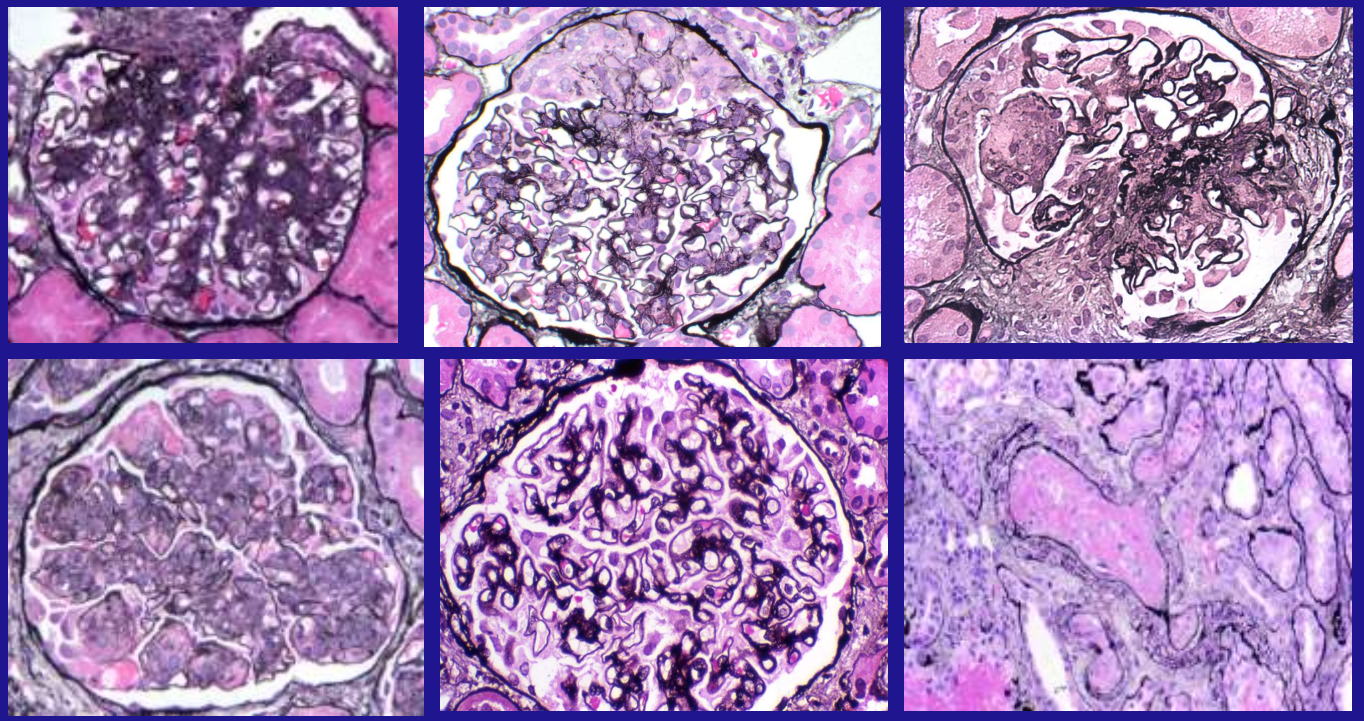
Спасибо за приглашение

Revision of the ISN/RPS classification for Lupus Nephritis

Charles E. Alpers
University of Washington

Lupus Nephritis has many Faces



The Classification of Lupus Nephritis

WHO Classifications of Lupus Nephritis

"Original WHO Classification"
Buffalo, NY, 1974; or Geneva, 1975

"Modified WHO Classification"
ISKDC, Paris, 1980 (Churg and Sobin, 1982)

"Modified WHO Classification"
Churg 1995

Classification of Lupus Nephritis

The classification of glomerulonephritis in systemic lupus erythematosus revisited

JAN J. WEENING, VIVETTE D. D'AGATI, MELVIN M. SCHWARTZ, SURYA V. SESHAN, CHARLES E. ALPERS, GERALD B. APPEL, JAMES E. BALOW, JAN A. BRUIJN, TERENCE COOK, FRANCO FERRARIO, AGNES B. FOGO, ELLEN M. GINZLER, LEE HEBERT, GARY HILL, PRUE HILL, J. CHARLES JENNETTE, NORELLA C. KONG, PHILIPPE LESAVRE, MICHAEL LOCKSHIN, LAI-MENG LOOI, HIROFUMI MAKINO, LUIZ A. MOURA, and MICHIO NAGATA, ON BEHALF OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY AND RENAL PATHOLOGY SOCIETY WORKING GROUP ON THE CLASSIFICATION OF LUPUS NEPHRITIS

Kidney International, Vo. 65 (2004), pp. 521-530

Proposal of the International Society of Nephrology and Renal Pathological Society Working Group on the Classification of Lupus Glomerulonephritis

"The major objective is to standardize definitions, emphasize clinically relevant lesions, and encourage uniform and reproducible reporting between centers."

Kidney Int 2004; 65:521-530 and J Am Soc Nephrol 2004, 15:241-250

ISN/RPS 2004 Classification Lupus Nephritis

Class I Minimal mesangial lupus nephritis

Class II Mesangial proliferative lupus nephritis

Class III Focal lupus nephritis* (<50% of glomeruli)
- III (A): active lesions
- III (A/C): active and chronic lesions
- III (C): chronic lesions

Class IV Diffuse lupus nephritis* (≥50% of glomeruli)
segmental (IV-S) or global (IV-G) lupus nephritis
- IV (A): active lesions
- IV (A/C): active and chronic lesions
- IV (C): chronic lesions

Class V Membranous lupus nephritis

Class VI Advanced sclerosing lupus nephritis
(≥90% globally sclerosed glomeruli without residual activity)

* Indicate the proportion of glomeruli with active and with sclerotic lesions
* Indicate the proportion of glomeruli with fibrinoid necrosis and with cellular crescents
* Class V may occur in combination with III or IV in which case both will be diagnosed

Classification of Lupus Nephritis

www.kidney-international.org meeting report

Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices

Ingeborg M. Bajema[1], Suzanne Wilhelmus[1], Charles E. Alpers[2], Jan A. Bruijn[1], Robert B. Colvin[3], H. Terence Cook[4], Vivette D. D'Agati[5], Franco Ferrario[6], Mark Haas[7], J. Charles Jennette[8], Kensuke Joh[9], Cynthia C. Nast[7], Laure-Hélène Noël[10], Emilie C. Rijnink[1], Ian S.D. Roberts[11], Surya V. Seshan[12], Sanjeev Sethi[13] and Agnes B. Fogo[14]

Kidney International (2018) **93,** 789–796

The classification of glomerulonephritis in systemic lupus erythematosus revisited

JAN J. WEENING, VIVETTE D. D'AGATI, MELVIN M. SCHWARTZ, SURYA V. SESHAN, CHARLES E. ALPERS, GERALD B. APPEL, JAMES E. BALOW, JAN A. BRUIJN, TERENCE COOK, FRANCO FERRARIO, AGNES B. FOGO, ELLEN M. GINZLER, LEE HEBERT, GARY HILL, PRUE HILL, J. CHARLES JENNETTE, NORELLA C. KONG, PHILIPPE LESAVRE, MICHAEL LOCKSHIN, LAI-MENG LOOI, HIROFUMI MAKINO, LUIZ A. MOURA, and MICHIO NAGATA, ON BEHALF OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY AND RENAL PATHOLOGY SOCIETY WORKING GROUP ON THE CLASSIFICATION OF LUPUS NEPHRITIS

Kidney International, Vo. 65 (2004), pp. 521-530

Immediate goals

Increase interobserver agreement (Phase 1):

1. Clarifying problematic terms
2. Unifying classification schemes
3. Omitting terms that had little distinctiveness

Identify areas that require research (Phase 2)

Group discussions

May 9–11, 2016, Leiden, Netherlands

Pre-meeting questionnaire

Multi-head sessions

Class I and Class II: Mesangial lupus nephritis

Variations on a theme

Class I: minimal mesangial lupus glomerulonephritis (LN)

- Normal glomeruli by LM, but mesangial immune deposits by IF and/or EM
- Uncommon finding in biopsies

Class II: Mesangial Proliferative Lupus Glomerulonephritis

- Purely mesangial hypercellularity of any degree and/or mesangial matrix expansion by LM with immune deposits, predominantly mesangial with none or few, isolated subepithelial and/or subendothelial deposits by IF and/or EM not visible by LM
- Mild hematuria, proteinuria, or both
- Favorable prognosis, 20% progression
- IF: mesangial IgG, some IgM, IgA

Class II: Mesangial Proliferative Lupus Glomerulonephritis

- Purely mesangial **hypercellularity** of any degree and/or mesangial matrix expansion by LM with immune deposits, predominantly mesangial with none or few, isolated subepithelial and/or subendothelial deposits by IF and/or EM not visible by LM
- Mild hematuria, proteinuria, or both
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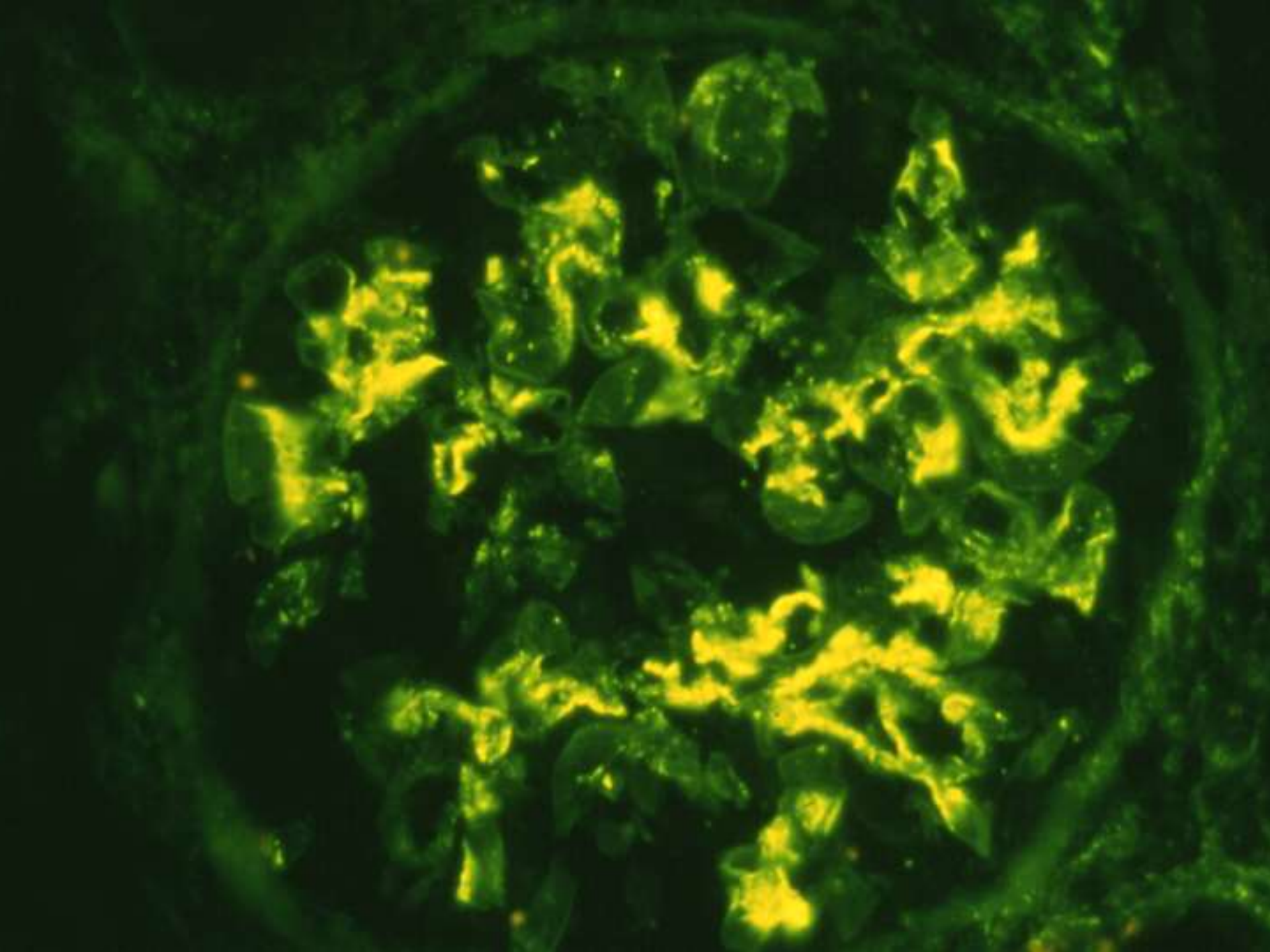
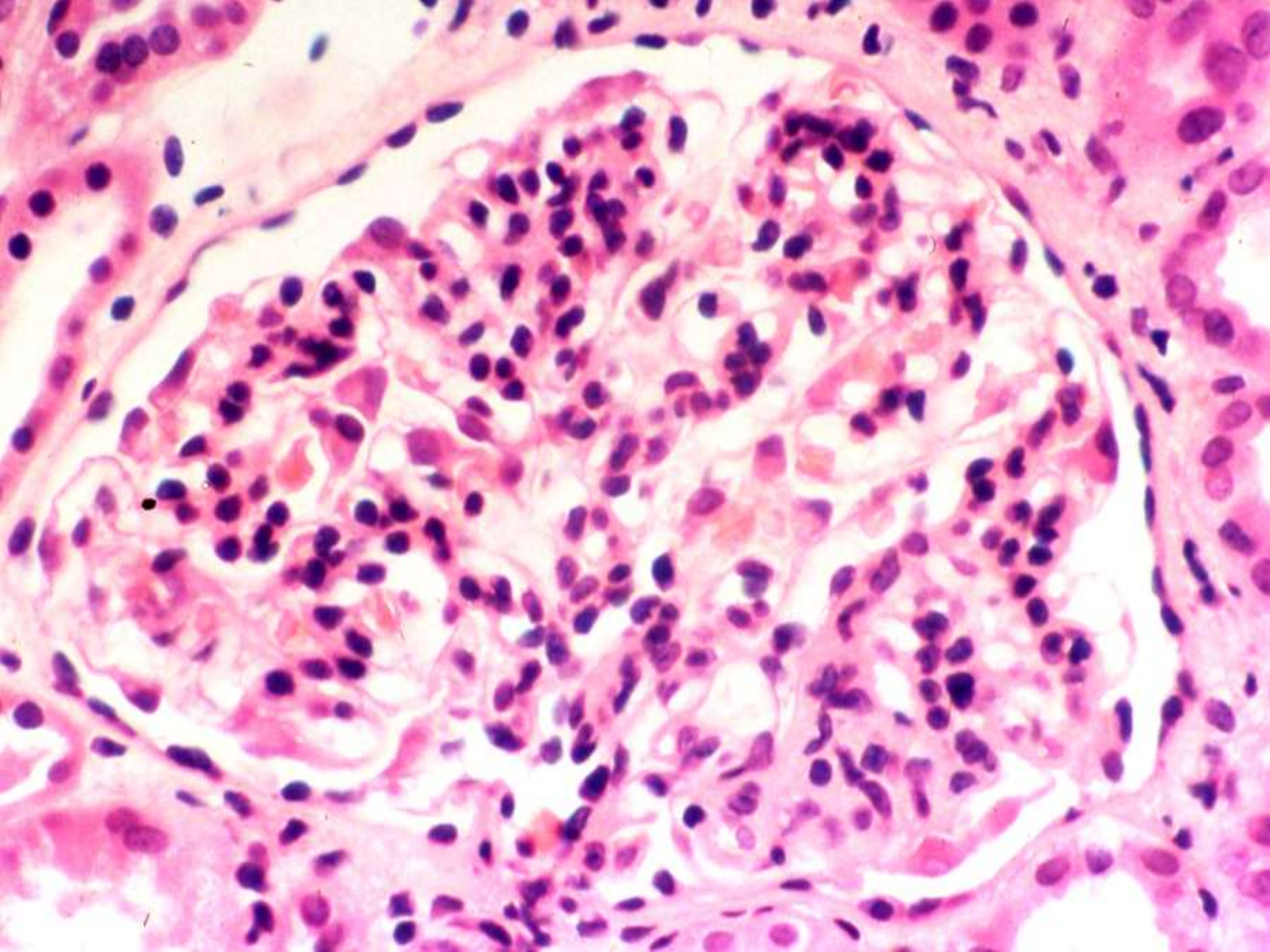
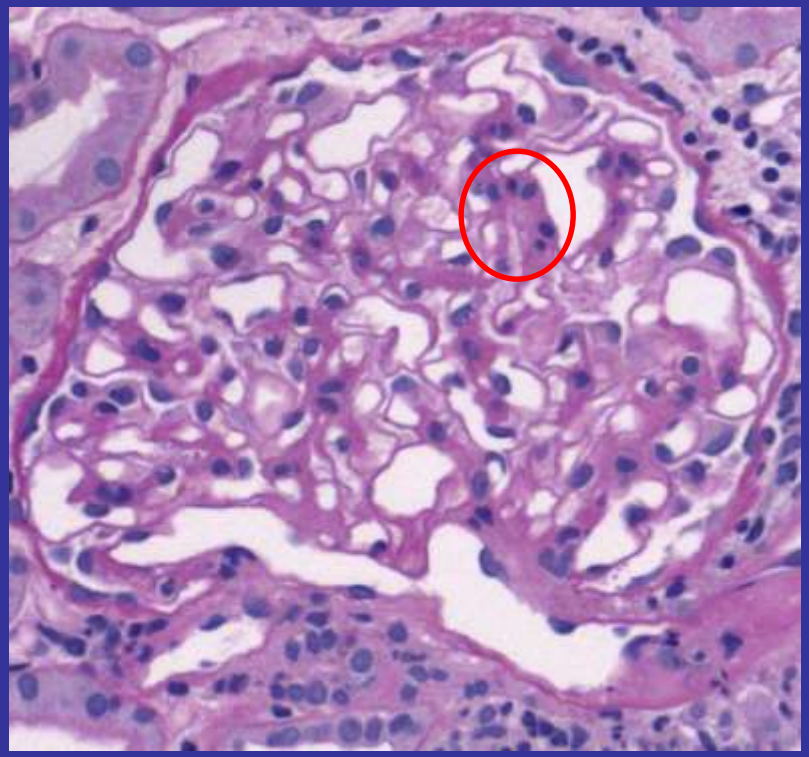




What should the threshold be for Class I to II transition?

Class I → Mesangial proliferation → Class II



Rheumatol Int (2012) 32:2459–2464

ORIGINAL ARTICLE

ISN/RPS 2003 class II mesangial proliferative lupus nephritis: a comparison between cases that progressed to class III or IV and cases that did not

Seung Geun Lee · Yong Mee Cho · Min Wook So · Sung Soo Kim · Yong-Gil Kim · Chang-Keun Lee · Bin Yoo

Based on this study, % of mesangial proliferation was not a predictor of histologic transformation

Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region	Cutoff for mesangial hypercellularity unclear

Bajema et al. Kidney Int 2018; 93:789

Class III and Class IV: Focal and Diffuse Lupus Glomerulonephritis

Variations on a theme

Class III and Class IV: Focal and Diffuse Lupus Glomerulonephritis

Variations on a theme

- Class III: Focal LN (involving less than 50% of the total number of glomeruli)

- Class IV: Diffuse LN (involving 50% or more of the total number of glomeruli)

Class III: focal lupus glomerulonephritis (involving less than 50% of the total number of glomeruli)

Active or inactive focal, segmental and/or global endo- and/or extracapillary GN, typically with focal, subendothelial immune deposits, with or without focal or diffuse mesangial alterations

- III (A) purely active lesions: active focal proliferative LN

- III (A/C) active and chronic lesions: active and sclerotic focal proliferative LN

- III (C) chronic inactive with glomerular scars: inactive sclerotic focal LN

* indicate the proportion of glomeruli with active and with sclerotic lesions

* indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular lesions

Class IV: diffuse LN (involving 50% or more of the total number of glomeruli)

Active or inactive diffuse, segmental or global endo- and/or extracapillary LN with diffuse subendothelial immune deposits, with or without mesangial alterations

- IV (A) active lesions: diffuse proliferative LN
- IV (A/C) active and chronic lesions: diffuse proliferative and sclerotic LN
- IV (C) inactive with glomerular scars: diffuse sclerotic LN

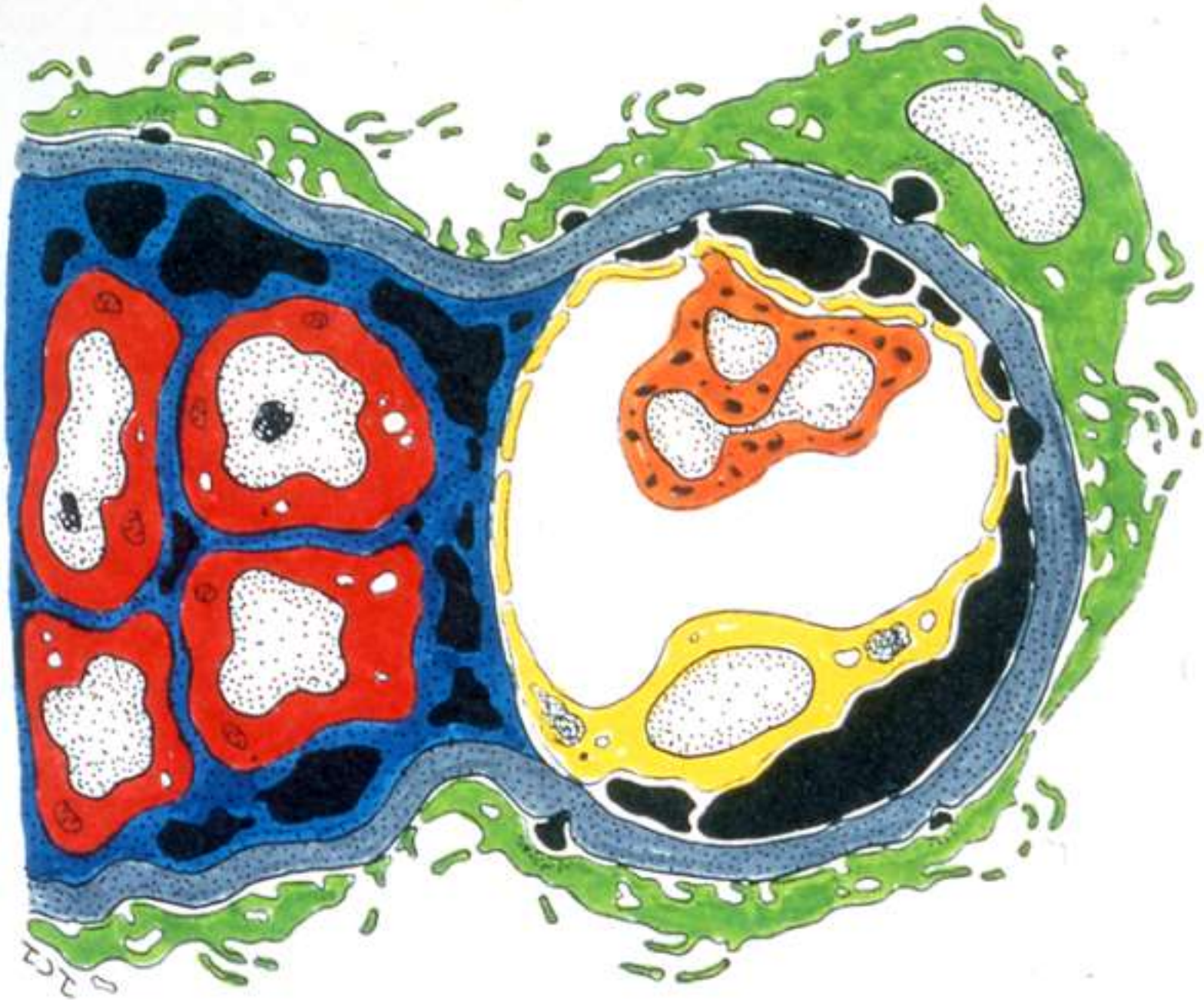
* indicate proportion of glomeruli with active and with sclerotic, and proportion with fibrinoid necrosis and/or crescents

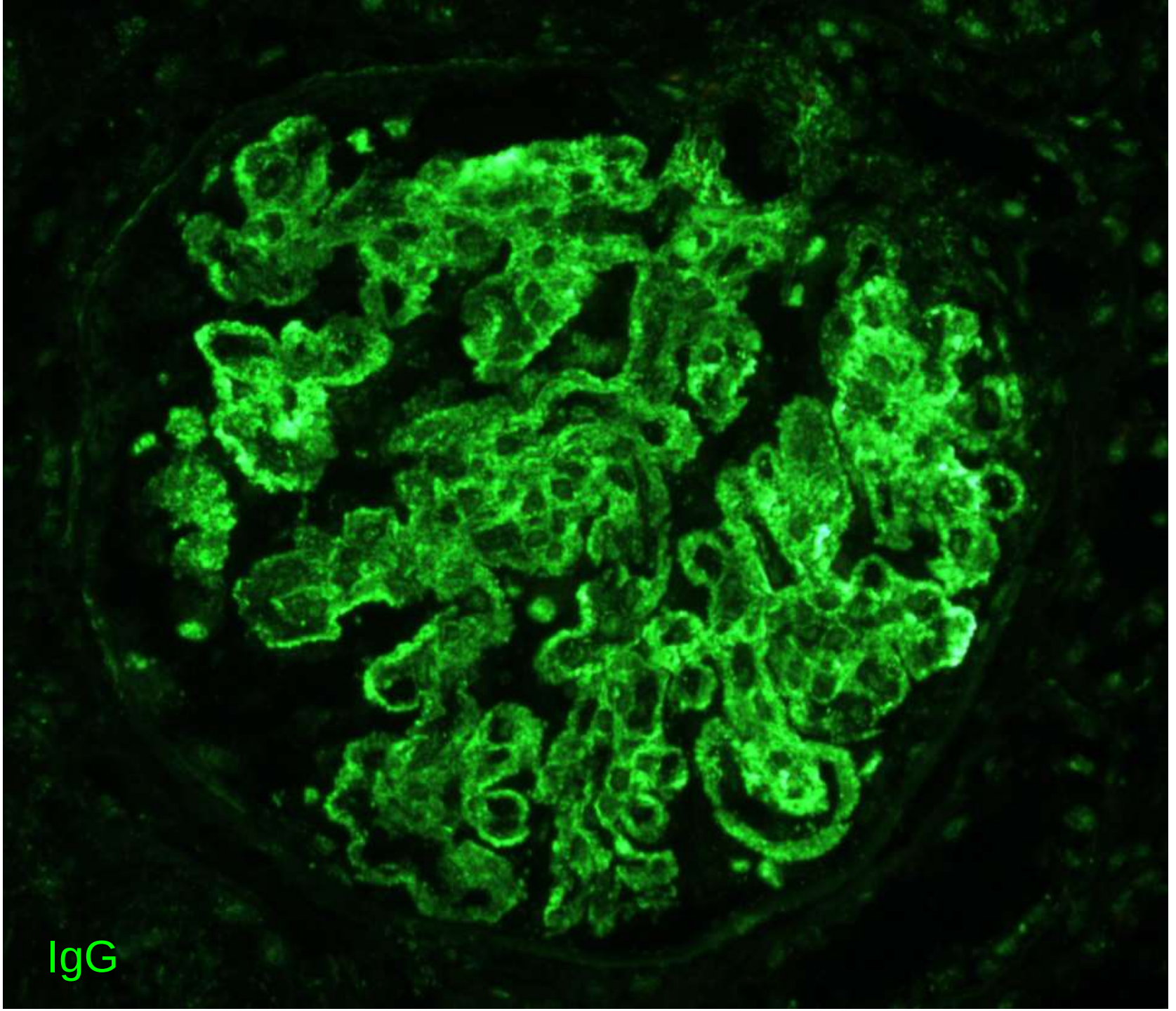
Class IV: diffuse LN (involving 50% or more of the total number of glomeruli)

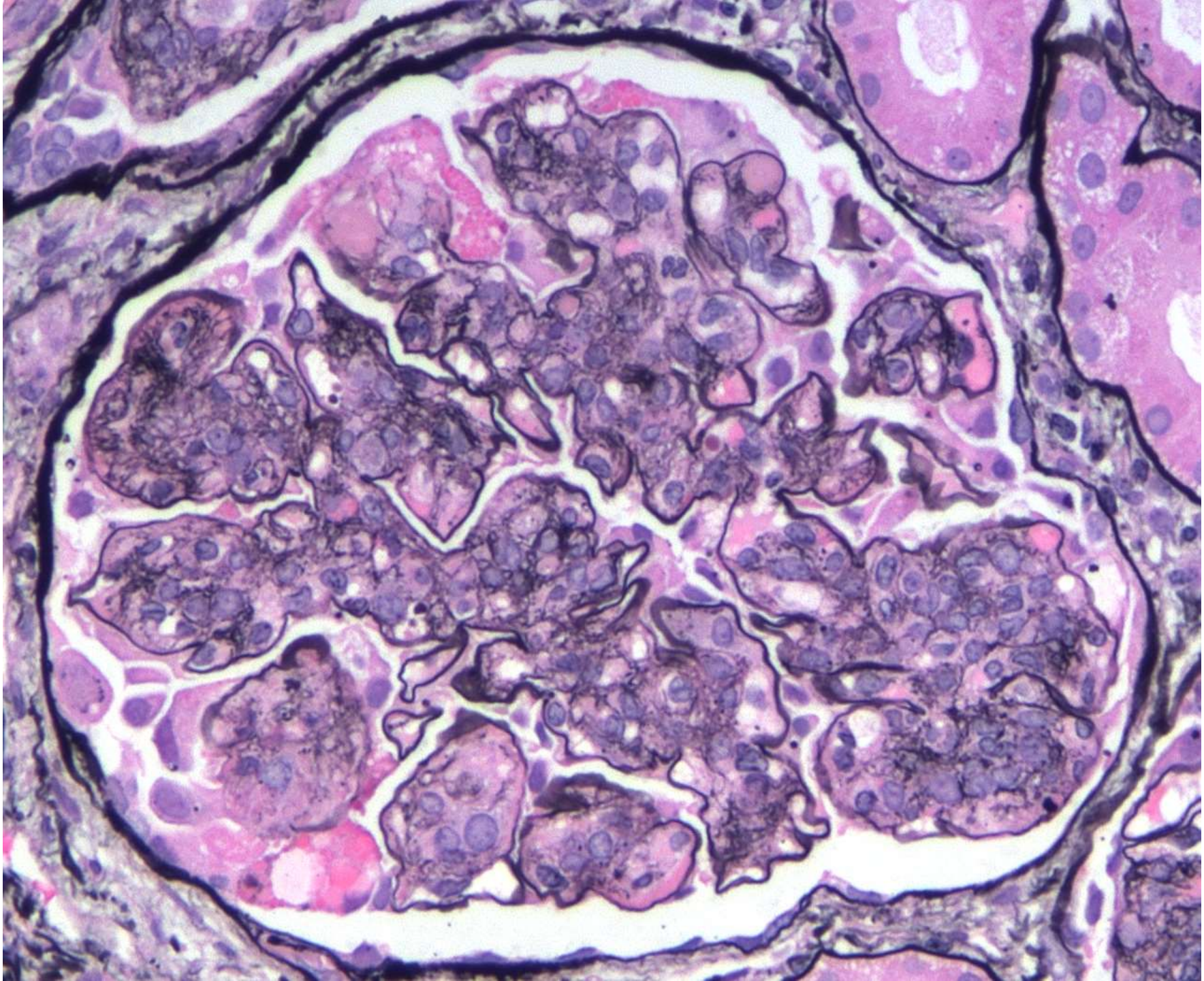
Active or inactive diffuse, segmental or global **endo- and/or extracapillary** LN with diffuse subendothelial immune deposits, with or without mesangial alterations

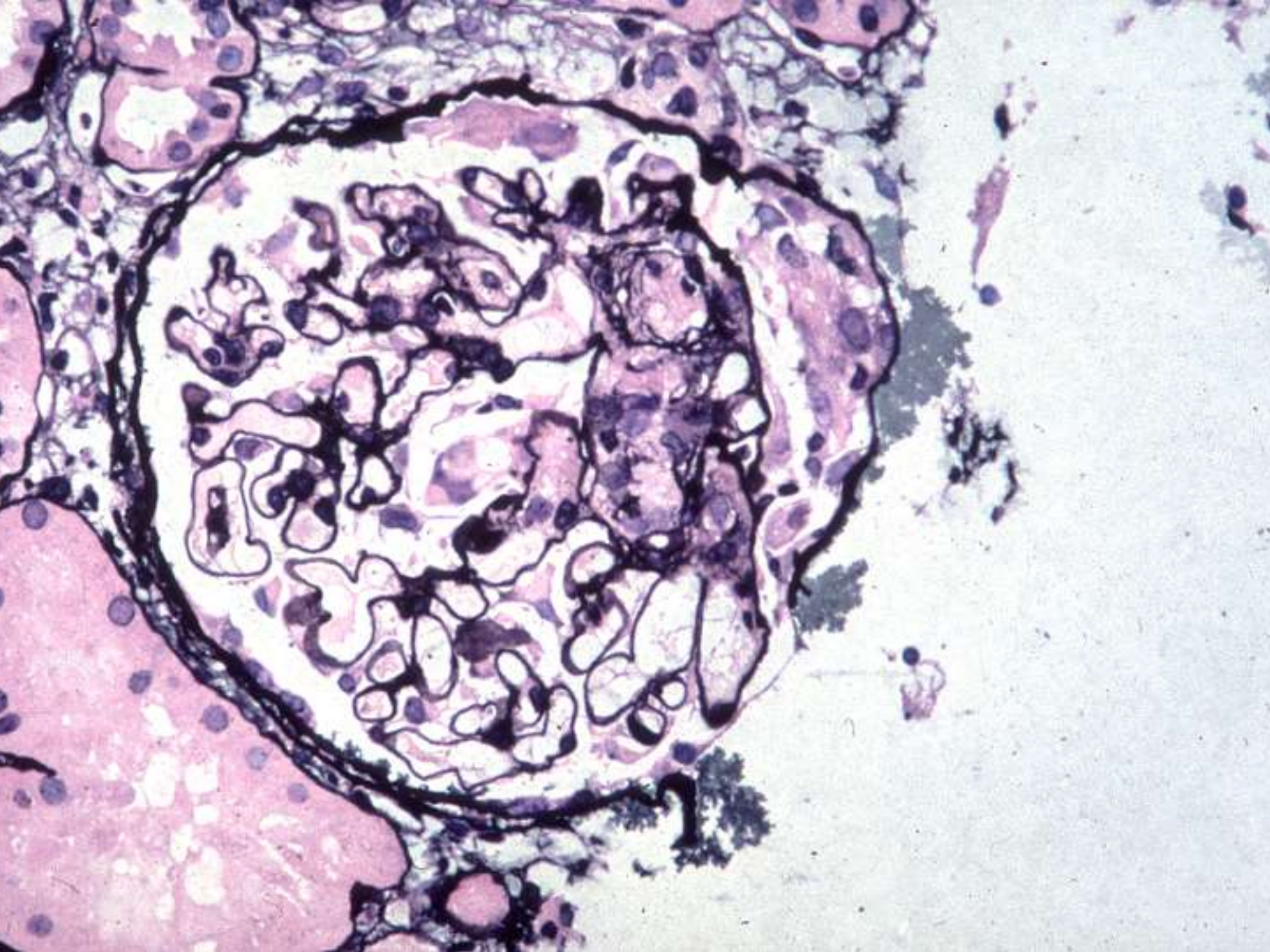
- **IV (A) active** lesions: diffuse proliferative LN
- IV **(A/C) active and chronic** lesions: diffuse proliferative and sclerotic LN
- IV **(C)** inactive with glomerular scars: diffuse sclerotic LN

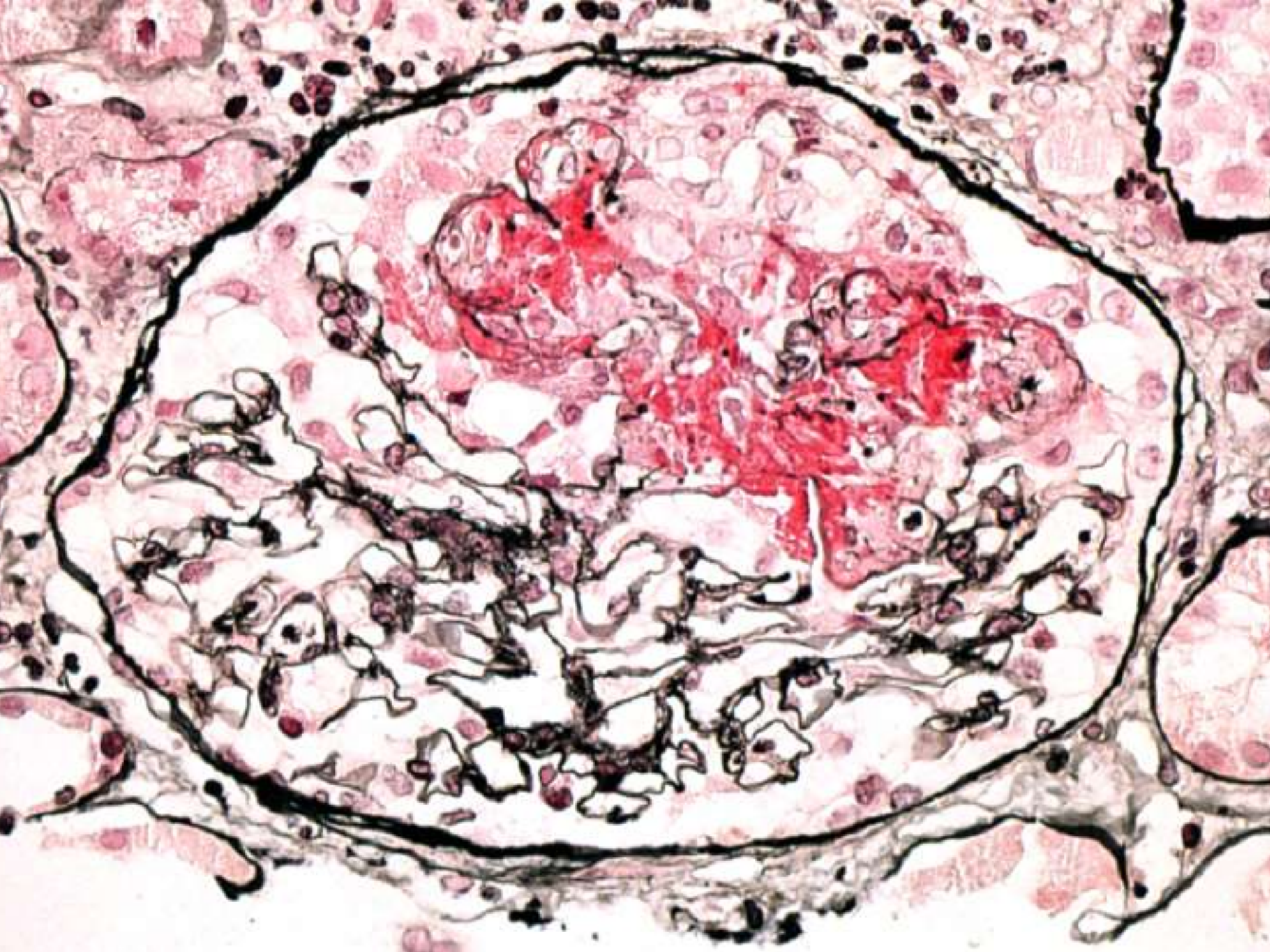
* indicate proportion of glomeruli with active and with sclerotic, and proportion with fibrinoid necrosis and/or crescents

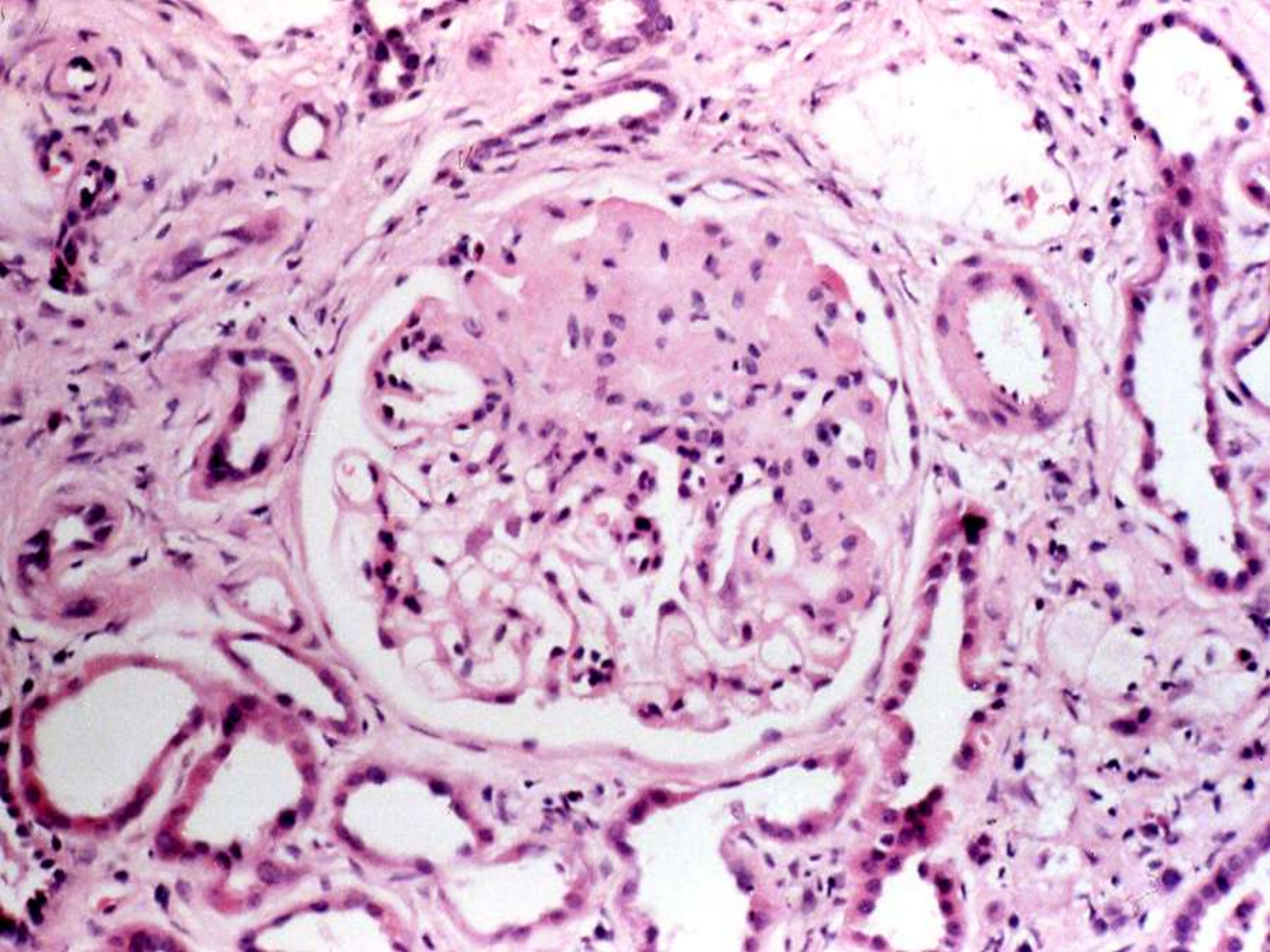


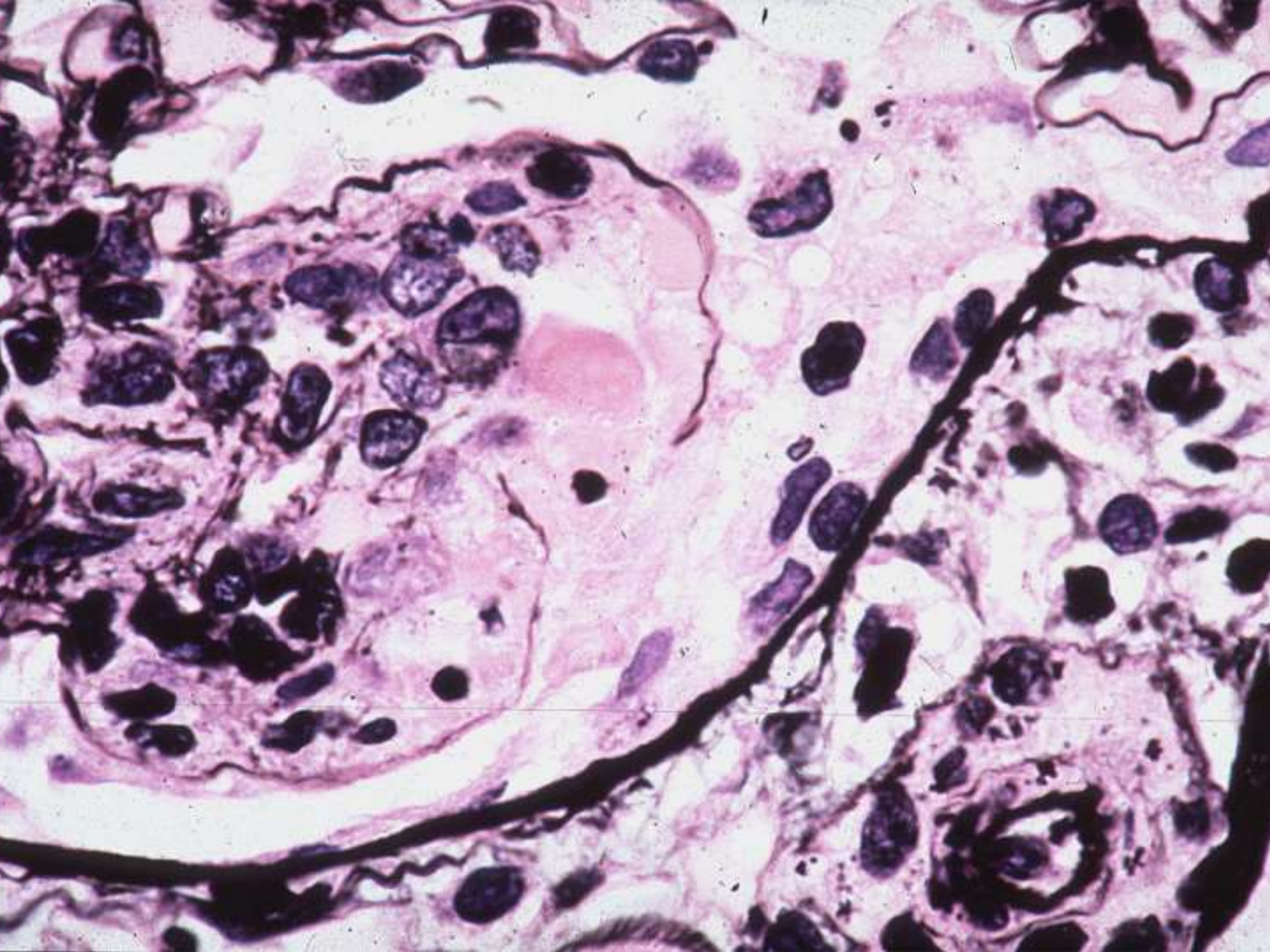

IgG

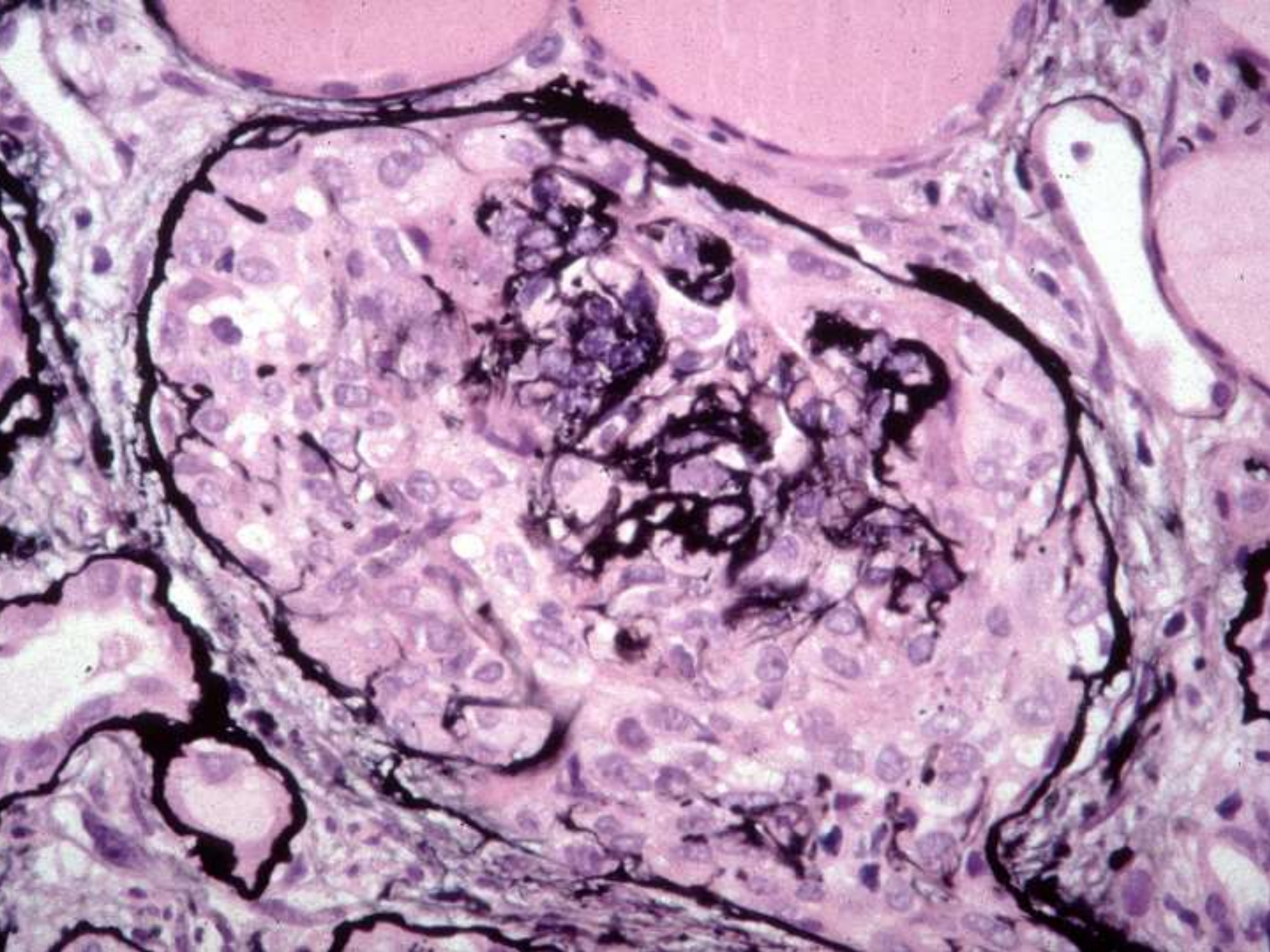


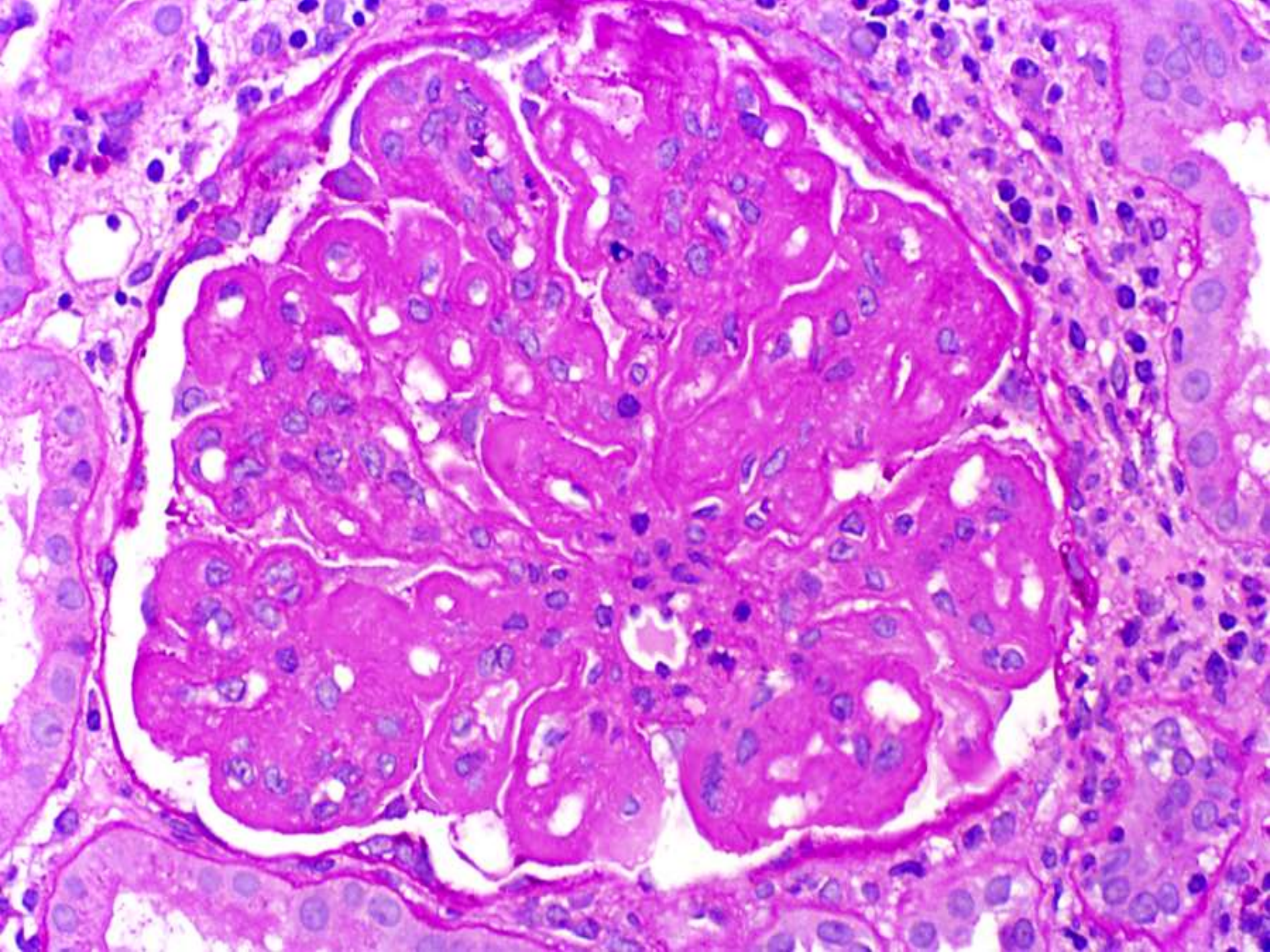


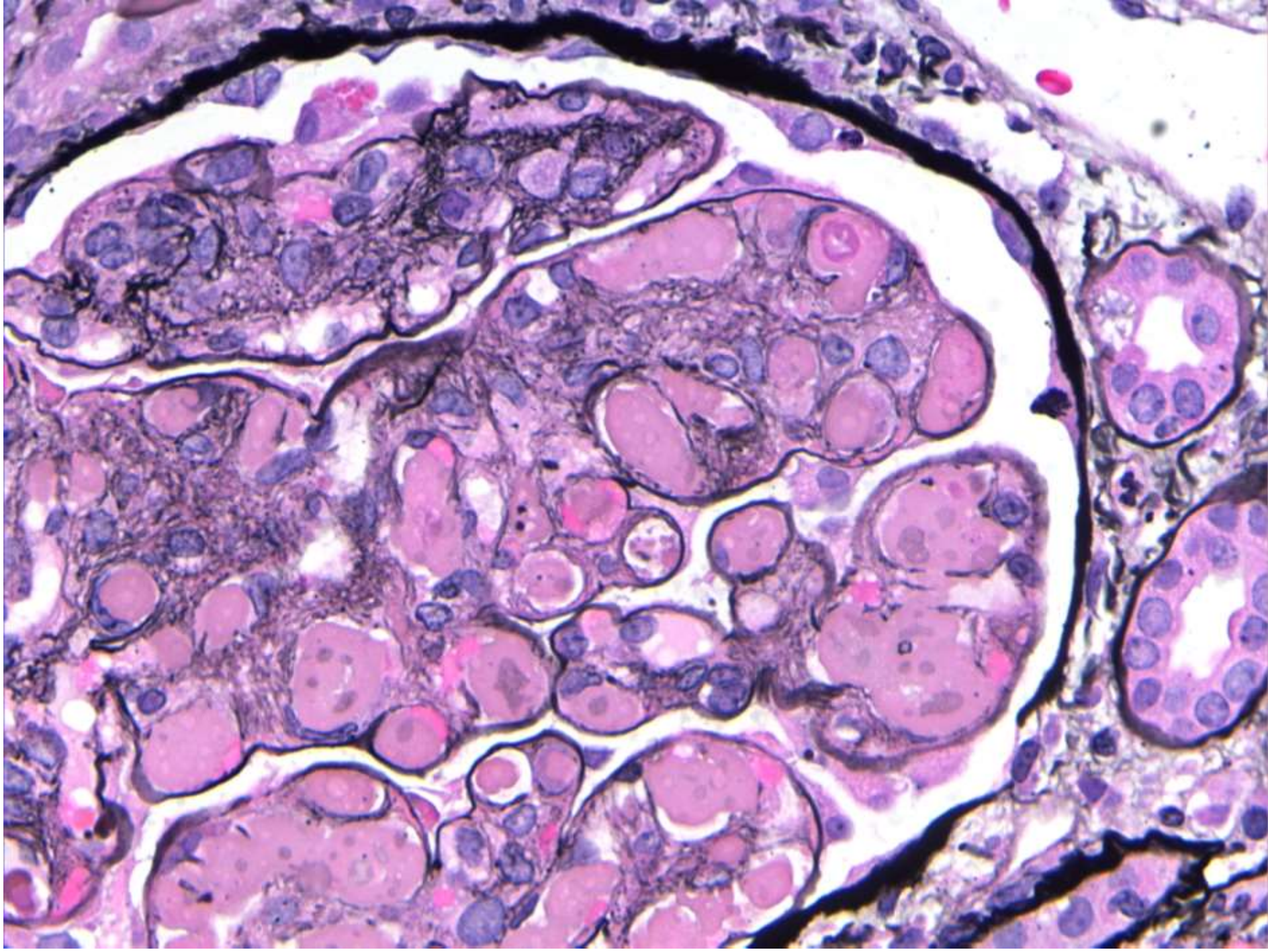


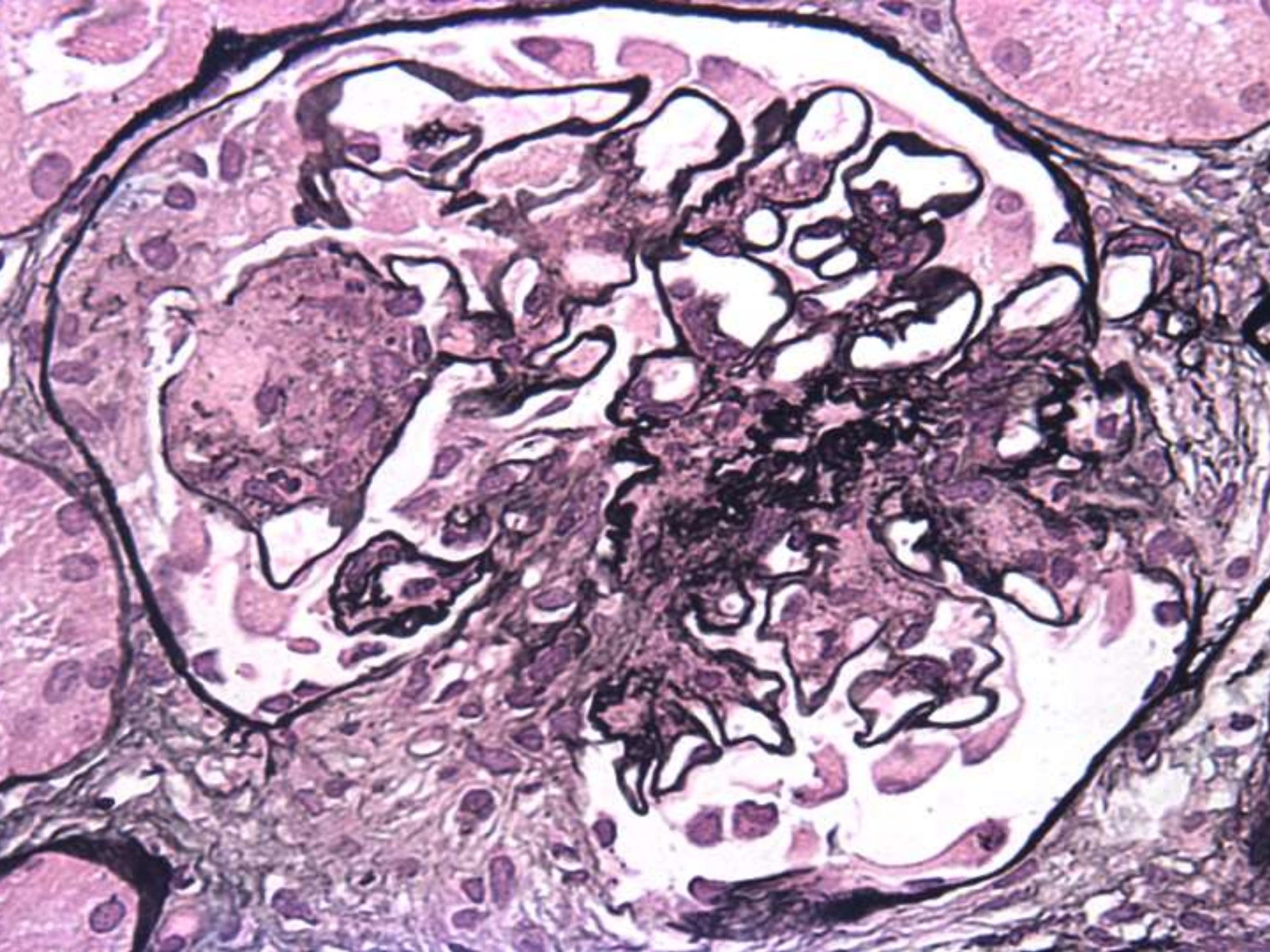


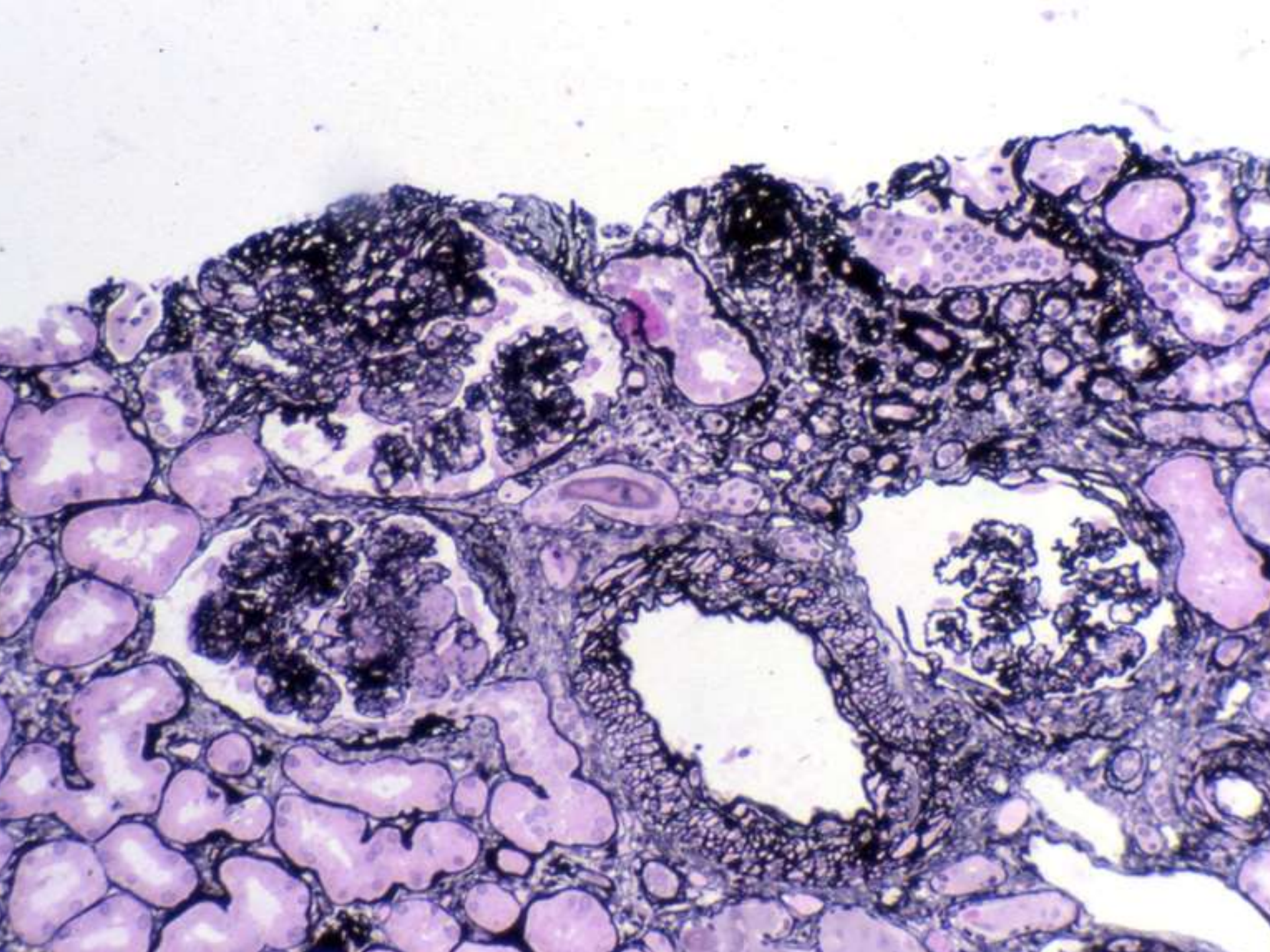




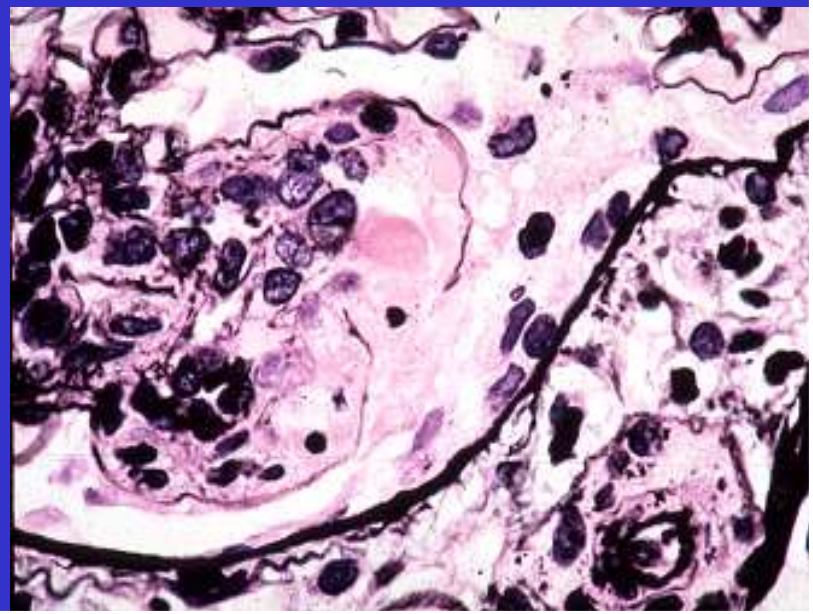


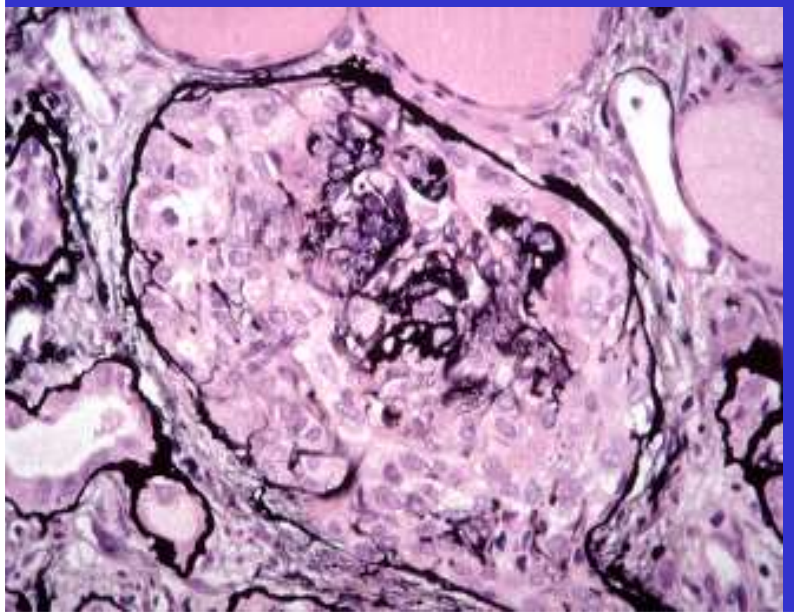


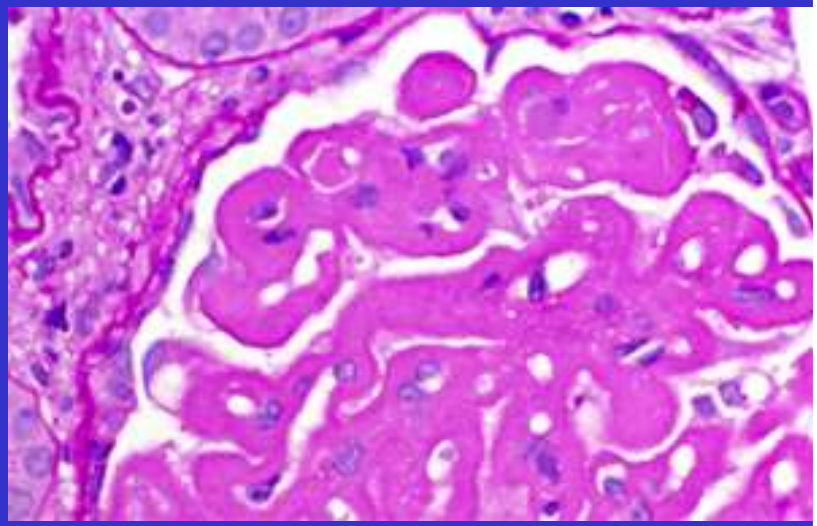


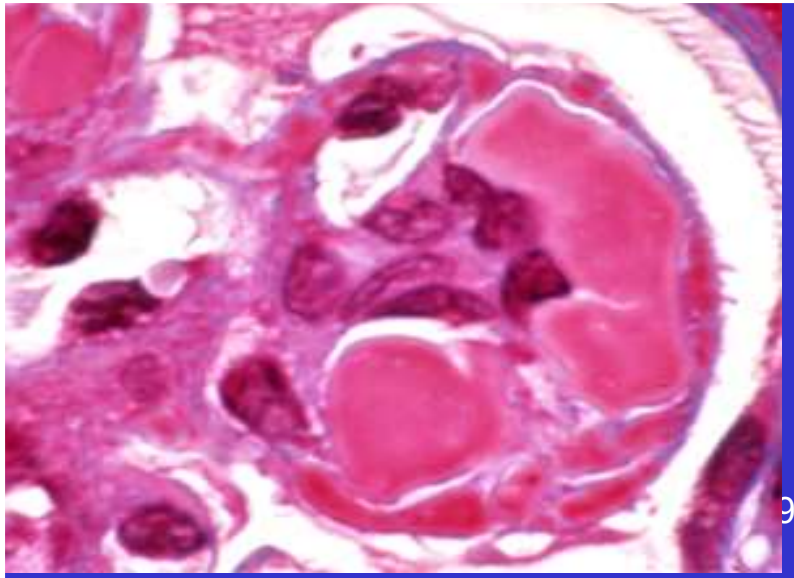


Lupus Activity

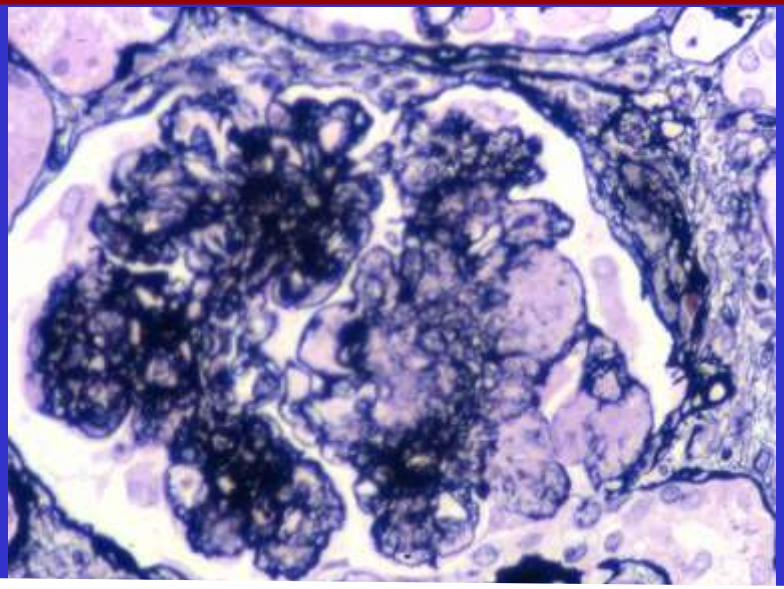


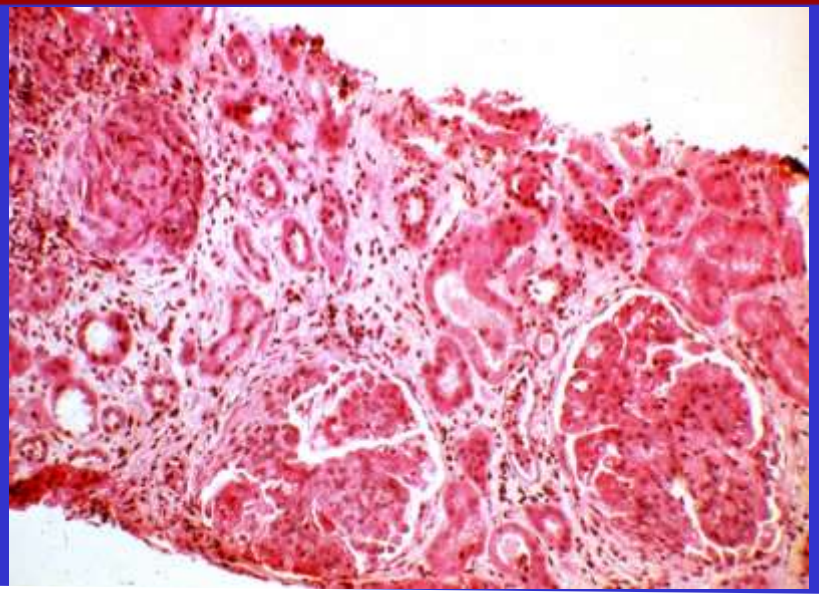


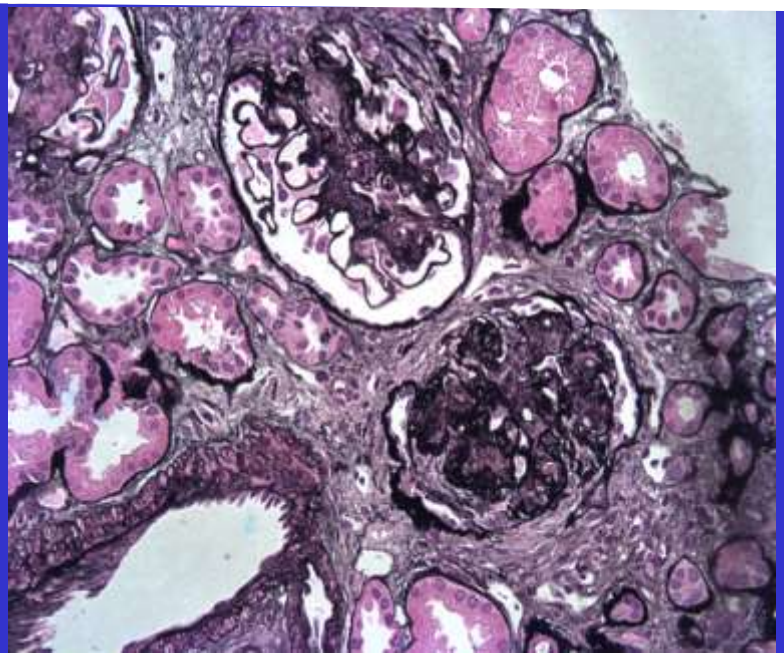


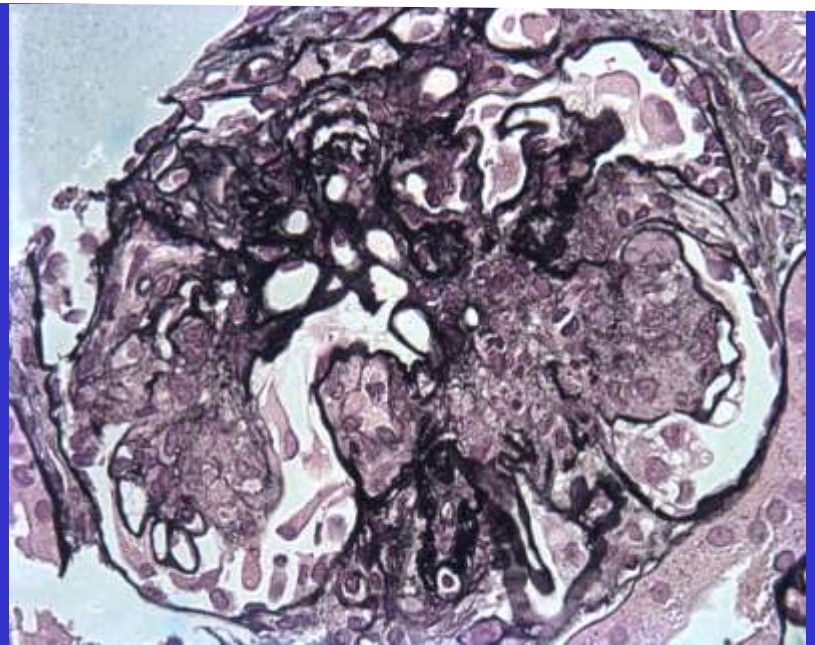


Lupus Chronicity









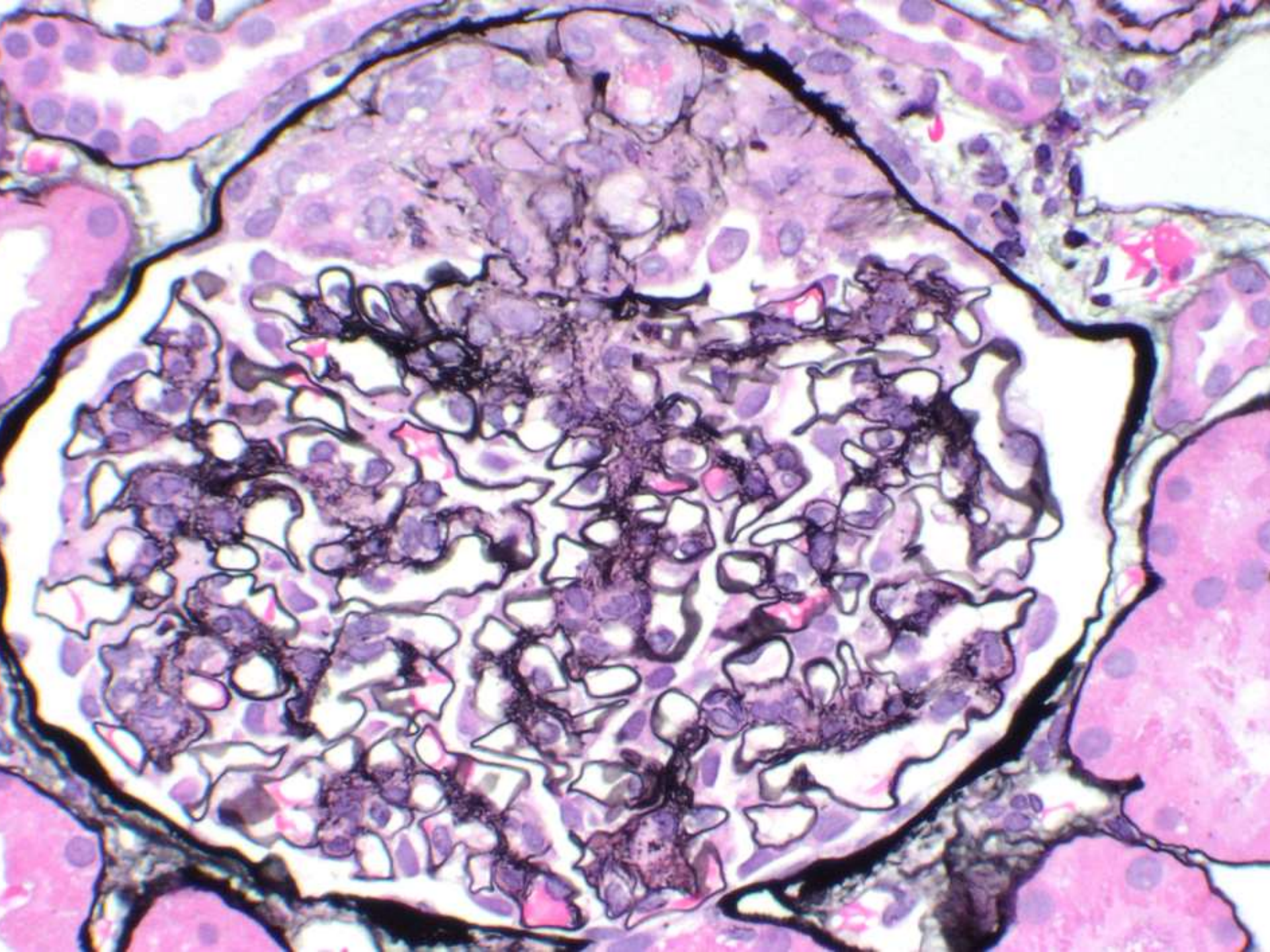
Active and Chronic Glomerular Lesions

Active lesions

- Endocapillary hypercellularity, with or without leukocyte infiltration and with substantial luminal reduction
- Karyorrhexis
- Fibrinoid necrosis
- Rupture of glomerular basement membrane
- Crescents, cellular or fibrocellular
- Subendothelial deposits, identifiable by LM (wireloops)
- Intraluminal immune aggregates (hyaline thrombi)

Chronic lesions

- Glomerular sclerosis (segmental, global)
- Fibrous adhesions
- Fibrous crescents



The prognosis of segmental glomerulonephritis in systemic lupus erythematosus

MELVIN M. SCHWARTZ, KAREN S. KAWALA, HOWARD L. CORWIN, and EDMUND J. LEWIS

Kidney Int 32:274-279, 1987

"The incidence of adverse outcomes, including death, end-stage kidney disease, and deterioration of renal function was similar in patients with severe Seg GN and DPGN."

"In SLE GN involvement of 50% or more of the glomeruli in a renal biopsy by active segmental lesions identifies a group of patients with a poor prognosis."

Proliferative Lupus Glomerulonephritis
2 Paradigms

Paradigm 1

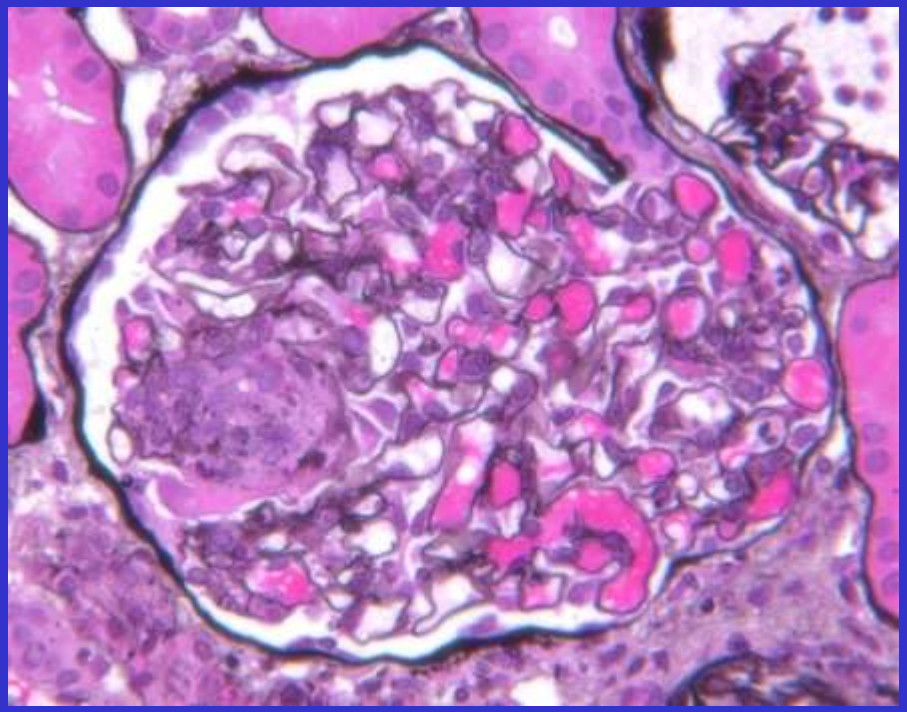
- Proliferative lupus nephritis is a continuum of injury.
- Focal and diffuse lupus nephritis differ only in extent.
- Therapy and prognosis largely the same.

Paradigm 2

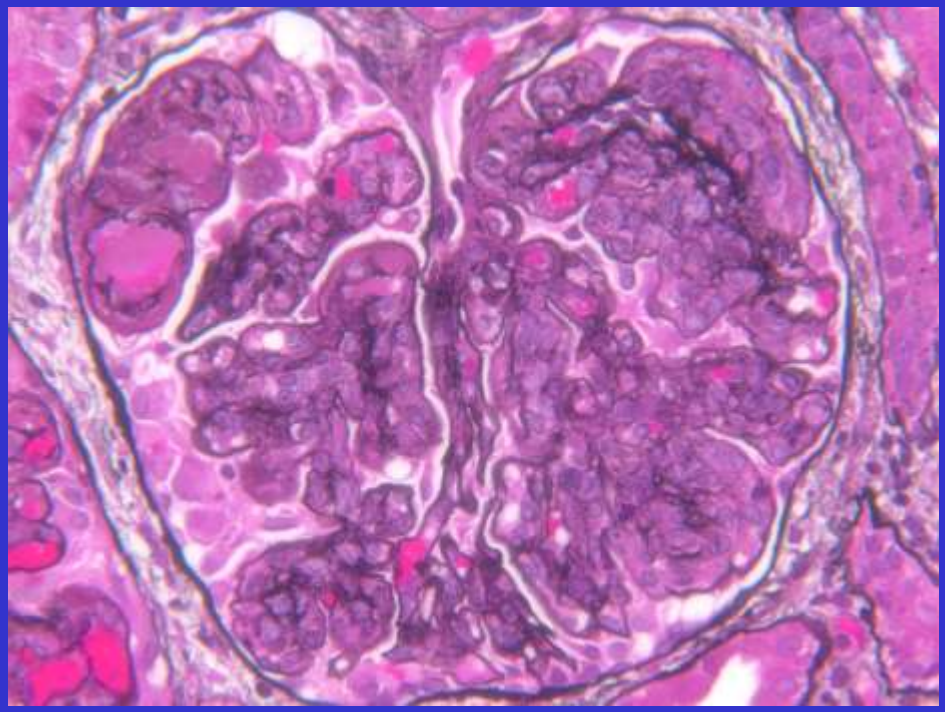
- Proliferative lupus nephritis has two distinct types of injury.
- Different pathogenesis (ANCA type vs. Immune complex deposition)
- Therapy and prognosis may differ.

Class IV: diffuse segmental (IV-S) or global (IV-G) LN

Class IV is further subdivided into:



Diffuse segmental (IV-S) when >50% of the involved glomeruli have segmental lesions



Diffuse global (IV-G) when >50% of the involved glomeruli have global lesions

Class IV Lupus Nephritis

IV-G vs. IV-S

Does it matter?

Consensus Findings-Studies of IV-G vs IV-S Lupus Nephritis

Table 2. Consensus Findings-Studies of IV-G vs IV-S Lupus Nephritis: Clinical/Morphologic Parameters and Outcomes

Study	Serum Creatinine	Renal Outcome
Najafi *et* al.[14]	G = S	G > S
Mittal *et* al. [15]	G > S	G = S
Yokoyama *et* al. [12]	G = S	G = S
Hill *et* al. [16]	G = S	G = S
Hiramatsu *et* al. [19]	G > S	G = S
Schwartz *et* al. [21]	G = S	G = S
Grootscholten *et* al. [13]	G > S	G = S
Yu *et* al. [17]	G > S	G = S
Kojo *et* al. [18]	Not Reported	G = S
Consensus	**G > S**	**G = S**

Haas M et al. Kidney Int. 2014; 85: 779-93

Class IV Lupus Nephritis

IV-G vs. IV-S

Does it matter?

Early indications: may not matter for patient outcome, but not adequately tested to date for differing therapeutic regimens.

Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class III and IV	The term **ENDOCAPILLARY PROLIFERATION** is replaced by **ENDOCAPILLARY HYPERCELLULARITY**	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise

Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class III and IV	The term **CRESCENT** is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved.	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents
	CELLULAR CRESCENT: more than 75% cells and fibrin and less than 25% fibrous matrix	
	FIBROUS CRESCENT: more than 75% fibrous matrix and less than 25% cells and fibrin	

Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class III and IV	**ADHESION**: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis	There was no definition for an adhesion
	FIBRINOID NECROSIS: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis	There was no definition for fibrinoid necrosis

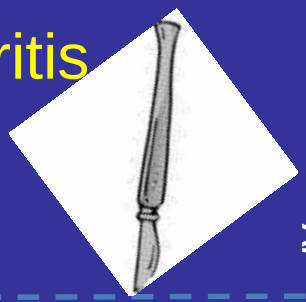
Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class III and IV	Elimination of segmental and global subdivions of class IV. **NO G OR S**	Definitions for segmental and global were unclear; interobserver variability was large; clinical significance uncertain

Phase 1 Recommendation for Lupus Nephritis Classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class III and IV	Modification of the NIH lupus nephritis **ACTIVITY AND CHRONICITY SCORING SYSTEM** to be used instead of the currently used A, C, and A/C parameters	Designation of activity/chronicity through A, C, and A/C considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions

Chronicity and Lupus nephritis



< 50% (focal) ≥ 50% (diffuse)

Class III ⟷ Class IV

~~Segmental/global~~

~~Active, A/C, Chronic~~ ~~Active, A/C, Chronic~~

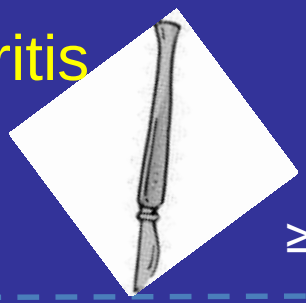
Kidney International, Vol. 25 (1984), pp. 689–695

Diffuse proliferative lupus nephritis: Identification of specific pathologic features affecting renal outcome

HOWARD A. AUSTIN III, LARRY R. MUENZ, KATHLEEN M. JOYCE, TATIANA T. ANTONOVYCH, and JAMES E. BALOW

Clinical Nephrology Service and Arthritis and Rheumatism Branch, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases; Clinical and Diagnostic Trials Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and the Nephropathology Section, Armed Forces Institute of Pathology, Washington, D.C.

Chronicity and Lupus nephritis



< 50% (focal) ≥ 50% (diffuse)

Class III ~~Segmental/global~~ Class IV

~~Active, A/C, Chronic~~ Active, ~~A/C, Chronic~~

Table 2 | Proposed modified NIH lupus nephritis activity and chronicity scoring system

Modified NIH activity index	Definition	Score
Endocapillary hypercellularity	Endocapillary hypercellularity in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Neutrophils/karyorrhexis	Neutrophils and/or karyorrhexis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Fibrinoid necrosis	Fibrinoid necrosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Hyaline deposits	Wire loop lesions and/or hyaline thrombi in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Cellular/fibrocellular crescents	Cellular and/or fibrocellular crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Interstitial Inflammation	Interstitial leukocytes in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–24***
Modified NIH chronicity index	**Definition**	**Score**
Total glomerulosclerosis score	Global and/or segmental sclerosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Fibrous crescents	Fibrous crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Tubular atrophy	Tubular atrophy in <25% (1+), 25%–50% (2+), or >50% (3+) of the cortical tubules	0–3
Interstitial fibrosis	Interstitial fibrosis in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–12***

NIH, National Institutes of Health.

Modified NIH ACTIVITY INDEX				
ACTIVITY INDEX	<25%	25%-50%	>50%	
Endocapillary Hypercellularity	1	2	3	0-3
Neutrophils/Karyorrhexis	1	2	3	0-3
Fibrinoid Necrosis	1	2	3	(0-3)x2
Hyaline deposits (WL/HT)	1	2	3	0-3
Cellular/fibrocellular crescents	1	2	3	(0-3)x2
Interstitial inflammation	1	2	3	(0-3)
Total				0-24

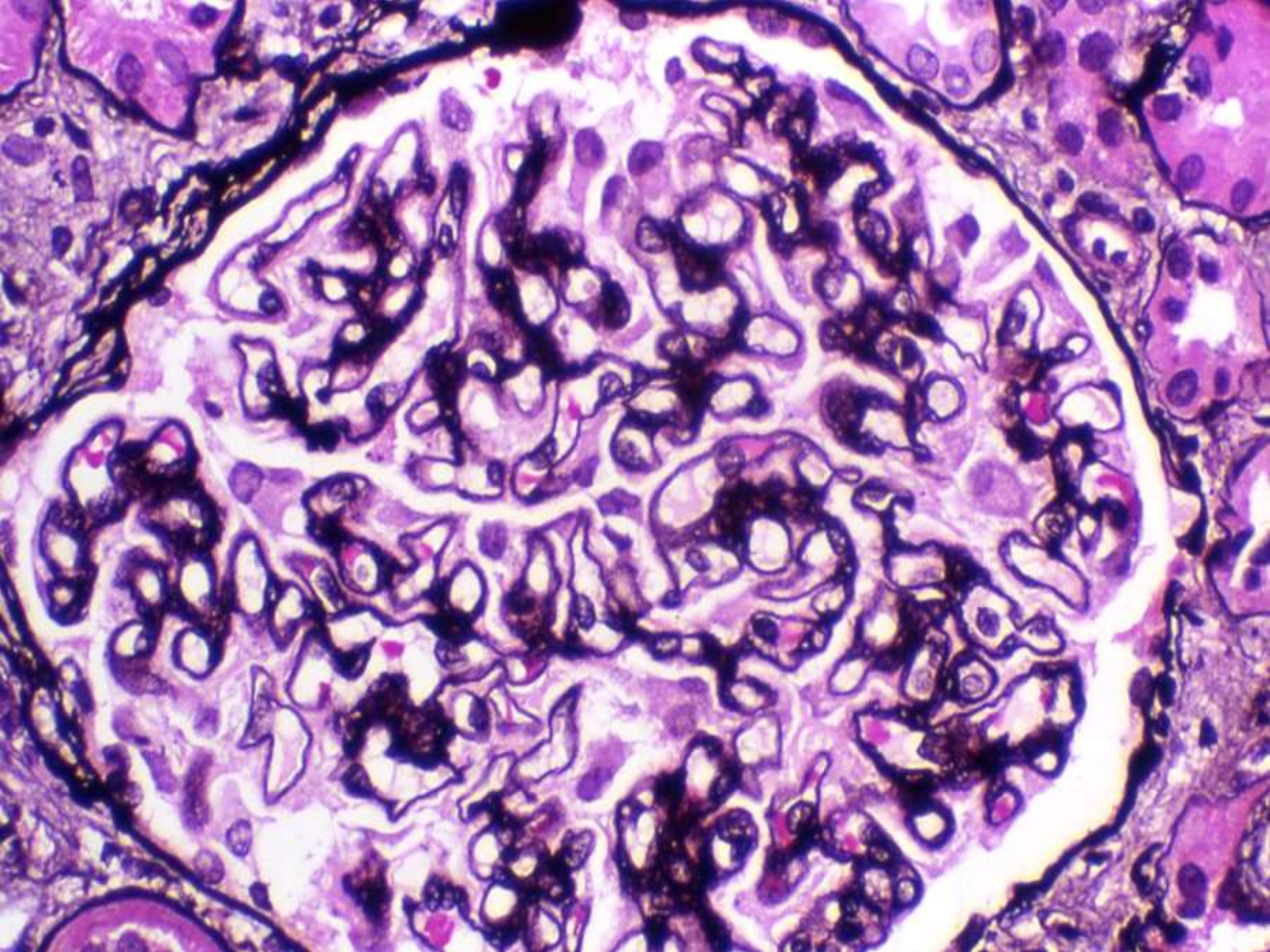
Modified NIH CHRONICTY INDEX				
ACTIVITY INDEX	<25%	25%-50%	>50%	
Glomerulosclerosis (global & segmental)	1	2	3	0-3
Fibrous crescents	1	2	3	0-3
Interstitial Fibrosis	1	2	3	0-3
Tubular Atrophy	1	2	3	0-3
Total				0-12

Phase 2 and Class III/IV

- *Endocapillary hypercellularity:*
  - Contribution of endothelial cell swelling?
  - # of cells required?
  - luminal narrowing?
  - Cellular interposition in subendothelial space?
- *Fibrinoid necrosis:*
  - Association with pauci Immune Complex/ANCA?
  - Importance in isolation or with Crescents?
  - Segmental vs global? (microscopic description)
- *Activity and Chronicity Index*

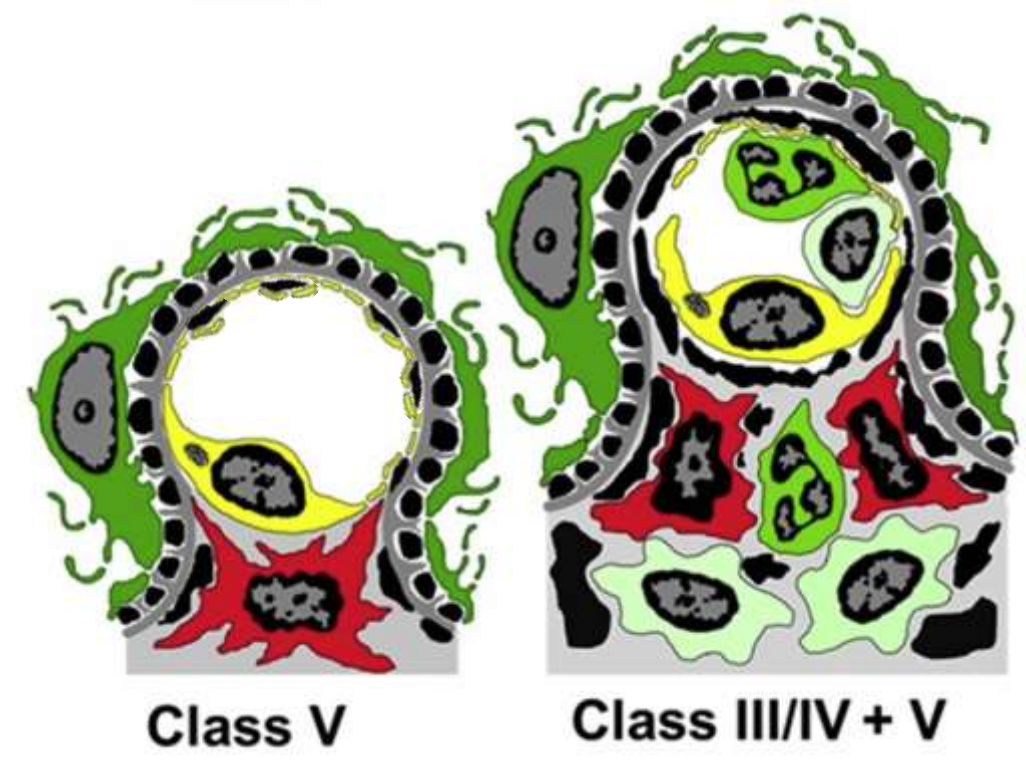
Class V: Membranous Glomerulonephritis

- Global or Segmental Granular Subepithelial Deposits
- Mesangial deposits common
- ANY degree of mesangial hypercellularity may be present
- Scattered subendothelial deposits by IF or EM may be present
- Subendothelial deposits visible by LM (i.e. “wire loops”) require a diagnosis of Class III or Class IV
- Class III or IV with >50% tuft of >50% glomeruli with demonstrable membranous lesions by LM or IF results in combined diagnosis (e.g. Class IV plus V)



Class V and Phase 2

- Class V with/without mesangial proliferation
- Extent of allowable non-wire loop subendothelial deposits



Class VI: Advanced Sclerotic LN

- > 90% of glomeruli globally sclerosed without residual activity
- Specific features of lupus nephritis may be lacking
- Interstitial fibrosis and tubular atrophy
- >> matrix deposition

Vascular lesions

- Lupus Vasculopathy:

  Luminal narrowing (arterioles/terminal ILAs), typically by immune deposits

  with fibrinoid change but no inflammation

Uncomplicated vascular immune complex deposition:

Vascular immune complex deposition, no luminal narrowing, no fibrinoid change, no inflammation

The 2004 ISN/RPS Revised Classification of Lupus Glomerulonephritis

What does the revision accomplish?

- Standardization and illustration of definitions
- Provides a means to ascertain potentially different subtypes of pathogenic and therapeutic importance within the Class III/IV proliferative categories, at a cost of some complexity
- Sets clear definitions of membranous GN in the context of coexisting proliferative lesions
- Introduces relative assessments of activity and chronicity into the diagnosis of focal and diffuse proliferative glomerulonephritis.

Kidney Int 2004; 65:521-530 and J Am Soc Nephrol 2004, 15:241-250

The 2004 ISN/RPS Revised Classification of Lupus Glomerulonephritis

What it doesn't accomplish:

- Does not provide a reproducible or quantitative measure of activity/chronicity
- Does not account for immune deposits in extraglomerular sites
- Does not account for interstitial nephritis
- Does not allow categorization of vasculopathies such as TMA due to anti-phospholipid or anti-cardiolipin antibodies or vasculitis

New Goals Accomplished

Increase interobserver agreement (Phase 1):

1. Clarifying problematic terms:

   Endocapillary proliferation; crescent

2. Unifying classification schemes:

   Mesangial proliferation (similar to Oxford IgA):

   ≥ 4 mes cell/area, all surrounded by matrix, excl vascular pole

3. Omitting terms that had little distinctiveness:

   Class IV-S vs IV-G

4. Added quantitative measures of activity and chronicity

Identified areas that require research (phase 2)

Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) Classification of Lupus Nephritis (2004)

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

Kidney Int 2004; 65:521-530 and J Am Soc Nephrol 2004, 15:241-250

ISN/RPS Classification of Lupus Nephritis

We are not yet done!

Спасибо