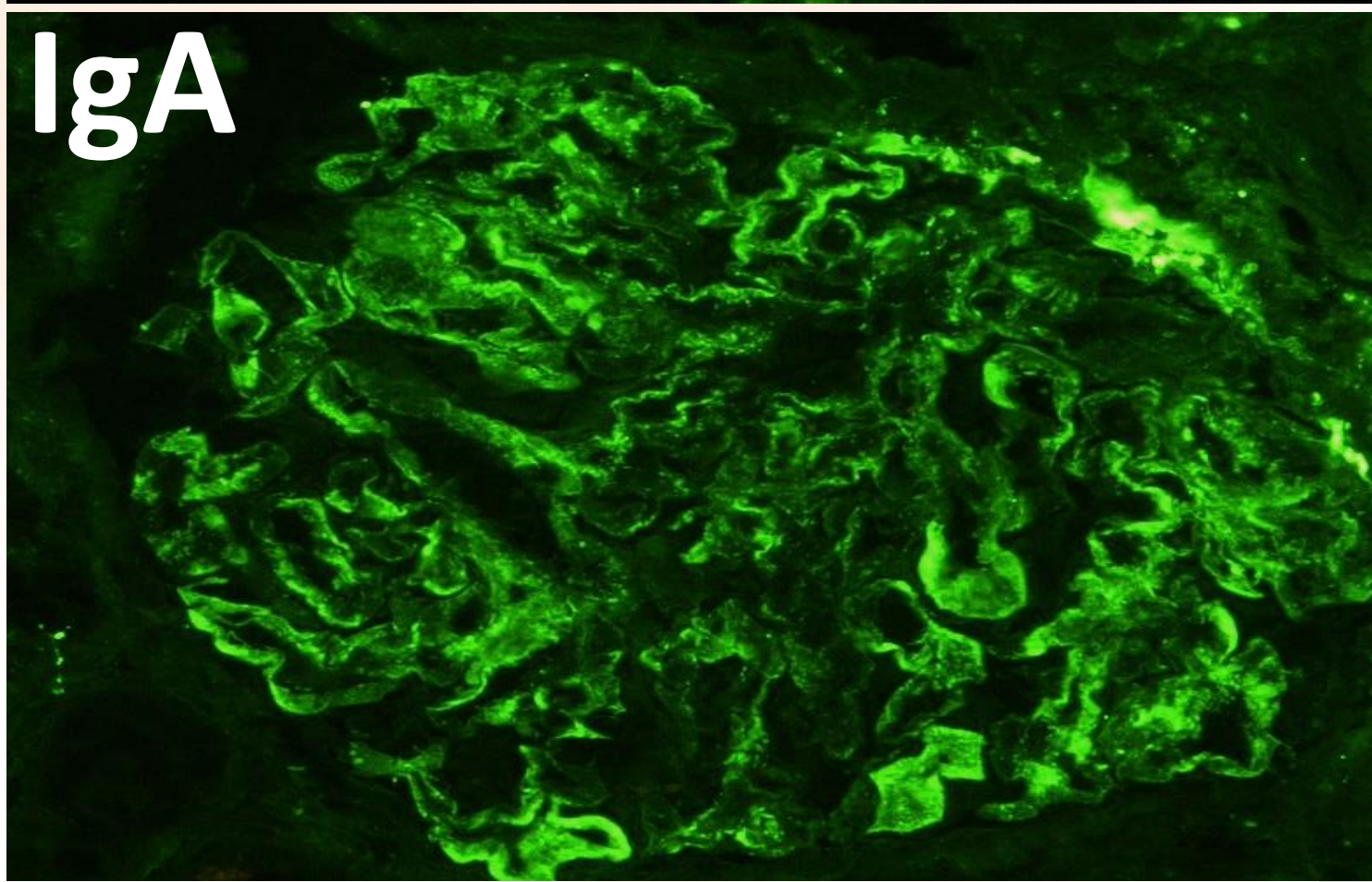
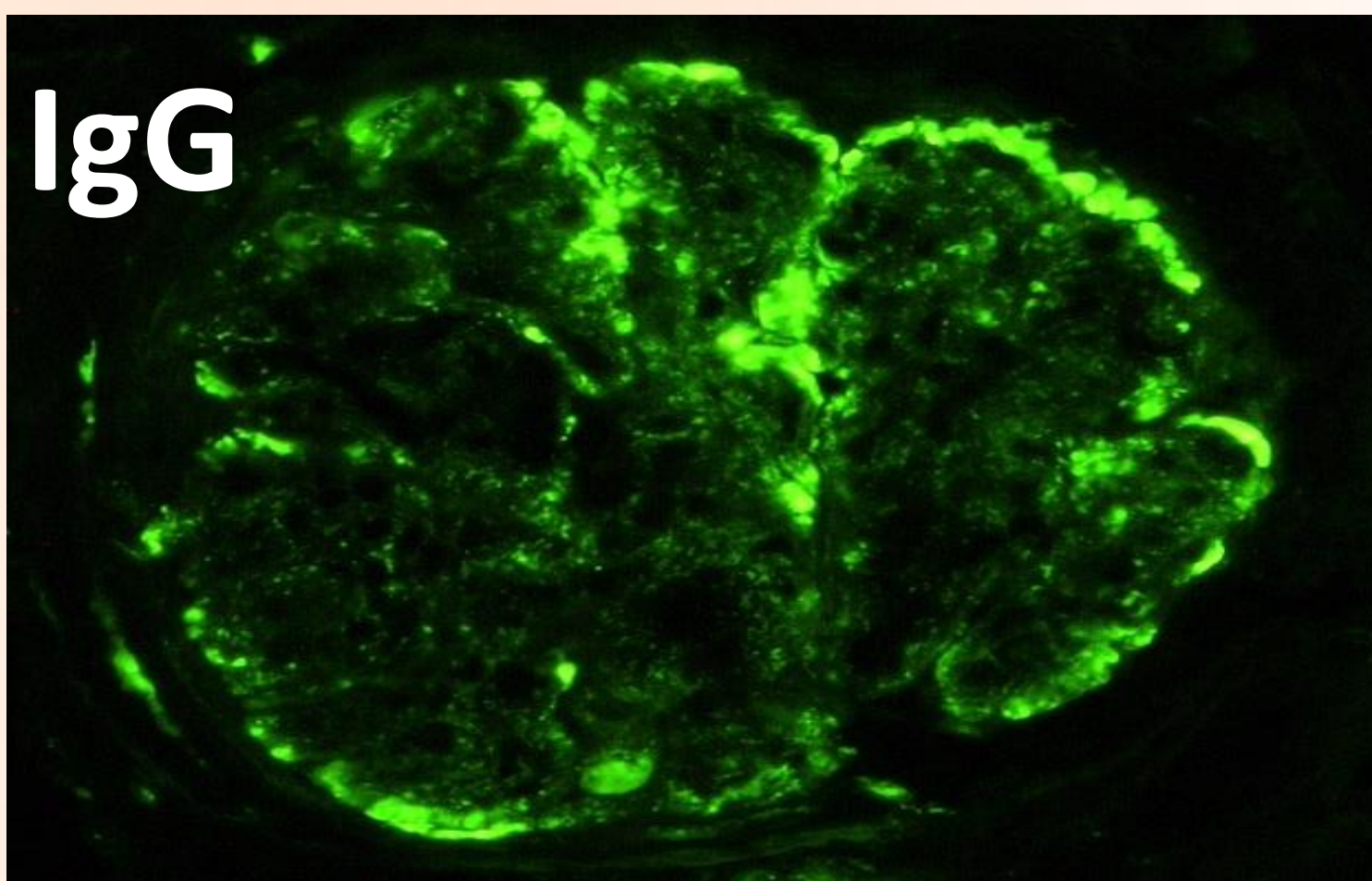


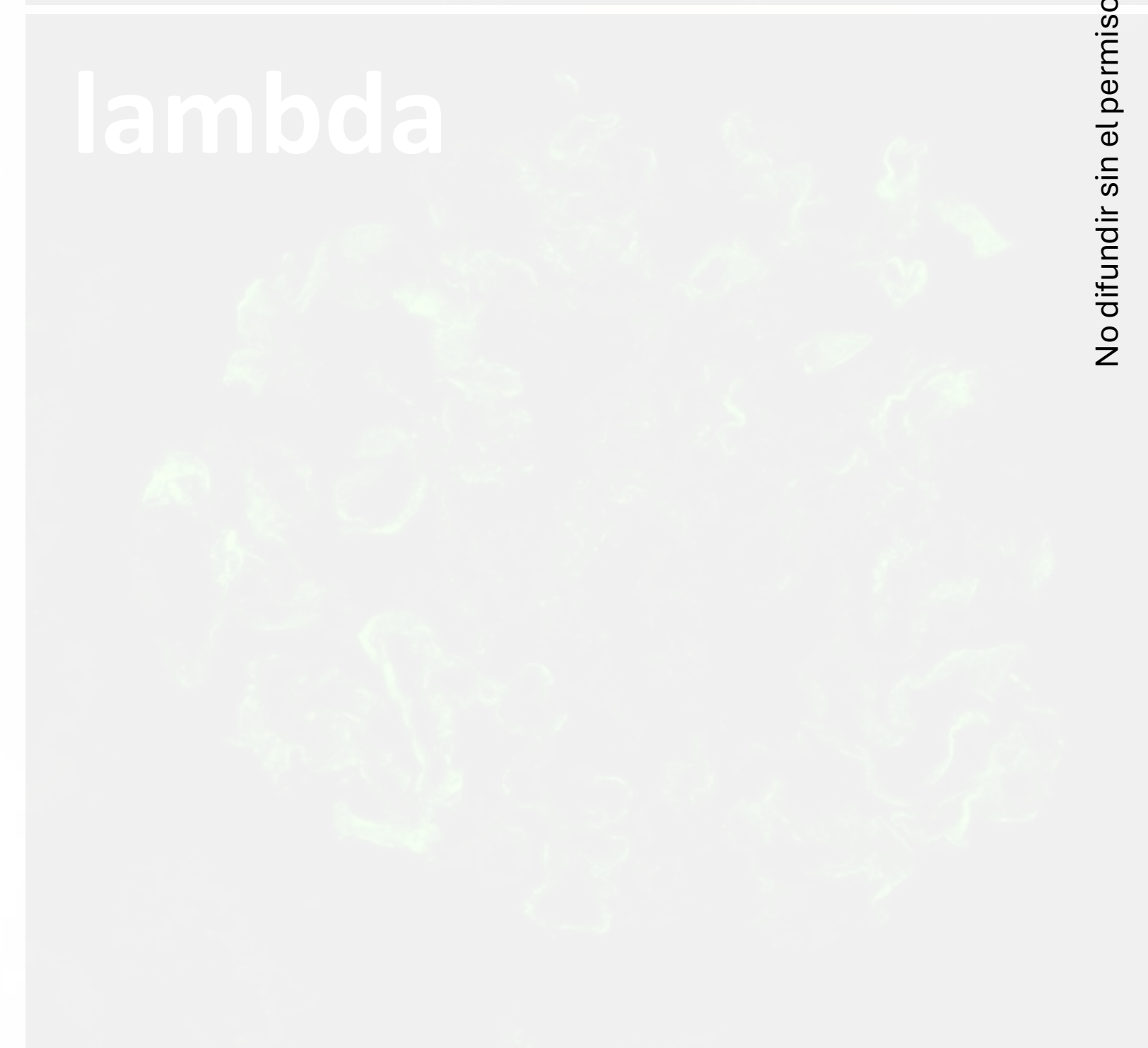
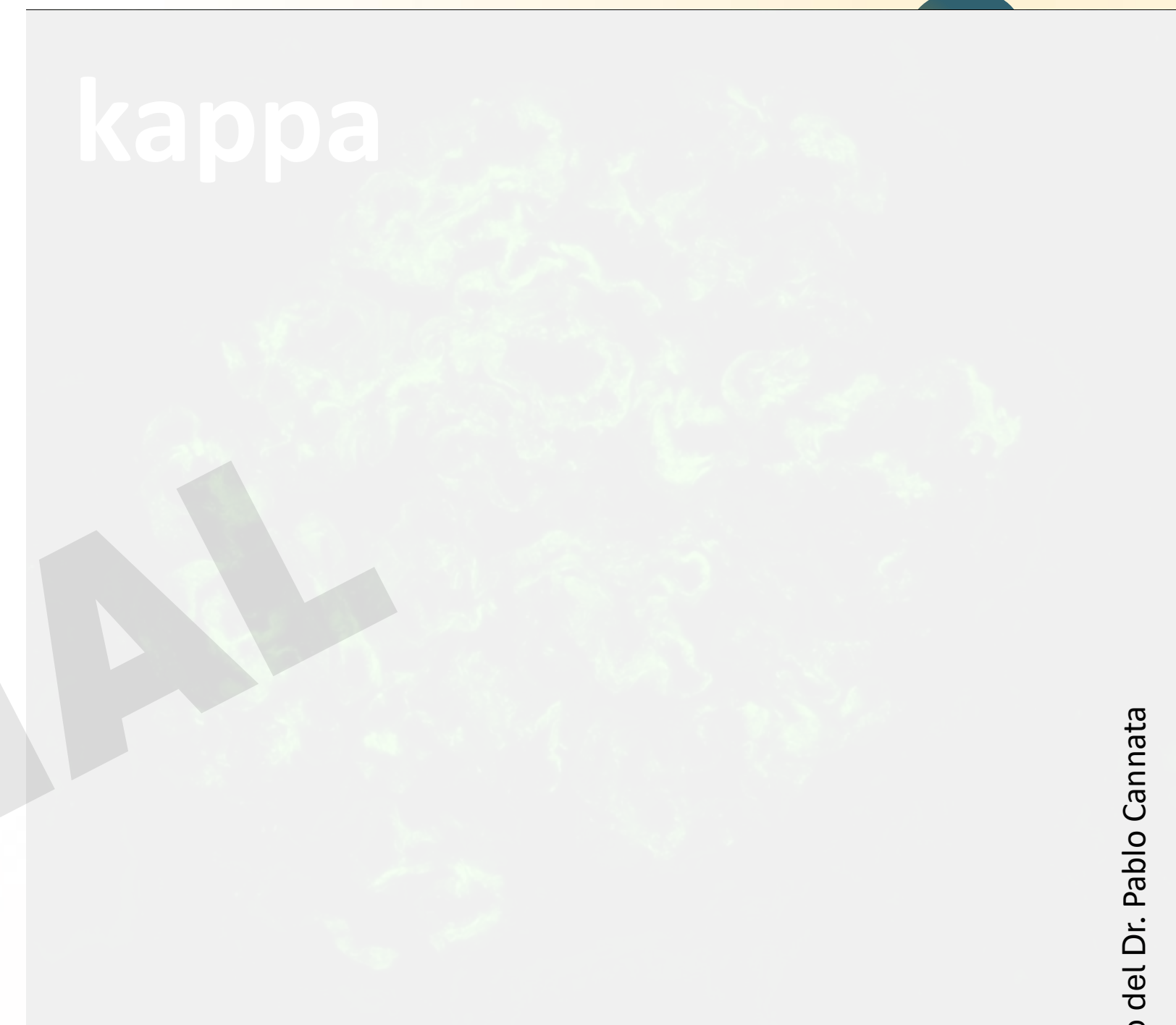
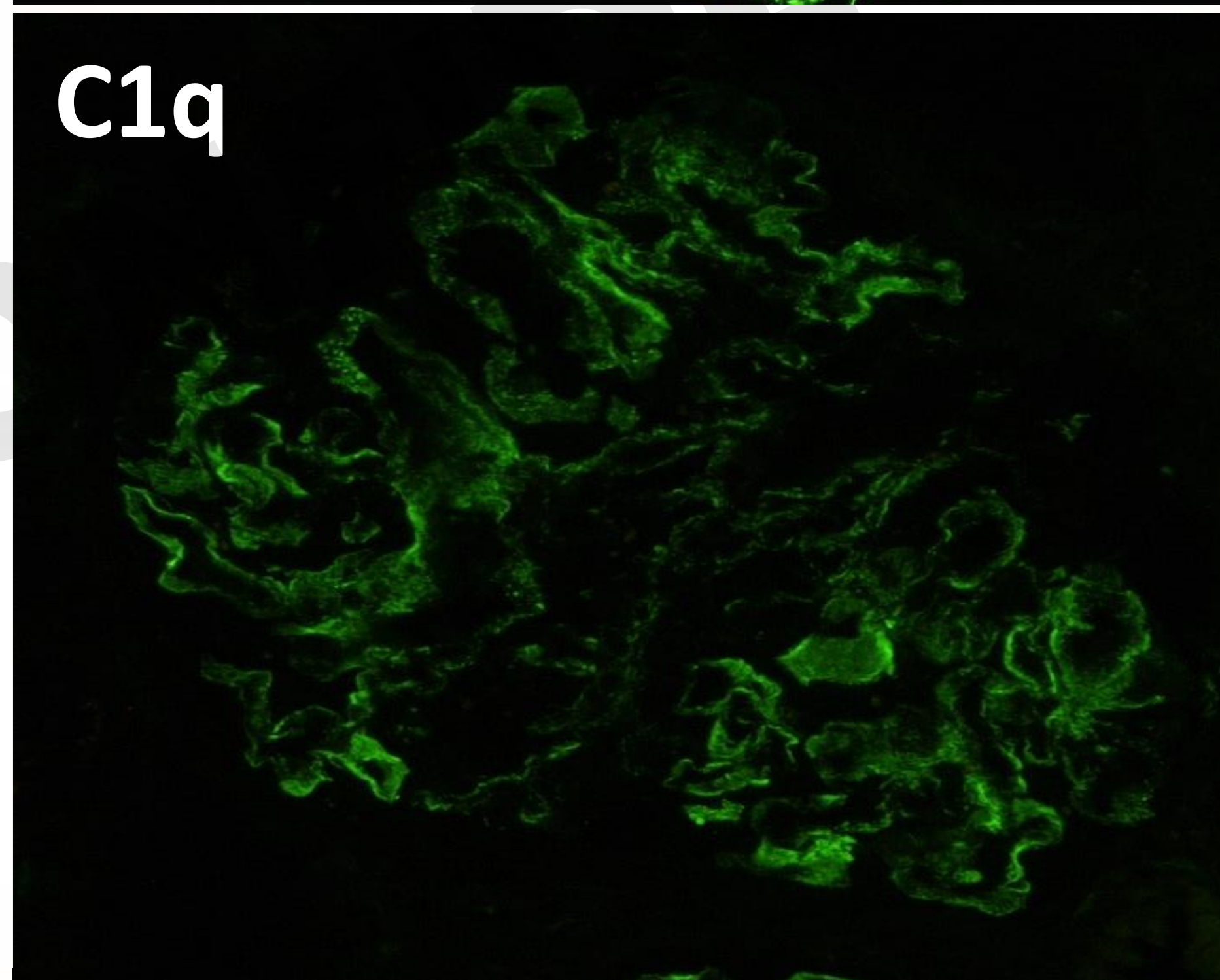
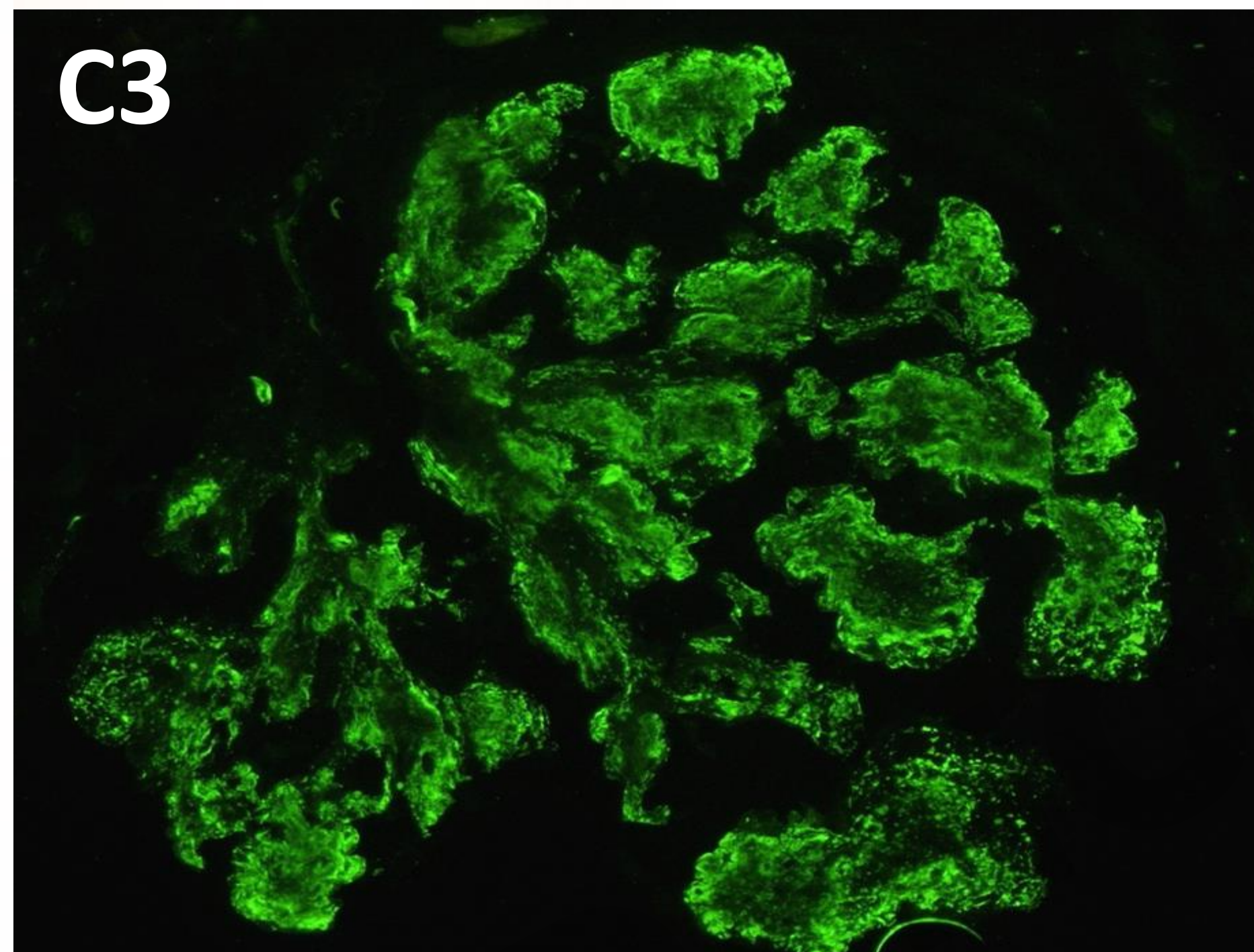
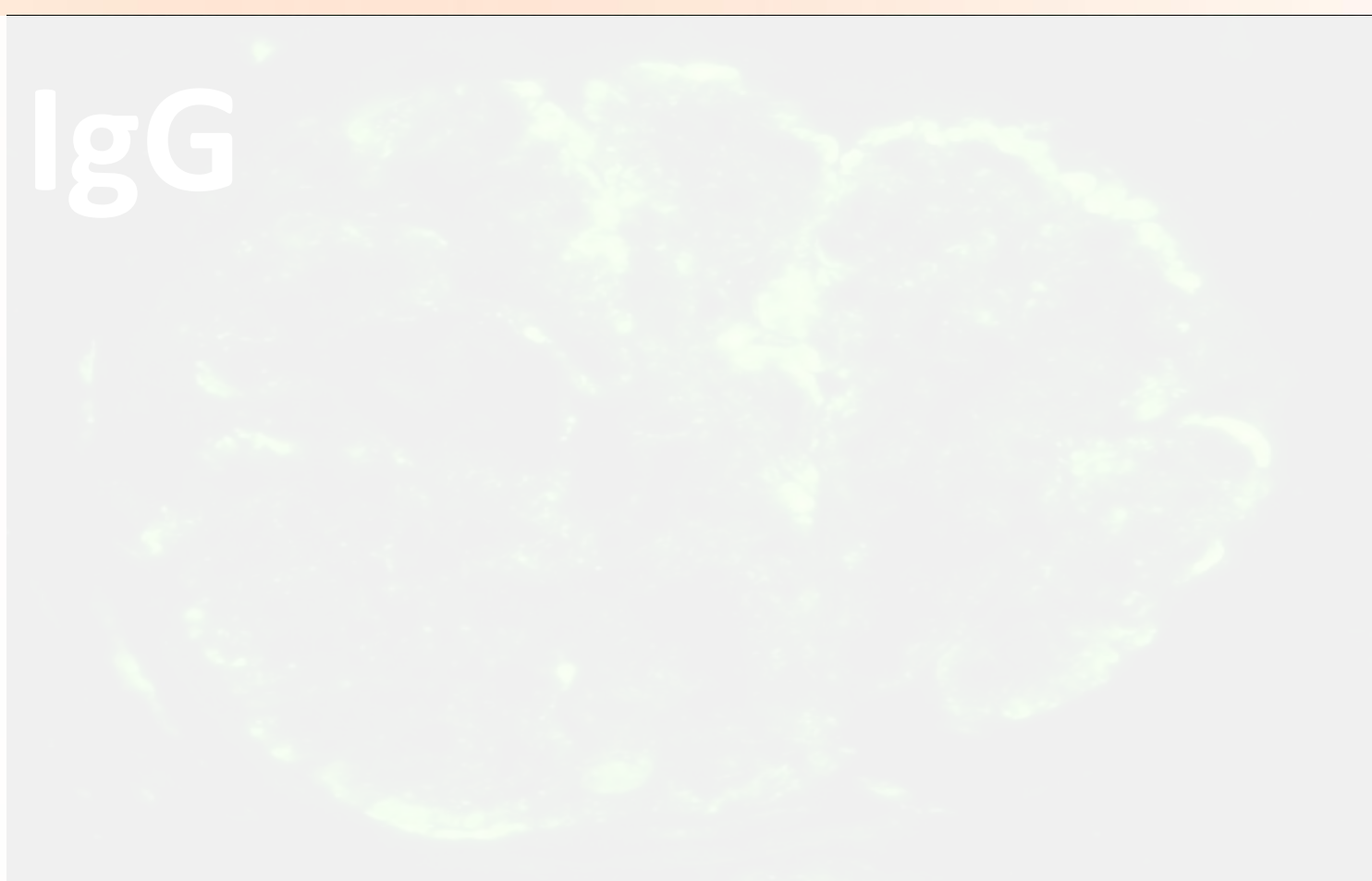
→ AI associated MPGN

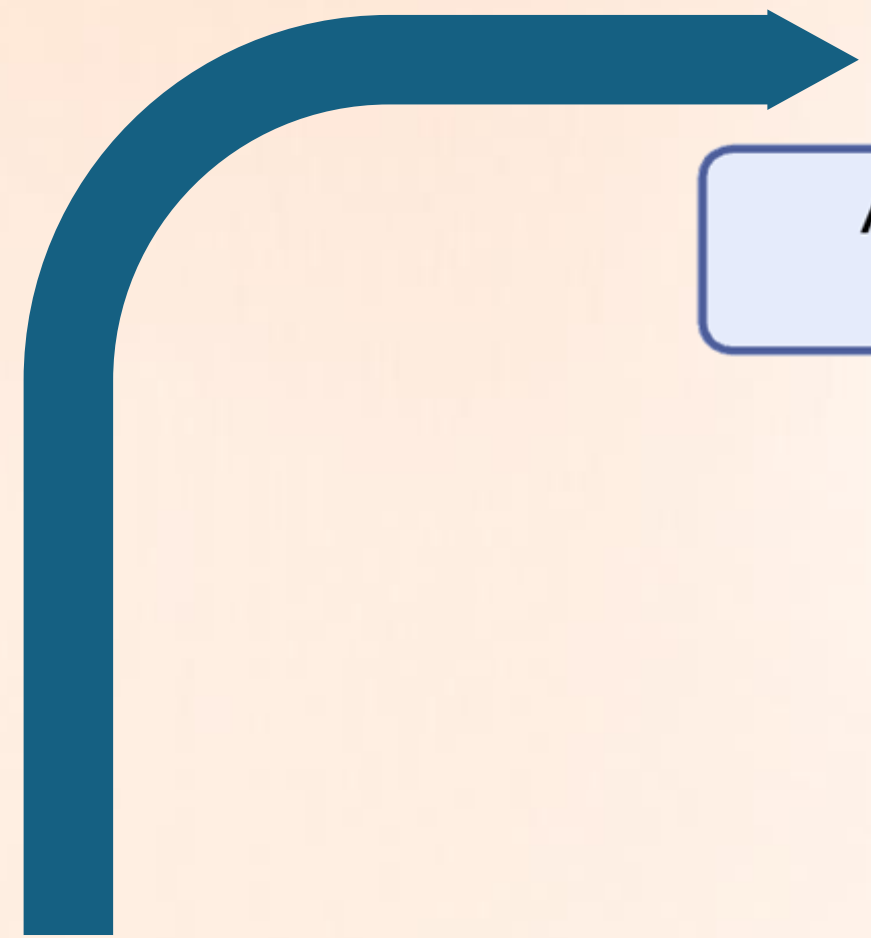


→ C3G

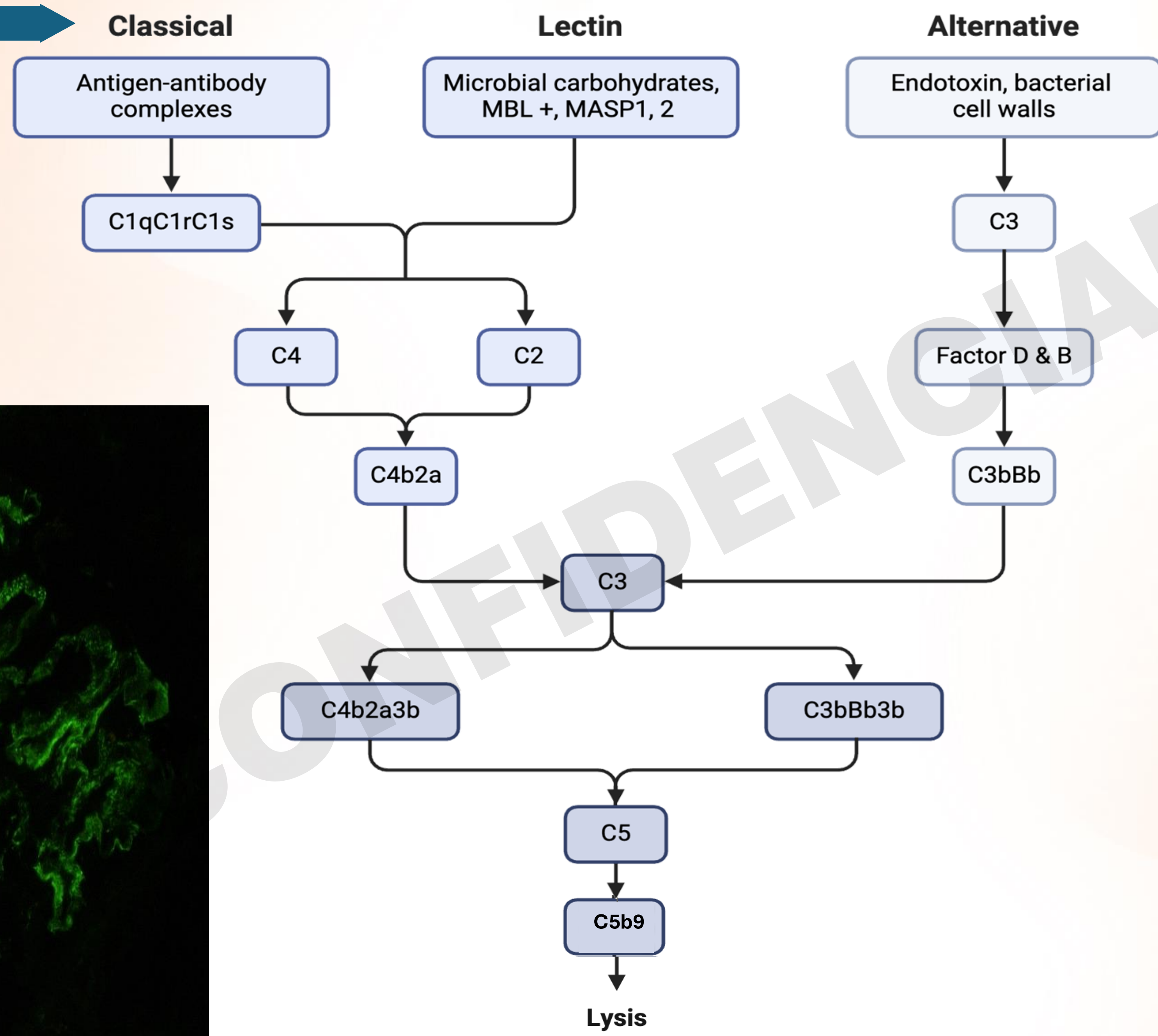
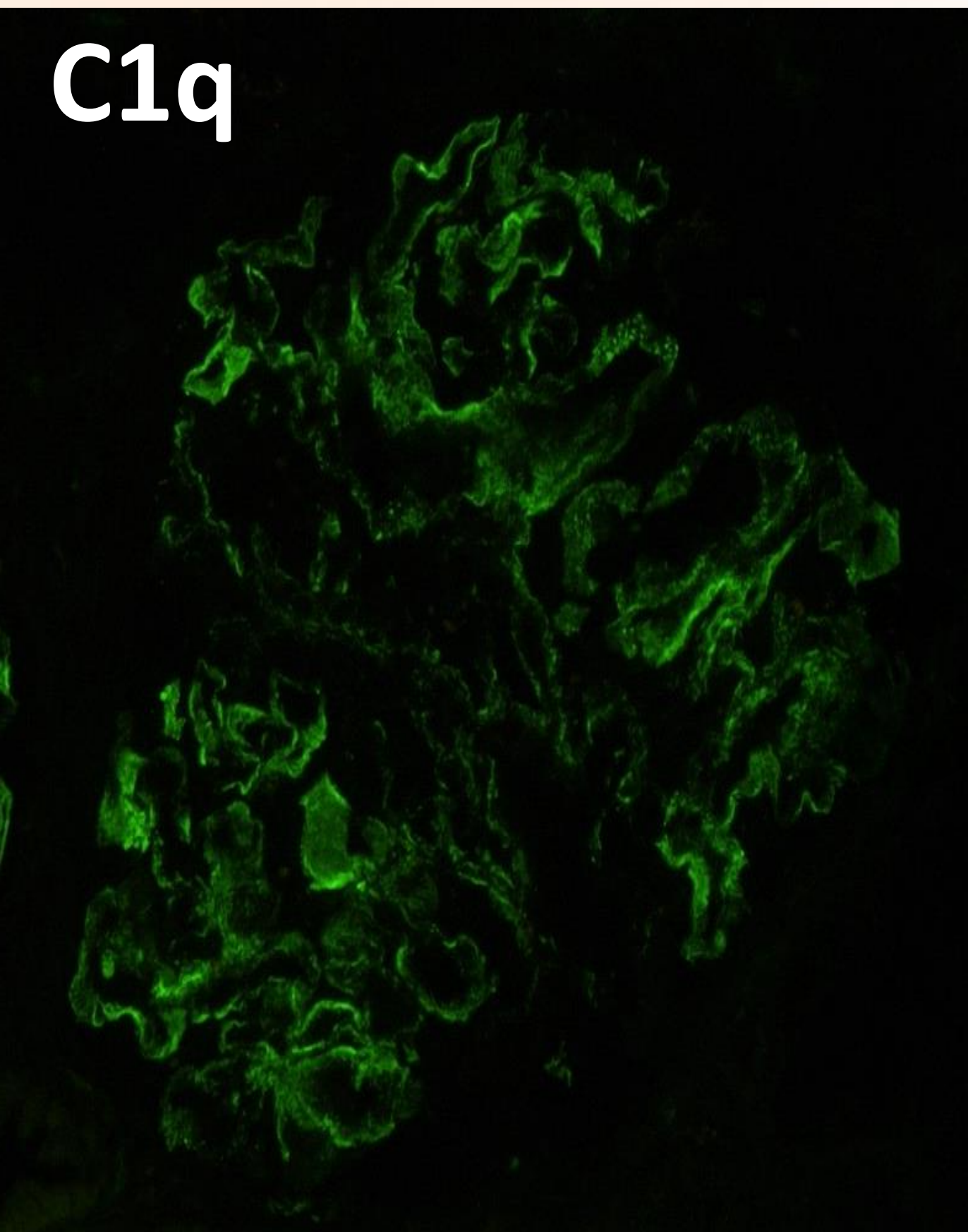
- C3GN
- DDD

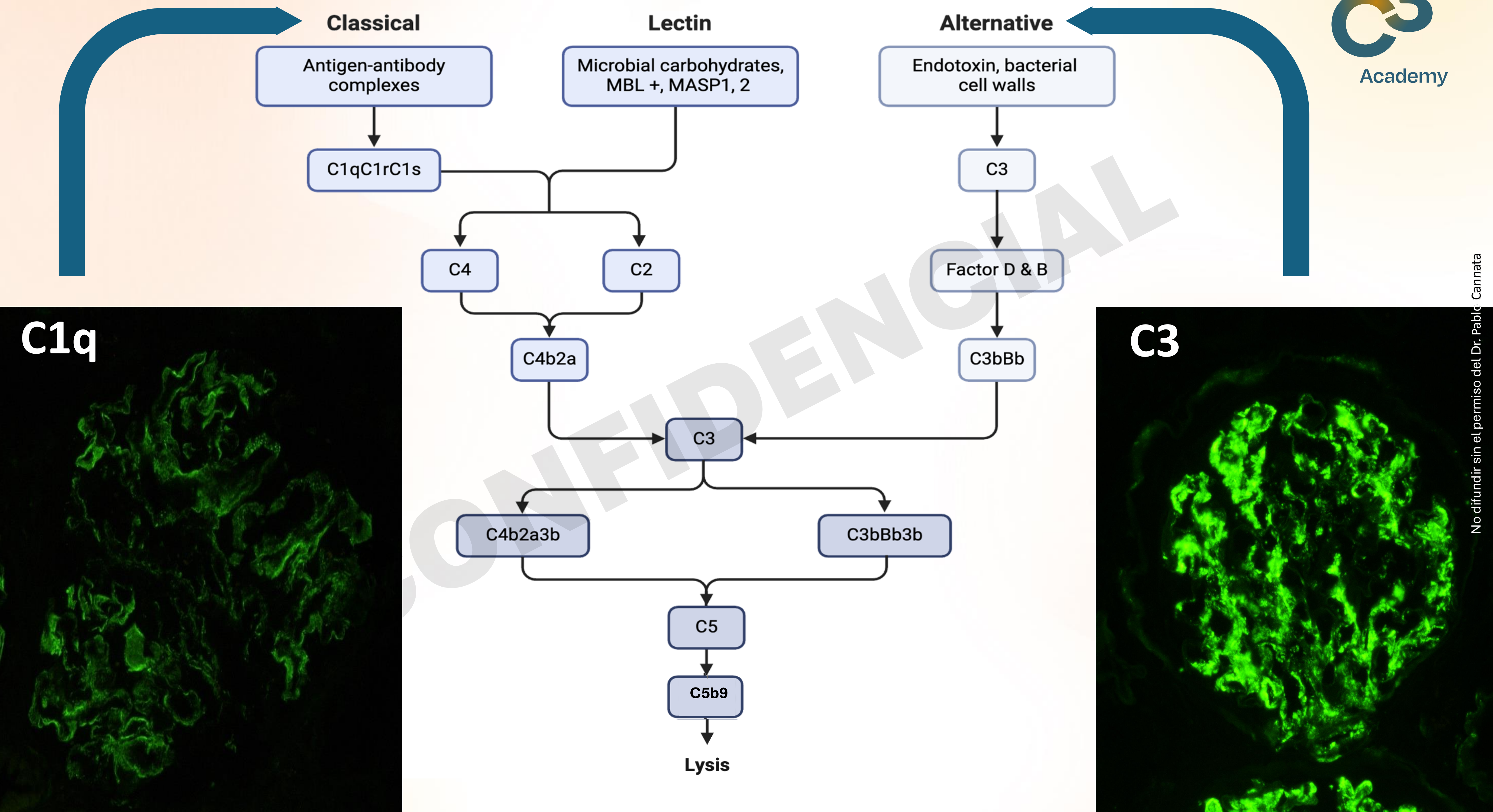






C1q





Kidney360 6: 645–647, April, 2025

n=108

Intensity of Glomerular C3 Deposits in IgA Nephropathy Predicts Early KRT

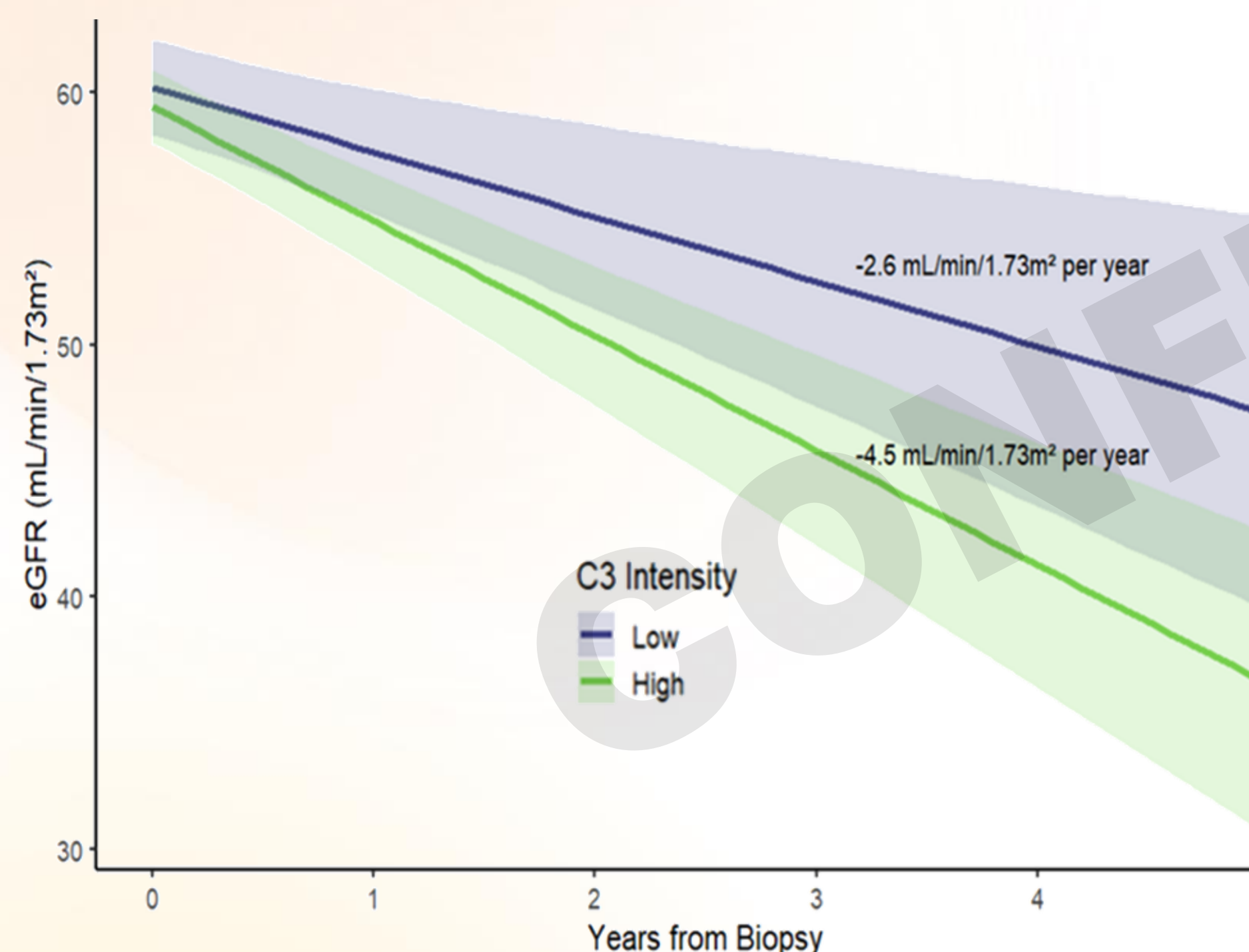
João Venda ¹, Beatriz Ferreira ¹, Andreia Henriques ¹, Pedro Castro ¹, Rita Leal ^{1,2}, Luís Rodrigues ^{1,2},
Vitor Sousa ^{2,3}, Ana Galvão^{1,2} and Rui Alves ^{1,2}

Kidney360 6: 645–647, 2025. doi: <https://doi.org/10.34067/KID.0000000735>

Glomerular C3 staining is an independent predictor of renal survival in IgAN: findings from the UK RaDaR cohort and its nested GPT-4o data extraction study

Sherry Masoud, David Pitcher, Katie Wong, Yunsoo Kim, Alex Shavick, Adam P Levine, Jonathan Barratt, Daniel P Gale, Ian SD Roberts

Figure 1. 5-year eGFR trajectory stratified by C3 intensity on biopsy (liner mixed model)*



n=571

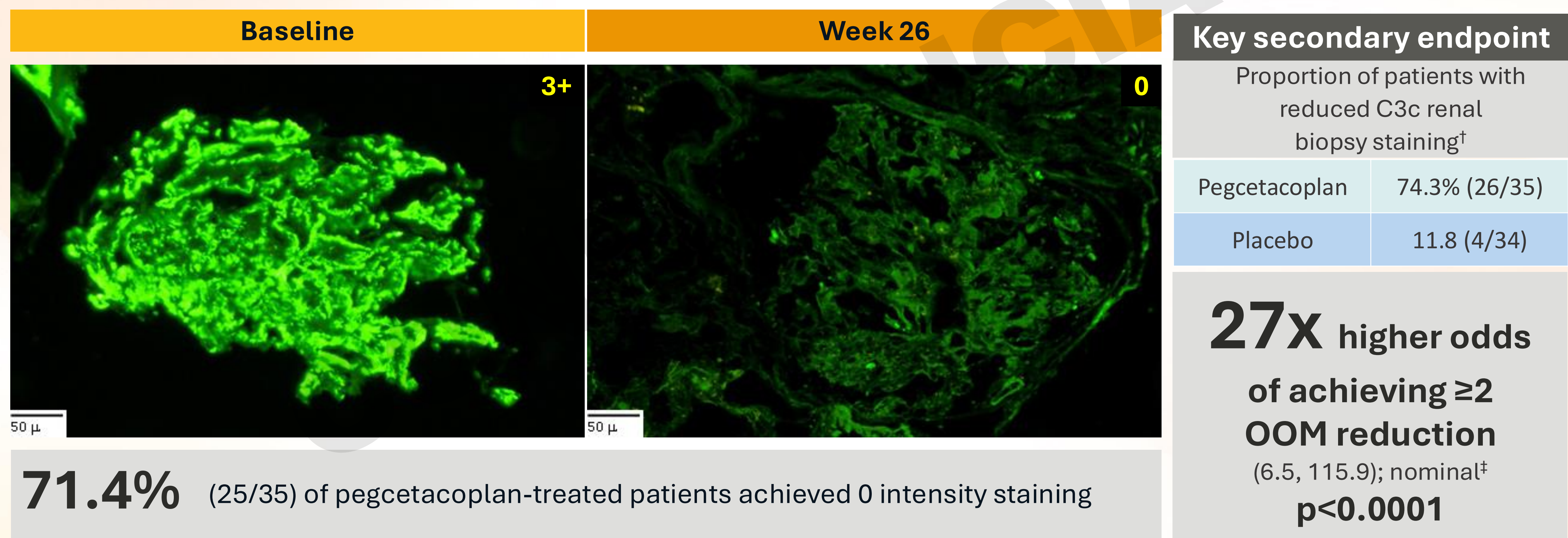
La intensidad glomerular de C3
<2+ (baja) vs. >2+ (alta)
predice la *pérdida de función renal* y *evolución a ERCA*.

* Adjusted for PCR, eGFR, Age, Sex, MEST-C scores

Phase 3 VALIANT secondary endpoint: Week 26

≥2 OOM C3c reduction in biopsy

Renal biopsies from a pegcetacoplan-treated C3G native kidney patient:



[†]Difference defined as ≥2 OOM at Week 26 vs baseline; in all adults. Baseline renal biopsies were not required for adolescent participants. [‡]Statistical testing stopped after first endpoint to not reach significance between treatment arms (i.e. change in activity score of C3G histological index score at Week 26 vs baseline). C3c, complement 3c; C3G, complement 3 glomerulopathy; OOM, orders of magnitude. Nester CM, et al. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

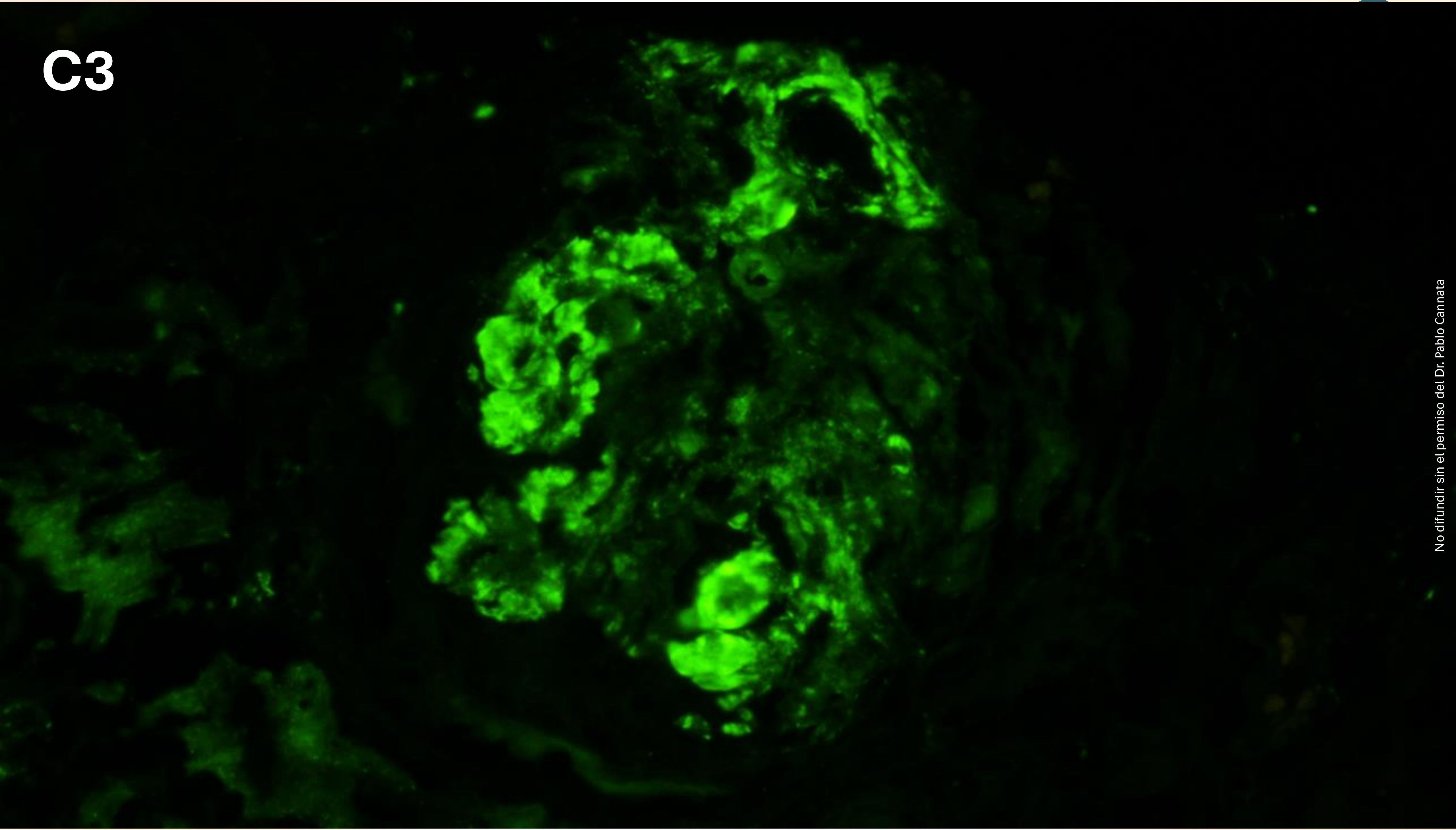
C3

3+

C3

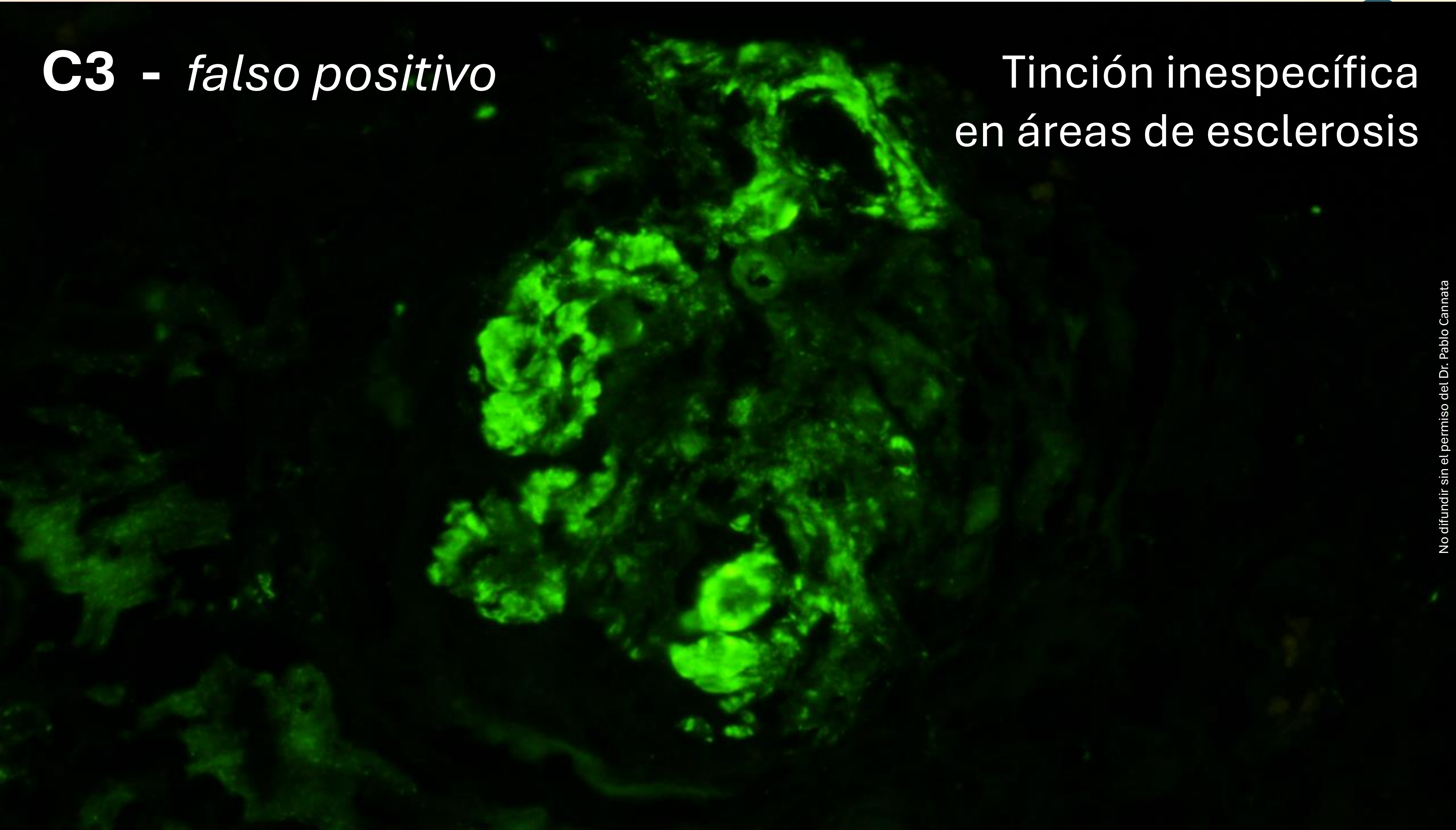
2+?

C3



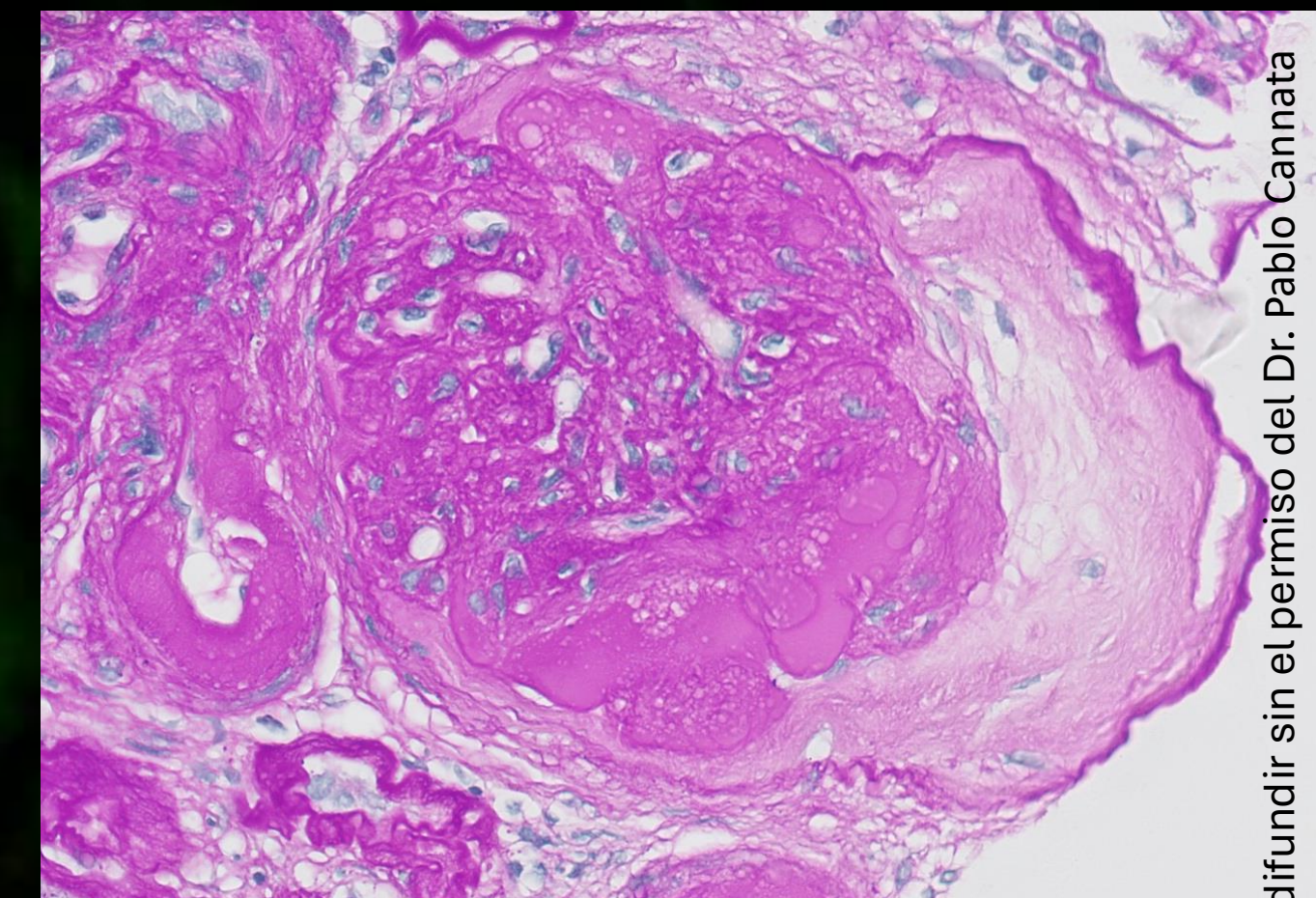
C3 - *falso positivo*

Tinción inespecífica
en áreas de esclerosis



C3 - *falso positivo*

Tinción inespecífica
en áreas de esclerosis



HE	IgG	IgA	IgM	C3	C1q	kap	Lam	Fibr	Alb
—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—

3. Cuando la rutina falla: Problemas técnicos, biopsias insuficientes...

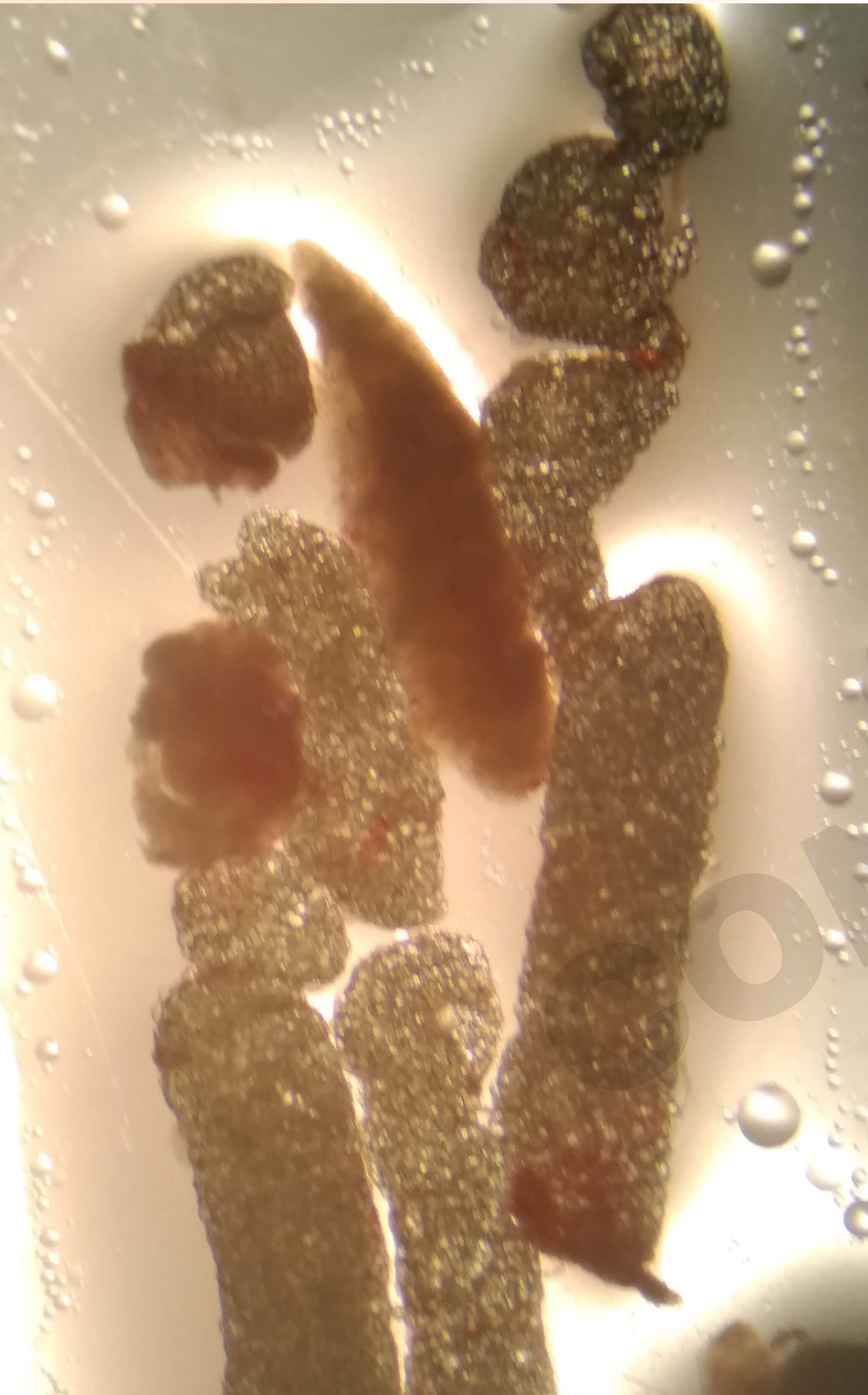
3. Cuando la rutina falla: Problemas técnicos, biopsias insuficientes...

Retos en el diagnóstico de la C3G

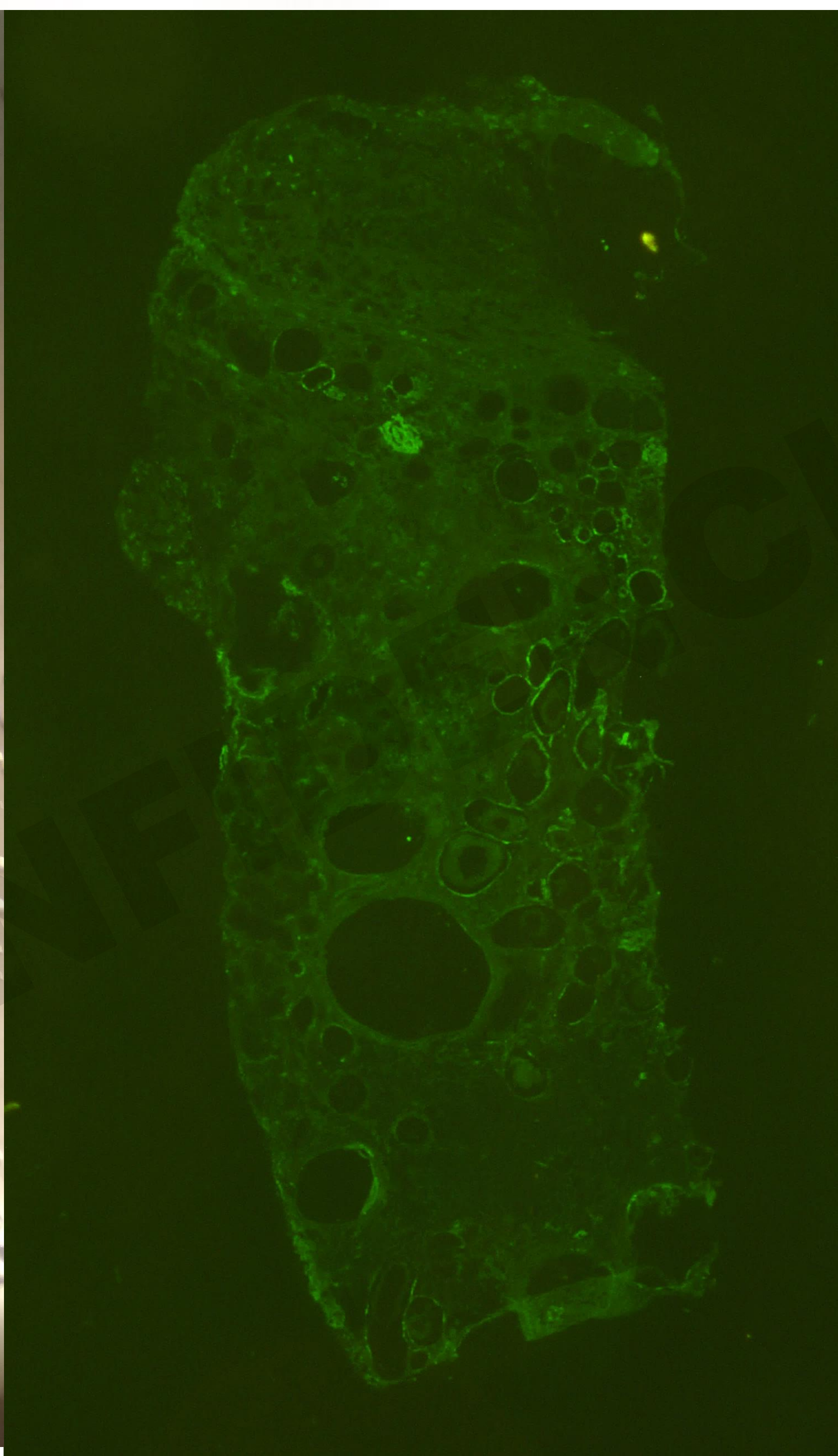
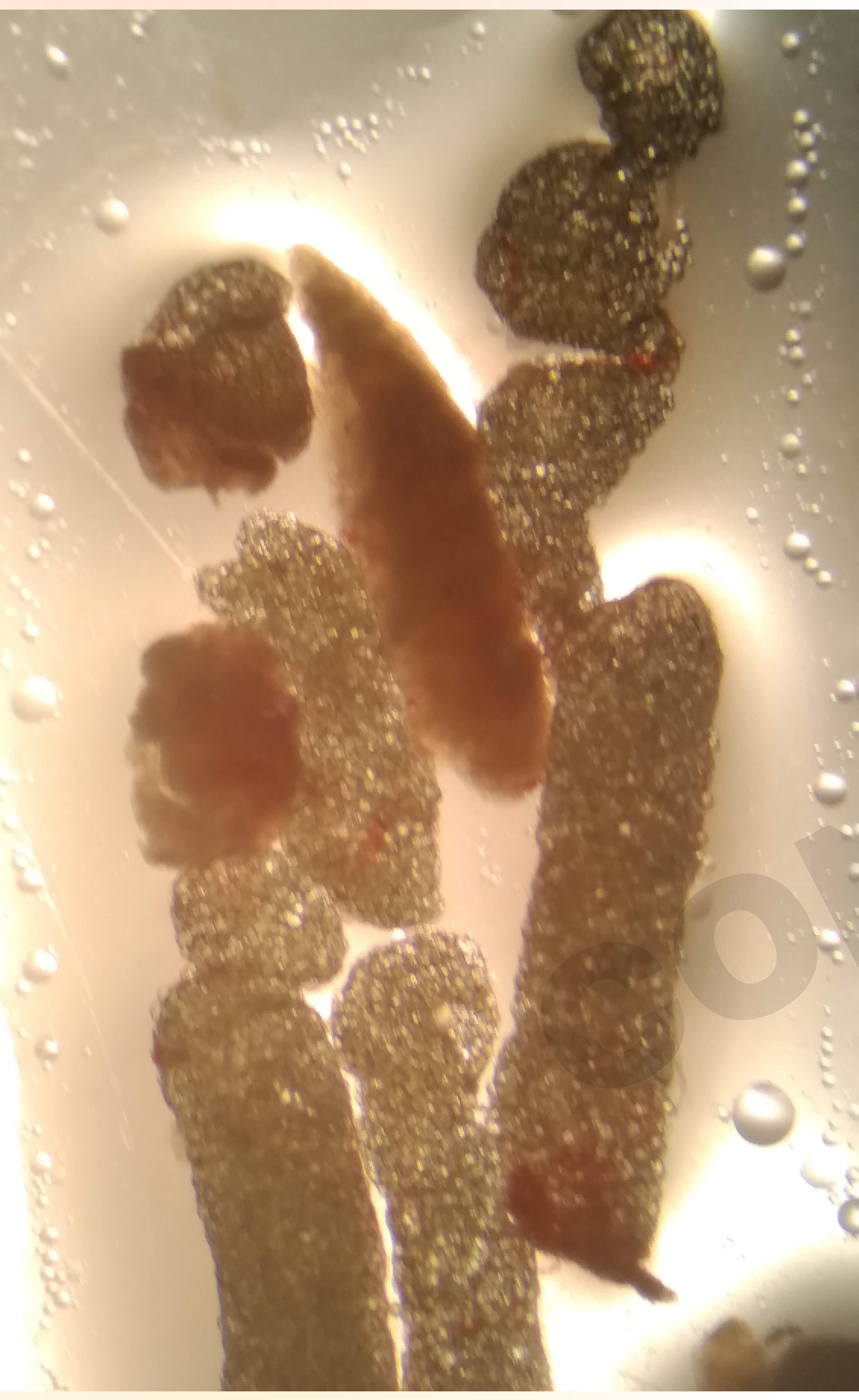
Retos en el diagnóstico de la C3G

- Escasez o ausencia de glomérulos en el segmento congelado para IFD.

CONFIDENCIAL



CONFIDENCIAL



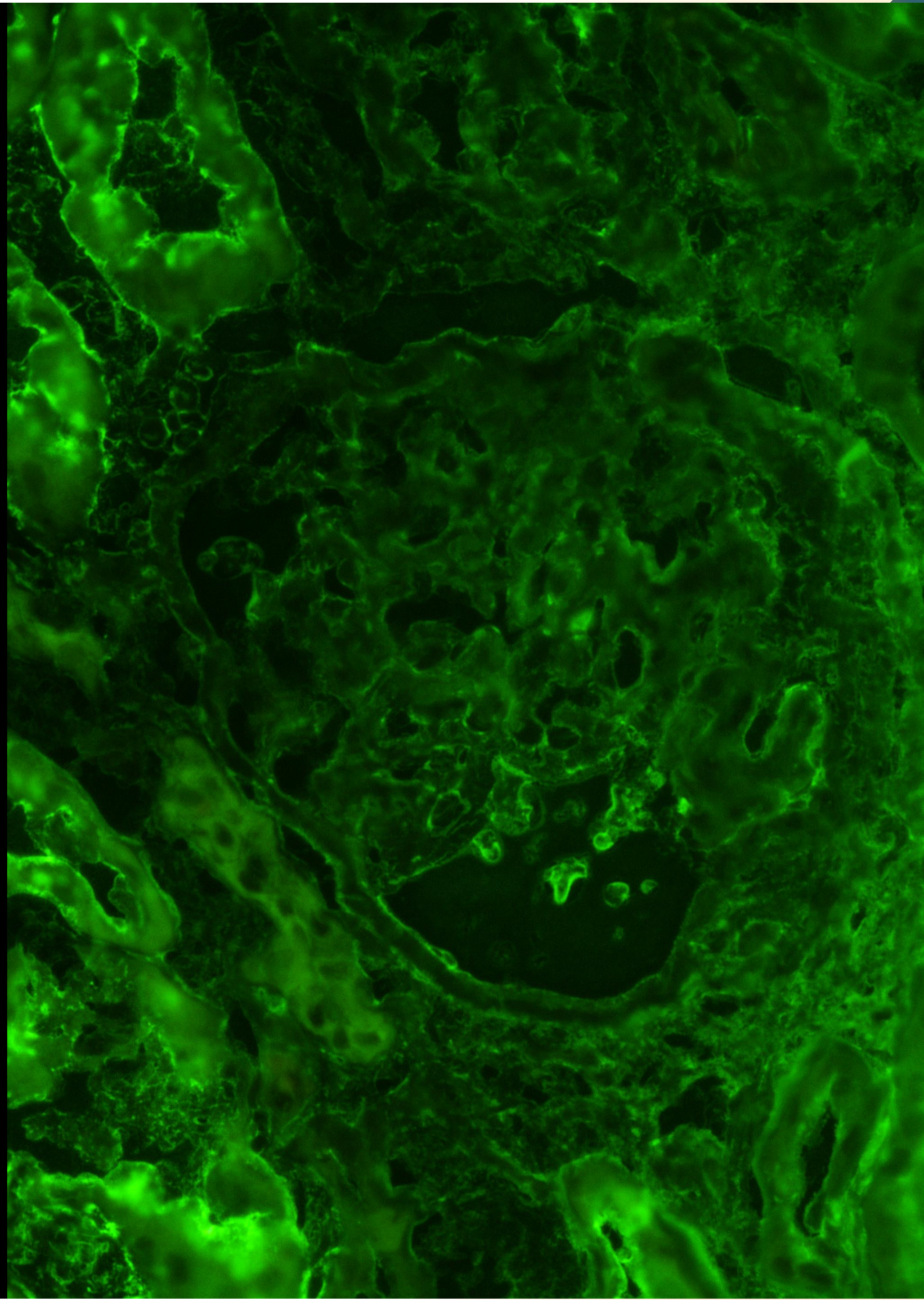
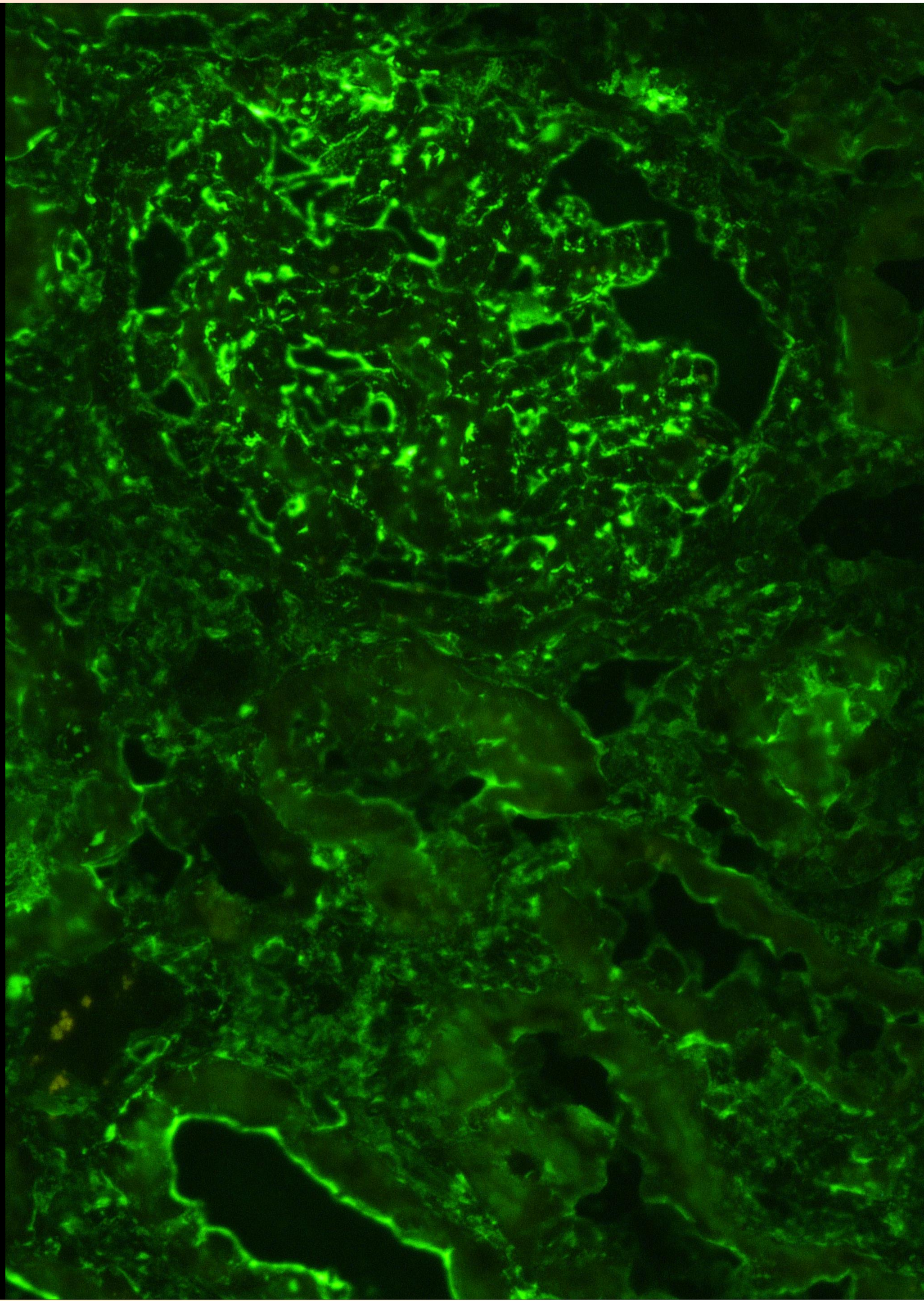
Retos en el diagnóstico de la C3G

- Escasez o ausencia de glomérulos en el segmento congelado para IFD.
- Ausencia de información clínica.

CONFIDENCIAL

Retos en el diagnóstico de la C3G

- Escasez o ausencia de glomérulos en el segmento congelado para IFD.
- Ausencia de información clínica.
- Biopsia remitida directamente en formol.



Paraffin immunofluorescence in the renal pathology laboratory: more than a salvage technique

Nidia C Messias, Patrick D Walker and Christopher P Larsen

Nephropath, Little Rock, AR, USA



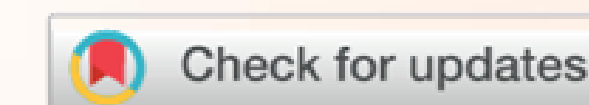
Kidney International Reports (2018) **3**, 1260–1266

REVIEW

Paraffin Immunofluorescence: A Valuable Ancillary Technique in Renal Pathology

Samih H. Nasr¹, Mary E. Fidler¹ and Samar M. Said¹

¹Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA



¿Cuándo debo realizar IF
en parafina?

Estandarización en la realización de estudios de inmunofluorescencia sobre tejido parafinado en la biopsia renal

PNT

PROCEDIMIENTO
NORMALIZADO DE TRABAJO

Hospital Universitario
Fundación Jiménez Díaz
Grupo  quirónsalud

Redactado por:	Aprobado por:
<i>Nombre: Pablo Javier Cannata Ortiz</i> <i>Cargo: coordinador de Patología renal</i> <i>Fecha: 24/04/2024</i>	<i>Nombre</i> <i>Cargo</i> <i>Fecha</i>

¿Cuándo debo realizar IF en parafina?

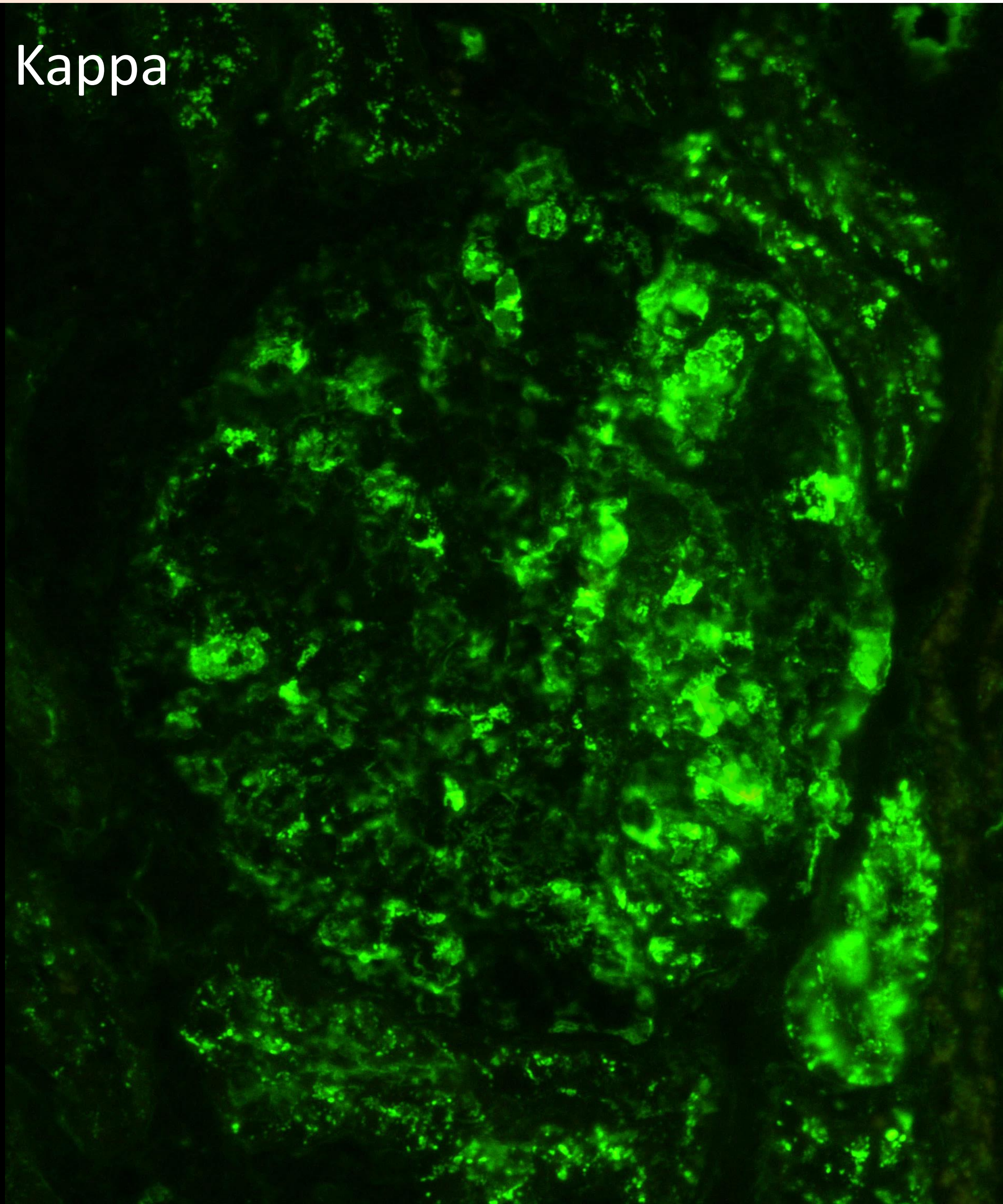
- Biopsia renal con escasa o nula representatividad de corteza renal.
- Biopsia renal sin glomérulos viables en el segmento congelado para IFD.
- Evidencia de artefacto o error en la técnica de IFD sobre tejido congelado.
- Biopsias que en la microscopía óptica muestran un patrón de afectación membranoproliferativo y negatividad en el estudio de inmunofluorescencia.
- Pacientes cuyo estudio analítico revele una paraproteína en orina y/o sangre en los que el estudio de IFD no revele una restricción de cadenas ligeras.

Inmunofluorescencia sobre tejido parafinado (IF/P)

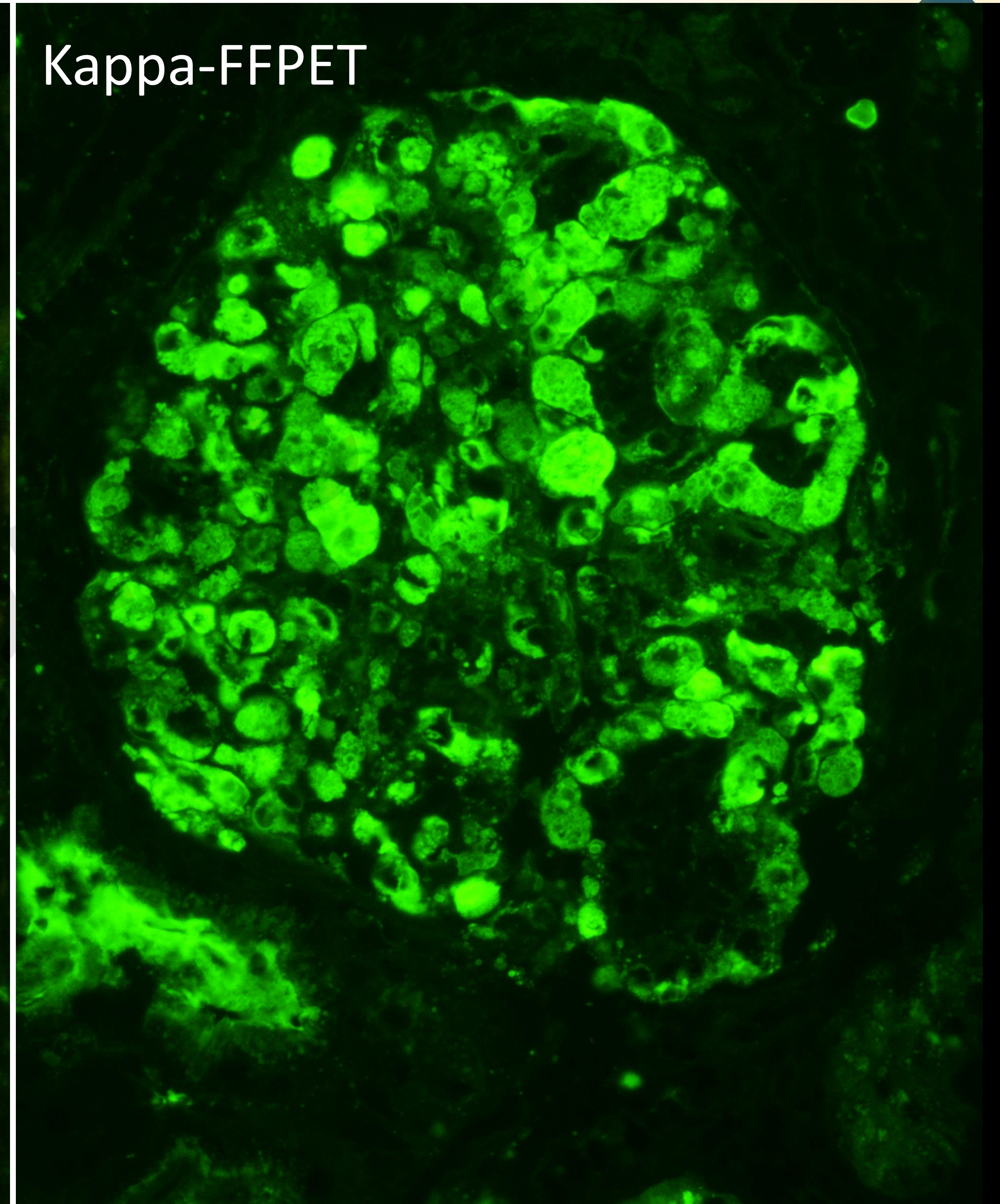
Ventajas

- Mejor preservación del tejido y localización topográfica exacta de los depósitos.
- En protocolos de corte y tinción dejando cortes intermedios sin teñir, permite tipificar hallazgos muy segmentarios presentes en solo unas micras salvando el temido: “*desaparece tras la seriación del tejido*”.

Kappa



Kappa-FFPET



Inmunofluorescencia sobre tejido parafinado (IF/P)

Ventajas

- Mejor preservación del tejido y localización topográfica exacta de los depósitos.
- En protocolos de corte y tinción dejando cortes intermedios sin teñir, permite tipificar hallazgos muy segmentarios presentes en solo unas micras salvando el temido: “*desaparece tras la seriación del tejido*”.

El gran inconveniente

- C3, muchos falsos negativos (NO ES FIABLE)

Paraffin Immunofluorescence: A Valuable Ancillary Technique in Renal Pathology

Samih H. Nasr¹, Mary E. Fidler¹ and Samar M. Said¹

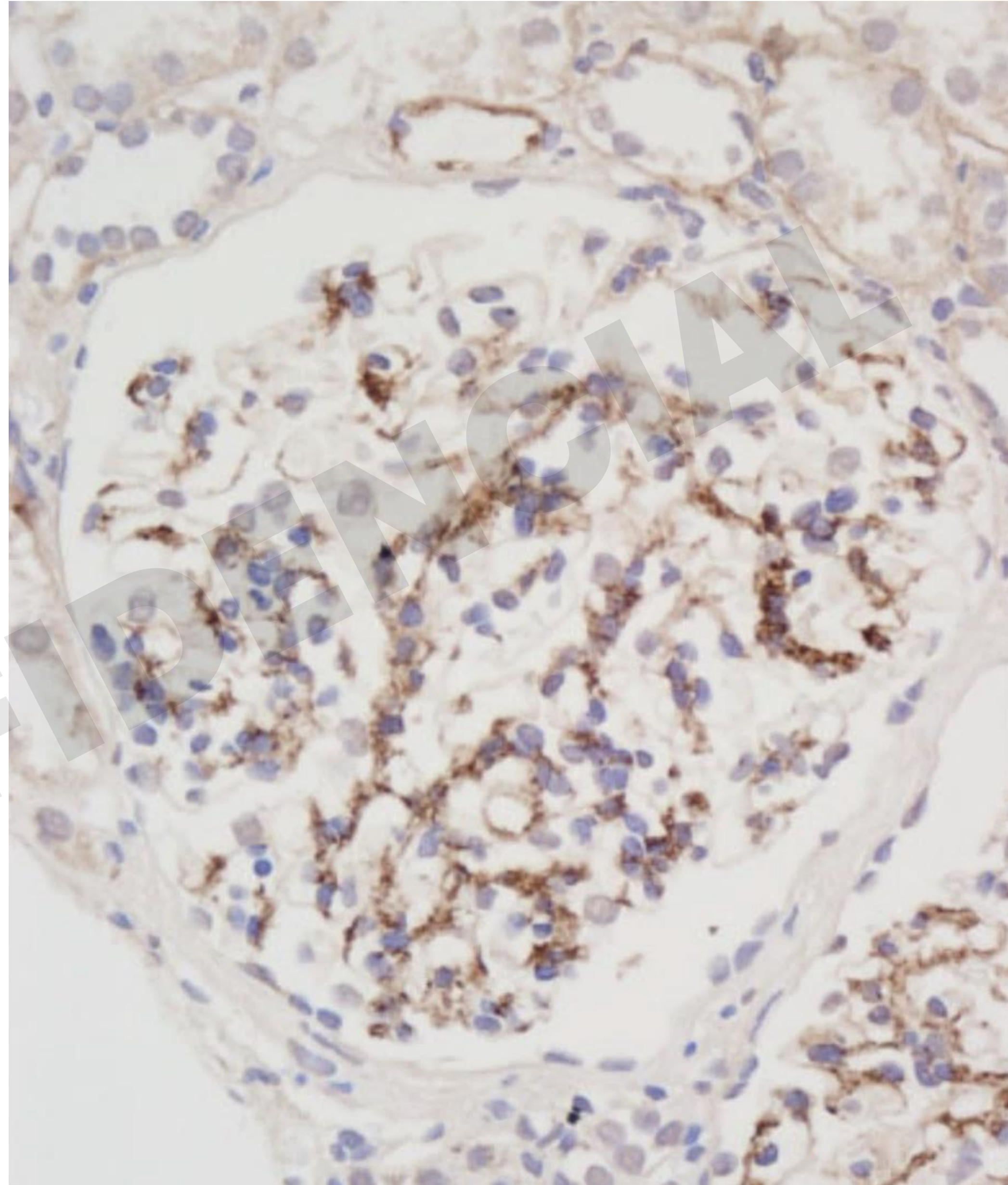
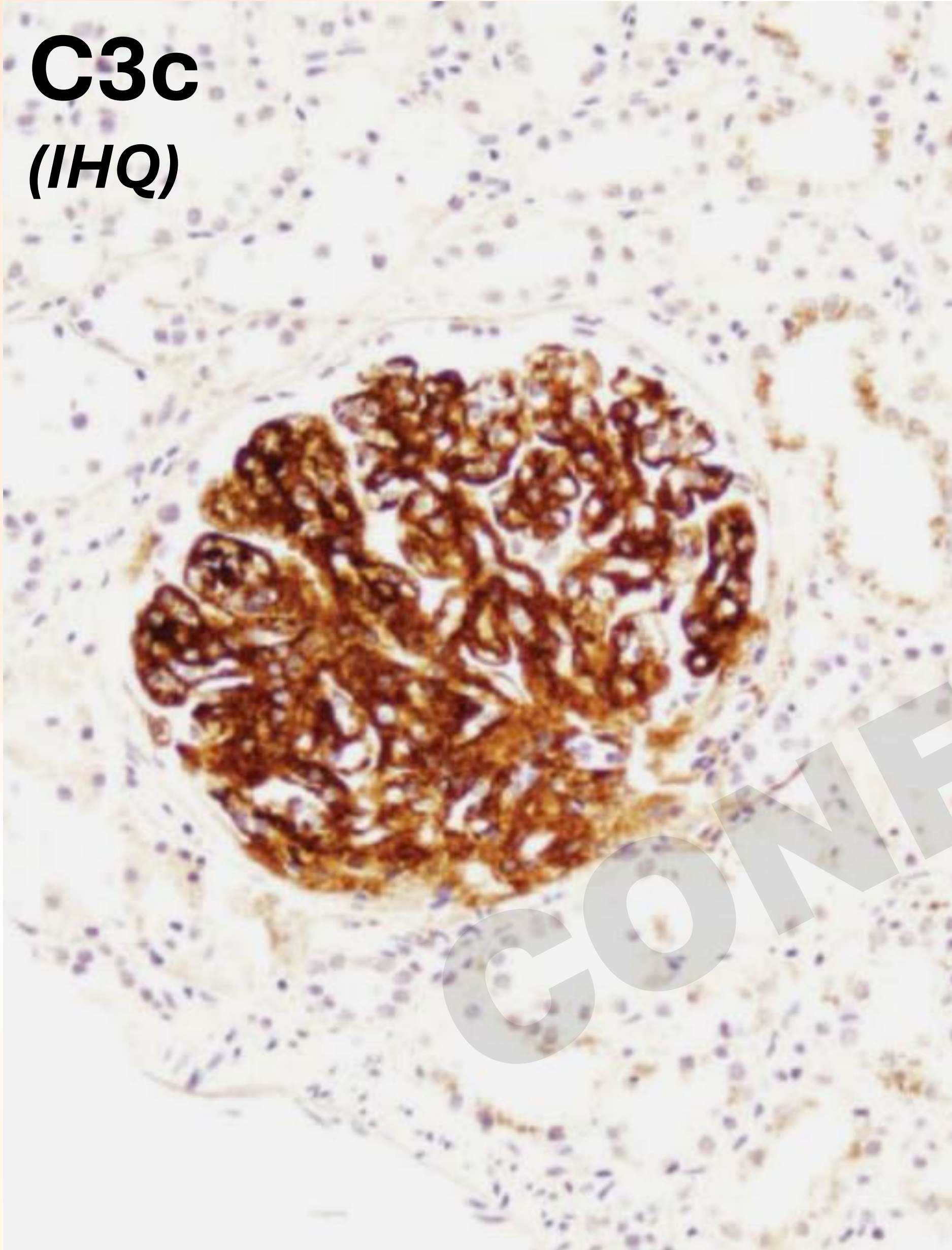
¹Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

glomerulonephritis (100%)¹⁴ (Figure 1c; Table 2). IF-P has a lower sensitivity than IF-F in primary membranous nephropathy (50%–78%),^{14,21} C3 glomerulonephritis,^{20,21} and anti-glomerular basement membrane (GBM) nephritis.^{14,20} In our laboratory, we use a case of diffuse proliferative lupus nephritis as our positive control for IF-P. (iii) The antigen tested: Good results can be obtained for IgG, kappa, and lambda (aside from cases of primary membranous nephropathy and anti-GBM nephritis), IgA, IgM, and C1q. IF-P is not sensitive for detecting C3 deposits.^{14,20} Therefore, C3 antibody is not included in our pronase IF-P staining panel.

El gran inconveniente

- C3, muchos falsos negativos (NO ES FIABLE)

C3c
(IHQ)



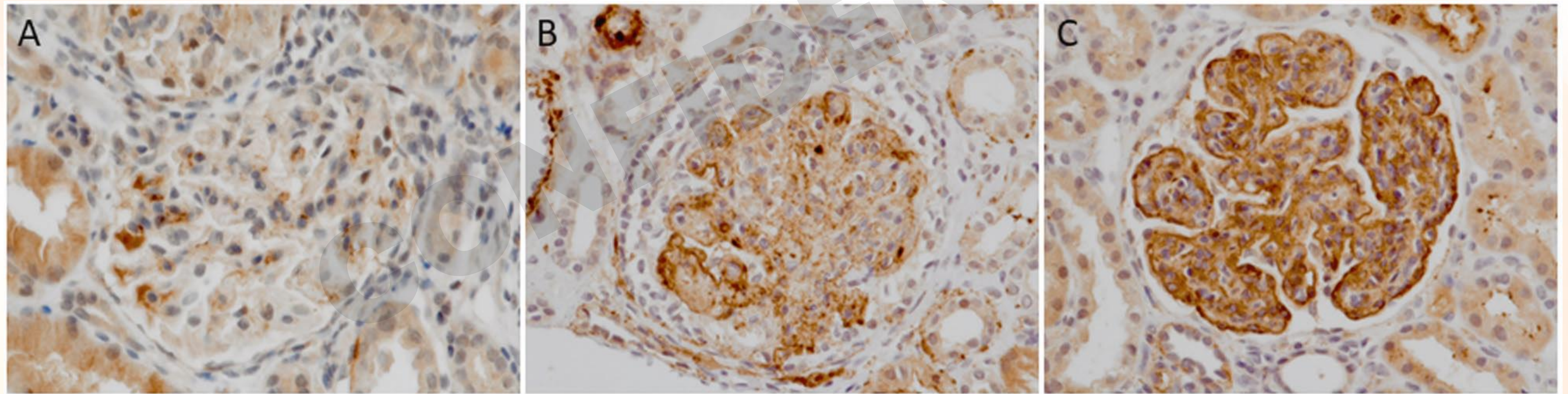
Heptinstall's Pathology of the Kidney 8th Edition



Utility of immunohistochemistry with C3d in C3 glomerulopathy

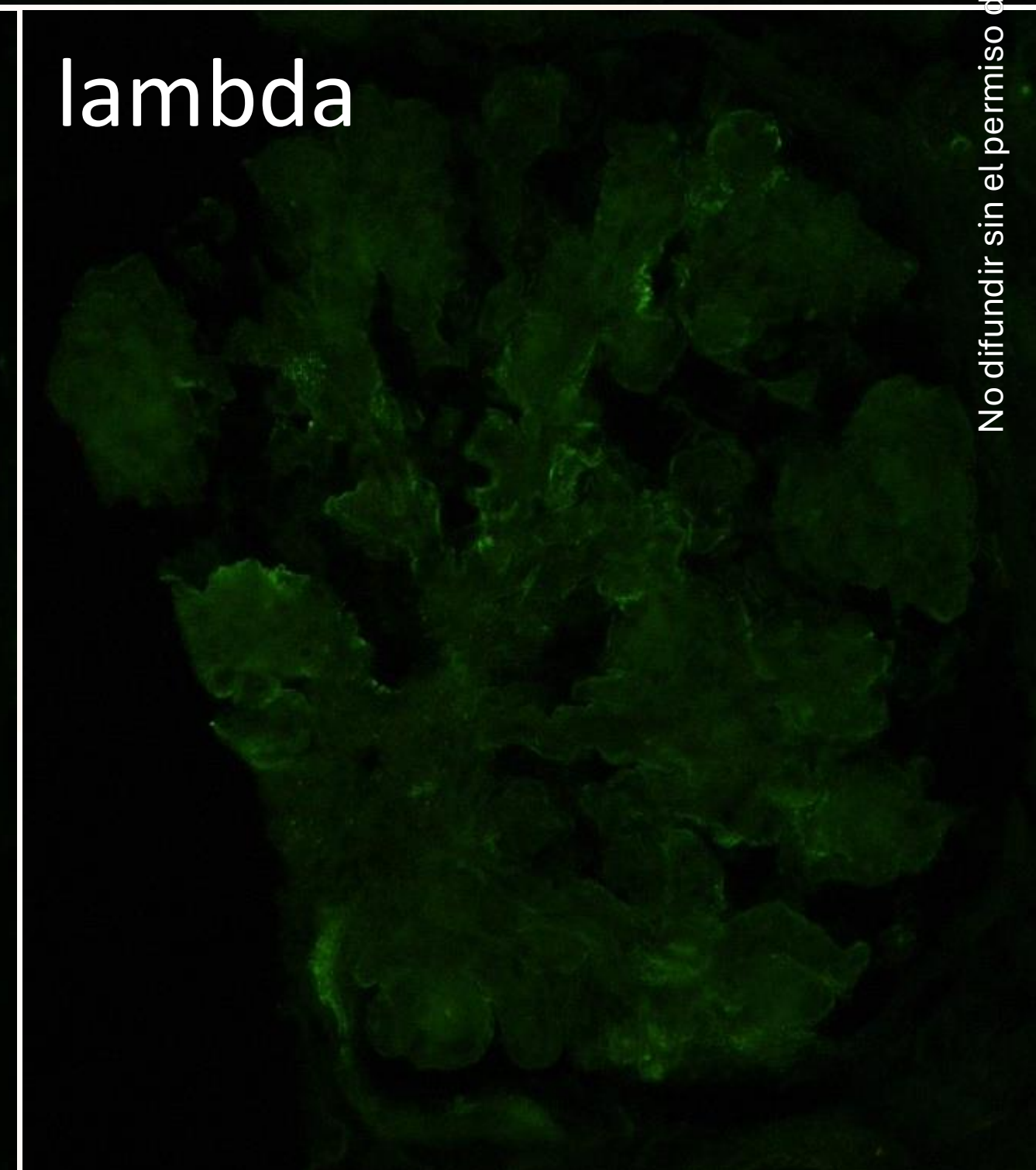
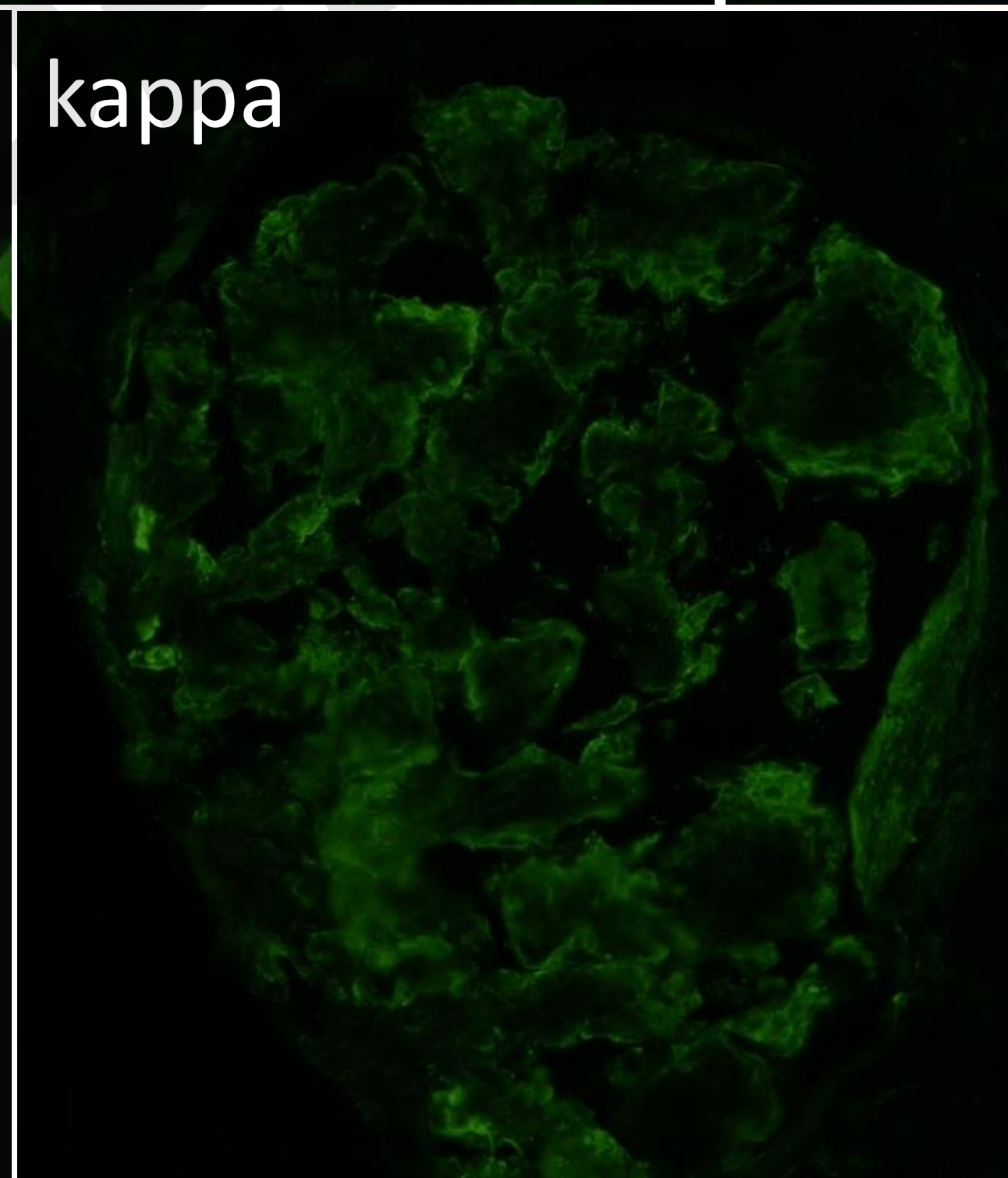
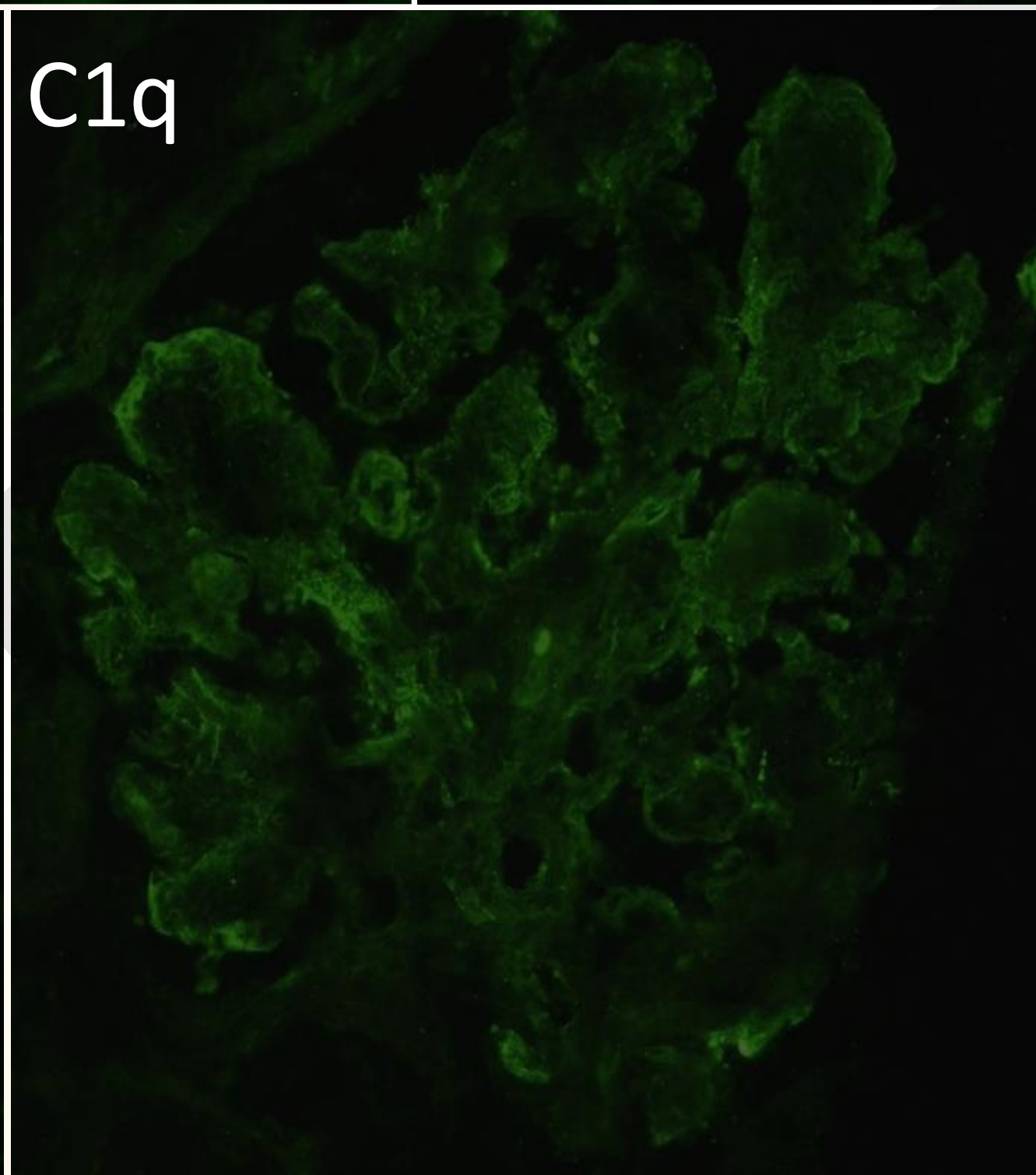
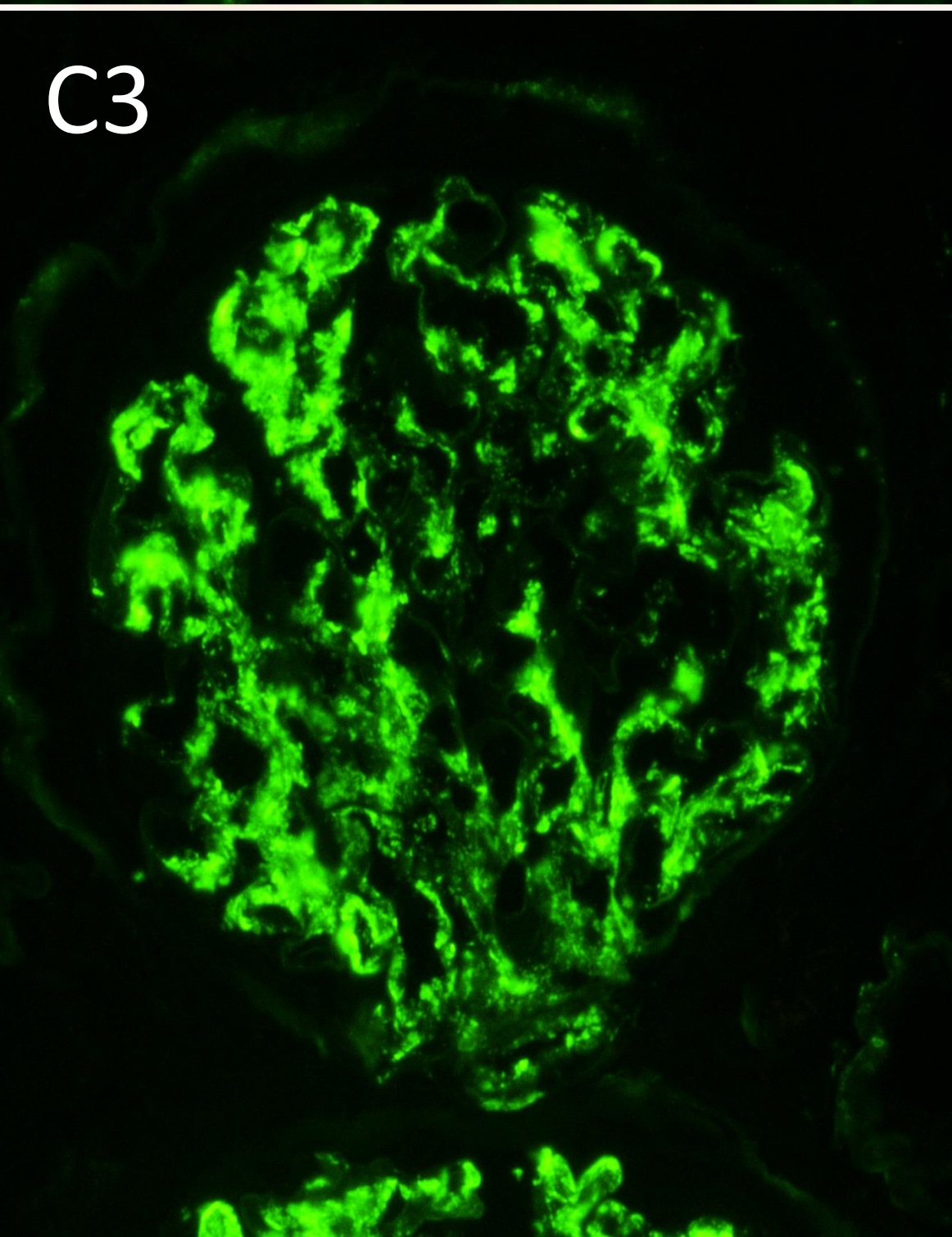
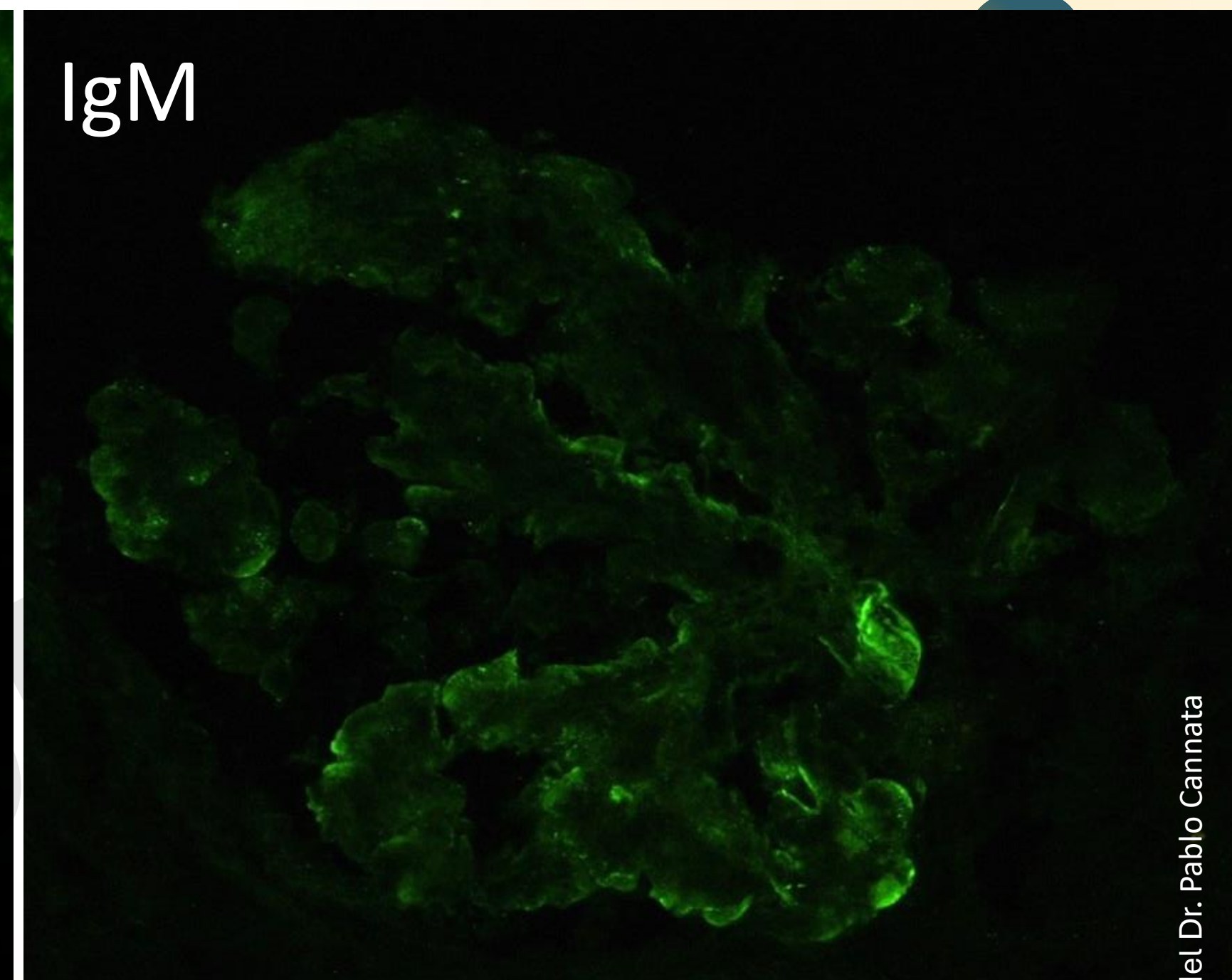
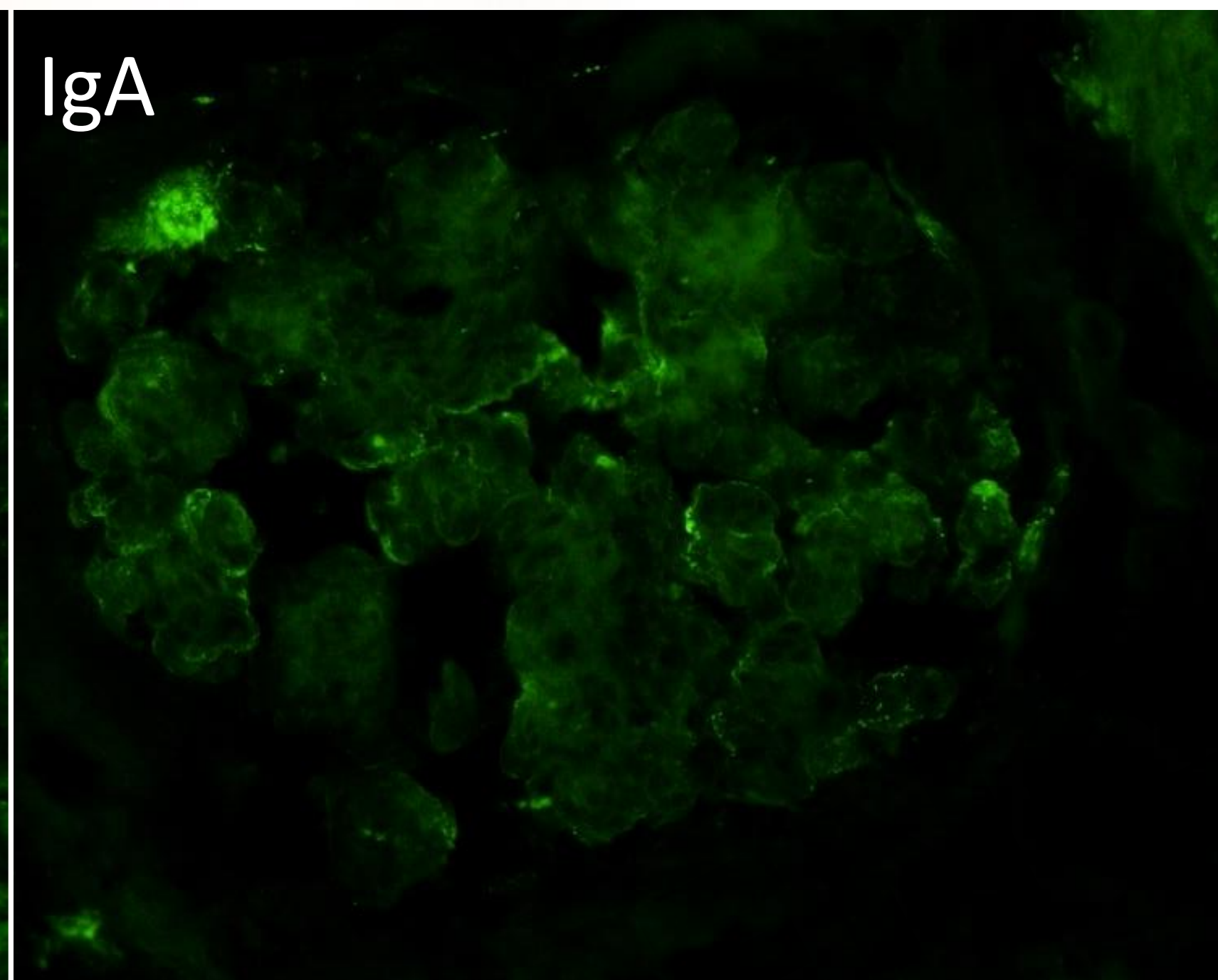
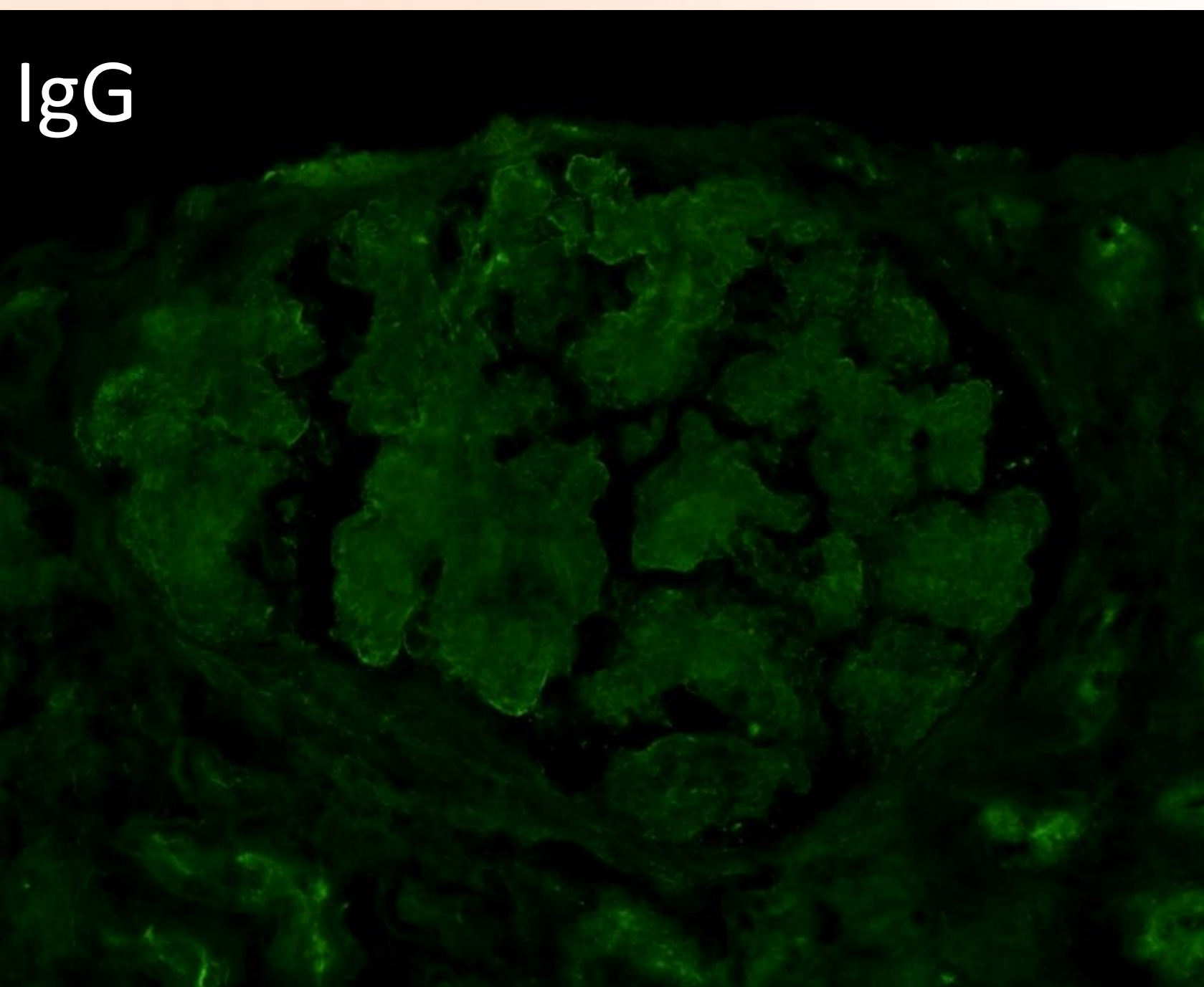
Malou L. H. Snijders¹ • Bojou J. van de Wall-Neecke¹ • Dennis A. Hesselink² • Jan U. Becker³ •
Marian C. Clahsen-van Groningen¹

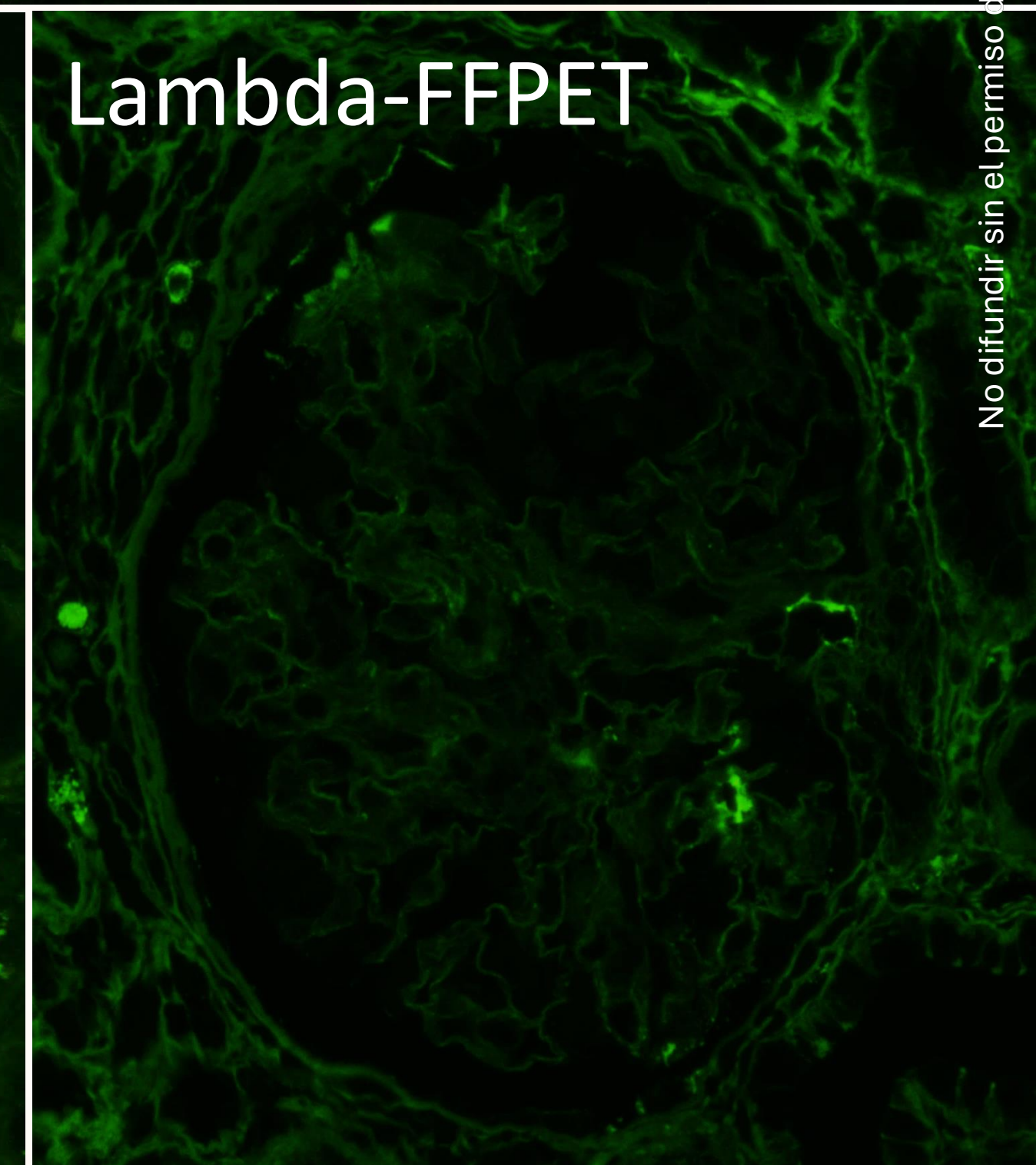
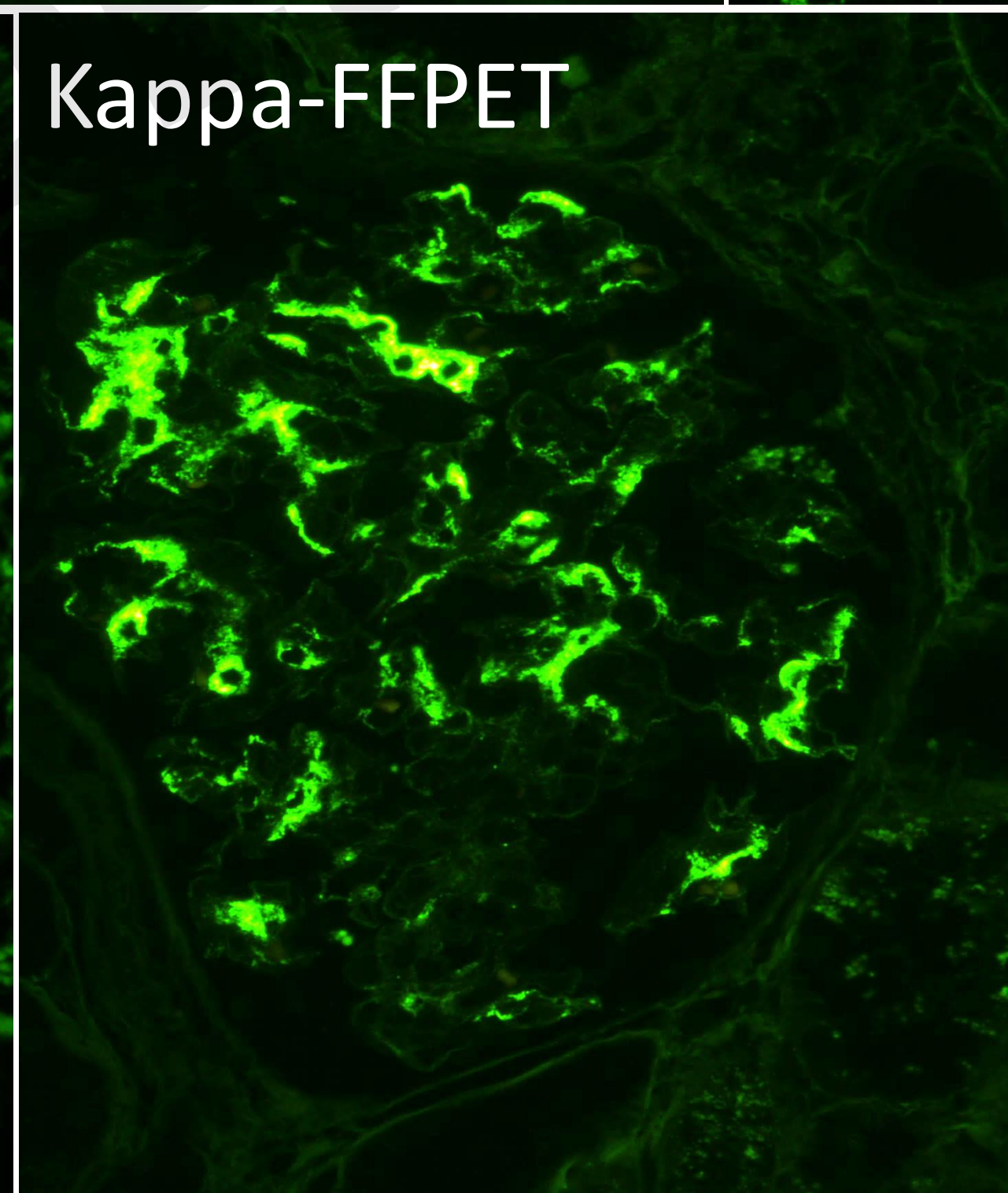
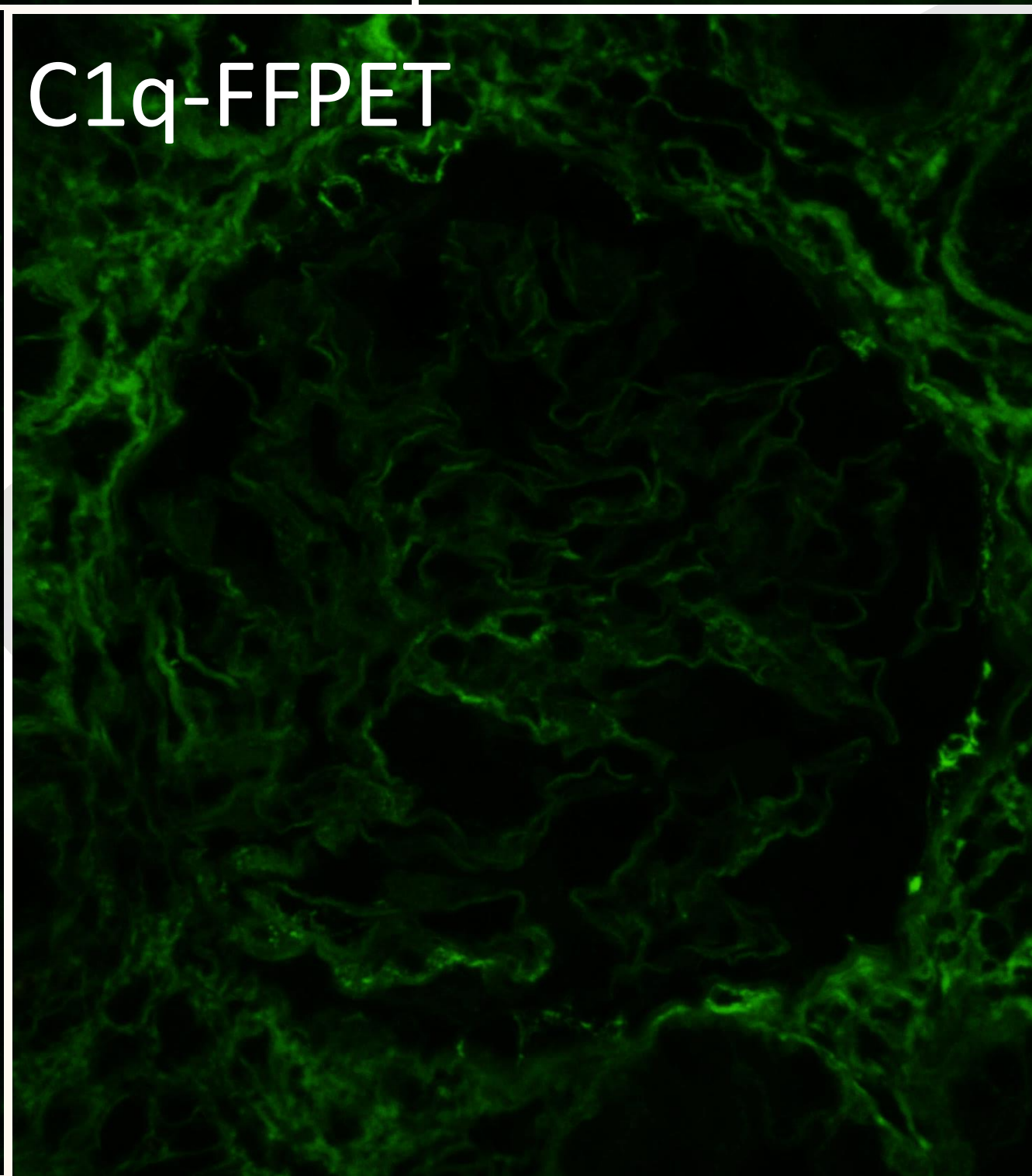
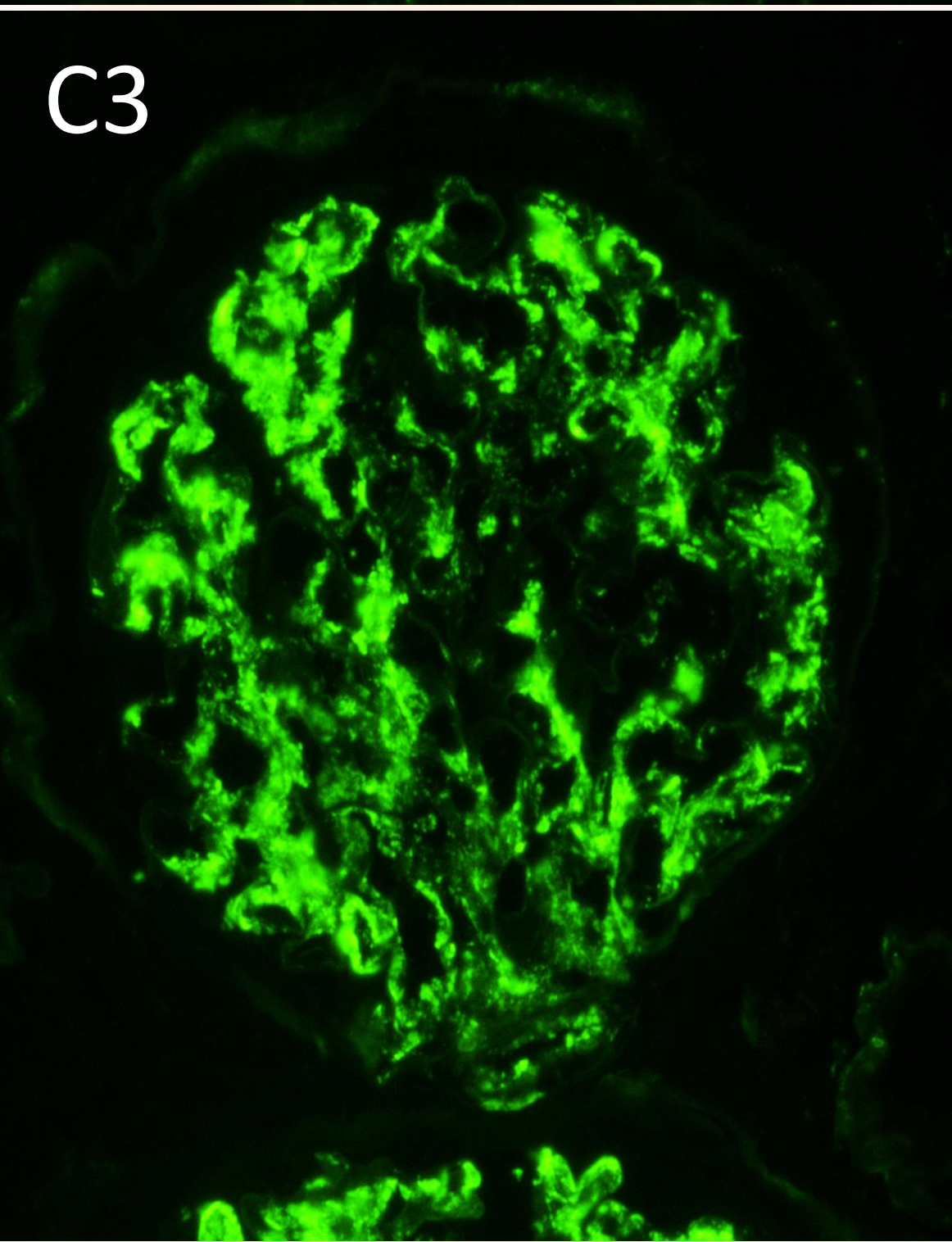
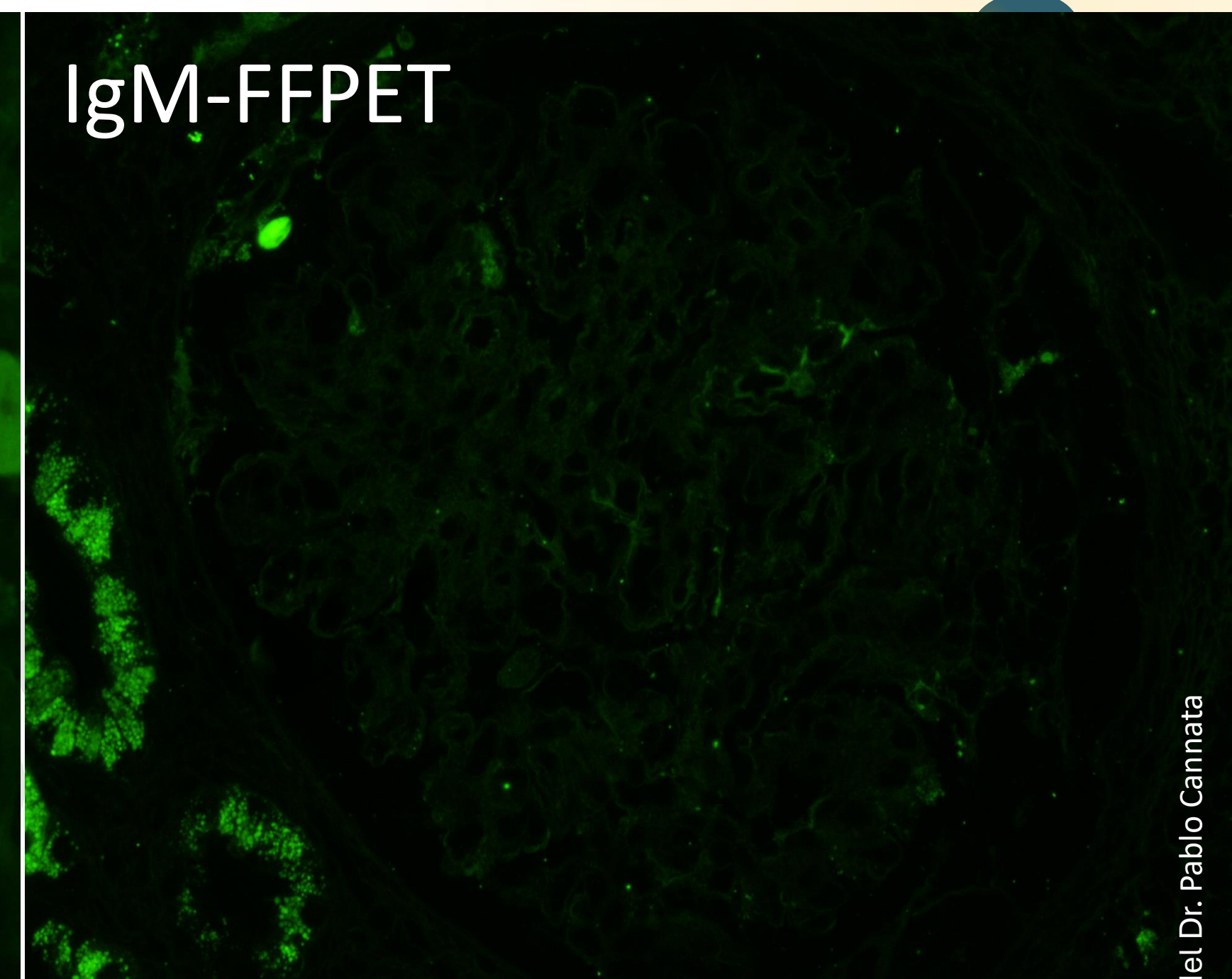
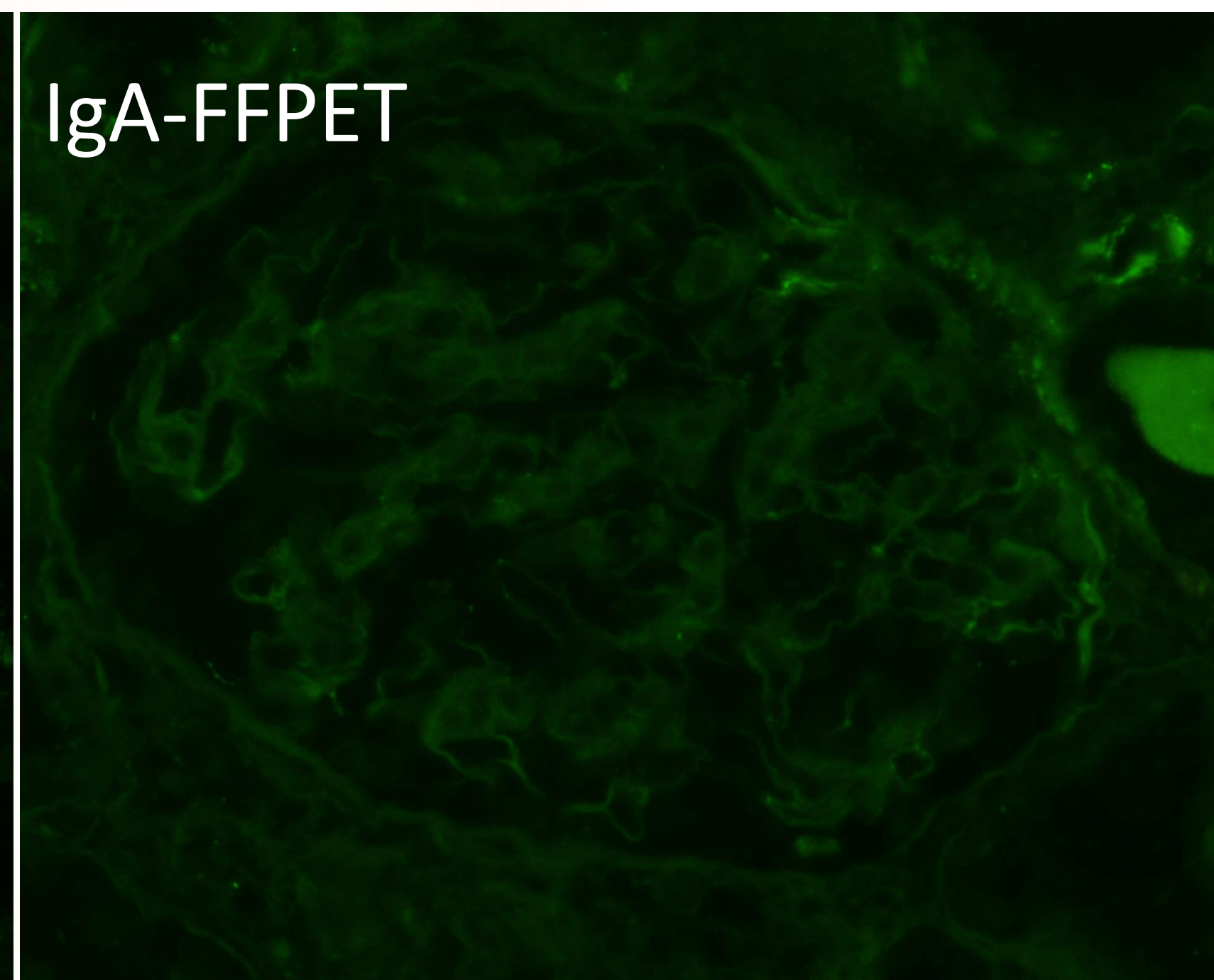
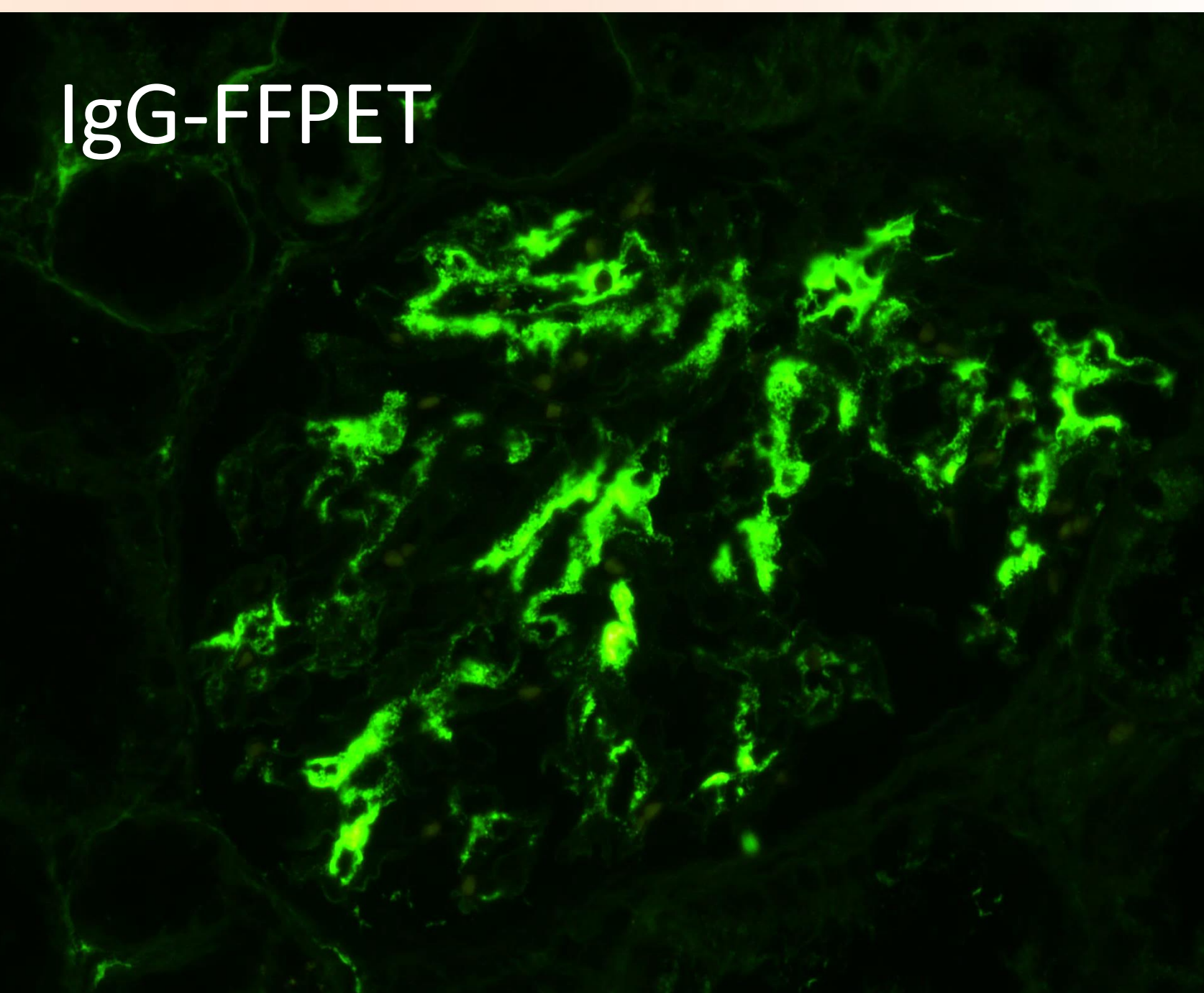
Received: 14 January 2019 / Revised: 30 July 2019 / Accepted: 30 July 2019 / Published online: 2 September 2019
© United States & Canadian Academy of Pathology 2019



El lobo con piel de cordero





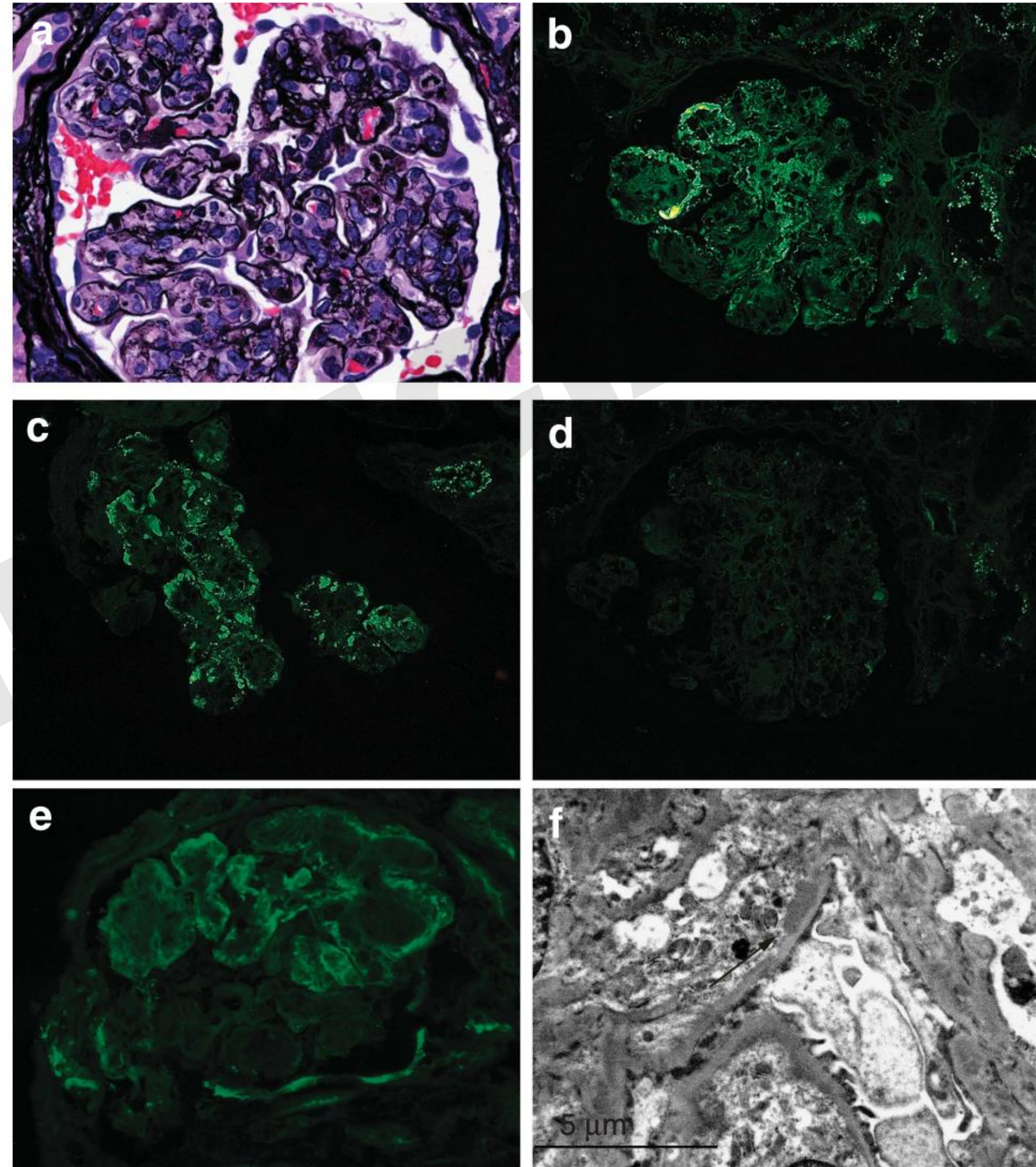


Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits

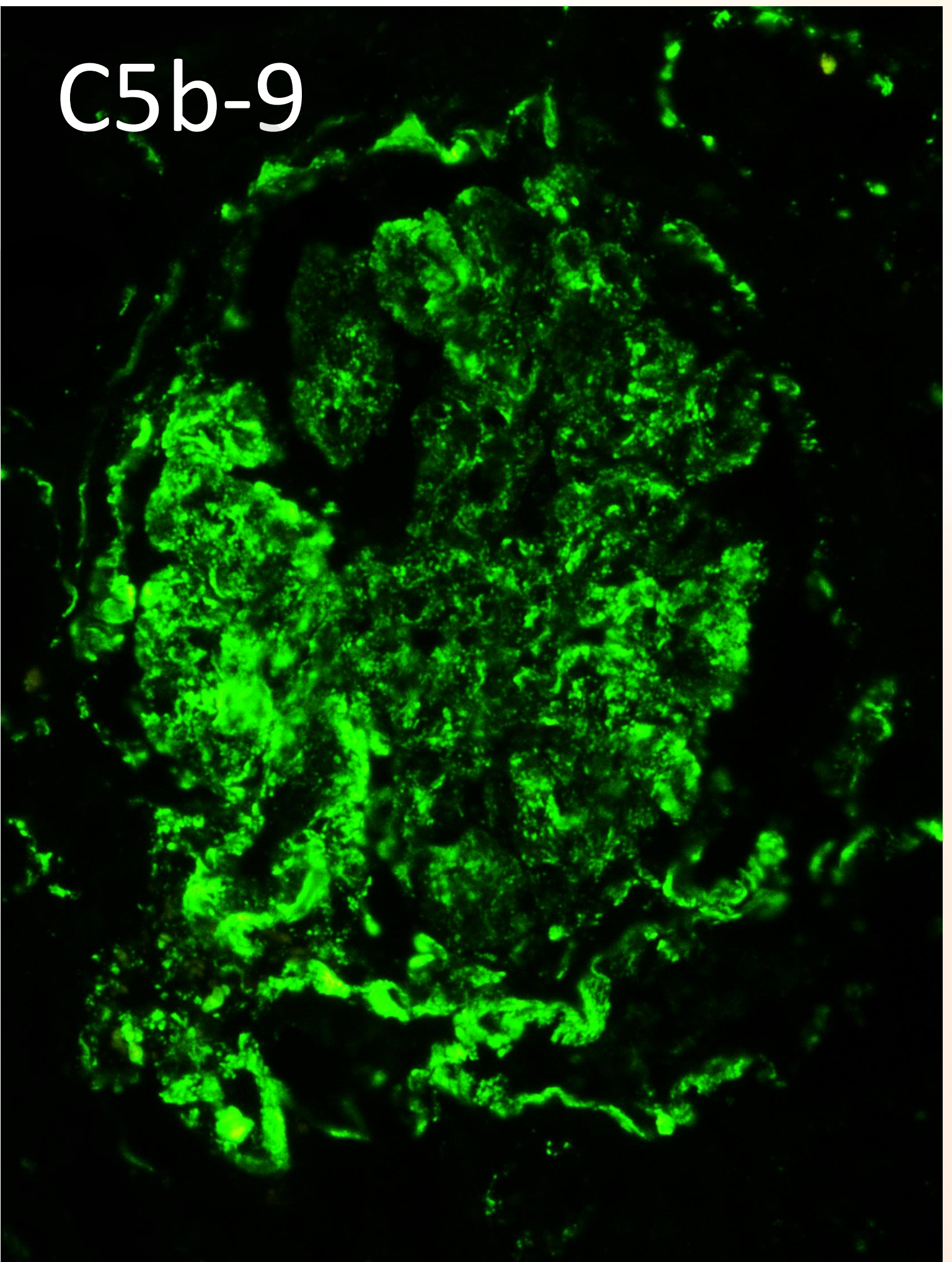
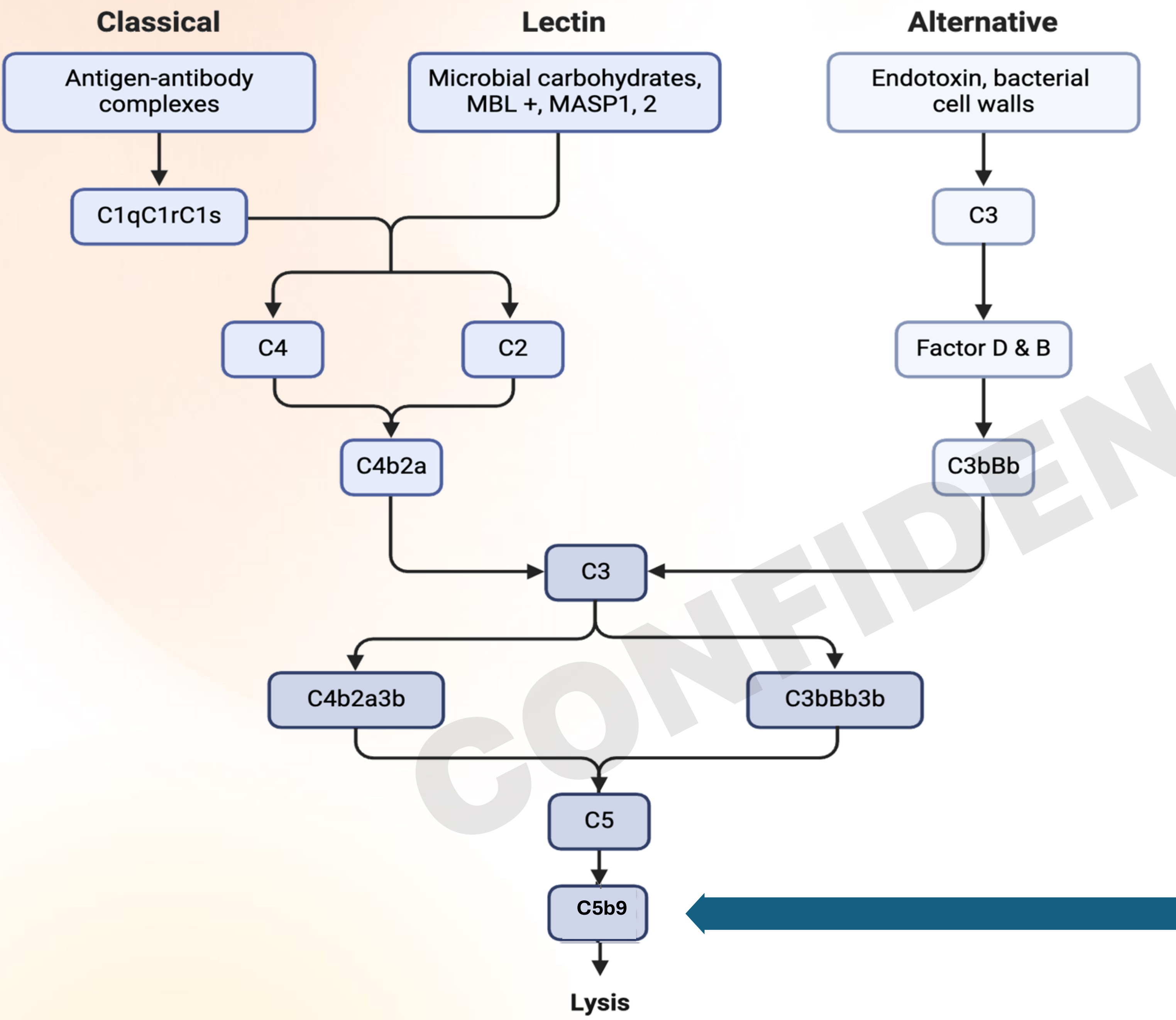
Christopher P. Larsen¹, Nidia C. Messias¹, Patrick D. Walker¹, Mary E. Fidler², Lynn D. Cornell², Loren H. Hernandez², Mariam P. Alexander², Sanjeev Sethi² and Samih H. Nasr²

¹Nephropath, Little Rock, Arkansas, USA and ²Division of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota, USA

We provide the first clinicopathological description of cases with an MPGN pattern of GN on biopsy with masked monotypic Ig deposits. This combination of findings is frequently associated with the presence of an underlying hematological disorder. A high index of suspicion is necessary to avoid misdiagnosis in these cases, as many would have been mistakenly diagnosed as C3 glomerulopathy or unclassified MPGN in the past. Paraffin IF is necessary to identify the Ig component and uncover the true nature of these deposits, avoiding misdiagnosis. It is important to identify the ‘masked’ Ig as this finding frequently informs our understanding of the true pathogenesis of the patient’s disease. As these cases are best considered a paraprotein-associated glomerulopathy, treatment directed against the underlying clonal hematological process is likely warranted to treat the GN.



4. Expandiendo la huella del complemento: C4d, C5b-9



No difundir sin el permiso del Dr. Pablo Cannata

CLINICAL TRIALS AND OBSERVATIONS

Dynamics of complement activation in aHUS and how to monitor eculizumab therapy

Marina Noris,¹ Miriam Galbusera,¹ Sara Gastoldi,¹ Paolo Macor,² Federica Banterla,¹ Elena Bresin,¹ Claudio Tripodo,³ Serena Bettoni,¹ Roberta Donadelli,¹ Elisabetta Valoti,¹ Francesco Tedesco,⁴ Alessandro Amore,⁵ Rosanna Coppo,⁵ Piero Ruggerenti,⁶ Eliana Gotti,⁶ and Giuseppe Remuzzi^{1,6}

¹IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, Bergamo, Italy and "Centro Anna Maria Astori" Science and Technology Park Kilometro Rosso, Bergamo, Italy; ²Department of Life Sciences, University of Trieste, Trieste, Italy; ³Tumor Immunology Unit, Human Pathology Section, Department of Health Sciences, University of Palermo, Palermo, Italy; ⁴IRCCS, Istituto Auxologico Italiano, Milan, Italy; ⁵Unit of Nephrology, Dialysis and Transplantation, Regina Margherita University Hospital, Turin, Italy; and ⁶Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

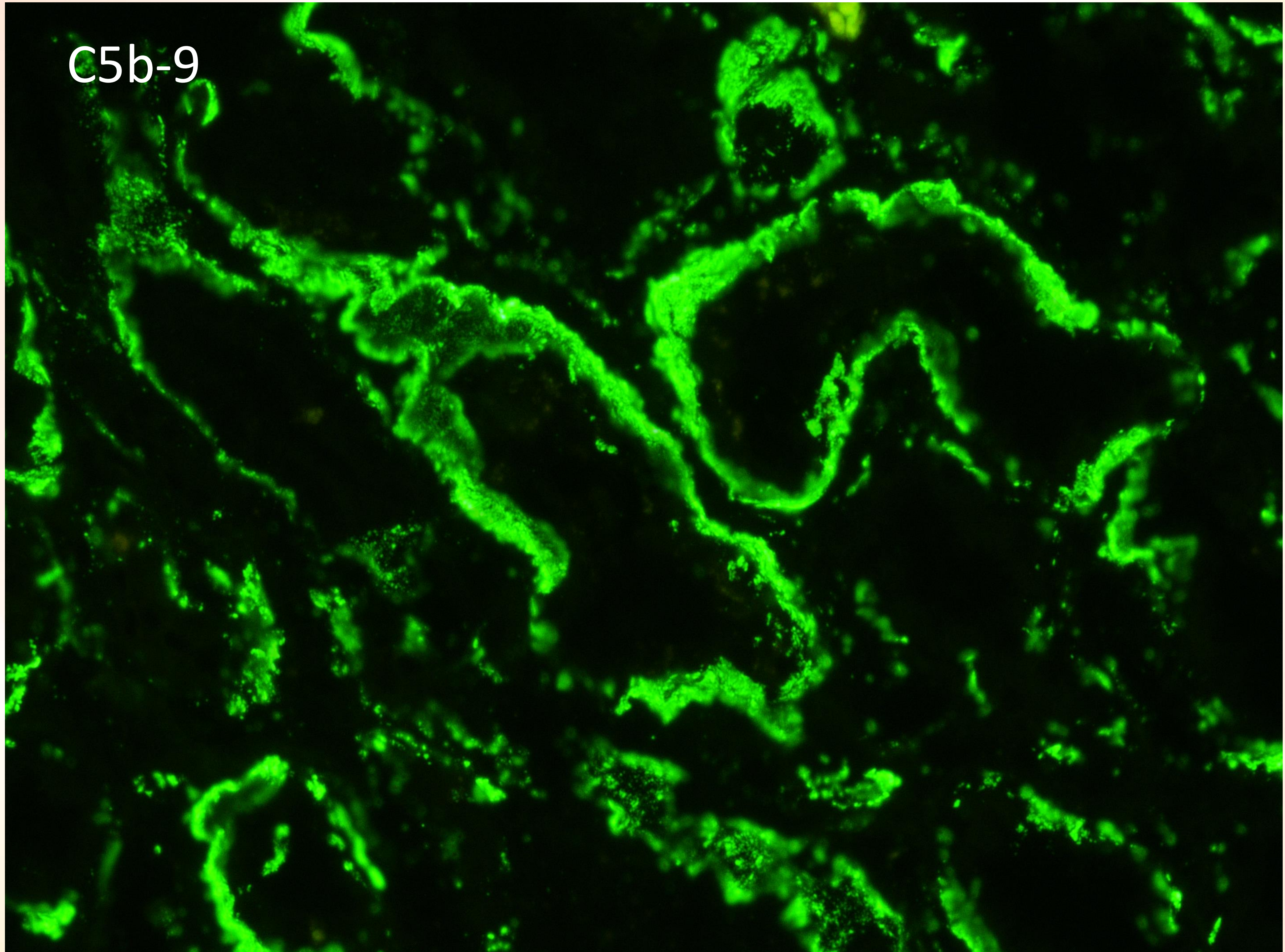
Key Points

- Endothelial-restricted complement activation occurs in aHUS, and clinical remission relies on efficient endothelial complement inhibition.
- Ex vivo serum-induced endothelial C5b-9 deposits are a sensitive tool to monitor complement activation and eculizumab effectiveness in aHUS.

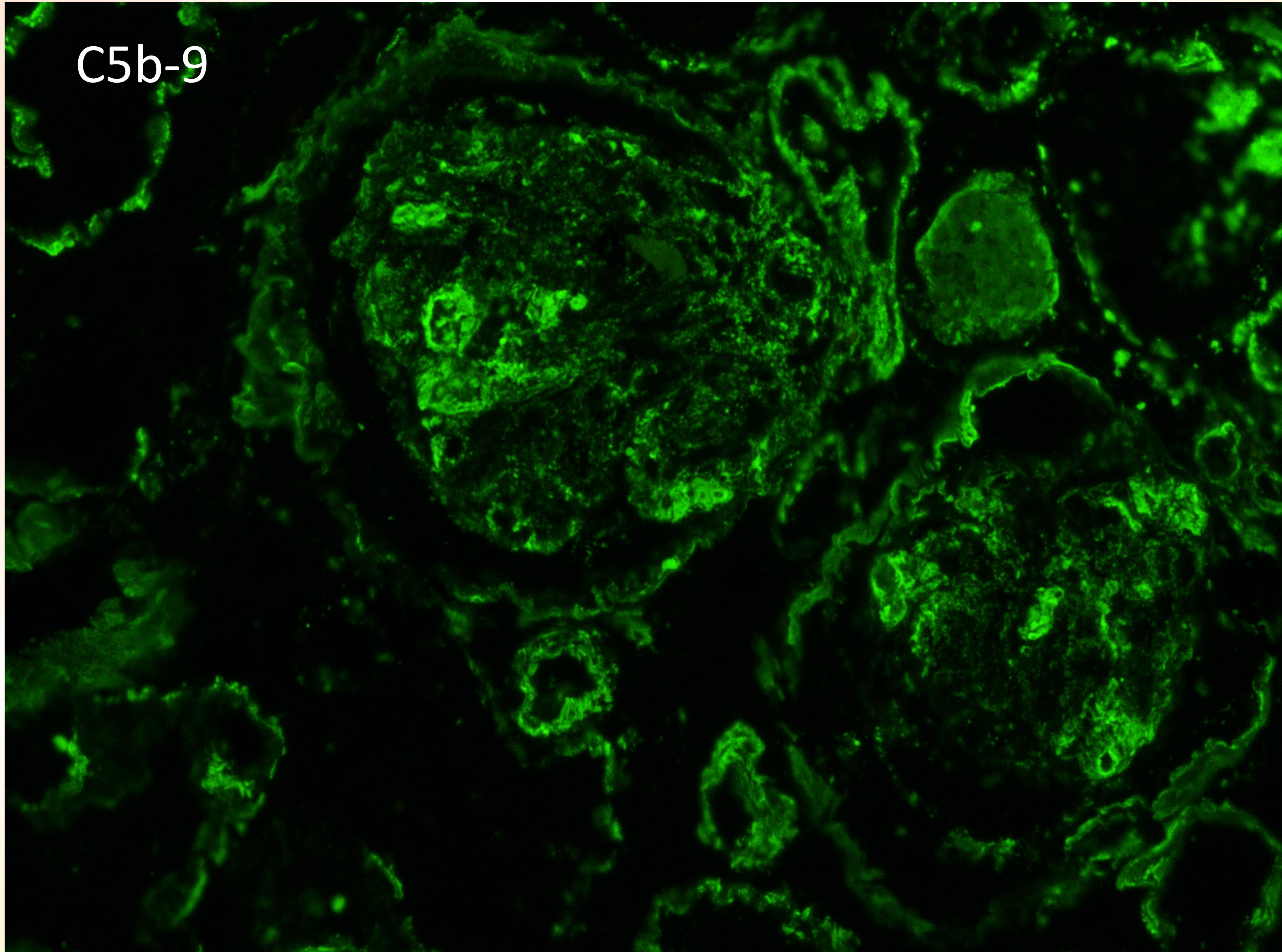
Atypical hemolytic-uremic syndrome (aHUS) is associated with genetic complement abnormalities/anti-complement factor H antibodies, which paved the way to treatment with eculizumab. We studied 44 aHUS patients and their relatives to (1) test new assays of complement activation, (2) verify whether such abnormality occurs also in unaffected mutation carriers, and (3) search for a tool for eculizumab titration. An abnormal circulating complement profile (low C3, high C5a, or SC5b-9) was found in 47% to 64% of patients, irrespective of disease phase. Acute aHUS serum, but not serum from remission, caused wider C3 and C5b-9 deposits than control serum on unstimulated human microvascular endothelial cells (HMEC-1). In adenosine 5'-diphosphate-activated HMEC-1, also sera from 84% and 100% of patients in remission, and from all unaffected mutation carriers, induced excessive C3 and C5b-9 deposits. At variance, in most patients with C3 glomerulopathies/immune complex-associated membranoproliferative glomerulonephritis, serum-induced endothelial C5b-9 deposits were normal. In 8 eculizumab-treated aHUS patients, C3/SC5b-9 circulating levels did not change posteculizumab, whereas serum-induced endothelial C5b-9 deposits normalized after treatment, paralleled or even preceded remission, and guided drug dosing and timing. These results point to efficient

complement inhibition on endothelium for aHUS treatment. C5b-9 endothelial deposits might help monitor eculizumab effectiveness, avoid drug overexposure, and save money considering the extremely high cost of the drug. (*Blood*. 2014;124(11):1715-1726)

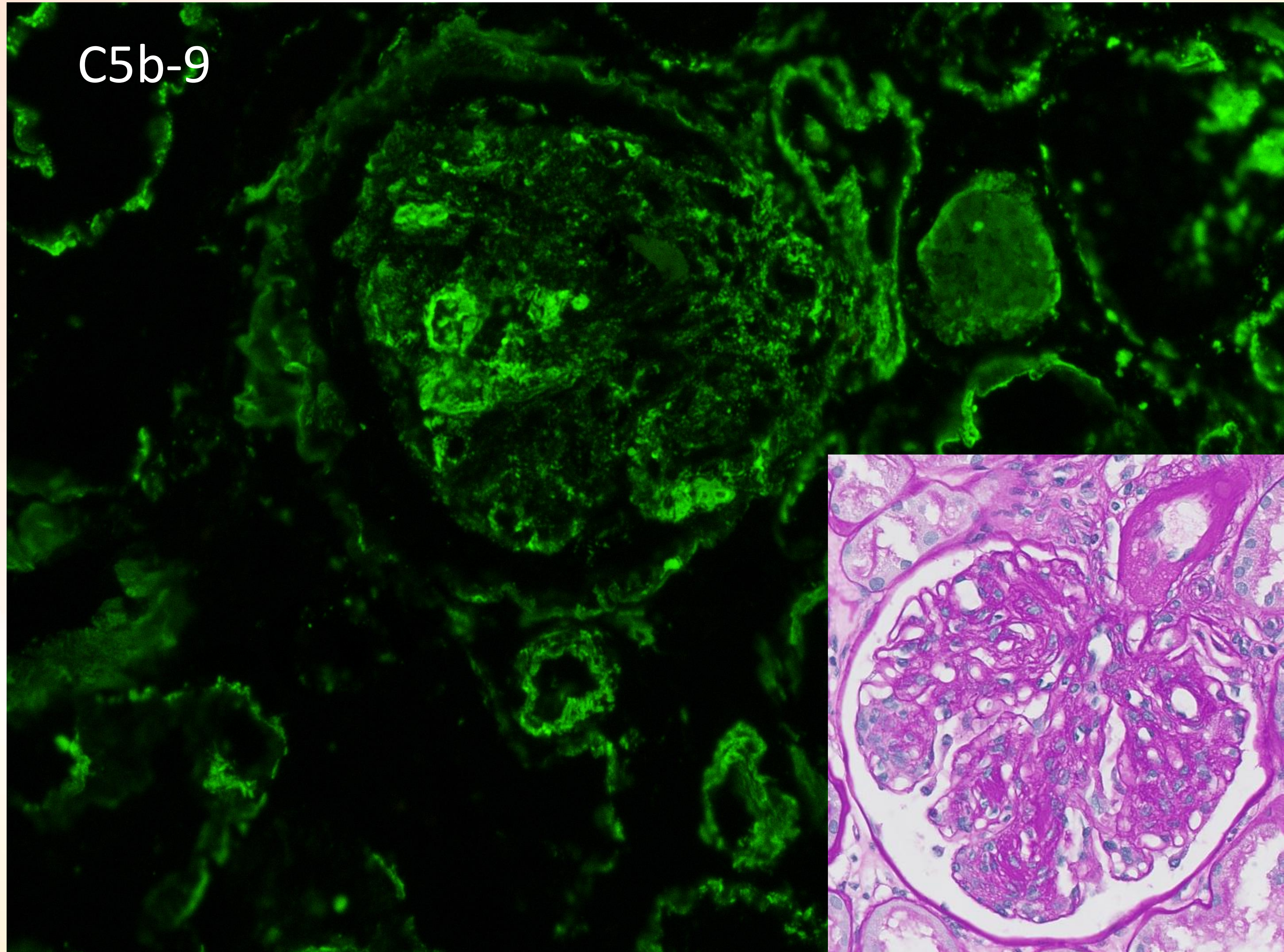
C5b-9



C5b-9



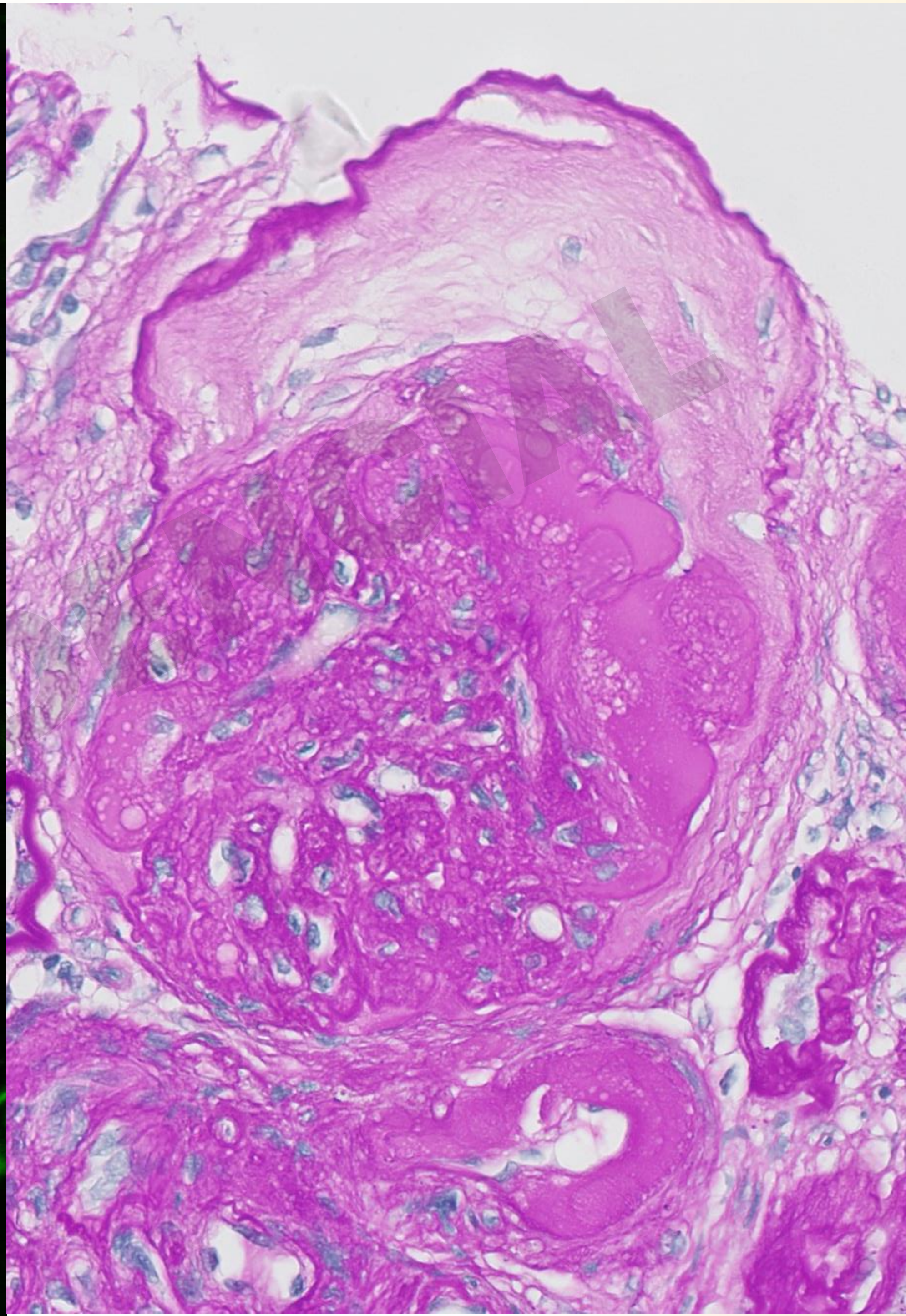
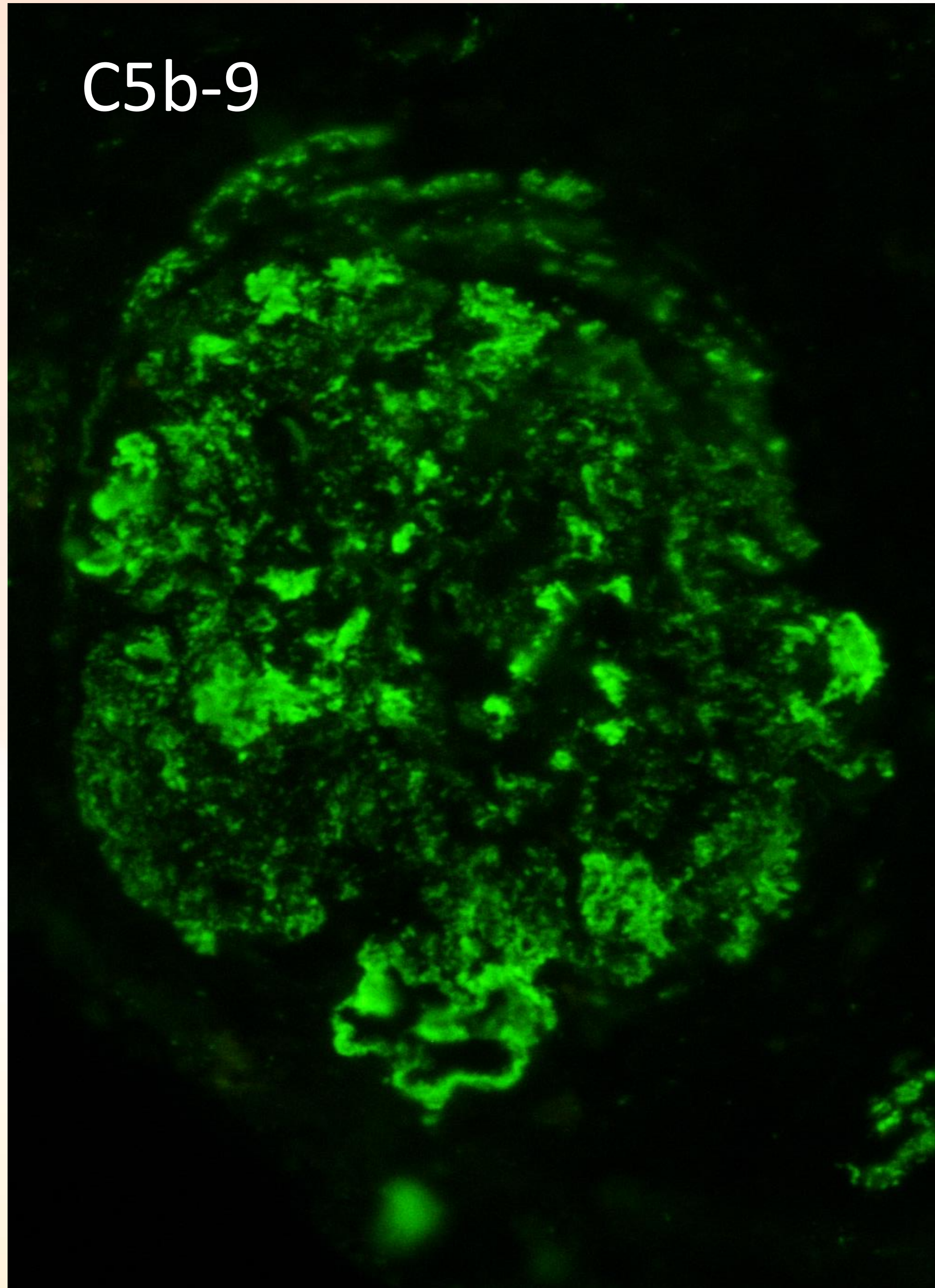
C5b-9



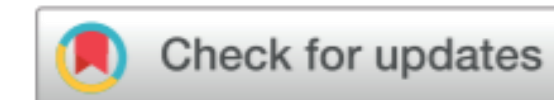
C5b-9

CONFIDENCIAL

C5b-9



Glomerular membrane attack complex is not a reliable marker of ongoing C5 activation in lupus nephritis

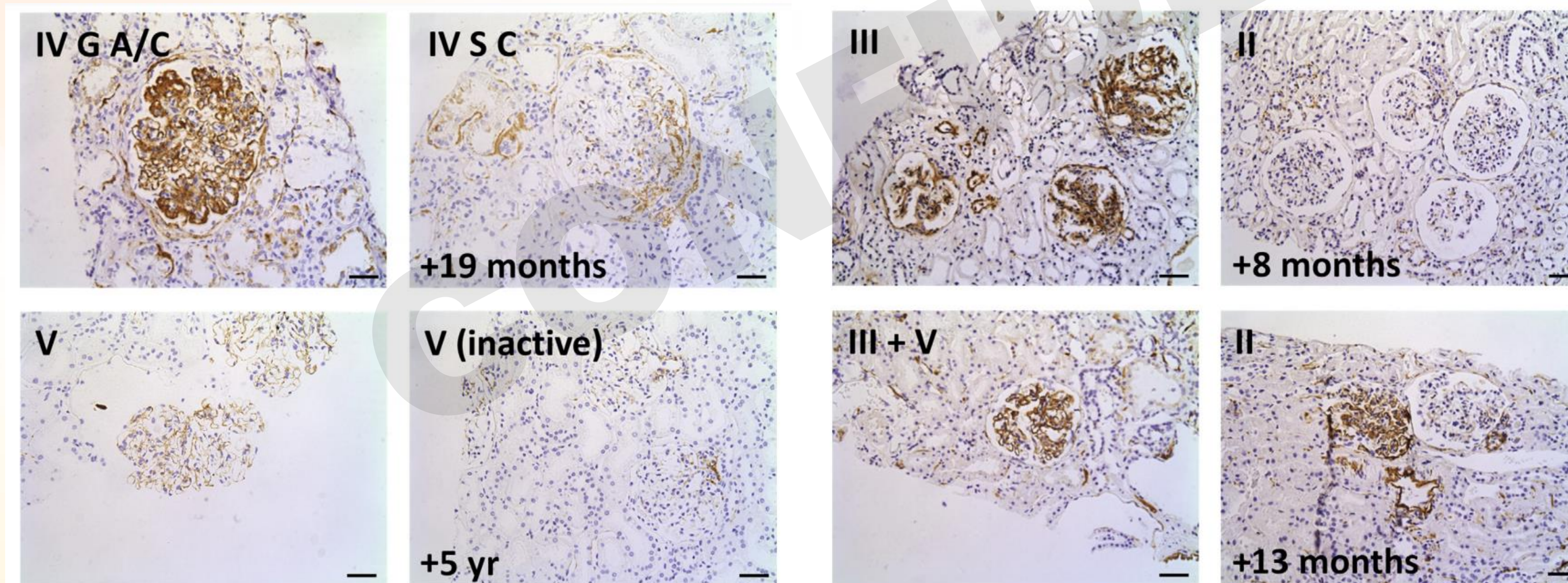


OPEN

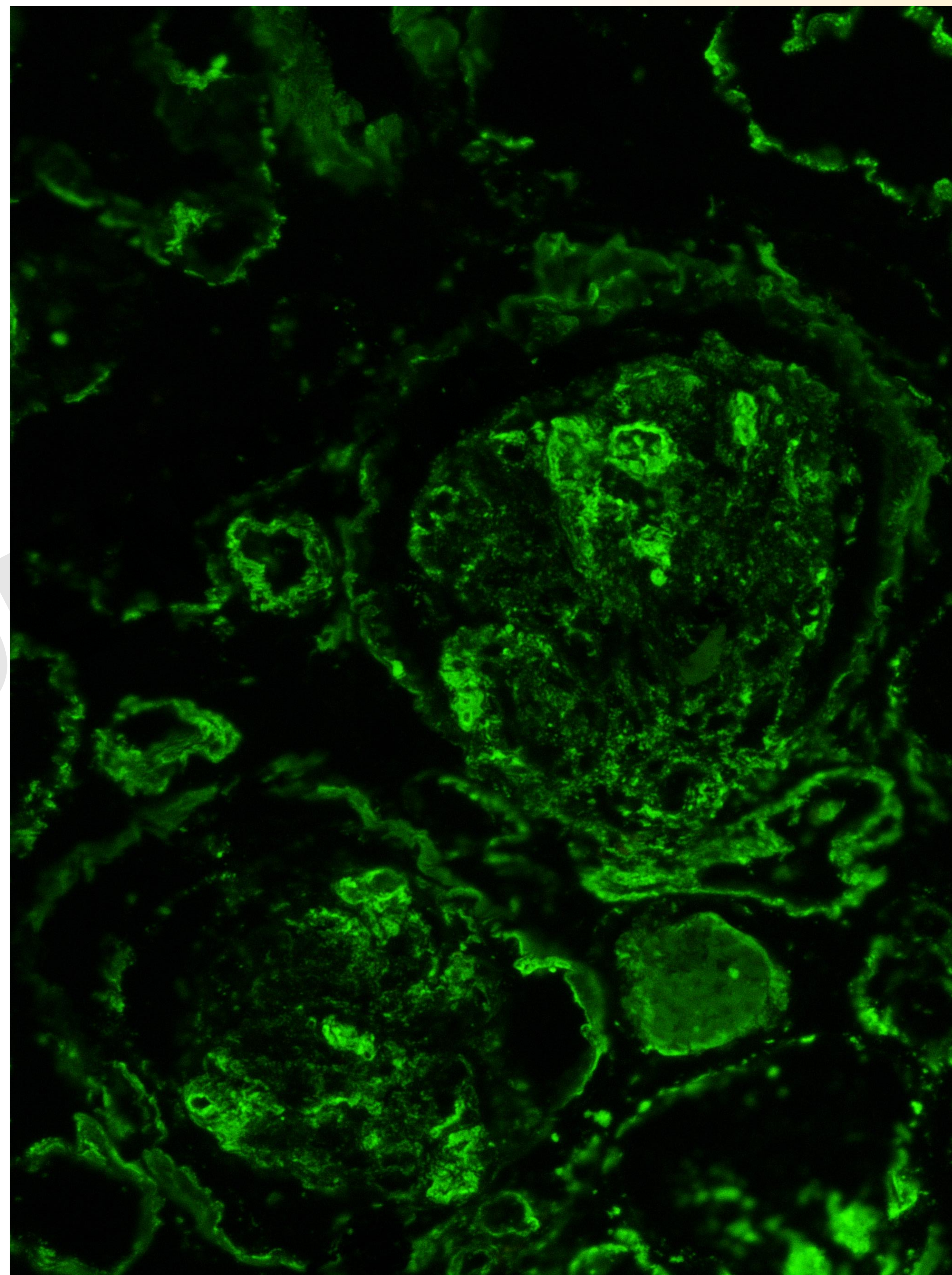
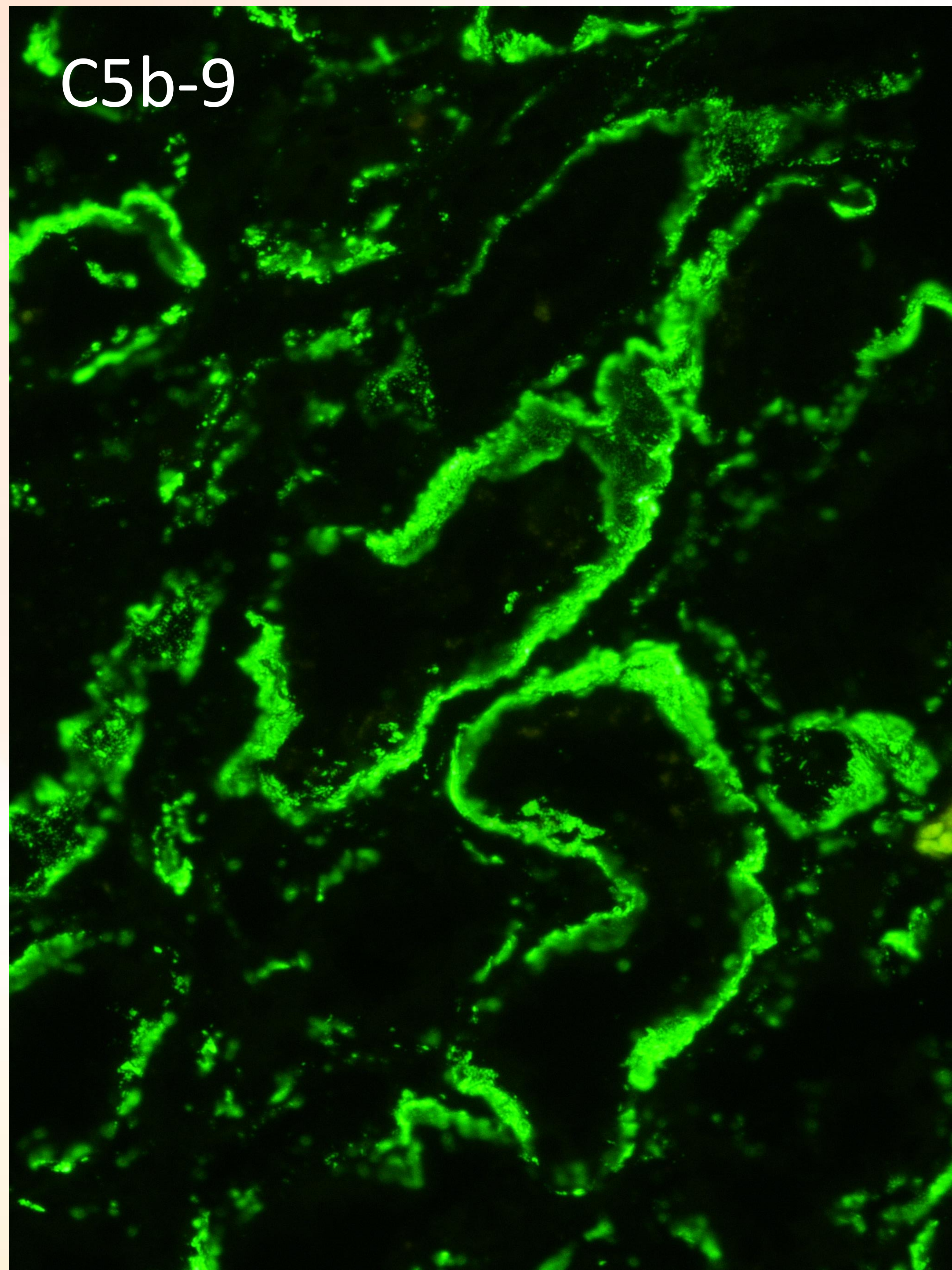
Hannah R. Wilson¹, Nicholas R. Medjeral-Thomas¹, Alyssa C. Gilmore¹, Pritesh Trivedi¹, Kathleen Seyb², Ramin Farzaneh-Far², Iva Gunnarsson³, Agneta Zickert³, Thomas D. Cairns¹, Liz Lightstone¹, H. Terence Cook^{1,4} and Matthew C. Pickering^{1,4}

¹Centre for Inflammatory Disease, Imperial College London, London, UK; ²Ra Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; and

³Division of Rheumatology, Department of Medicine, Karolinska Institutet and Rheumatology, Karolinska University Hospital, Stockholm, Sweden



Wilson et al. Kidney International (2019) 95, 655-665.



Immunohistochemical study of the C5b-9 complex of complement in human kidneys

NICOLE HINGLAIS, MICHEL D. KAZATCHKINE, SUCHARIT BHAKDI,
MARIE-DOMINIQUE APPAY, CHANTAL MANDET, JEANINE GROSSETETE, and JEAN BARIETY

INSERM U 28, Hôpital Broussais, Paris, France, and Institute of Medical Microbiology, Giessen, Federal Republic of Germany

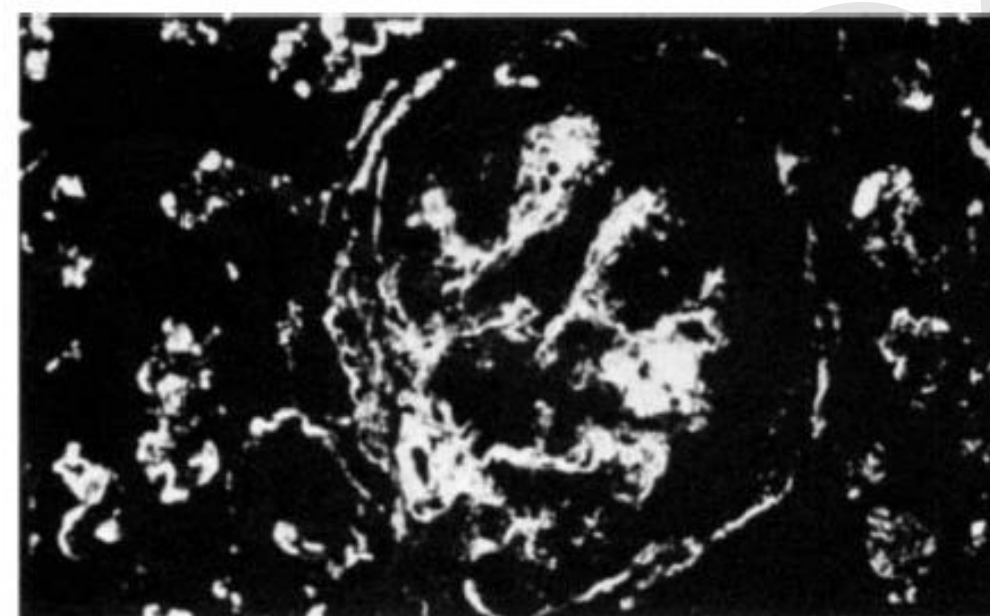
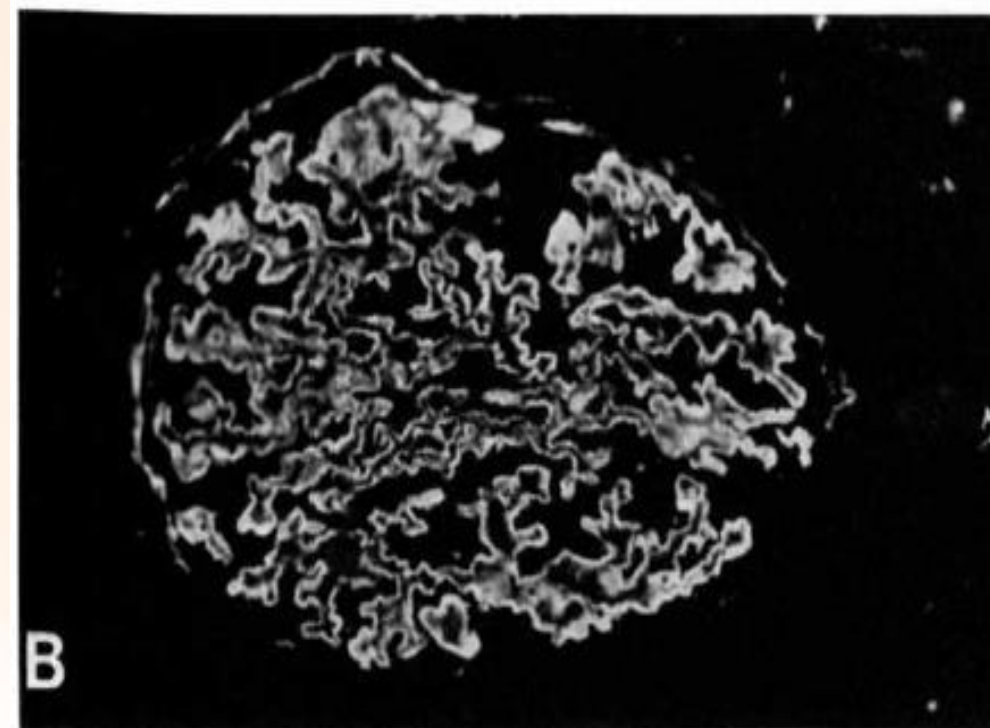
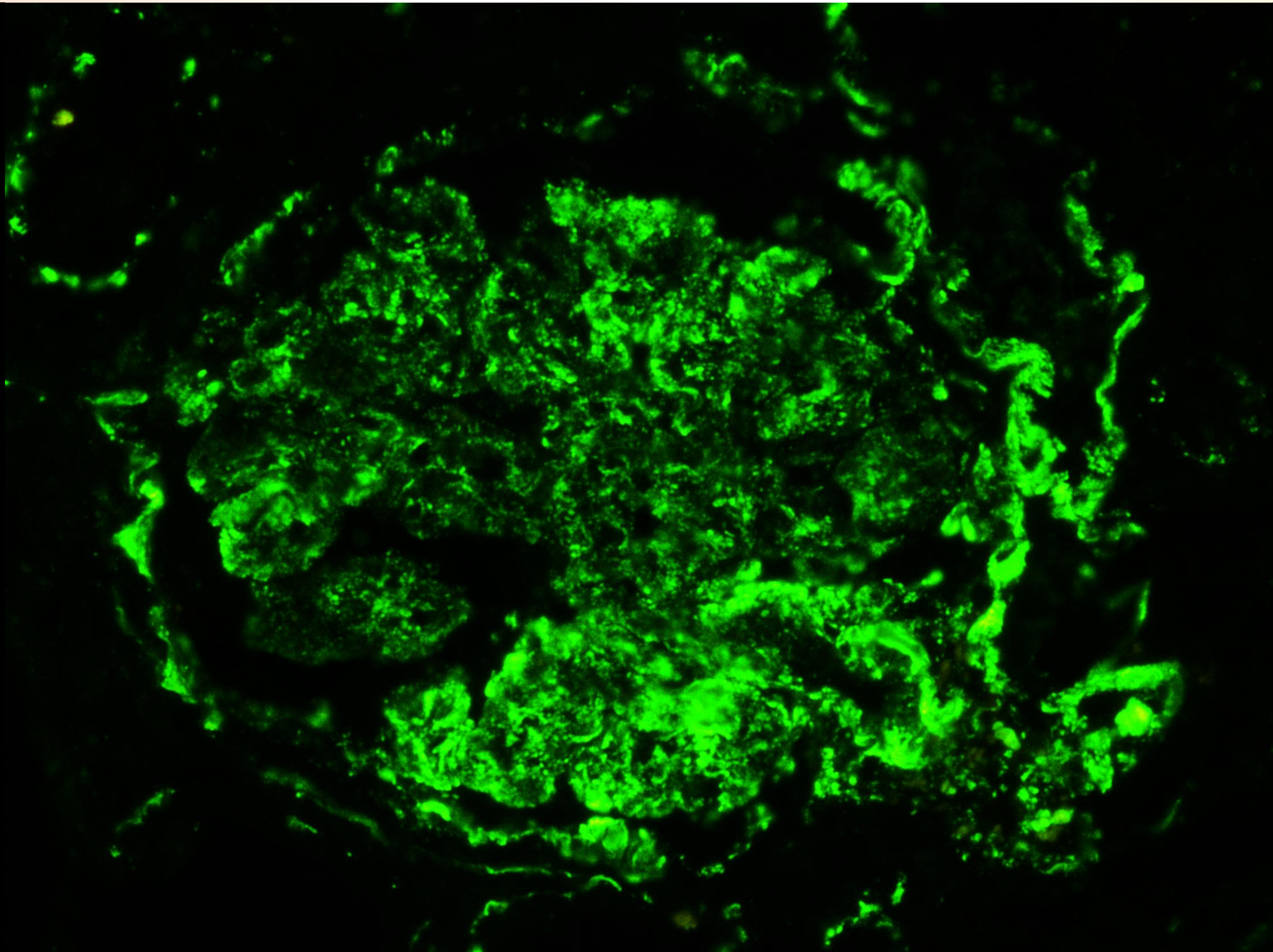


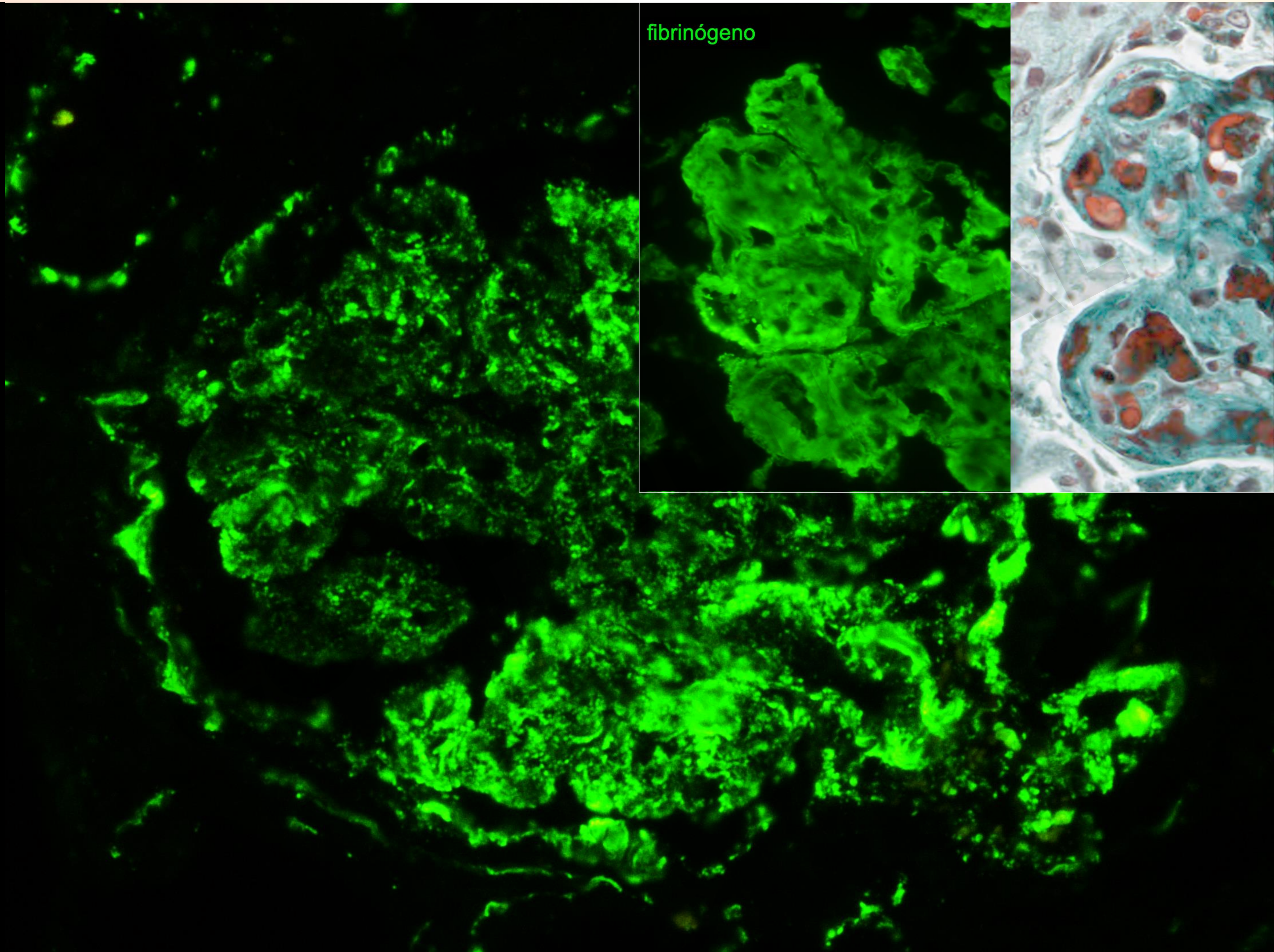
Fig. 14. Diabetic glomerulosclerosis. Staining with anti-C9 neoantigens antibodies. Extensive C5b-9 deposits are seen in nodular mesangial areas; $\times 310$.

Evaluation of immunohistochemical data on renal biopsies stained with anti-C5b-9 antibodies requires careful interpretation; sparse and granular labeling in connective matrices should not be regarded as abnormal, since C5b-9 is normally found on cell remnants that are embedded in connective matrices. Conversely, the presence of C5b-9 neoantigens is of pathological significance when the antigens are found within immune deposits and/or are present in abundant clusters in sclerotic matrices because of the increased density of labeled cell remnants in the latter circumstances. The pathological occurrence of C5b-9 neoantigens does not strictly correlate with positivity for C3, that is, some biopsies were negative for C3 but positive for C5b-9, which may derive from the extreme stability of C5b-9 as opposed to C3 antigens.

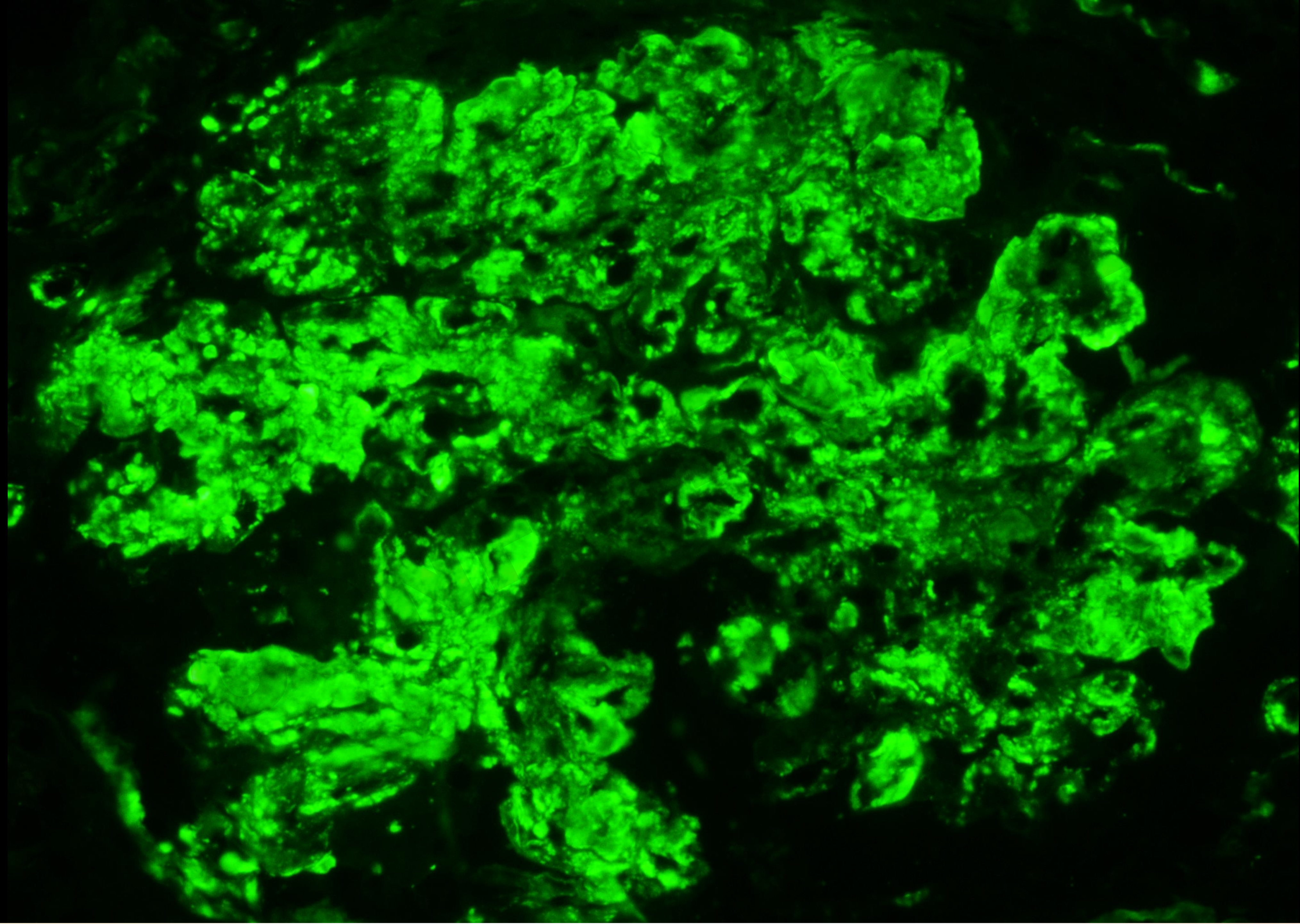
C5b-9



C5b-9



C3



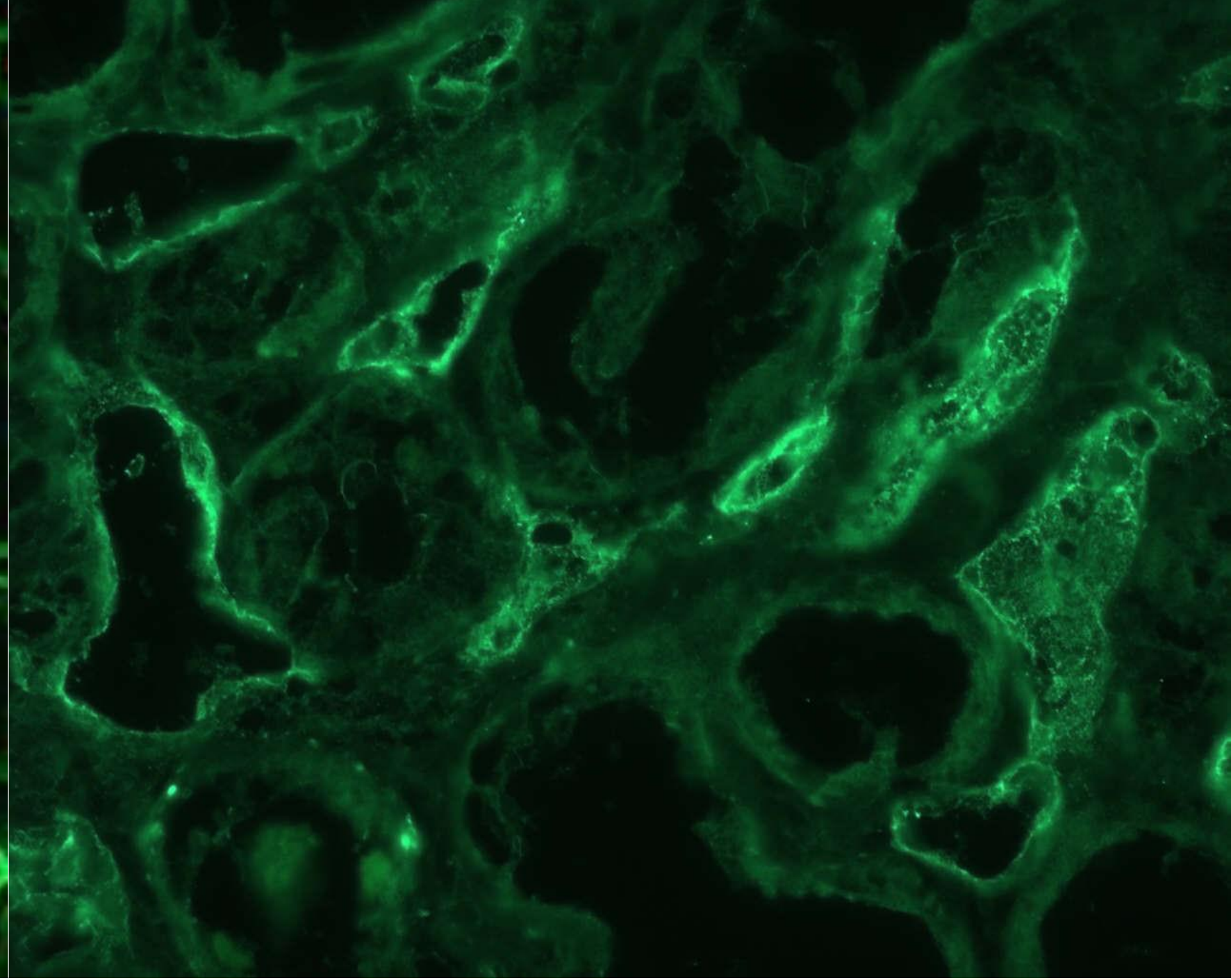
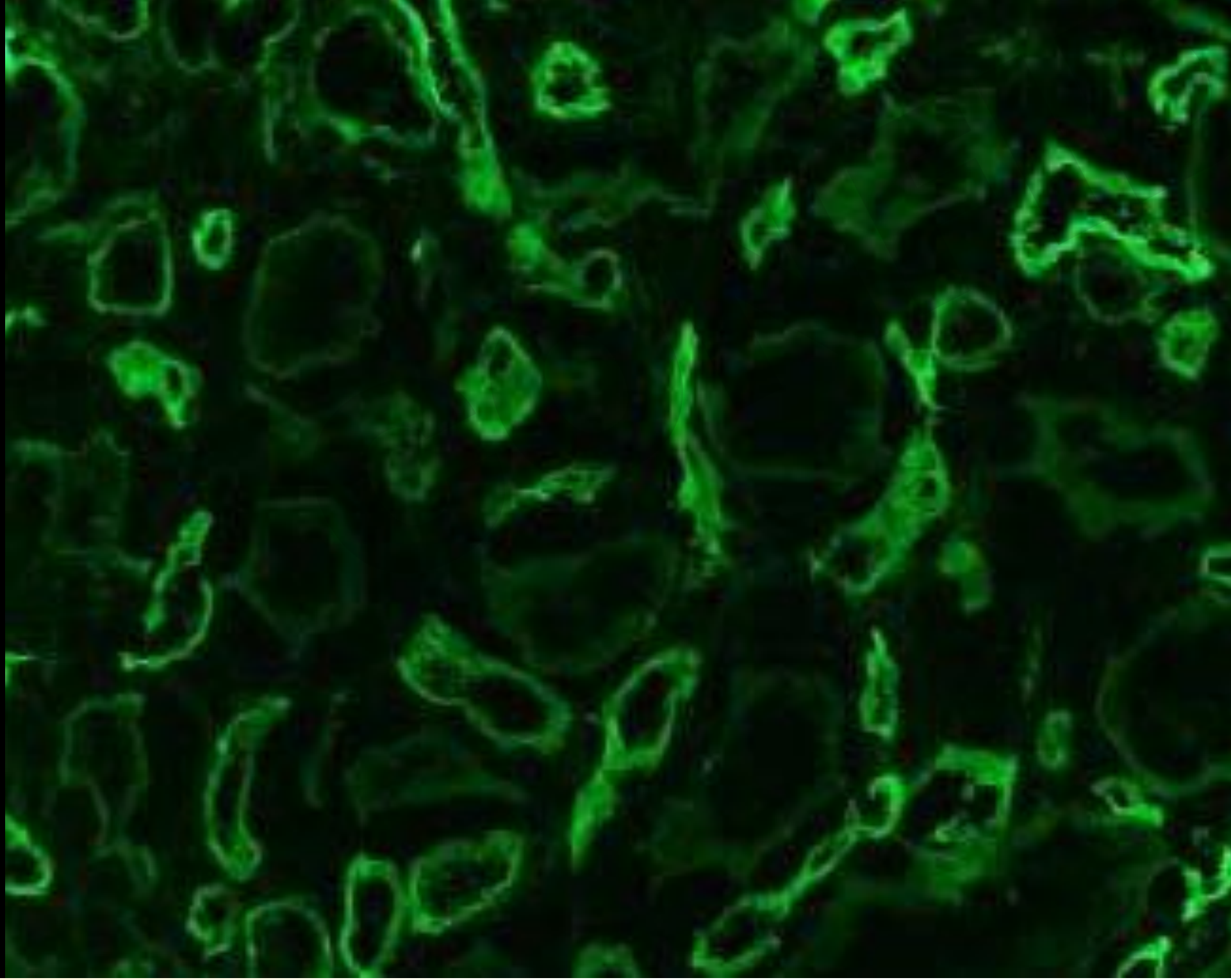
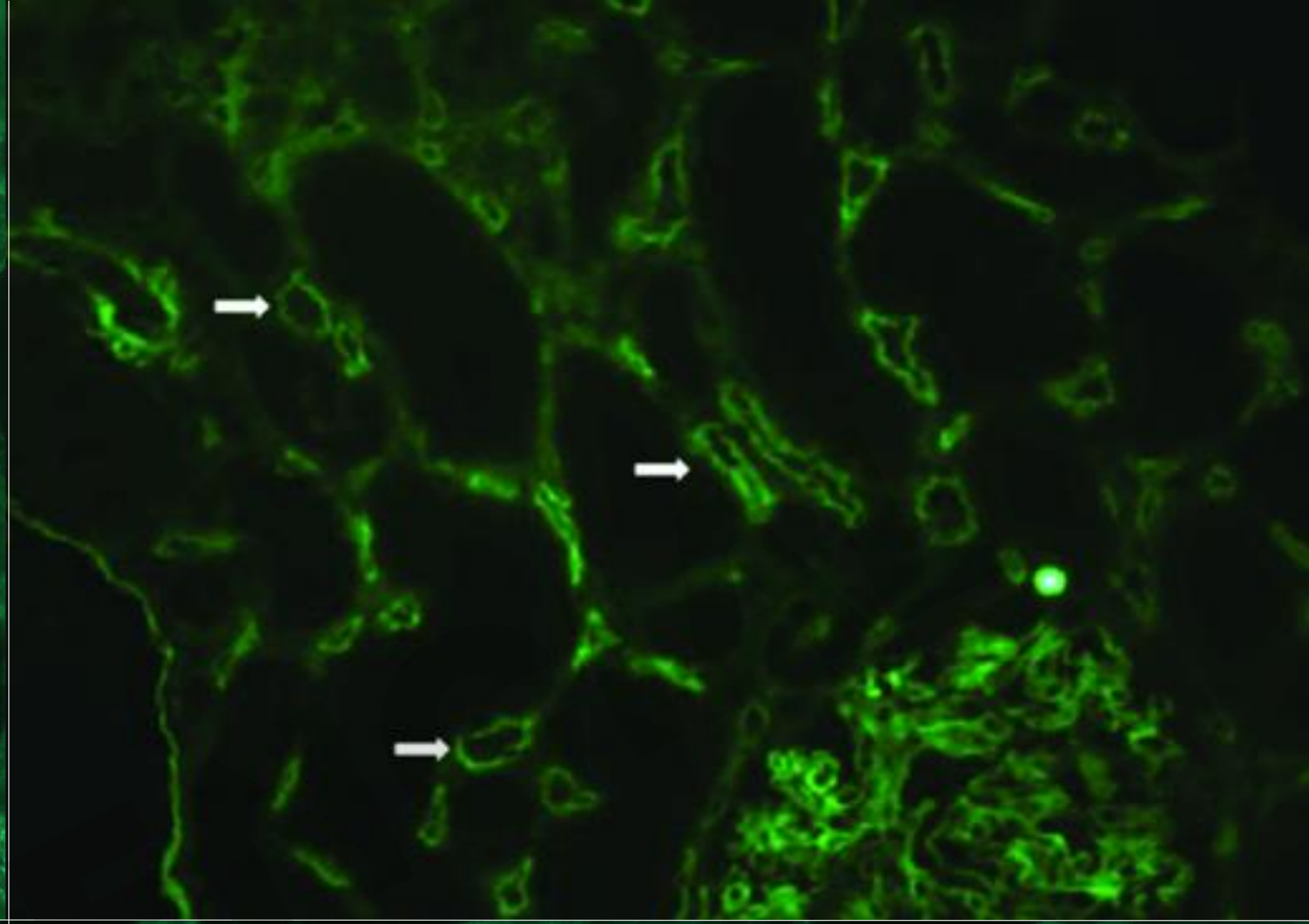
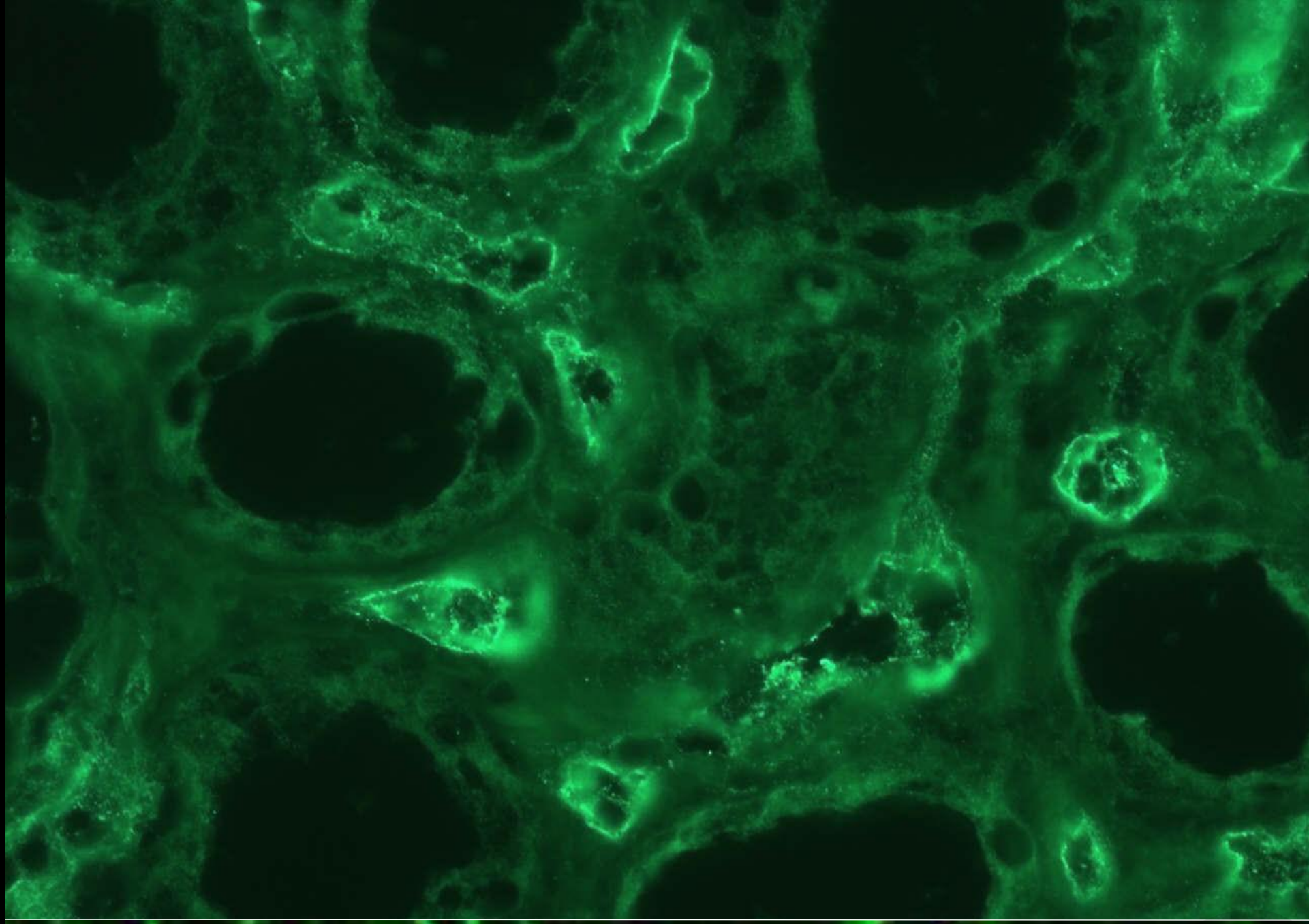
Kidney International, Vol. 43 (1993), pp. 1333–1338

Capillary deposition of C4d complement fragment and early renal graft loss

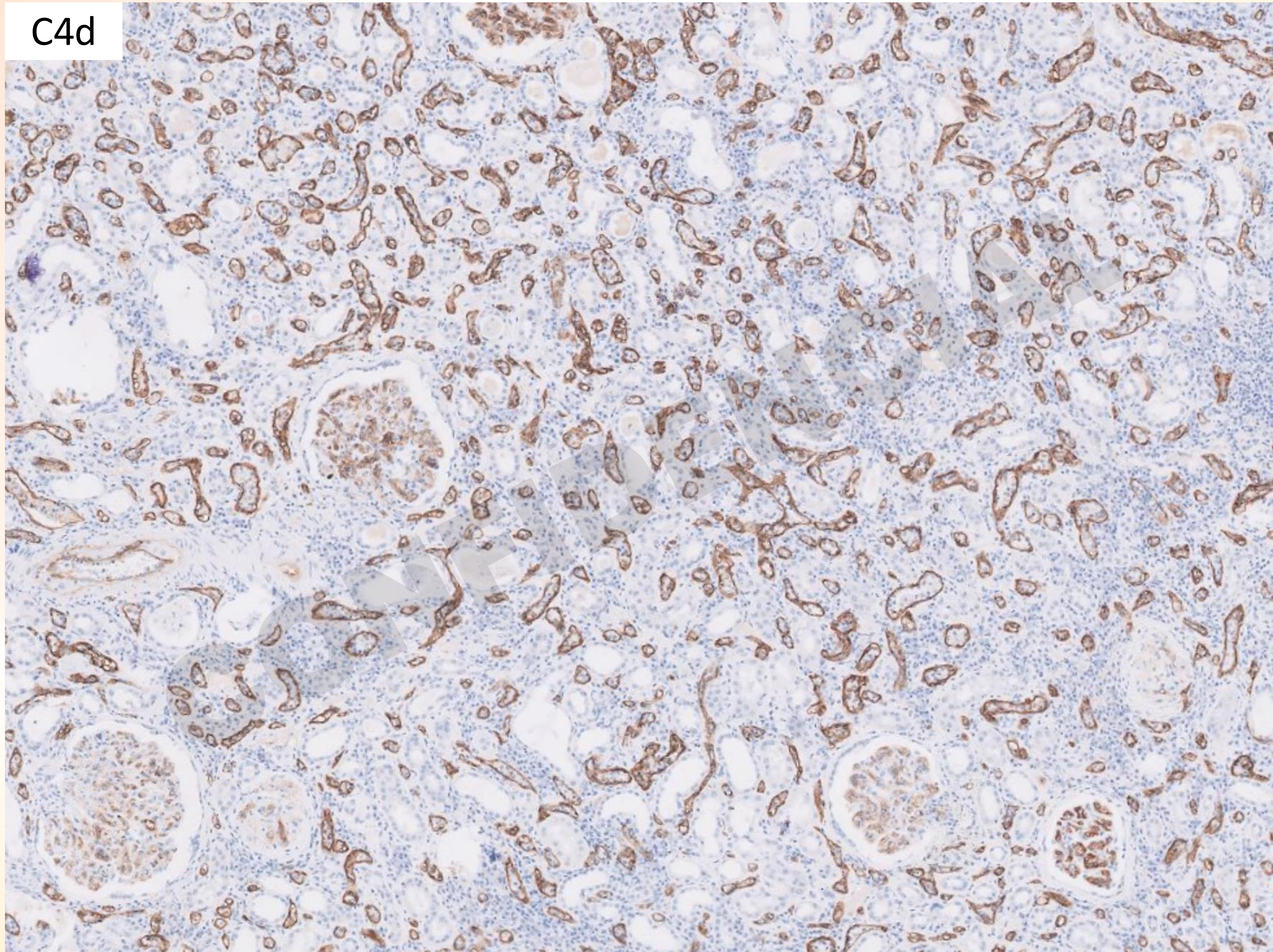
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MAX WEISS, GERT RIETHMÜLLER, WALTER LAND, and EKKEHARD ALBERT

Department of Internal Medicine, Klinikum Innenstadt; Institute of Immunology; Division of Transplant Surgery, Department of Surgery and Nephrology Division, Department of Internal Medicine I, Klinikum Großhadern; Institute of Pathology and Department of Paediatrics, University of Munich, Munich, Germany

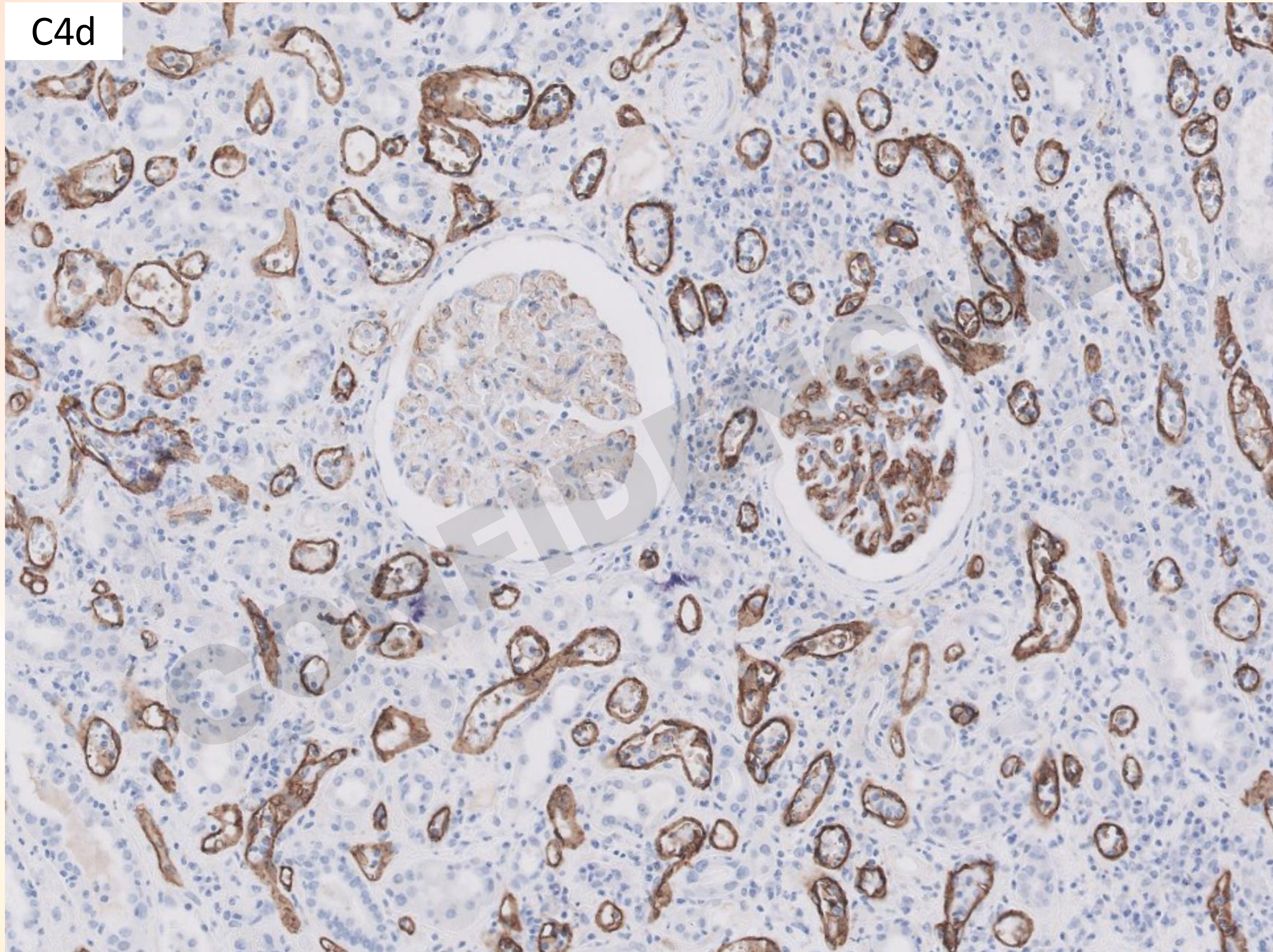
C4d



C4d



C4d



C4d



C4d

Mas allá del rechazo



ARTHRITIS & RHEUMATISM
Vol. 58, No. 8, August 2008, pp 2460–2469

Potential for Glomerular C4d as an Indicator of Thrombotic Microangiopathy in Lupus Nephritis

Danielle Cohen, Marije Koopmans, Idske C. L. Kremer Hovinga, Stefan P. Berger, Marian Roos van Groningen, Gerda M. Steup-Beekman, Emile de Heer, Jan Anthonie Bruijn, and Ingeborg M. Bajema

Glomerular endothelial activation, C4d deposits and microangiopathy in immunoglobulin A nephropathy



ndt
Nephrology Dialysis Transplantation

Hernán Trimarchi ¹ and Rosanna Coppo²

Nephrol Dial Transplant (2019) 1–6
doi: 10.1093/ndt/gfz241

CLINICAL RESEARCH

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Complement Factor C4d Is a Common Denominator in Thrombotic Microangiopathy

Jamie S. Chua,* Hans J. Baelde,* Malu Zandbergen,* Suzanne Wilhelmus,* Leendert A. van Es,* Johan W. de Fijter,[†] Jan A. Bruijn,* Ingeborg M. Bajema,* and Danielle Cohen*

Glomerular C4d deposits can mark structural capillary wall remodelling in thrombotic microangiopathy and transplant glomerulopathy: C4d beyond active antibody-mediated injury: a retrospective study

Adil H. Gasim, Jamie S. Chua, Ron Wolterbeek, John Schmitz, Eric Weimer, Harsharan K. Singh, Volker Nickeleit

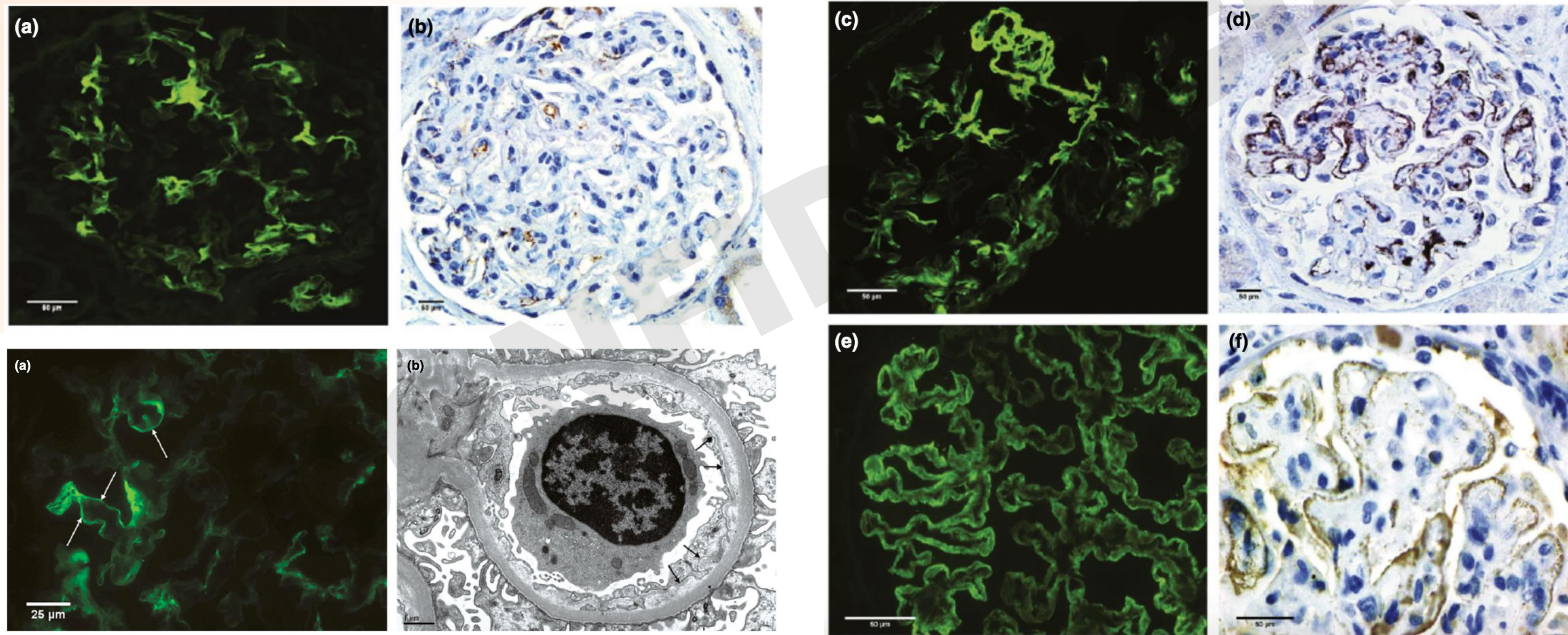
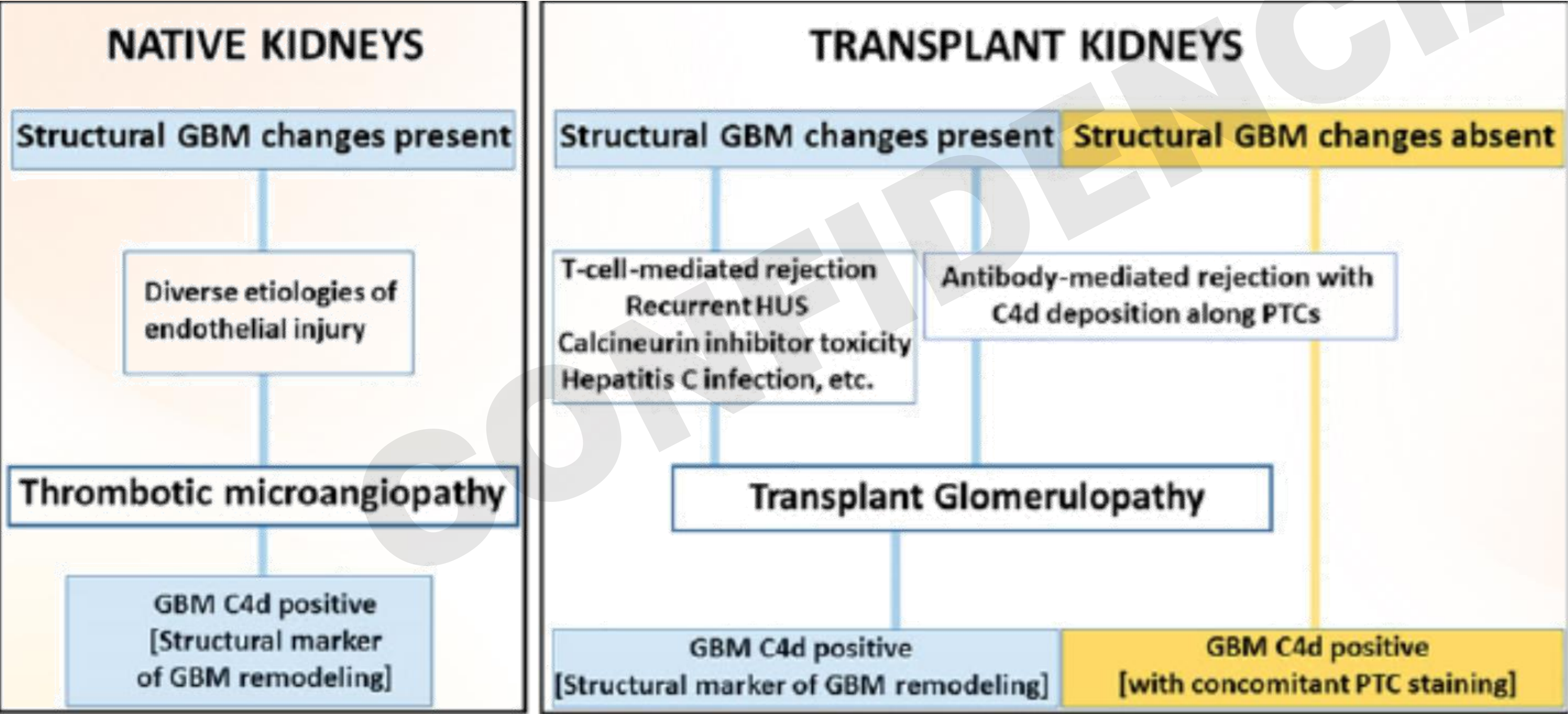


Figure 2 (a and b) – GBM-C4d deposits associated with structural capillary wall remodelling: Minor GBM duplication, often limited to few glomerular capillaries and only noted by electron microscopy, can be reflected by segmental pseudolinear GBM-C4d staining. (a) GBM-C4d staining by IF is seen along few peripheral glomerular capillary walls (arrows); mesangial C4d deposits are considered to be nondiagnostic. (b) Corresponding EM illustrates minor structural capillary wall changes with thin layers of rudimentary new dense (arrows) under activated glomerular endothelial cells. The newly formed subendothelial lamina densa is considered to be the morphologic correlate for the GBM-C4d deposits. The illustrated changes can be seen in native kidney biopsies with TMA or in early transplant glomerulopathy. Indirect immunofluorescence microscopy with a monoclonal antibody directed against C4d, $\times 600$ oil (a); transmission electron microscopy, uranyl acetate staining, $\times 6000$ (b).

C4d as a structural damage marker

Cases with GBM – C4d deposition



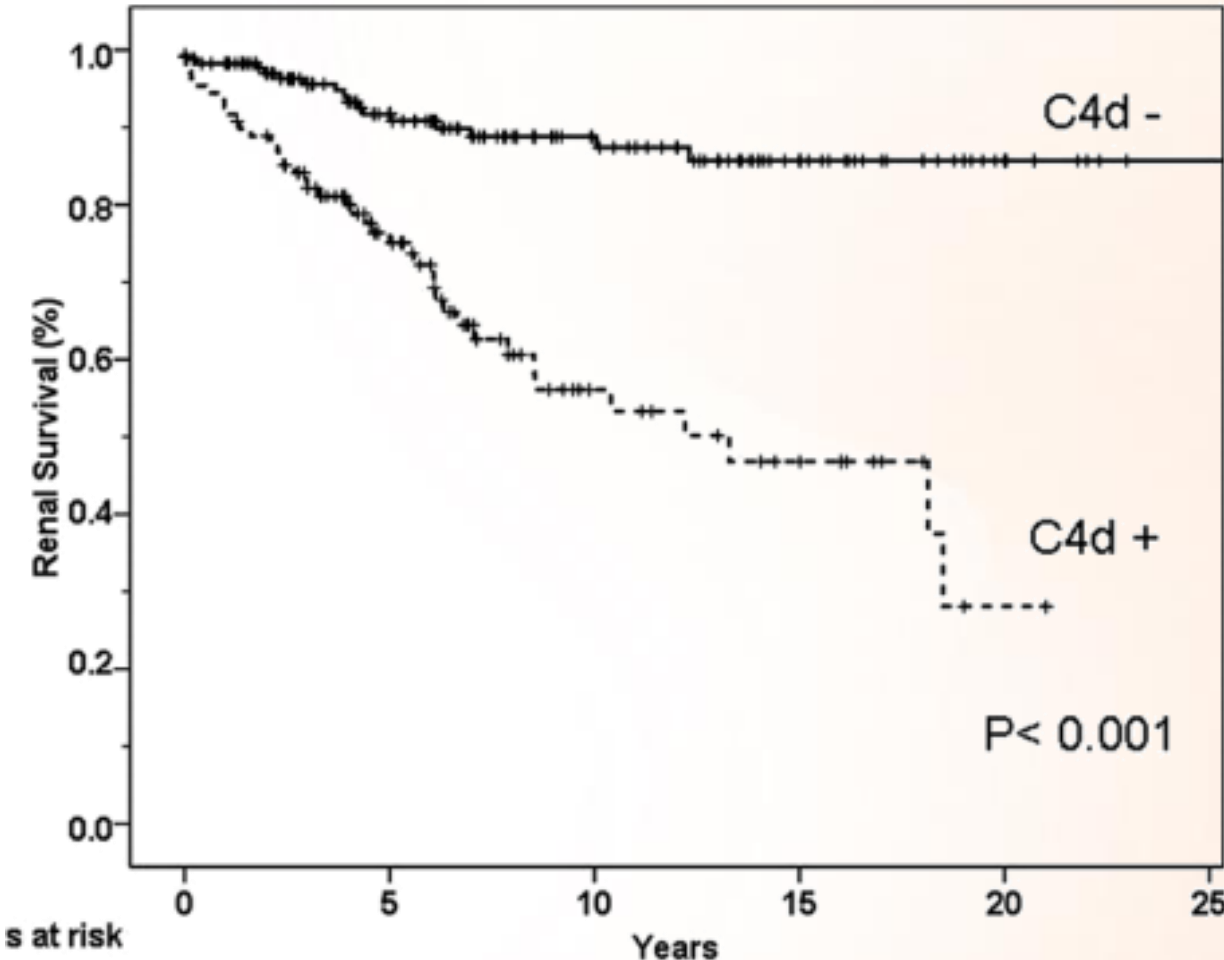
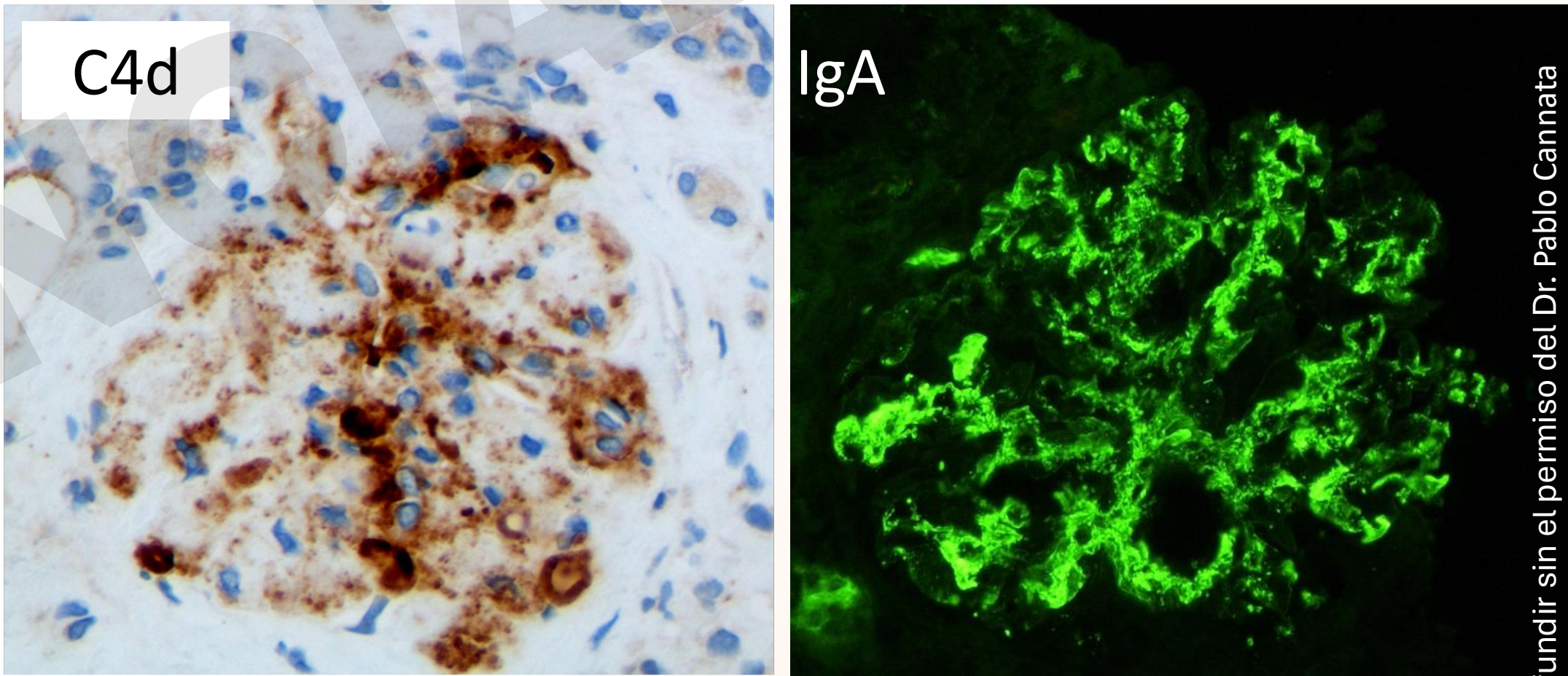
C3
Academy

Association of C4d Deposition with Clinical Outcomes
in IgA Nephropathy

Mario Espinosa, Rosa Ortega, Marina Sánchez, Alfons Segarra, Maria Teresa Salcedo, Fayna González, Rafael Camacho, Miguel Angel Valdivia, Rocio Cabrera, Katia López, Fernando Pinedo, Eduardo Gutierrez, Alfonso Valera, Miryam Leon, Maria Angeles Cobo, Rosa Rodriguez, Jose Ballarín, Yolanda Arce, Beatriz García, María Dolores Muñoz, and Manuel Praga for the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

Clin J Am Soc Nephrol 9: 897–904, 2014.

Table 1. Clinical and histologic characteristics of the patients at baseline and during the follow-up period according to C4d staining				
Variable	Total (N=283)	C4d-Positive (n=109)	C4d-Negative (n=174)	P Value
Mean age (yr)	39.1±17.2	38.6±15.0	39.4±18.5	0.72
Male sex	208 (73.8)	81 (74.3)	127 (73.4)	0.89
Macroscopic hematuria	129 (45.6)	43 (39.4)	86 (49.4)	0.06
Hypertension	155 (55.2)	78 (71.6)	77 (44.8)	<0.001
eGFR (ml/min per 1.73 m²)	67.7±35.9	58.9±34.1	73.2±36.0	0.001
Stage (eGFR in ml/min/1.73 m²)				0.02
1 (≥90)	84 (29.7)	22 (20.2)	62 (35.8)	
2 (60–89)	69 (24.4)	26 (23.9)	43 (24.9)	
3 (30–59)	82 (29.0)	38 (34.9)	44 (25.4)	
4 (15–29)	29 (10.2)	16 (14.7)	13 (7.5)	
5 (<15)	18 (6.4)	7 (6.4)	11 (6.4)	
Median urinary protein excretion (g/d)	1.9 (1.0–3.0)	2.2 (1.4–3.6)	1.7 (1.0–2.6)	<0.001
Urinary protein excretion (g/d)				0.01
<0.30	13 (4.6)	1 (0.9)	12 (6.9)	
0.30–0.99	42 (14.8)	14 (12.8)	28 (16.1)	
1–2.99	150 (53.0)	53 (48.6)	97 (55.7)	
≥3.0	78 (27.6)	41 (37.6)	37 (21.3)	
Proteinuria≥1 g/d	228 (80.6)	94 (86.2)	134 (77.0)	0.03
Oxford classification				
M1	183 (64.7)	77 (73.3)	106 (66.3)	0.13
E1	62 (21.9)	28 (25.7)	34 (19.5)	0.14
S1	57 (20.1)	35 (32.4)	22 (12.6)	<0.001
Tubular atrophy/interstitial fibrosis (%)				<0.001
T0 (<25)	112 (39.6)	15 (13.8)	97 (55.7)	
T1 (25–50)	90 (31.8)	41 (37.6)	49 (28.2)	
T2 (>50)	81 (28.6)	53 (48.6)	28 (16.1)	
Use of ACEI/ARB	225 (79.5)	90 (89.1)	135 (87.1)	0.39
Use of prednisone	100 (35.3)	35 (33.7)	65 (38.2)	0.51
Any other immunosuppressive treatment ^a	60 (21.2)	23 (23.2)	37 (23.9)	>0.99
Median follow-up period (yr)	6.0 (3.0–11.7)	5.3 (2.9–8.3)	6.6 (3.0–13.1)	0.03
Evolution to ESRD in the follow-up ^b	58 (20.5)	41 (37.6)	17 (9.8)	<0.001

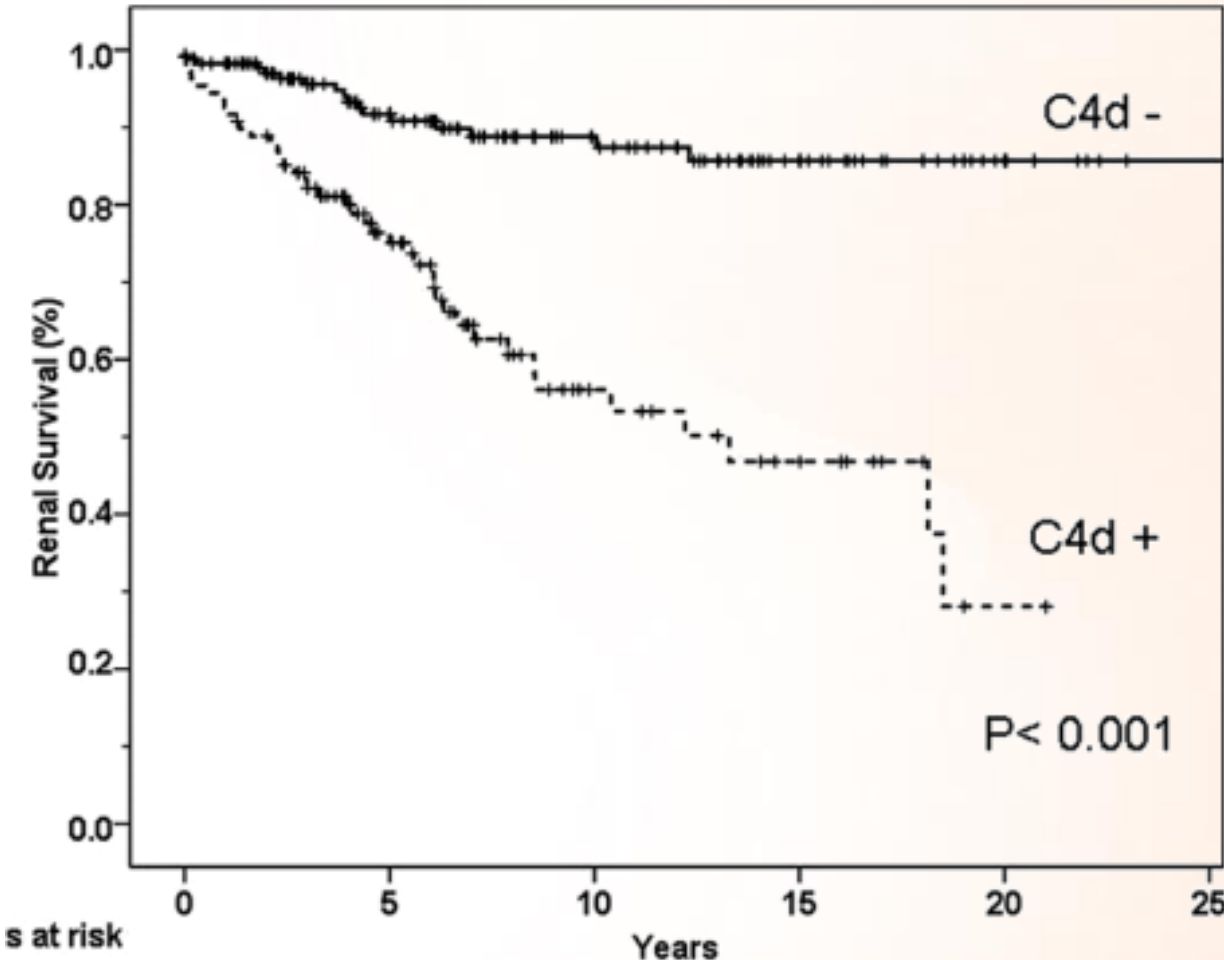
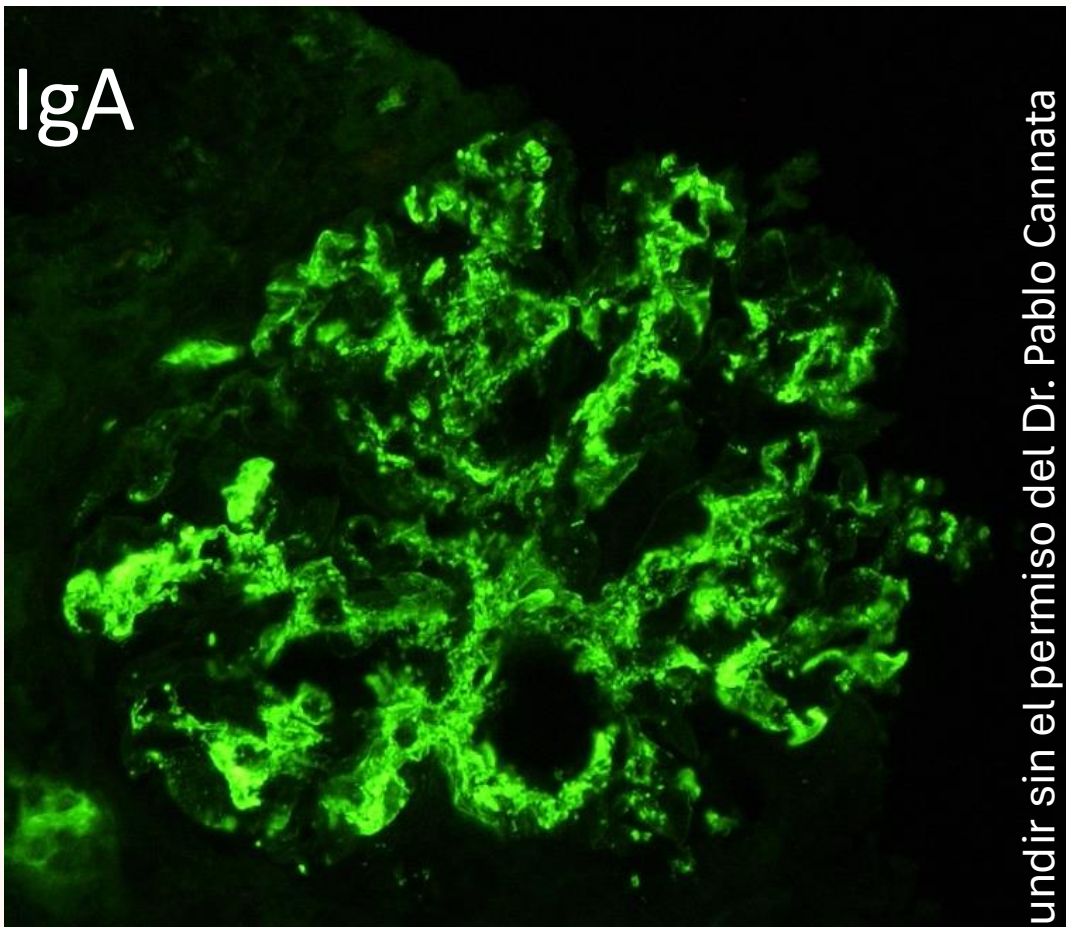
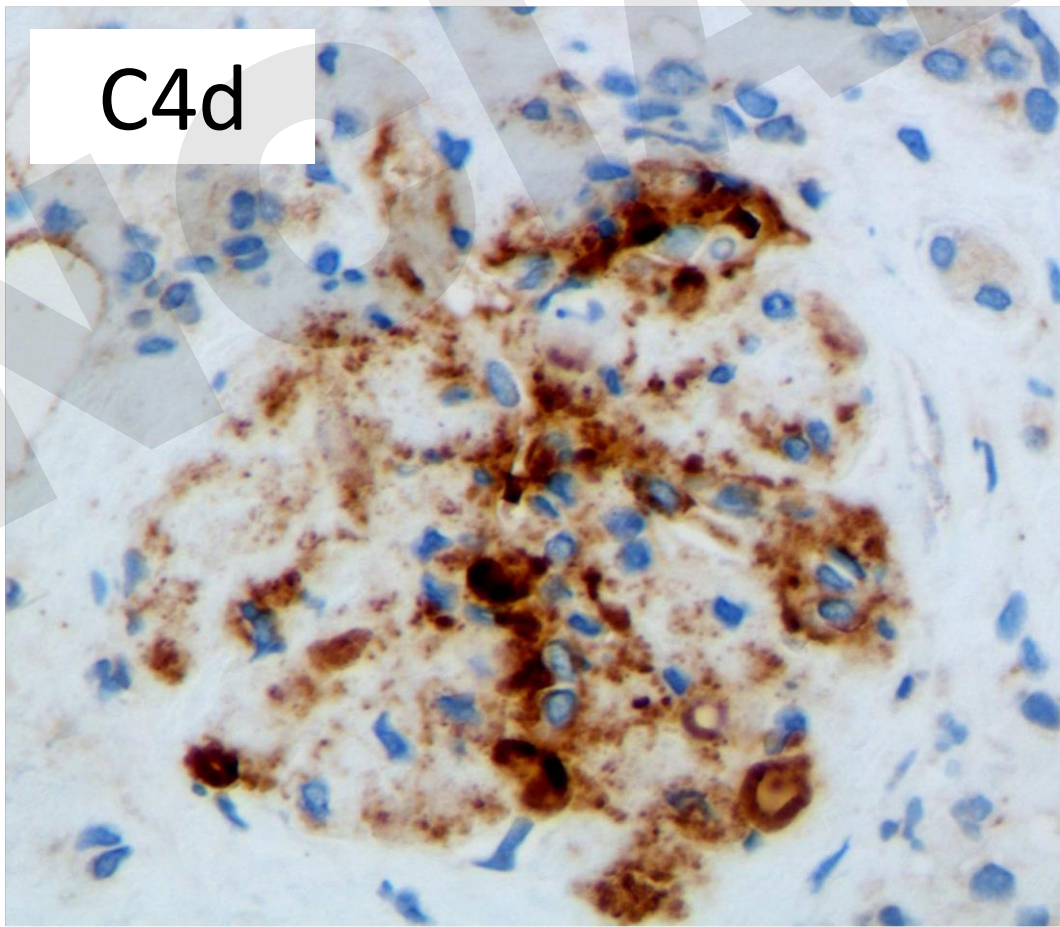


Association of C4d Deposition with Clinical Outcomes in IgA Nephropathy

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Clin J Am Soc Nephrol 9: 897–904, 2014.

Table 1. Clinical and histologic characteristics of the patients at base		38.5%	61.5%	C4d staining
Variable	Total (N=283)	C4d-Positive (n=109)	C4d-Negative (n=174)	P Value
Mean age (yr)	39.1±17.2	38.6±15.0	39.4±18.5	0.72
Male sex	208 (73.8)	81 (74.3)	127 (73.4)	0.89
Macroscopic hematuria	129 (45.6)	43 (39.4)	86 (49.4)	0.06
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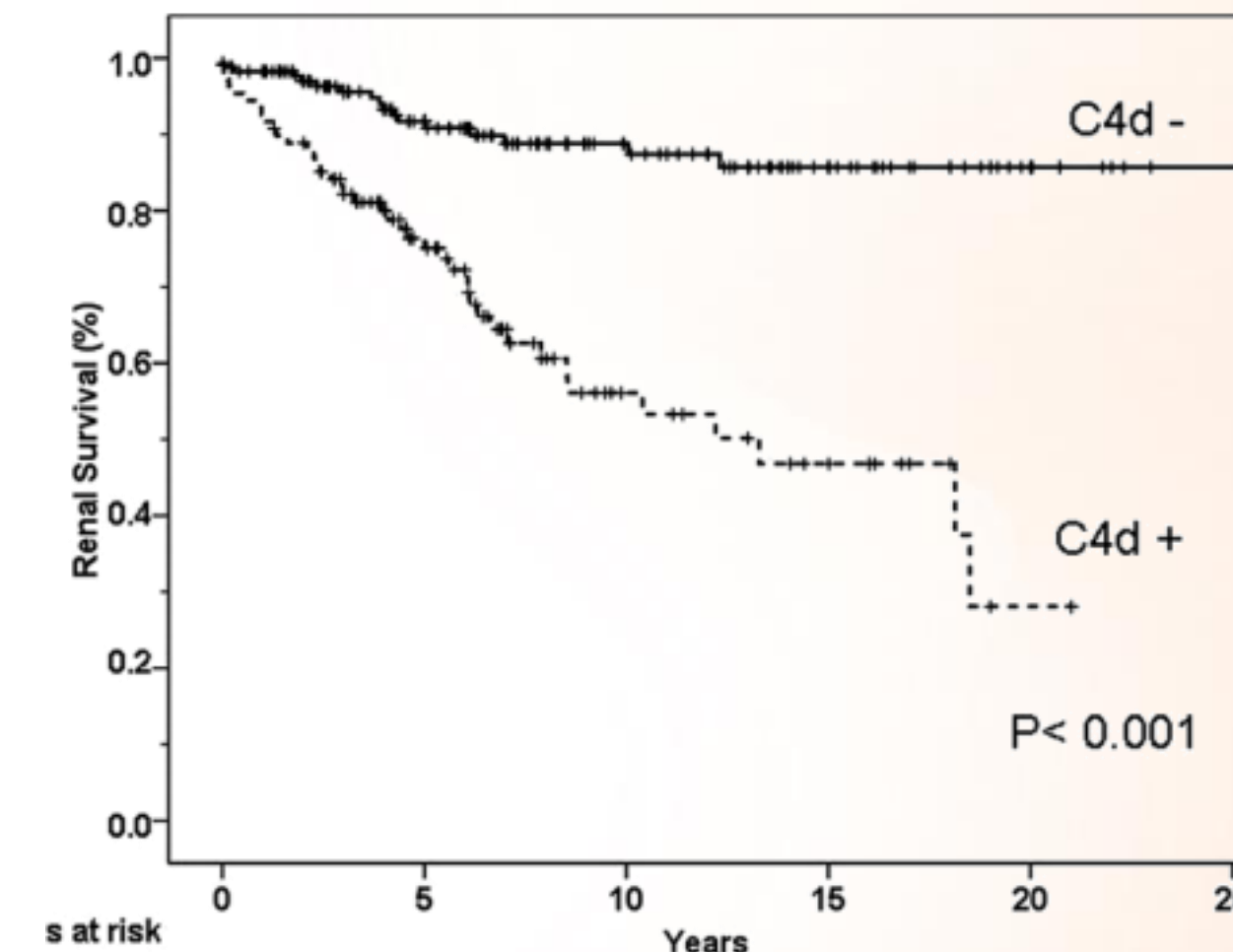
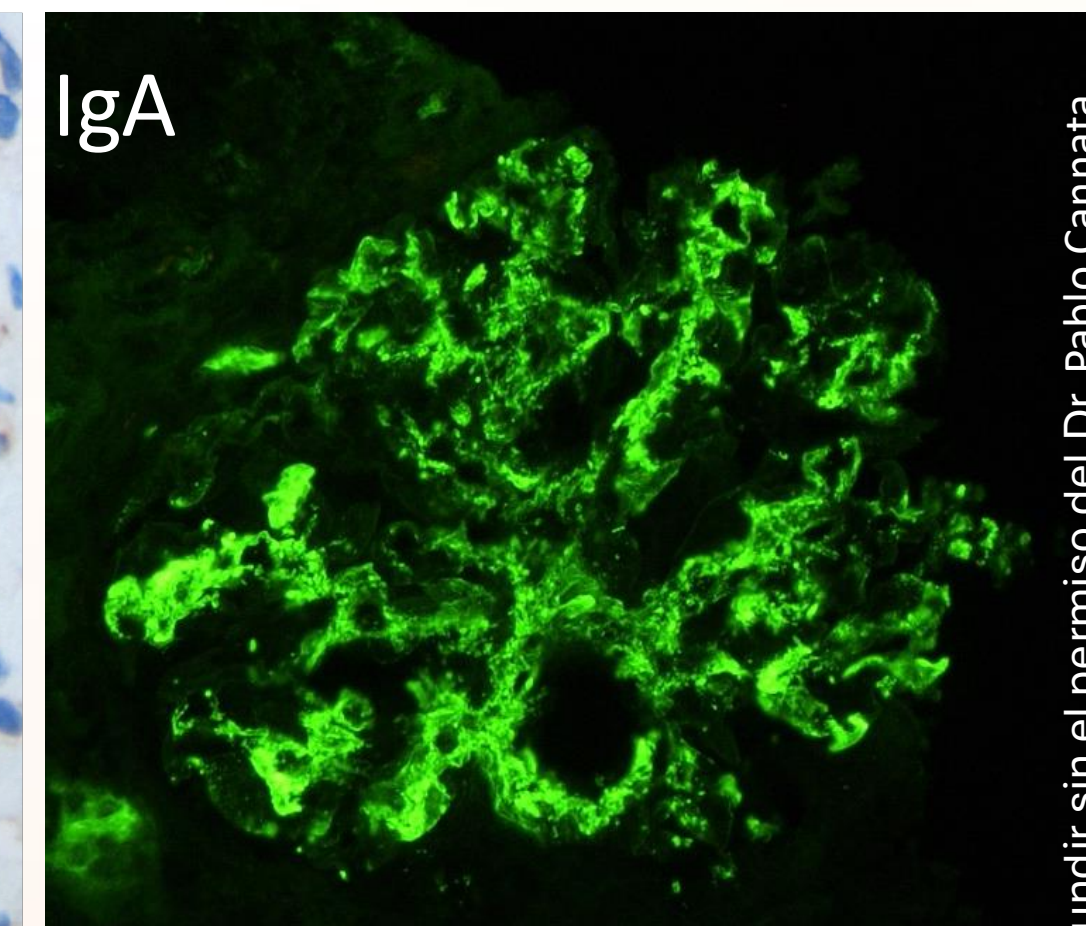
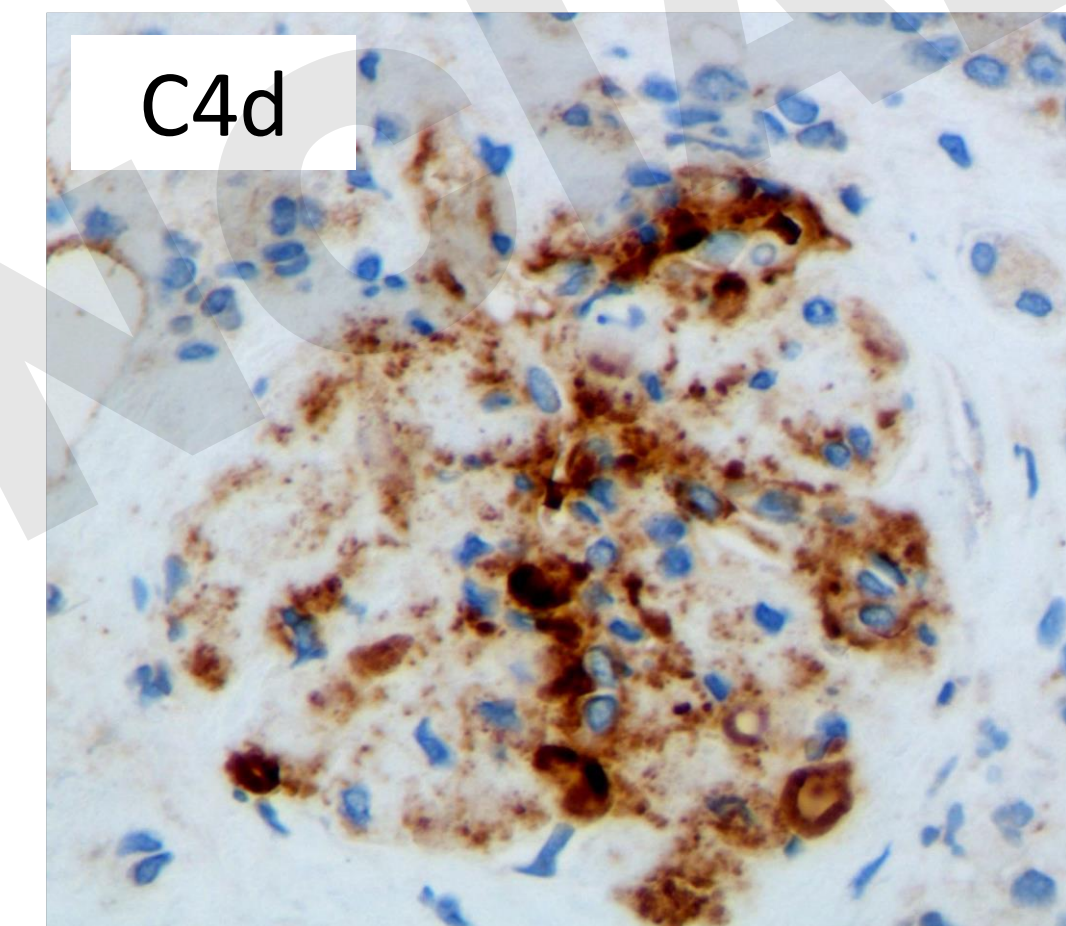


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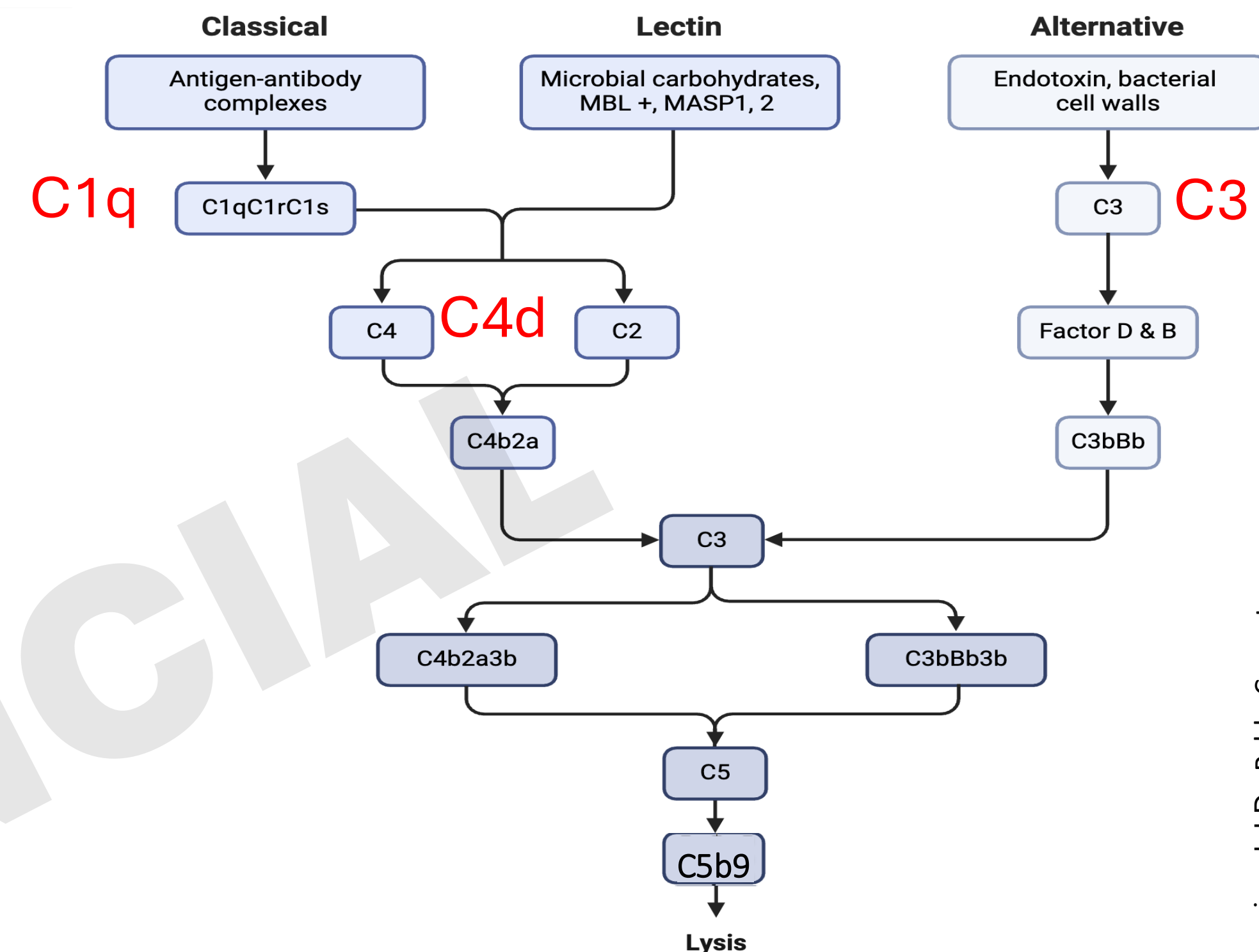
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C4d as a Diagnostic Tool in Proliferative GN

Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,[†] and Fernando C. Fervenza[‡]

*Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology and [‡]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and [†]Division of Nephrology, AZ Sint-Jan Brugge, Brugge, Belgium



Glomerular Staining in Immune Complex-Mediated GN

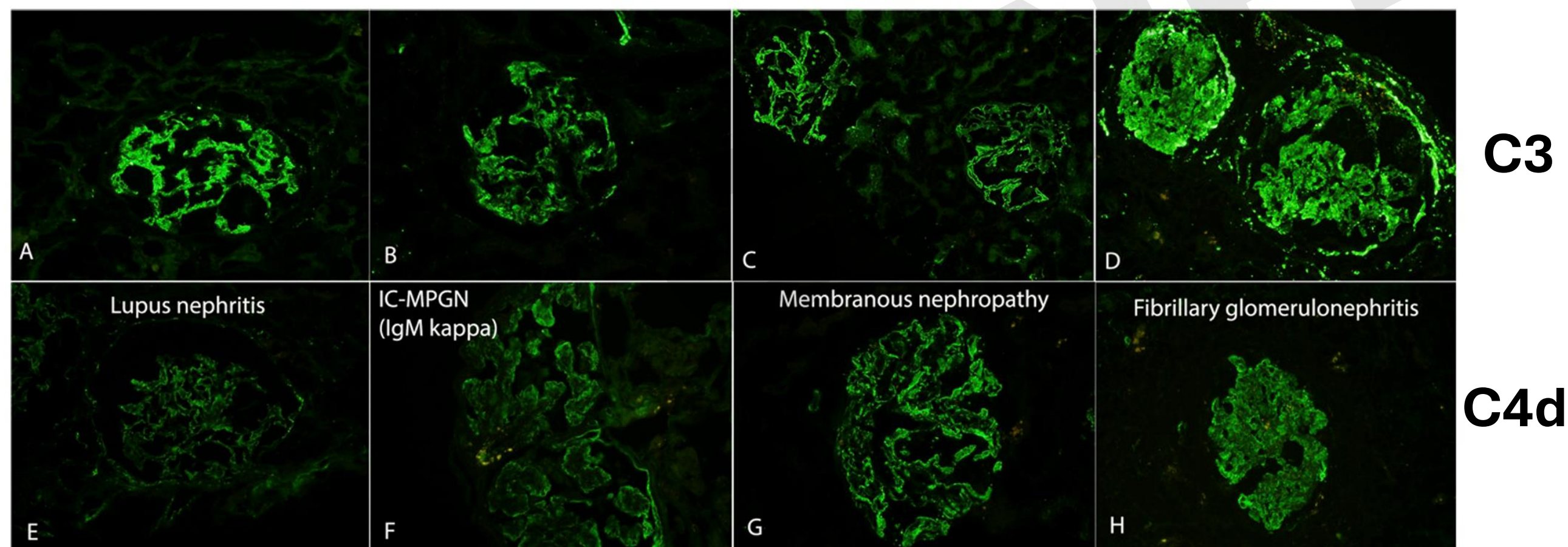


Figure 1. C3 and C4d staining in immune complex (IC)-mediated GN. Top panel shows staining for C3, and bottom panel shows staining for C4d. Each vertical panel represents one patient: (A) and (E) show lupus nephritis, (B) and (F) show MPGN because of monoclonal Ig deposits, (C) and (G) show membranous nephropathy, and (D) and (H) show fibrillary GN.

Glomerular Staining in C3 Glomerulopathy

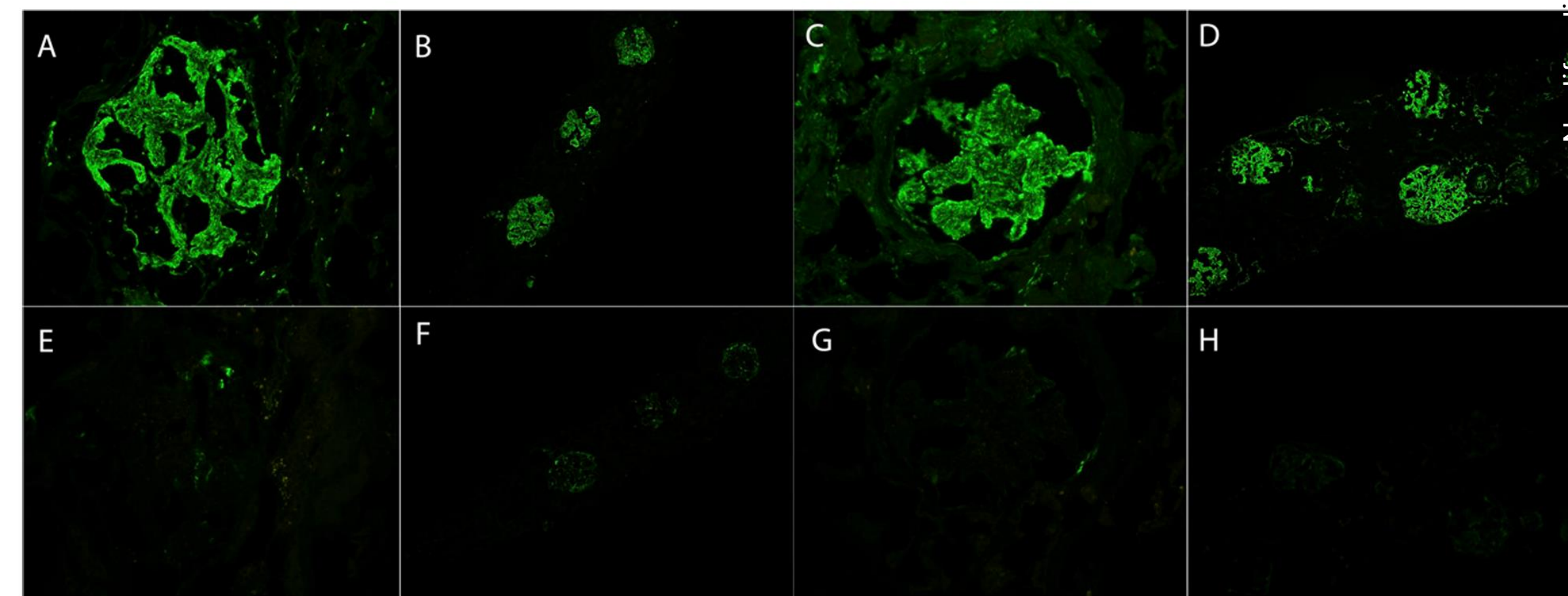
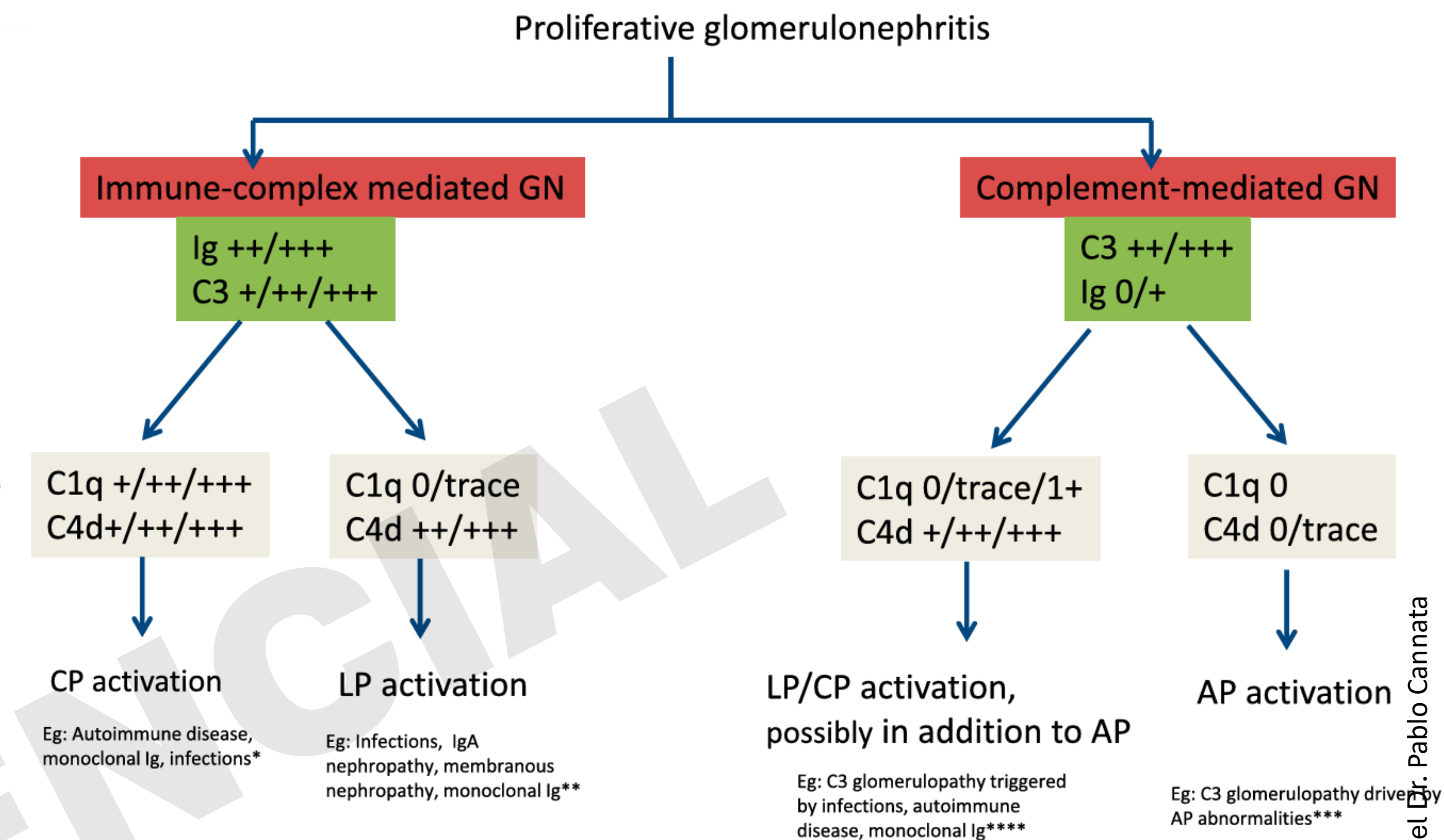


Figure 2. C3 and C4d staining in C3 GN. Top panel shows staining for C3, and bottom panel shows staining for C4d. Each vertical panel represents one patient: (A) and (E), (B) and (F), (C) and (G), and (D) and (H) represent one patient of C3 GN.

C4d as a Diagnostic Tool in Proliferative GN

Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,[†] and Fernando C. Fervenza[‡]

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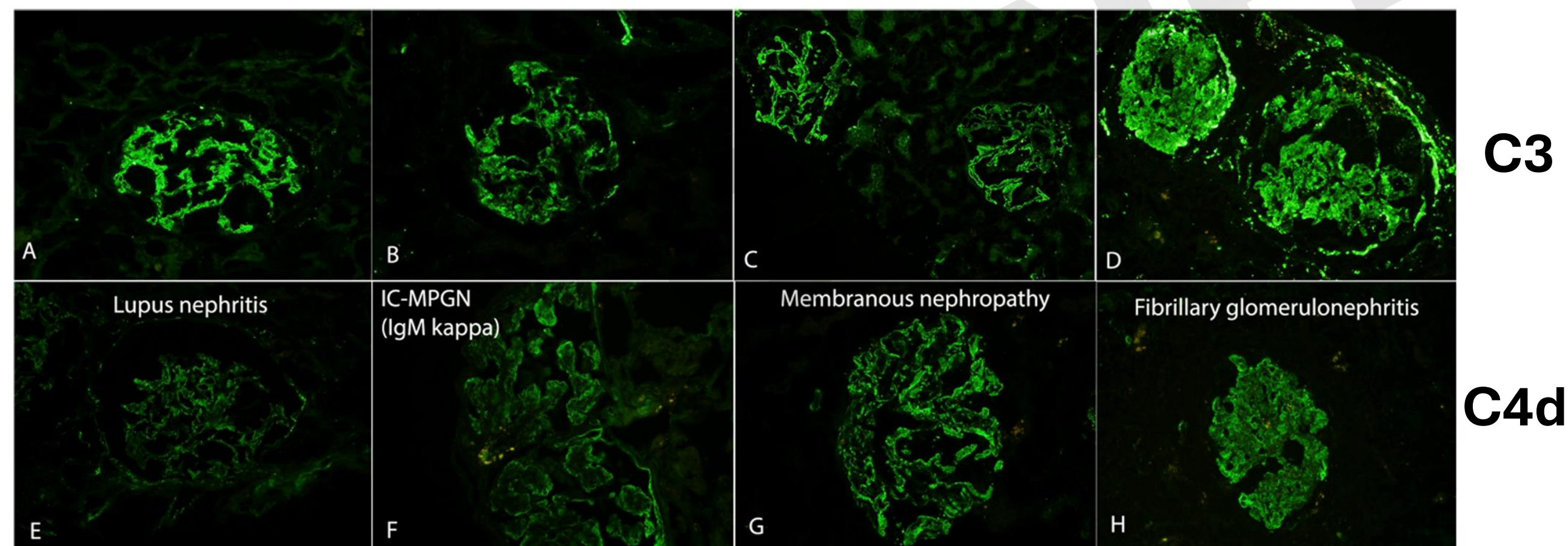


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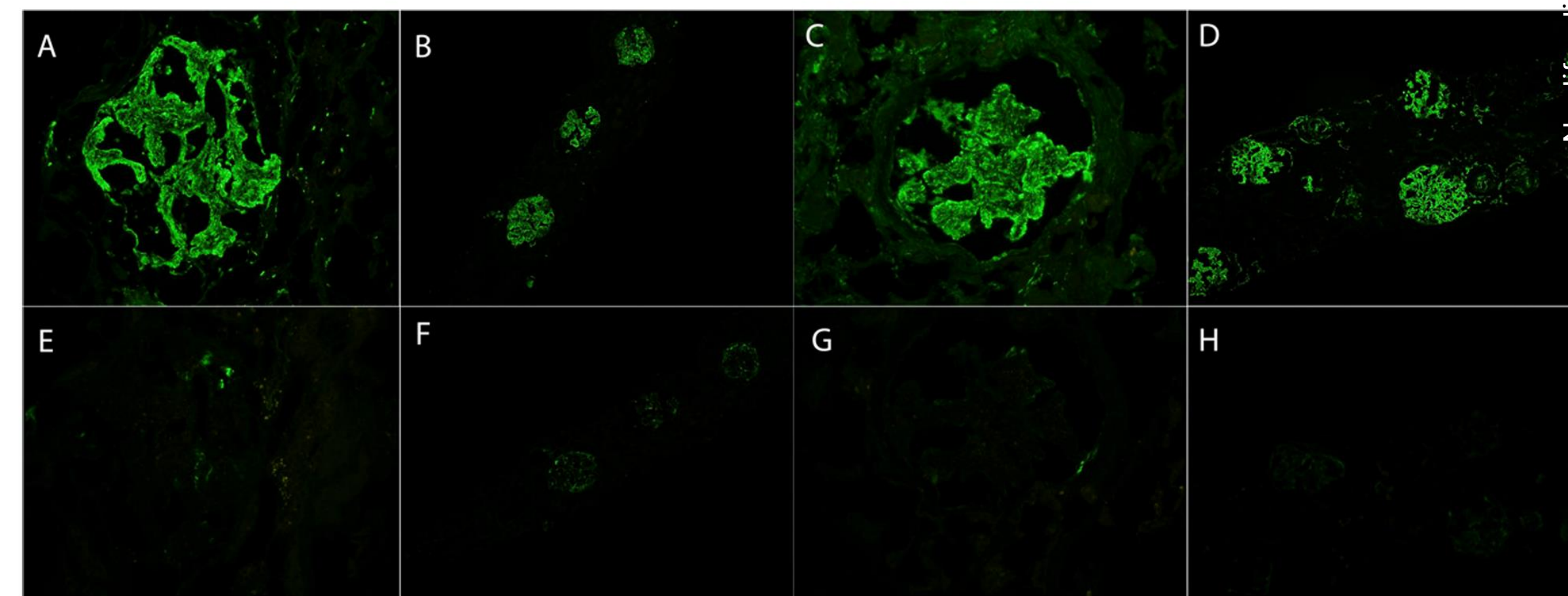
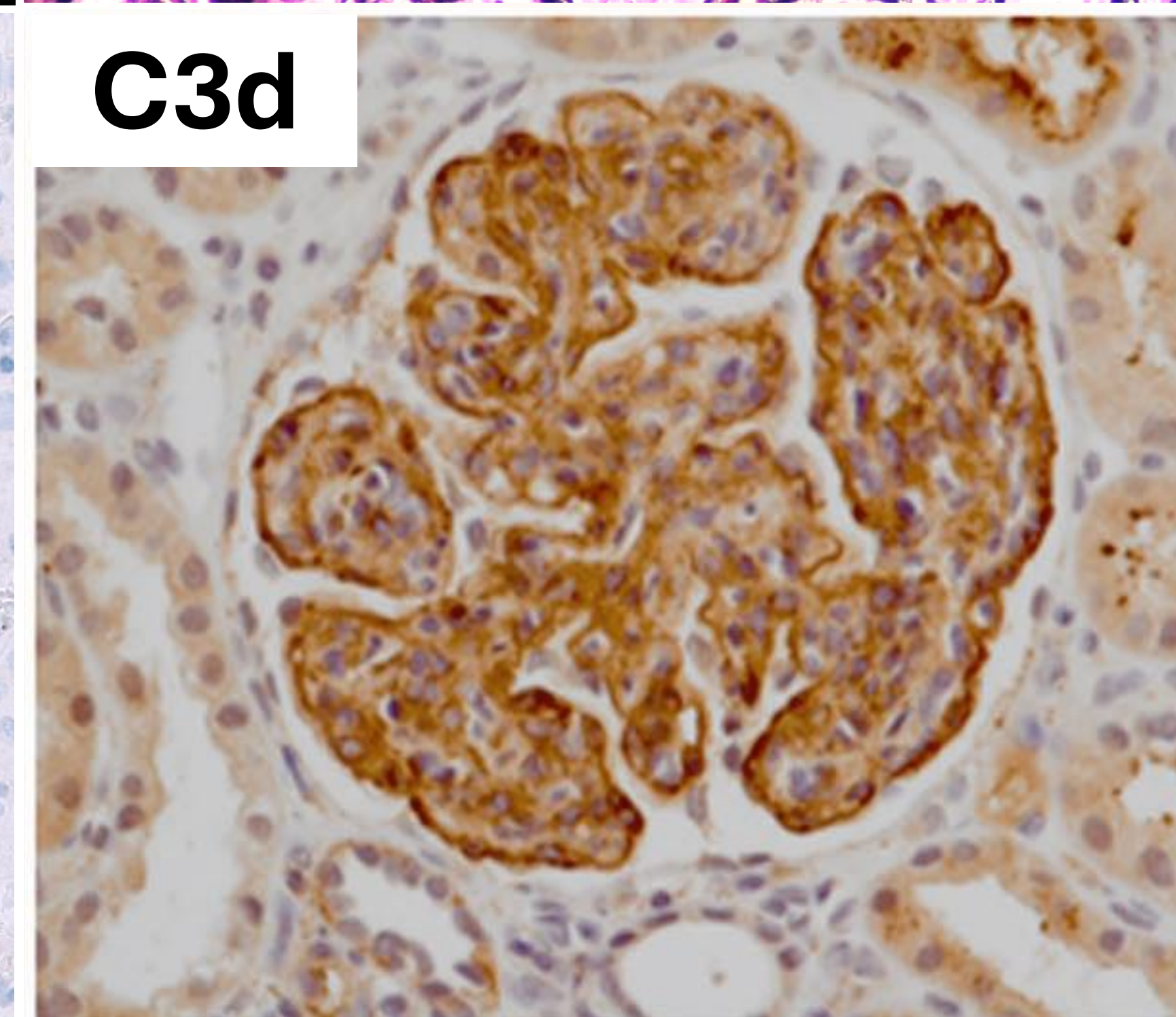
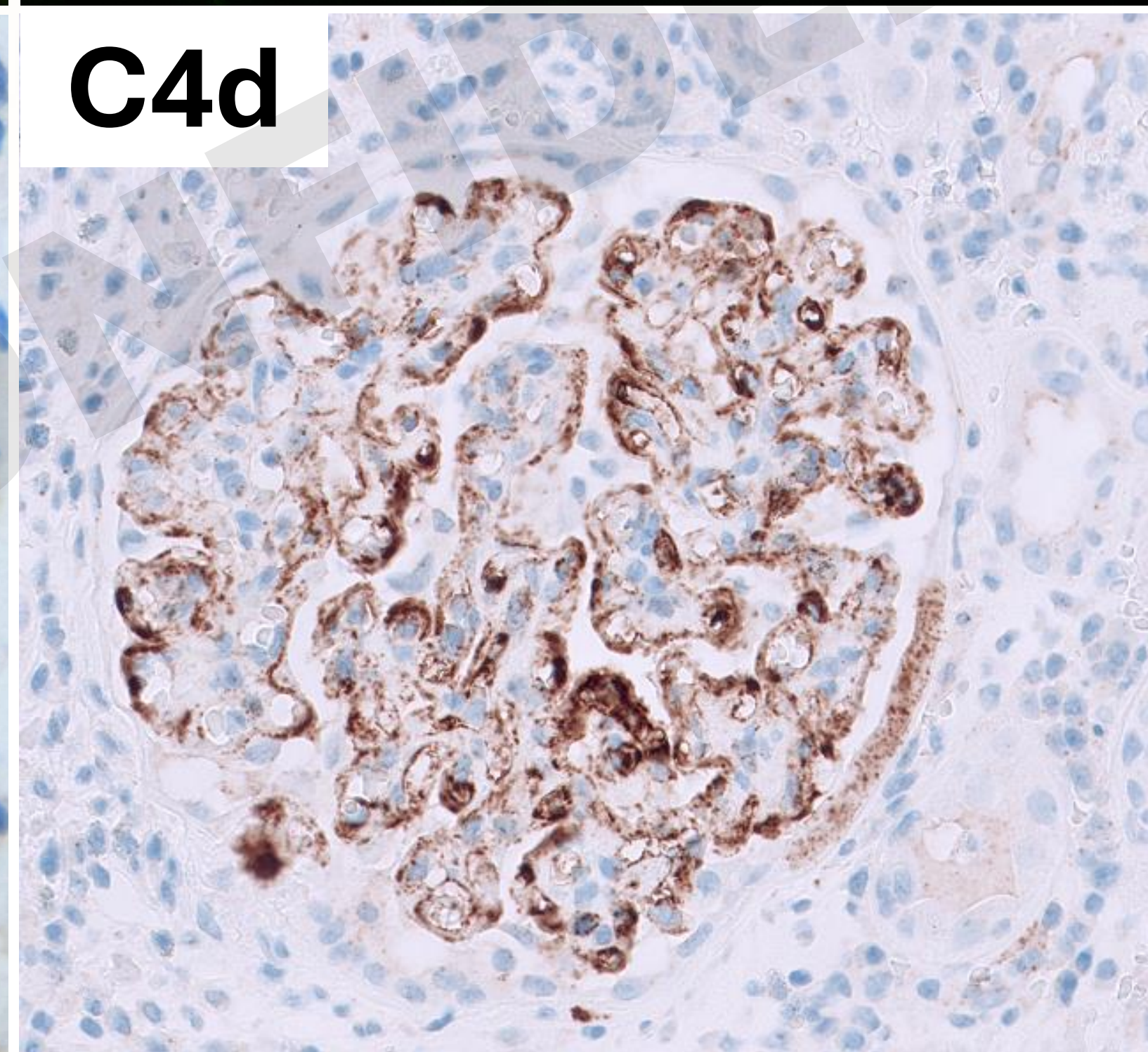
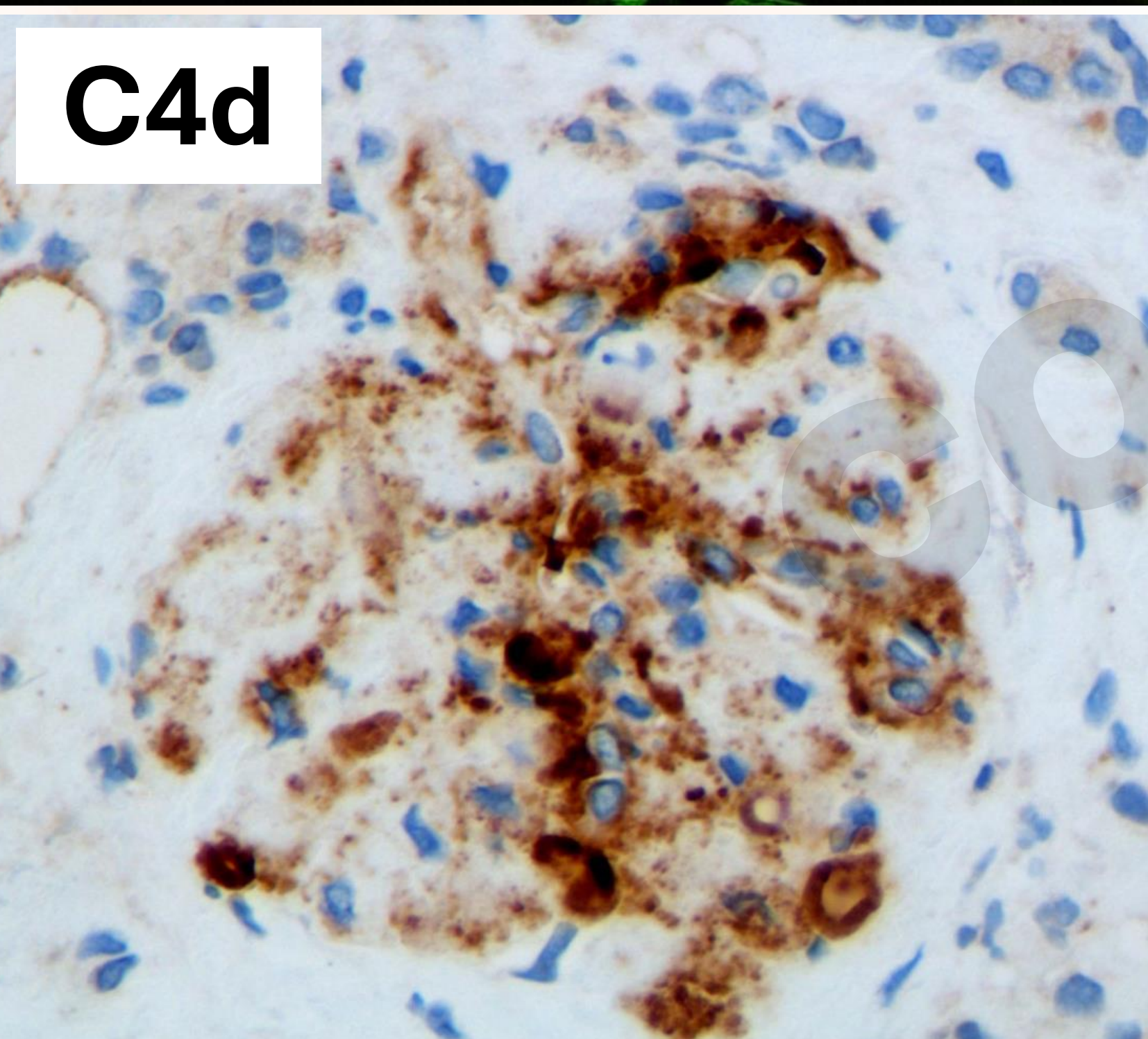
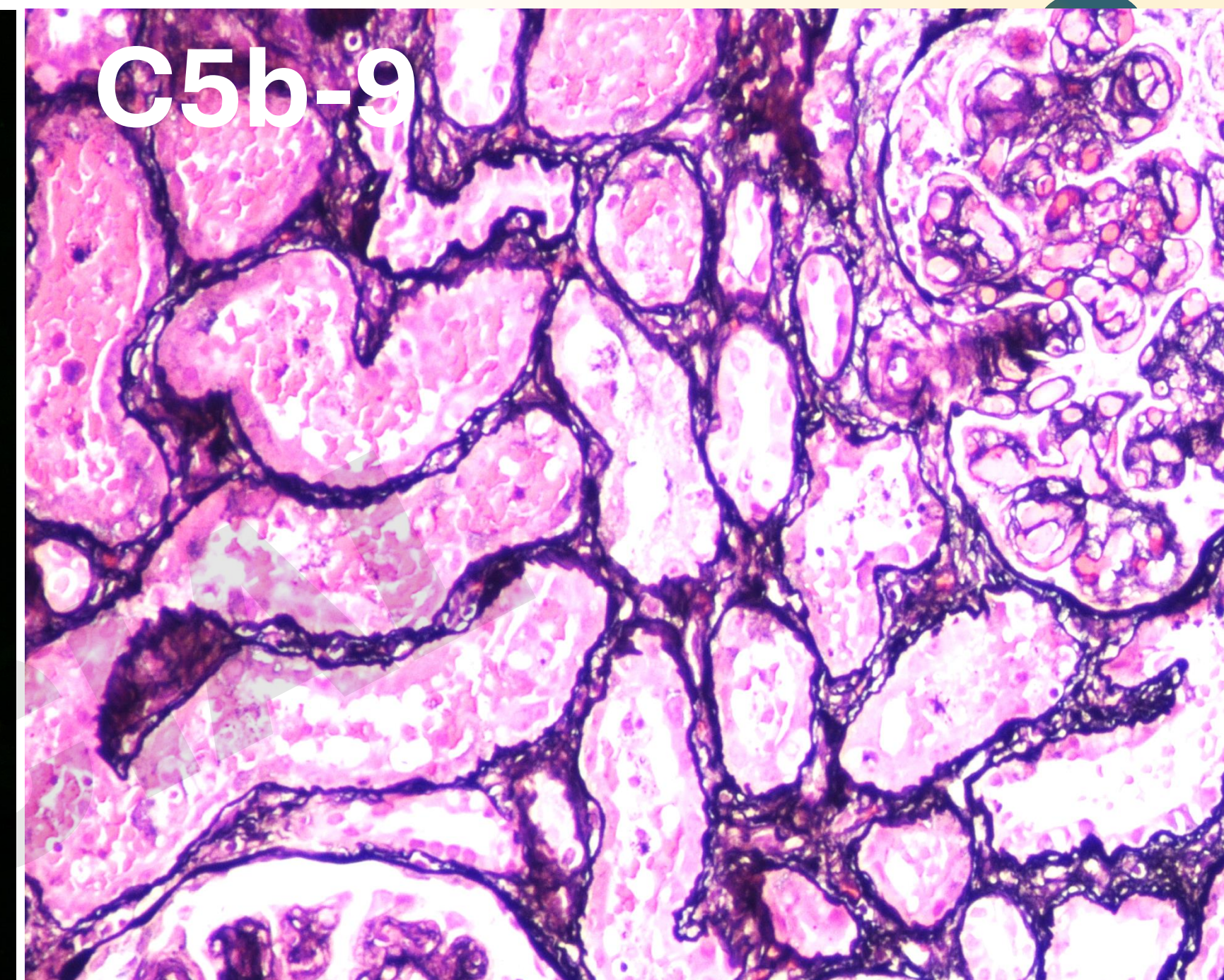
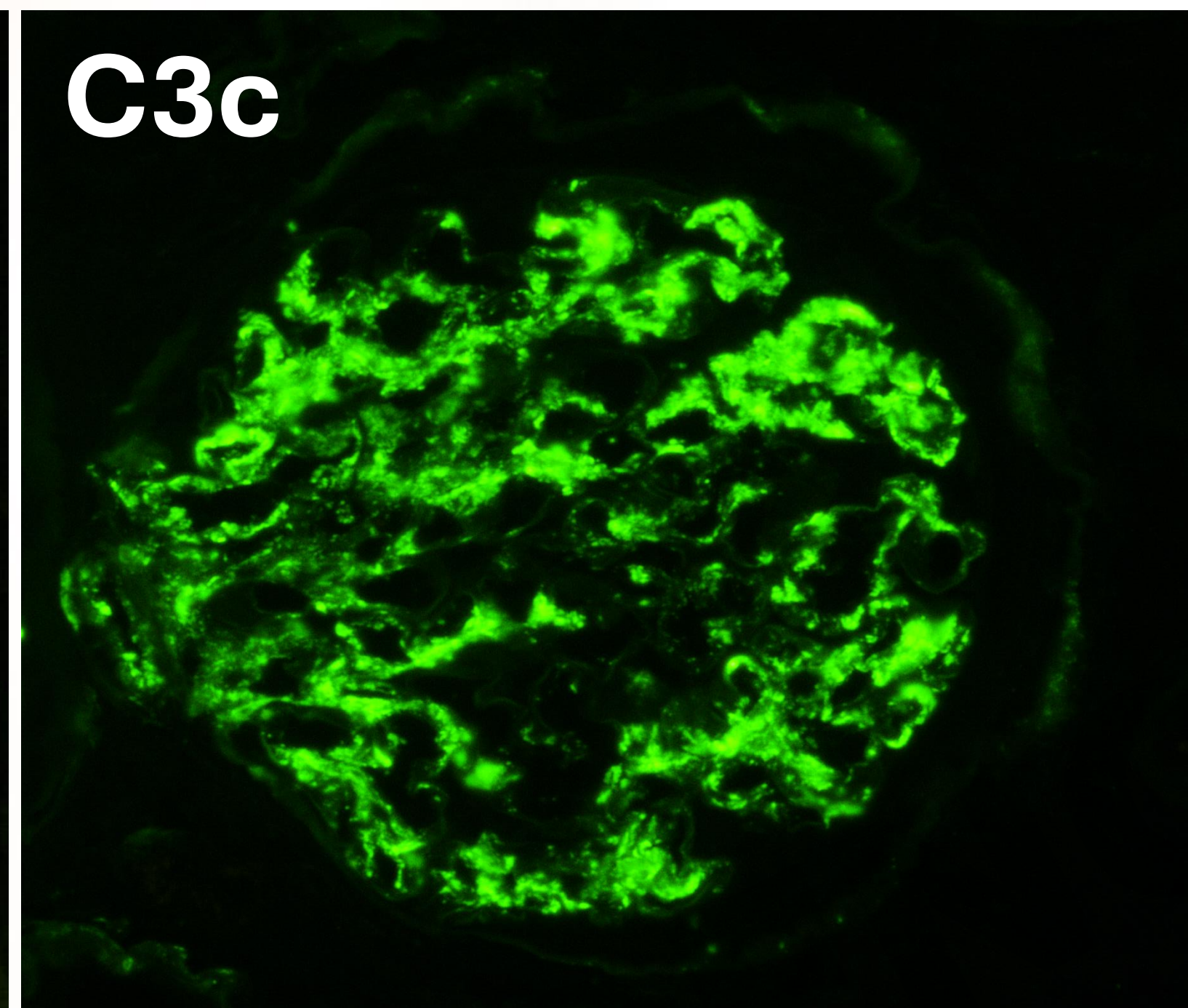
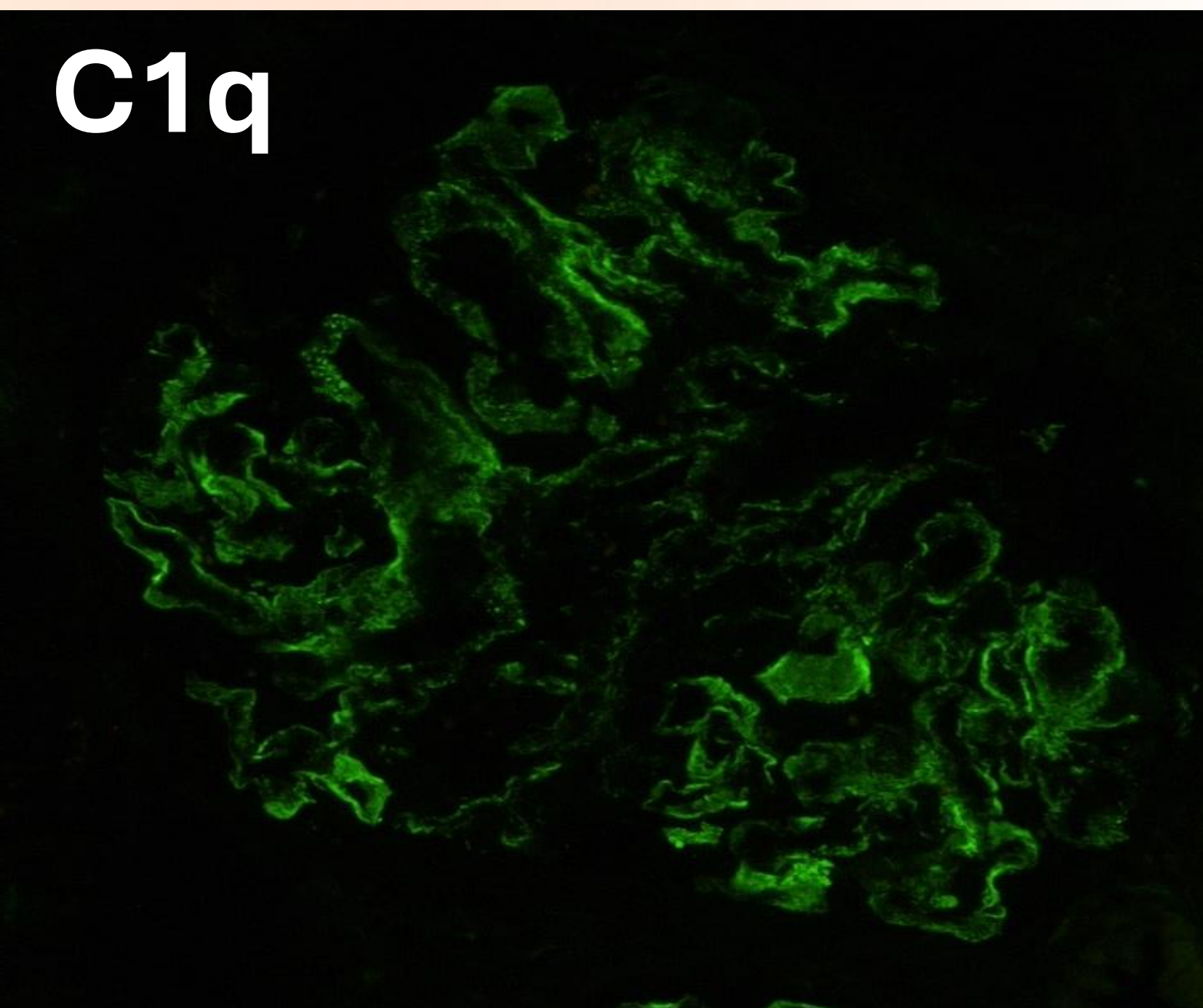


Figure 2. C3 and C4d staining in C3 GN. Top panel shows staining for C3, and bottom panel shows staining for C4d. Each vertical panel represents one patient: (A) and (E), (B) and (F), (C) and (G), and (D) and (H) represent one patient of C3 GN.





¡Muchas gracias!
pablo.cannata@fjd.es