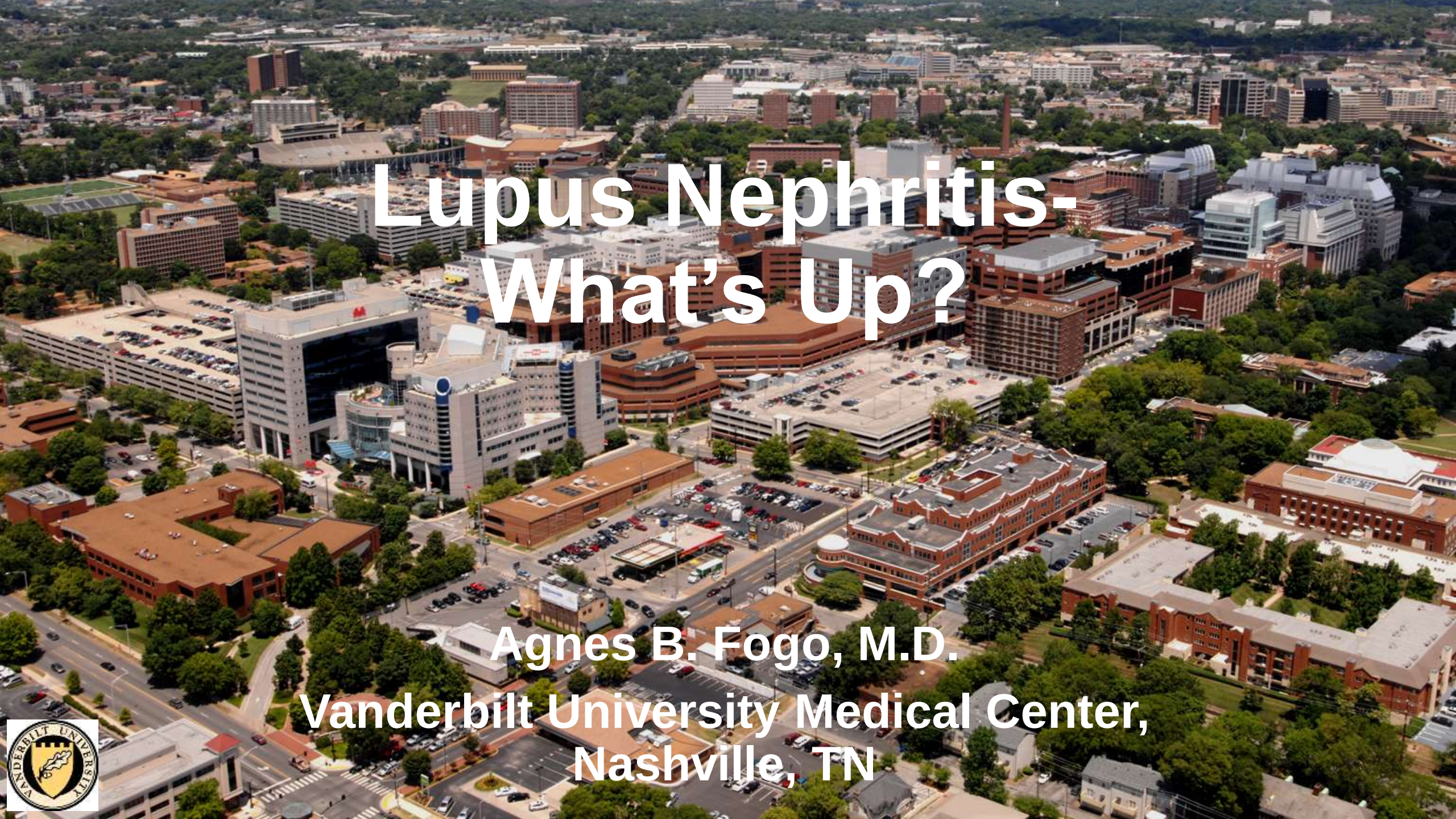


Lupus Nephritis- What's Up?

Agnes B. Fogo, M.D.

Vanderbilt University Medical Center, Nashville, TN

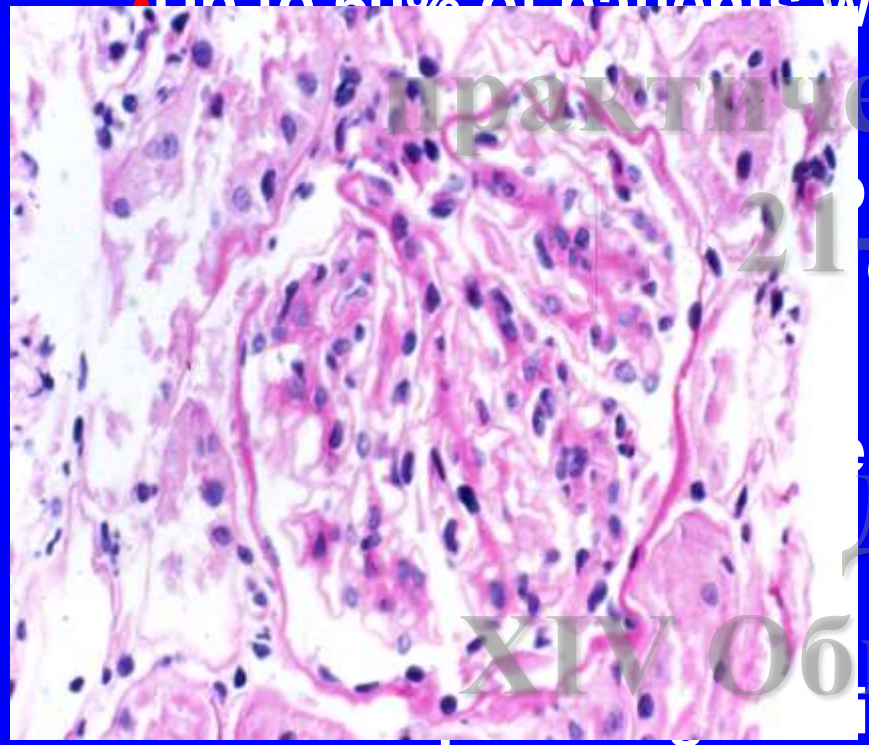
27 yo man with SLE

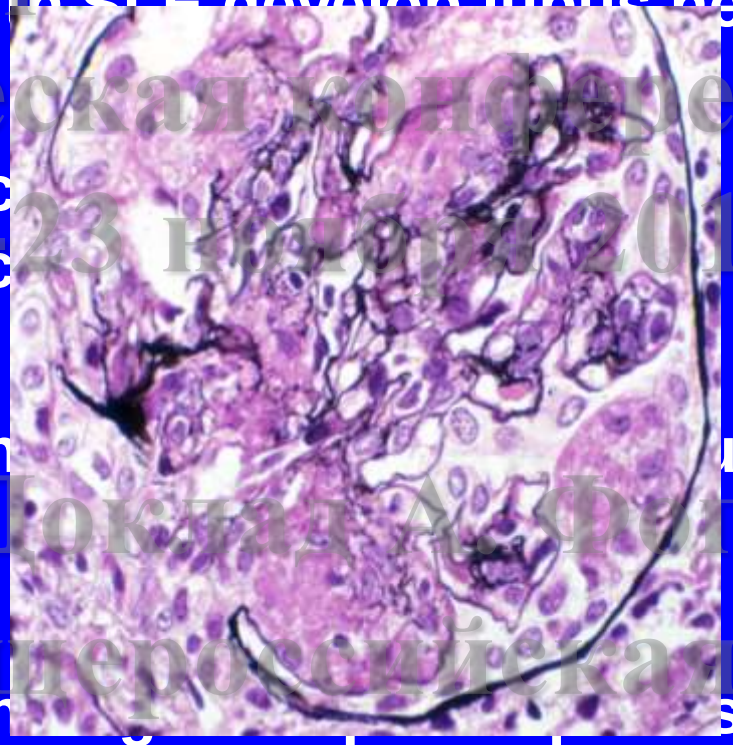
- Previous bx 2009:
  - Membranous class V and diffuse LN class IV
- One glomerulus with collapse
- Remission in response to aggressive RX

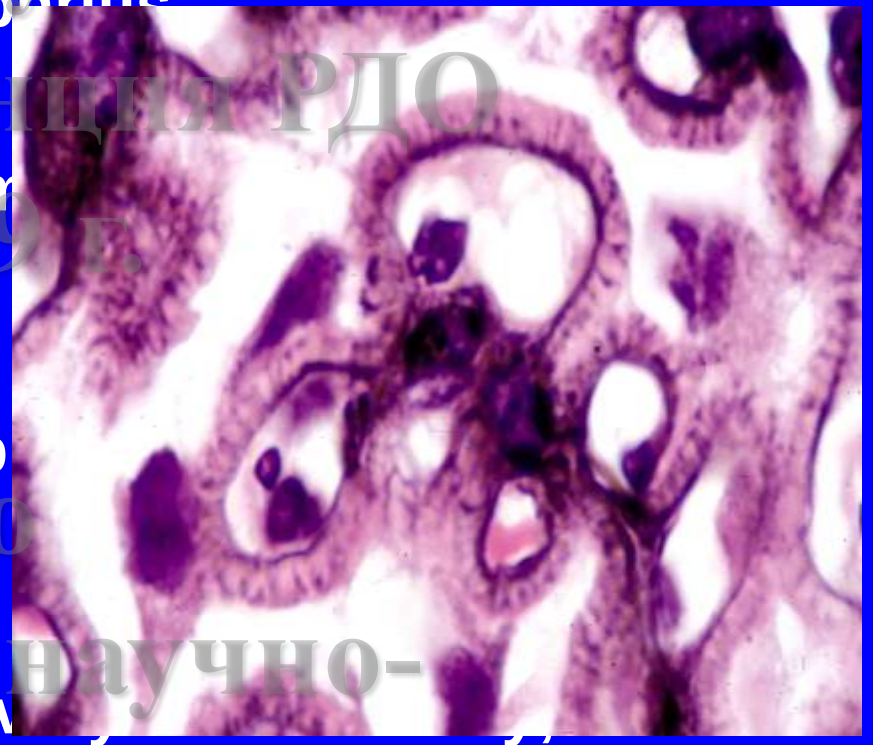
- Now marked NS, increased Screat
- Renal biopsy is essential
- What do we expect, what can we learn from biopsy in this patient?

Lupus Nephritis- Not Just One Entity

- Up to 60% of patients with SLE develop lupus nephritis







classification of lupus nephritis is essential for treatment decisions

The diagnosis of SLE is NOT made by renal biopsy

RATHER

Renal biopsy defines the TYPE of renal lesion in a patient with SLE

Renal Biopsy Questions to Answer in the Patient with SLE and Kidney Disease

-Lupus nephritis (IC in glomeruli)

If present, what class?

Active or chronic?

-Vascular lesion- TMA/vasculitis

-Tubular deposits

-"Podocytopathy"- MCD like or collapsing lesions

-Non-lupus renal disease

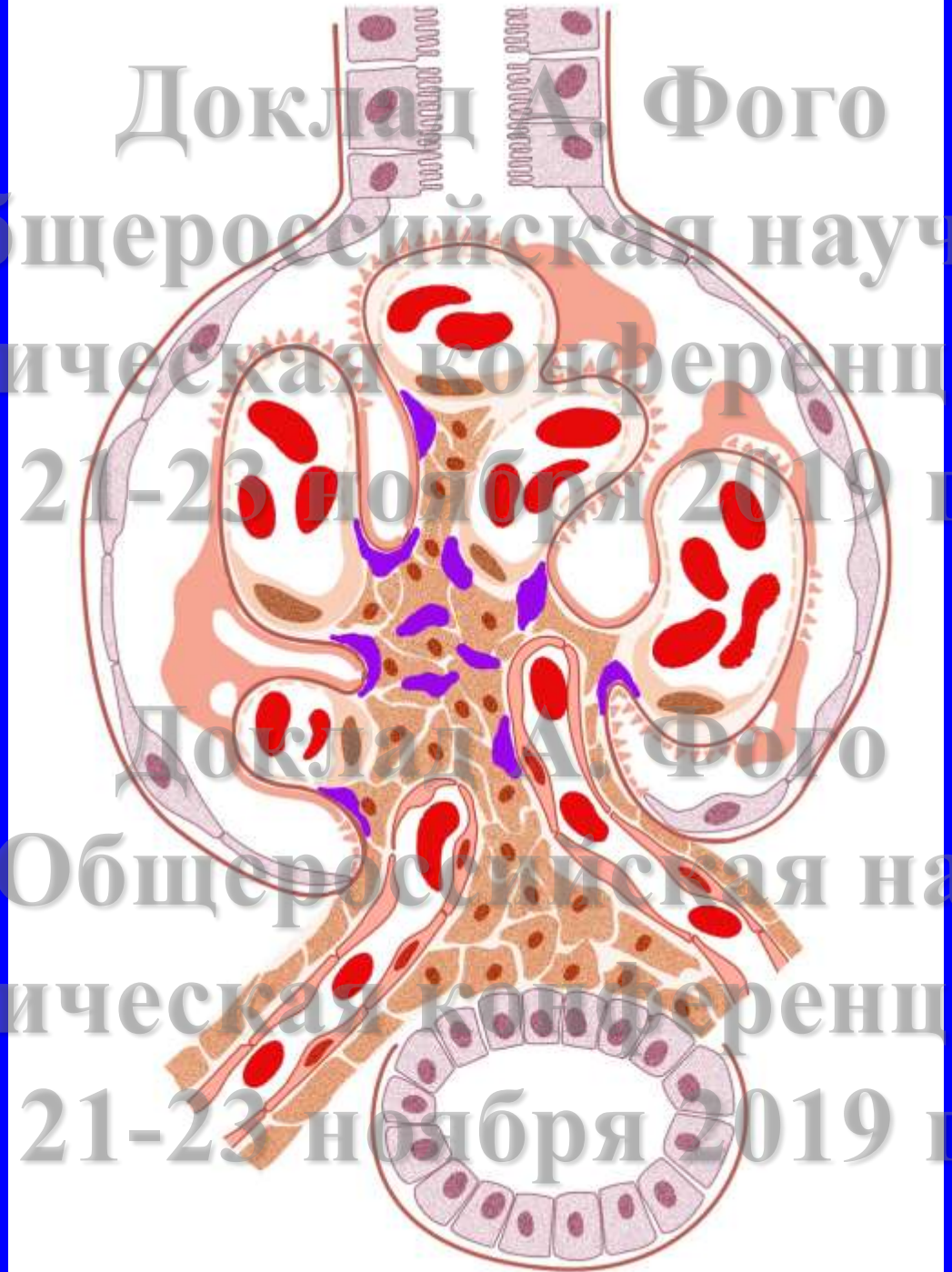
-Lupus + non-lupus disease

Wide Spectrum of Lesions
Wide Spectrum of Implications
Need for Classification

Доклад А. Фого
XIV Общероссийская научно-практическая конференция РДО
21-23 ноября 2019 г.

Abbreviated Current ISN/RPS classification of lupus glomerulonephritis

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



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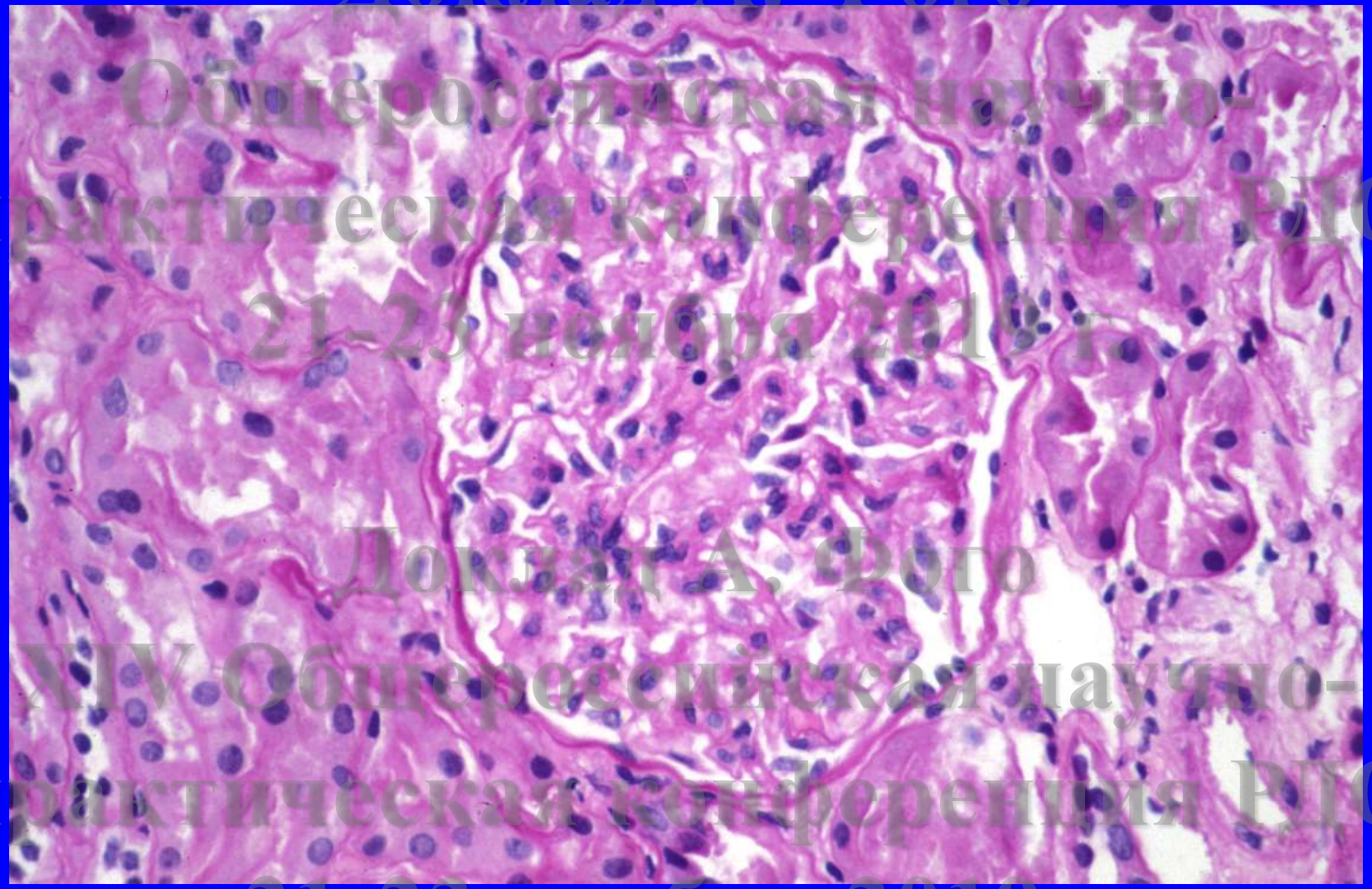

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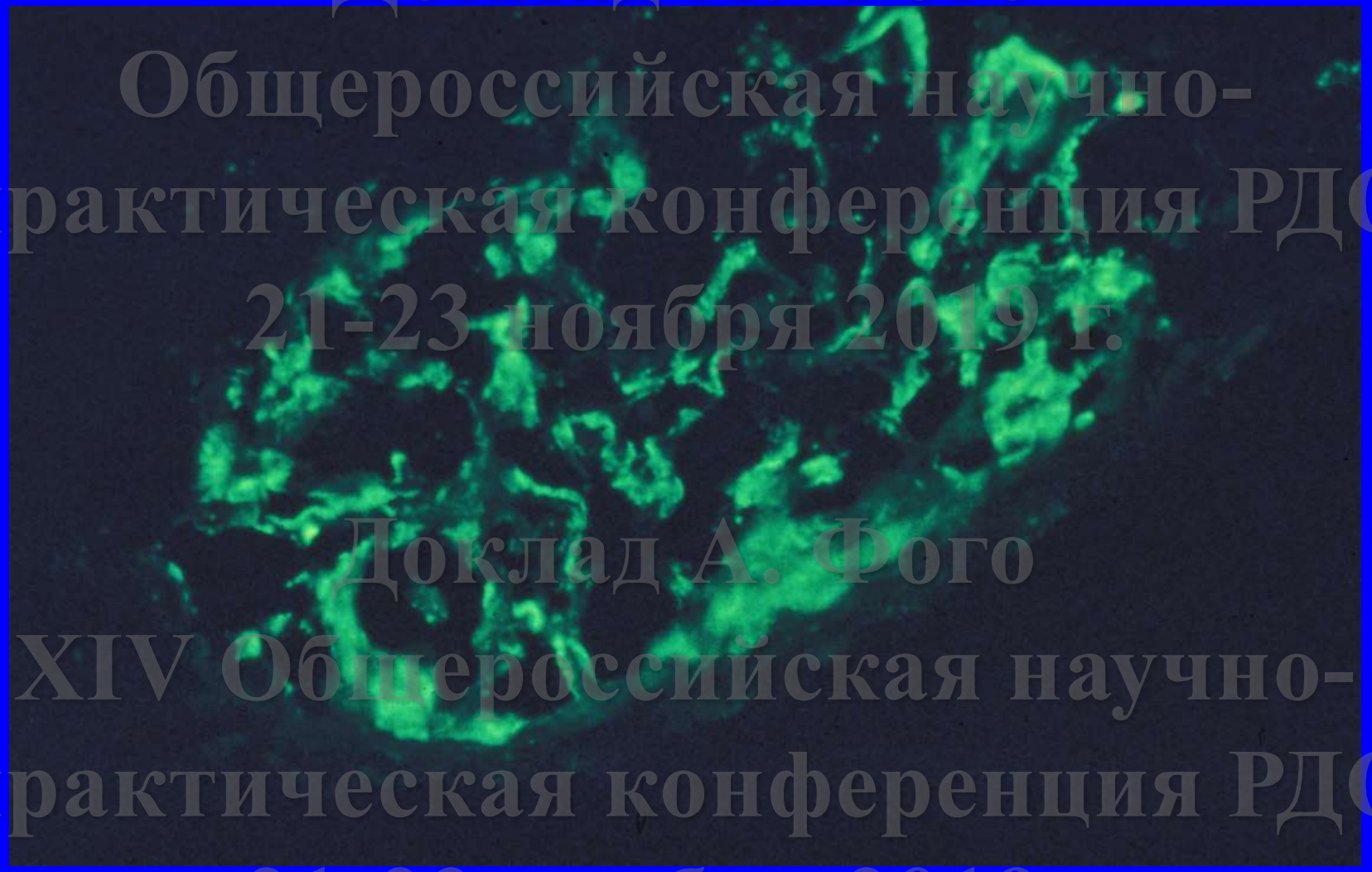

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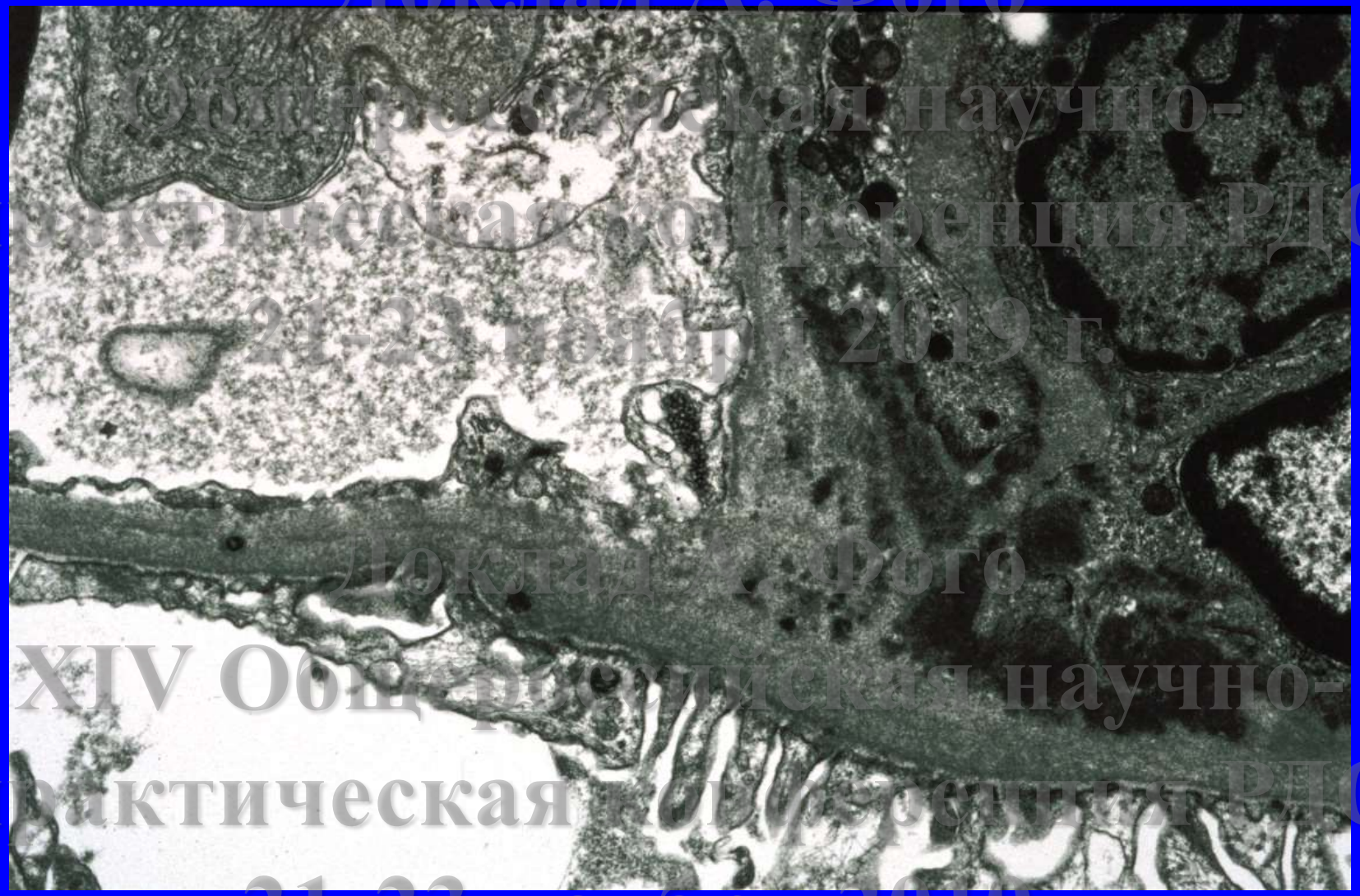

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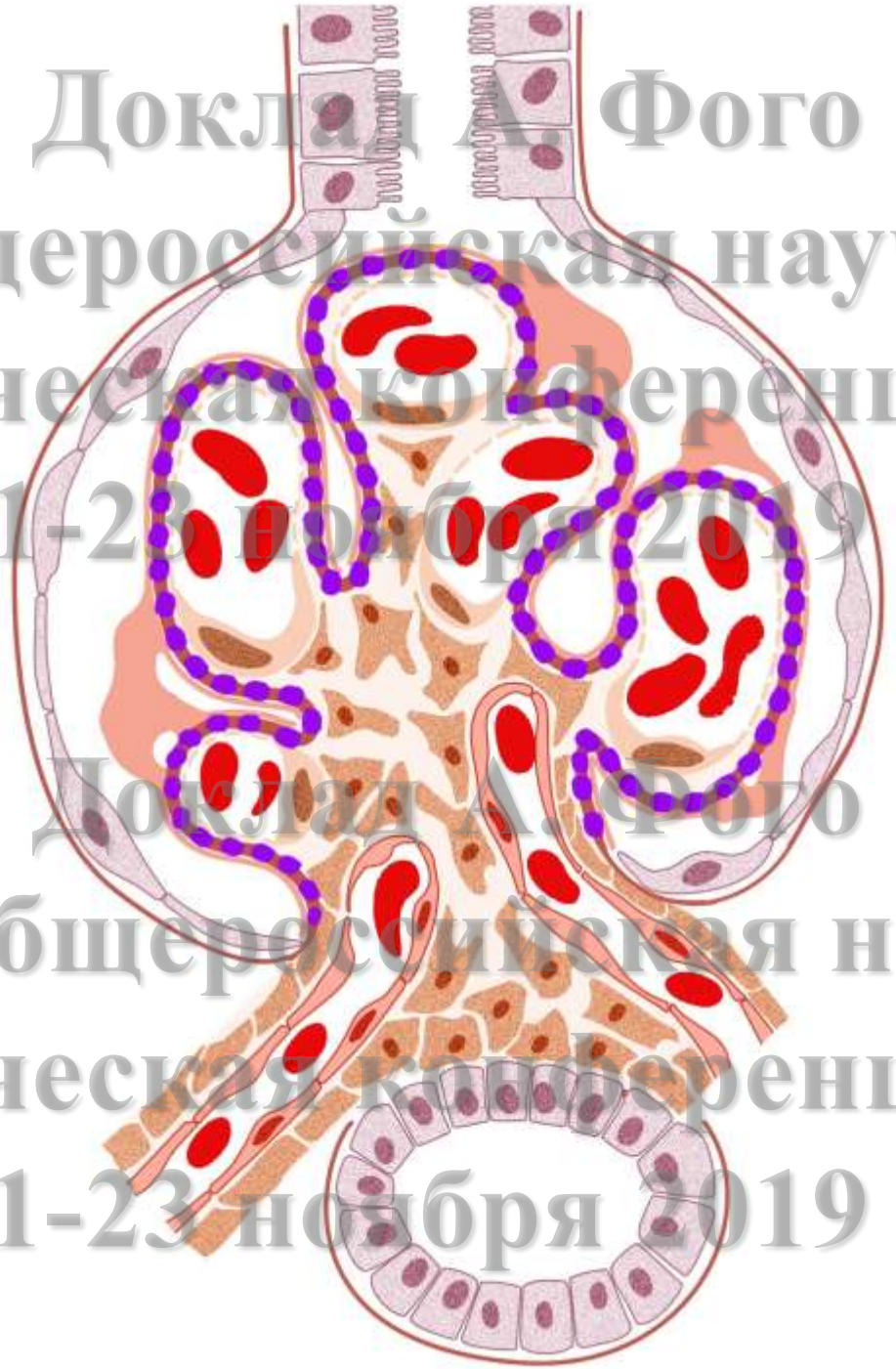
Membranous Lupus Nephritis

- Subepithelial deposits
- IgG, C3
- Varying GBM reaction ±sclerosis



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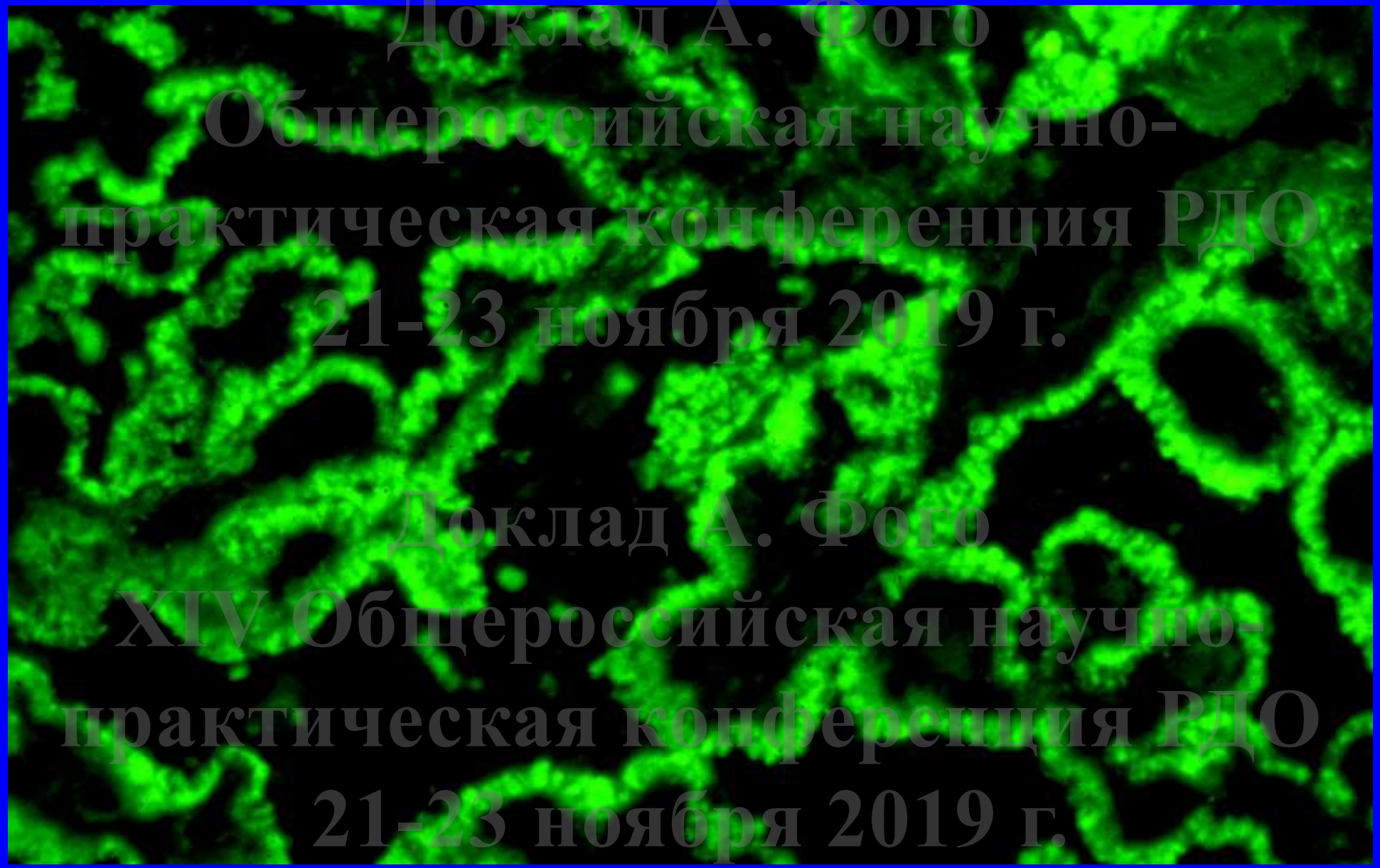

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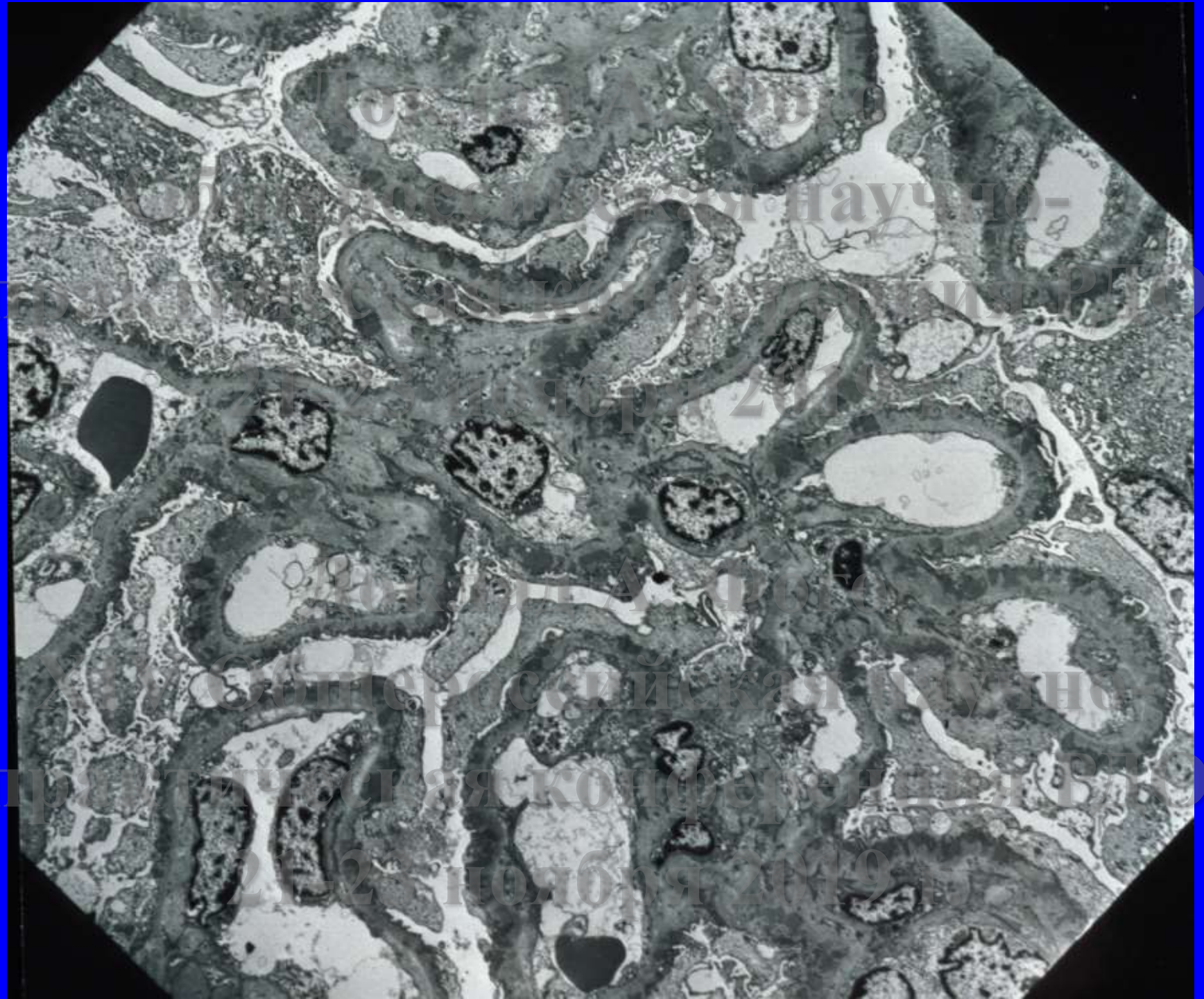

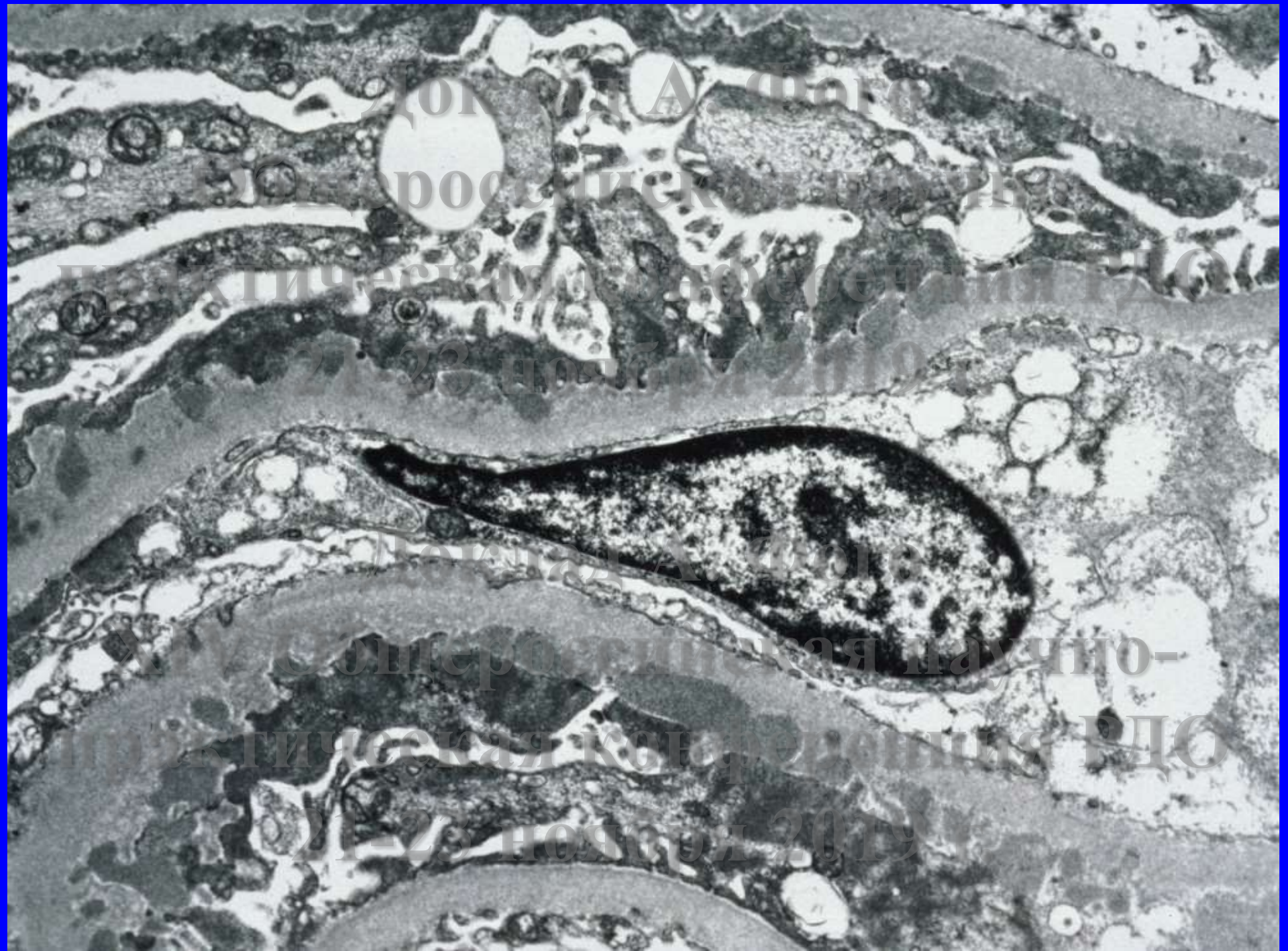

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Lupus Nephritis- Class III and IV

- **Often nephritic ± nephrotic proteinuria**

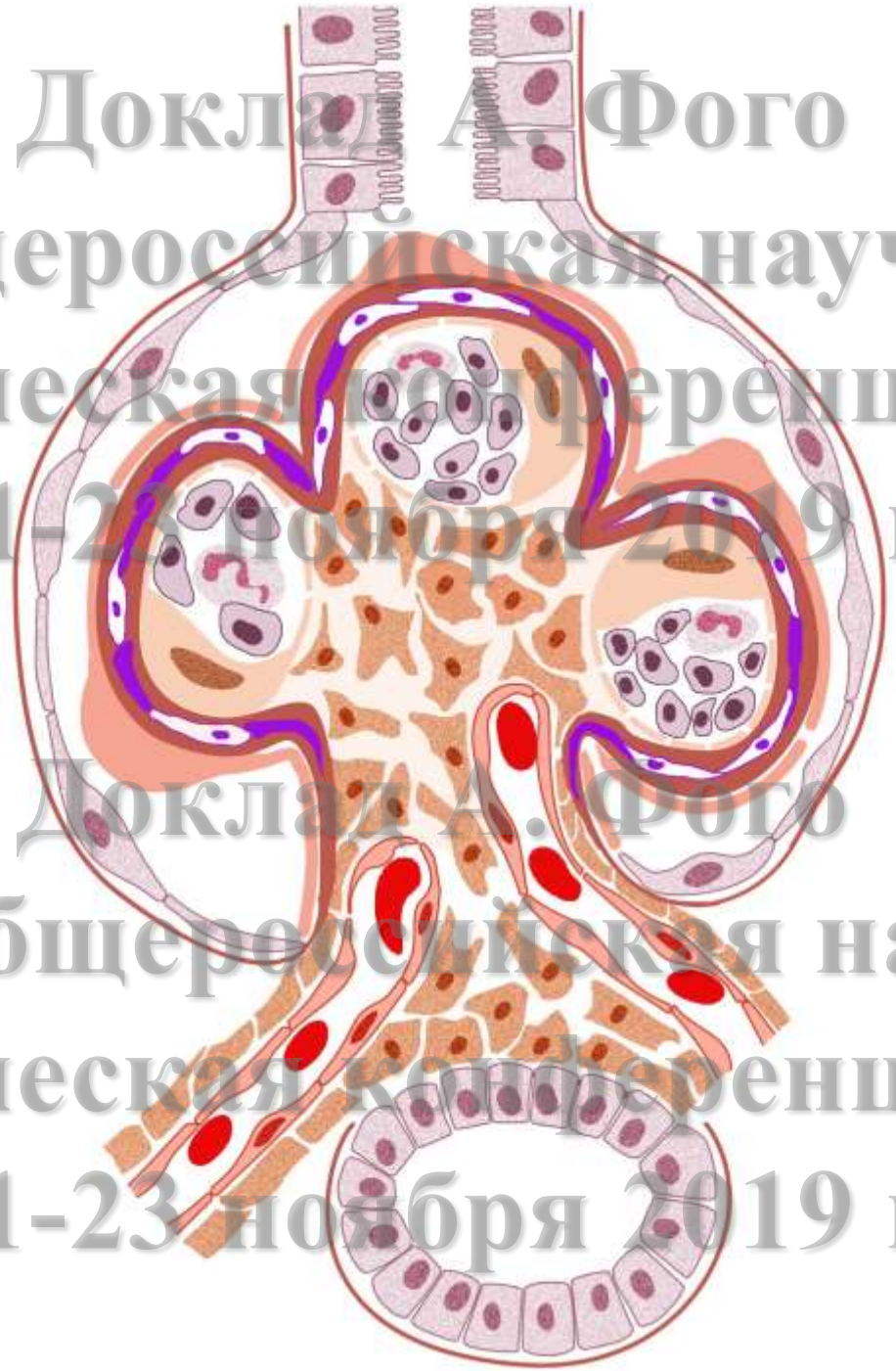
  (subendothelial deposits)

  “Bad active” lesions- cellular crescents, necrosis, proliferative,

  Or

  “Bad chronic”- fibrous/fibrocellular crescents, sclerosis

- **Bad prognosis**



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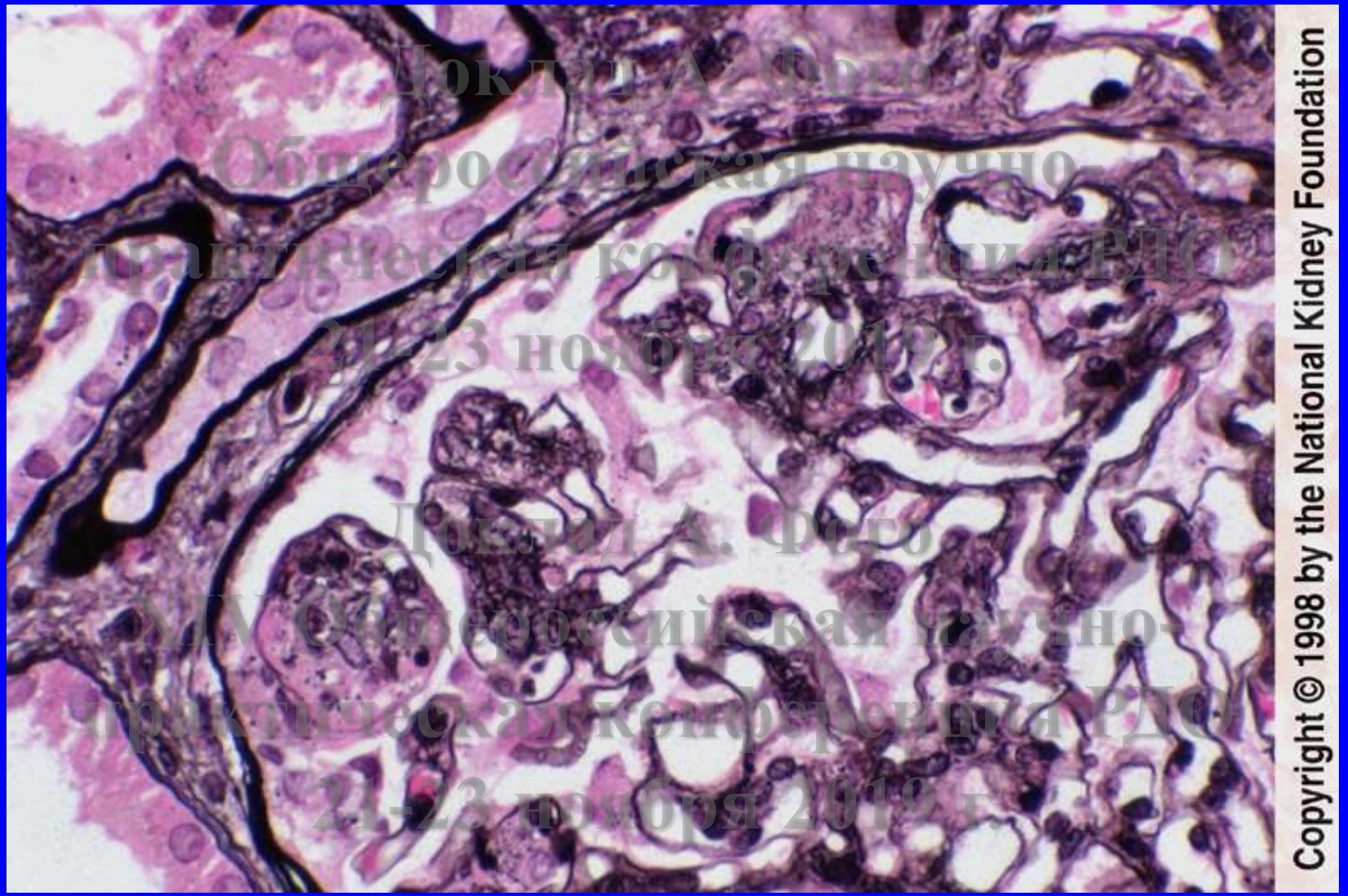

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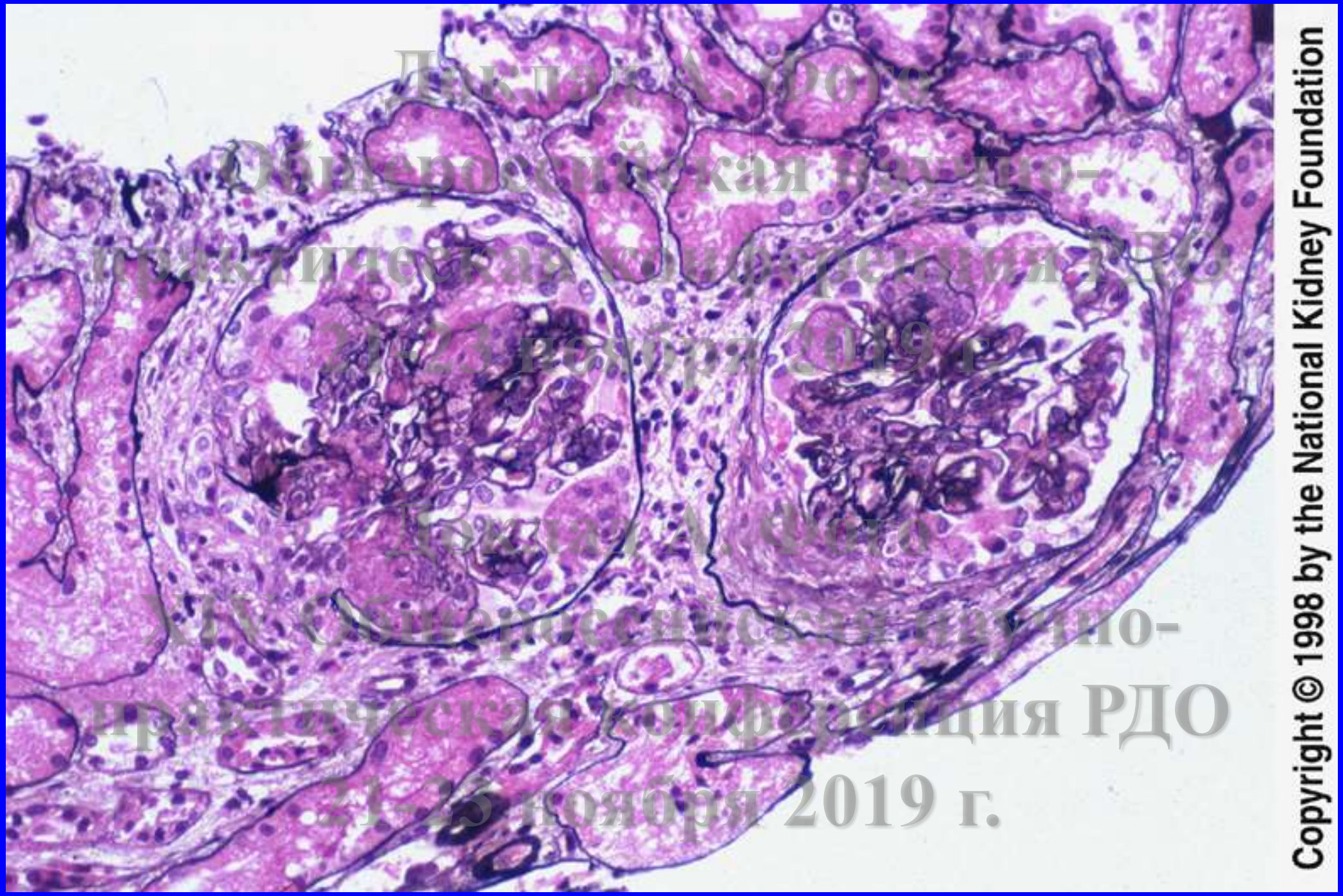

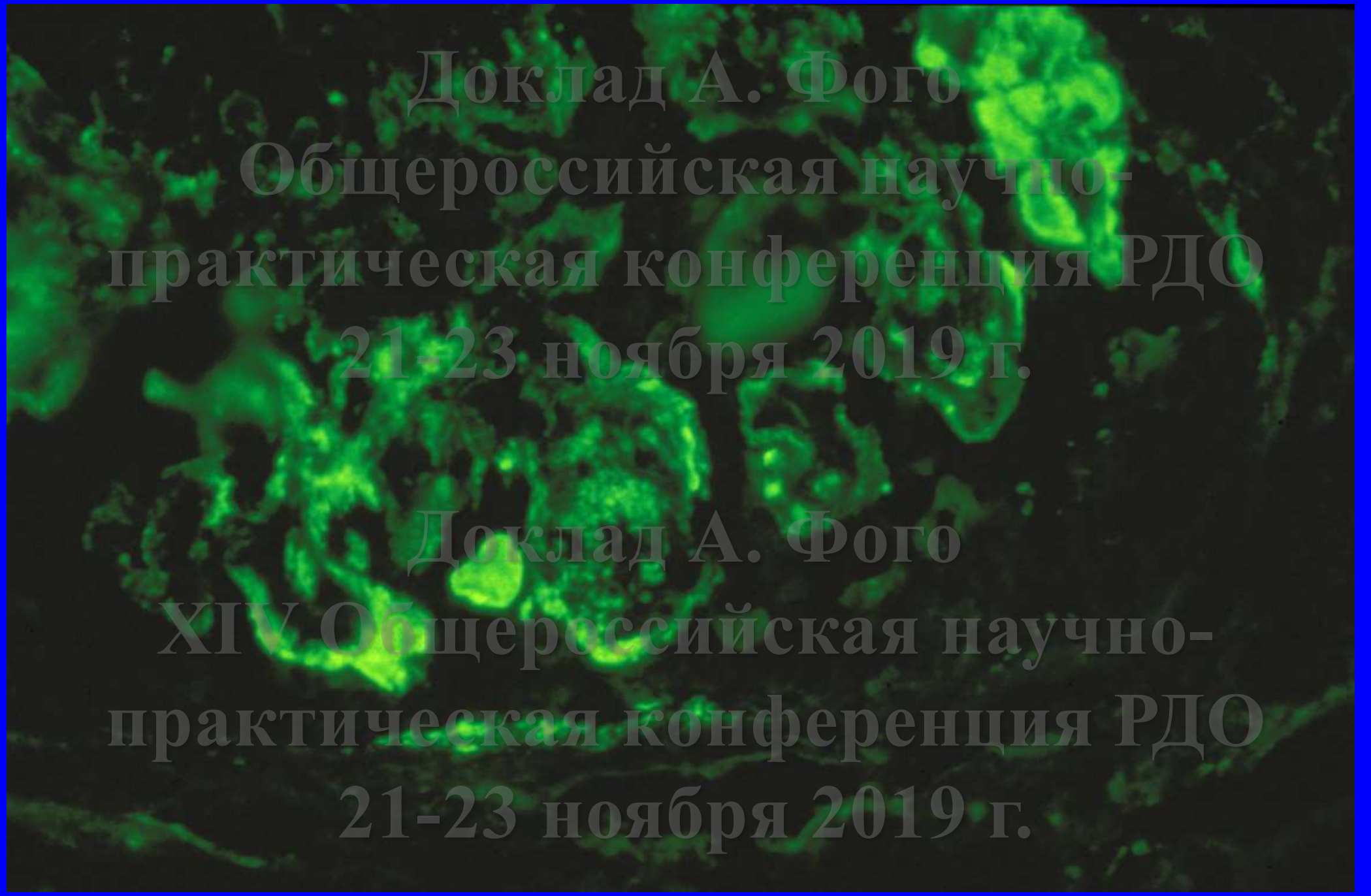

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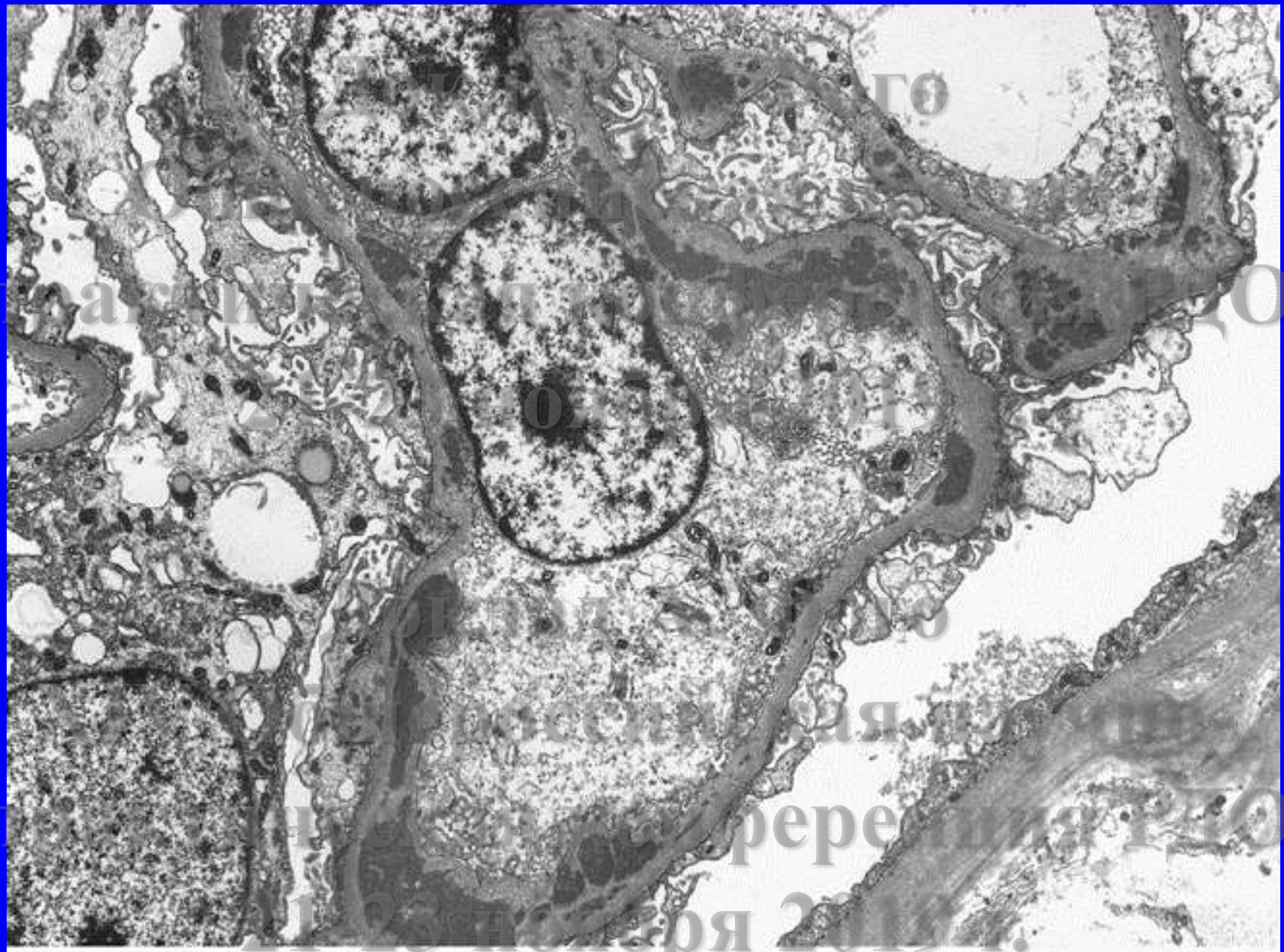
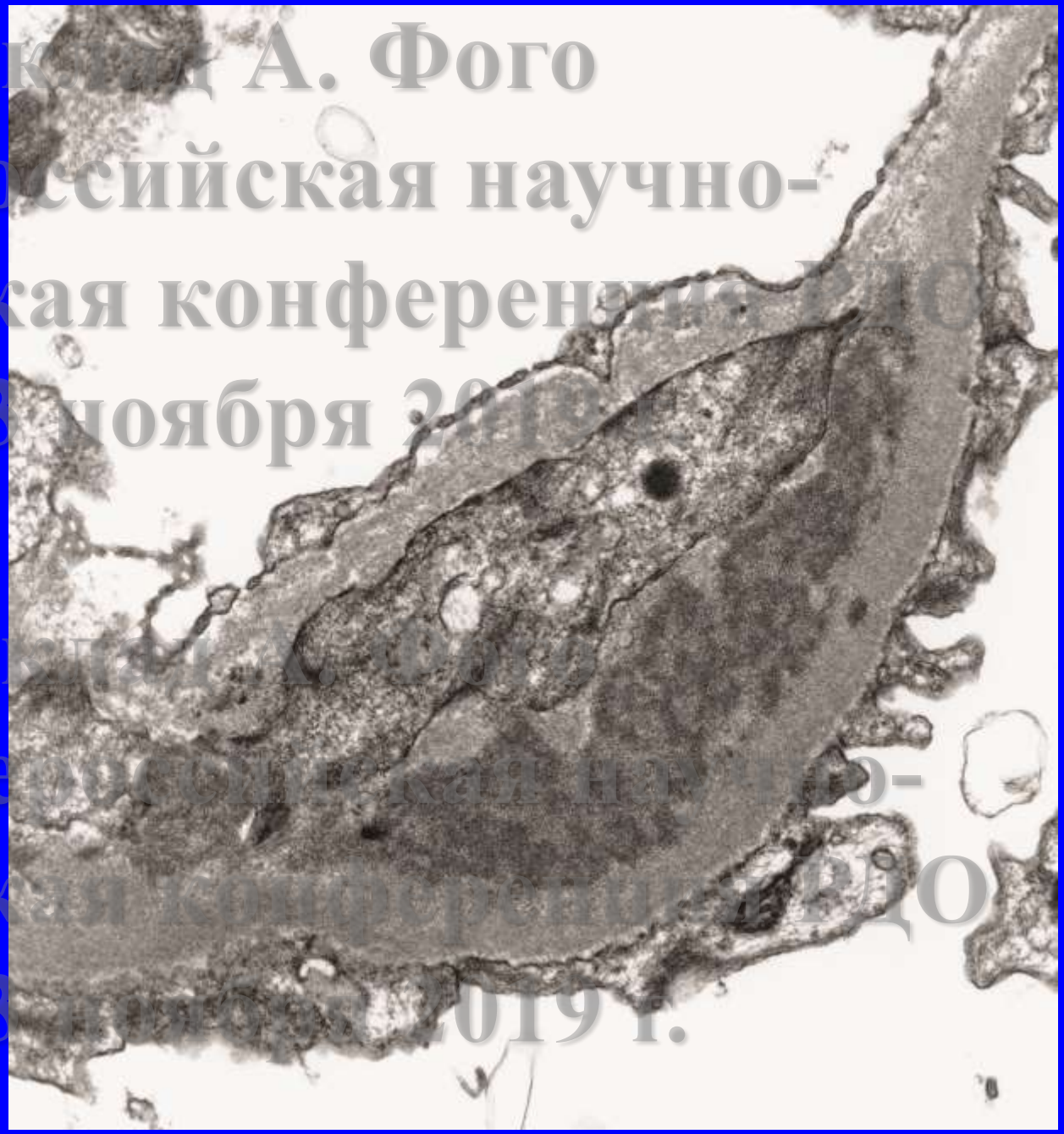


Subendothelial deposits-
In Class III and IV LN



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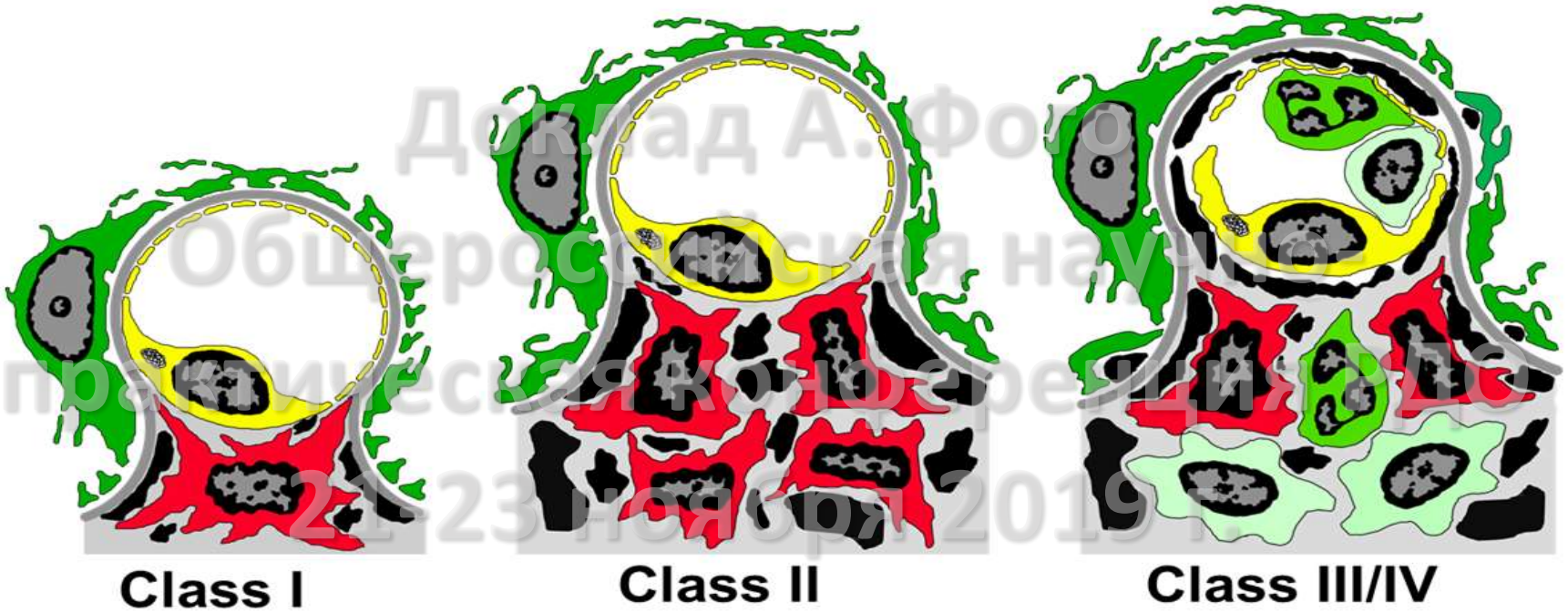
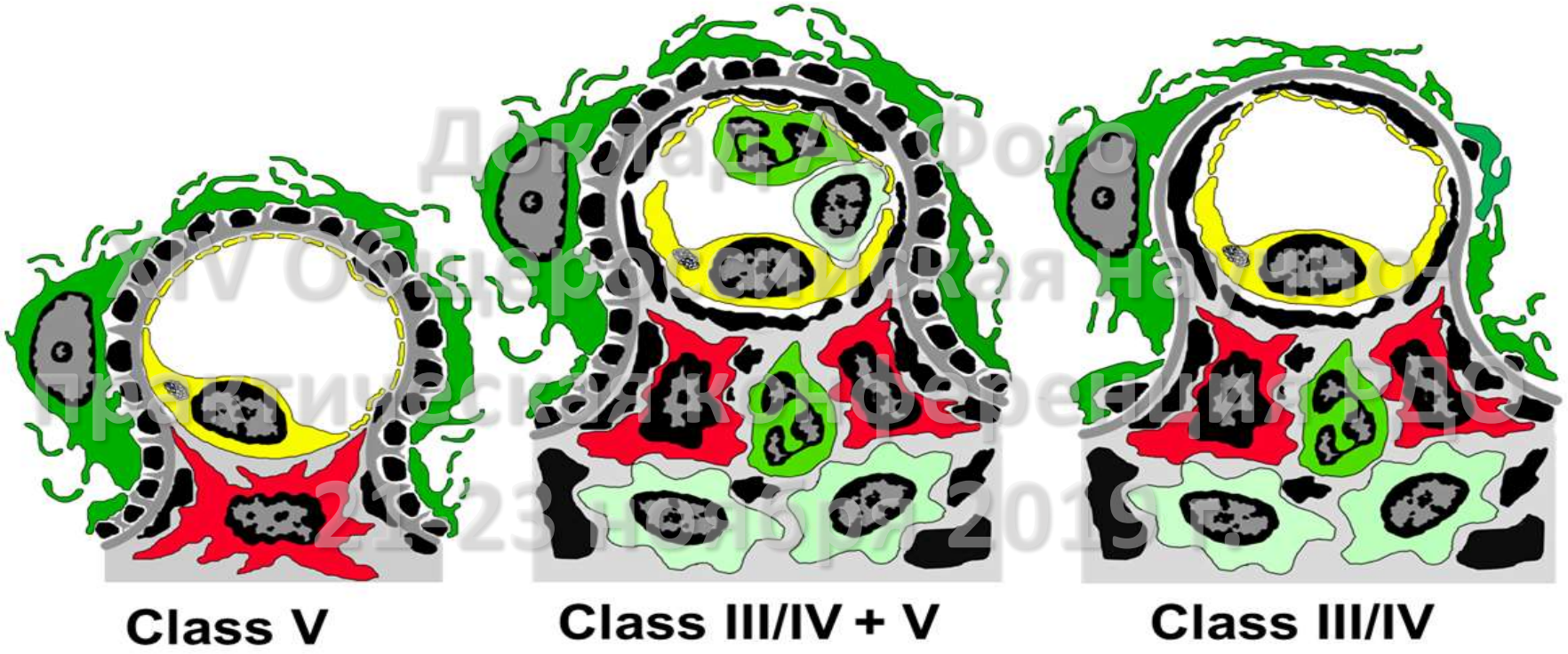
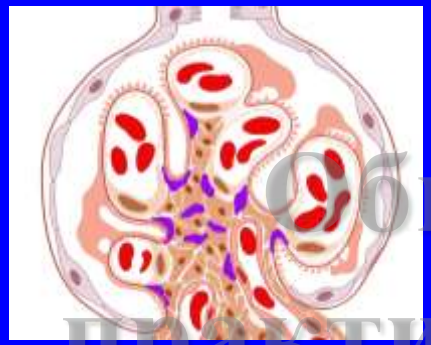
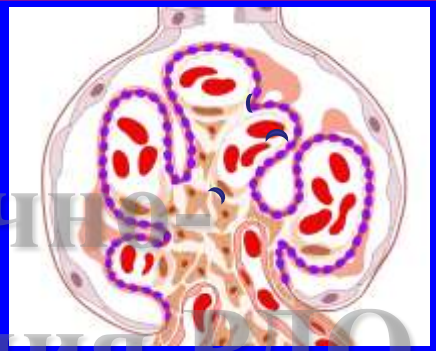
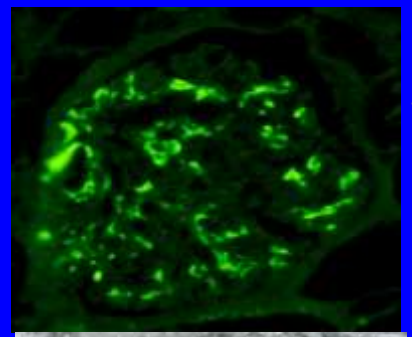
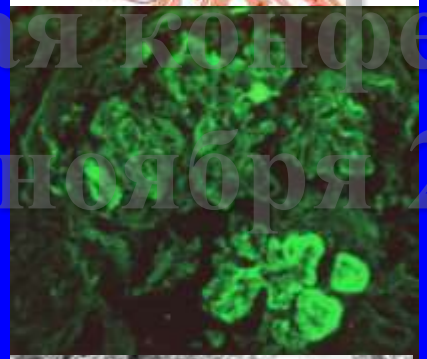
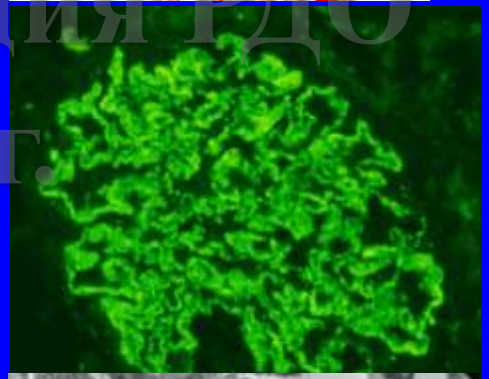


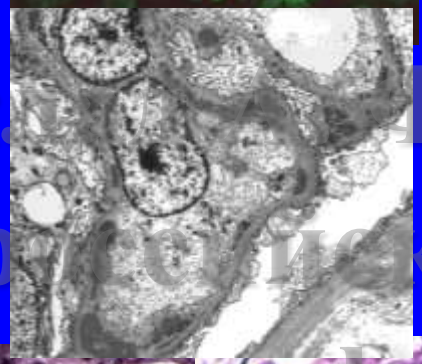
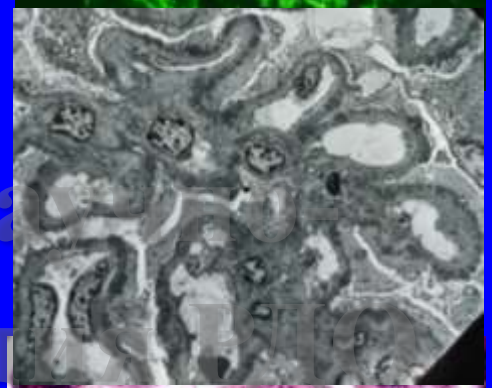
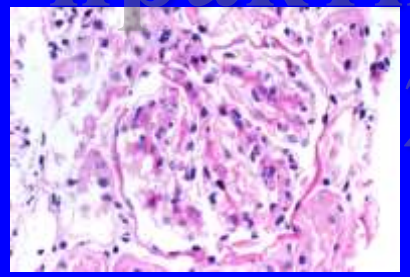
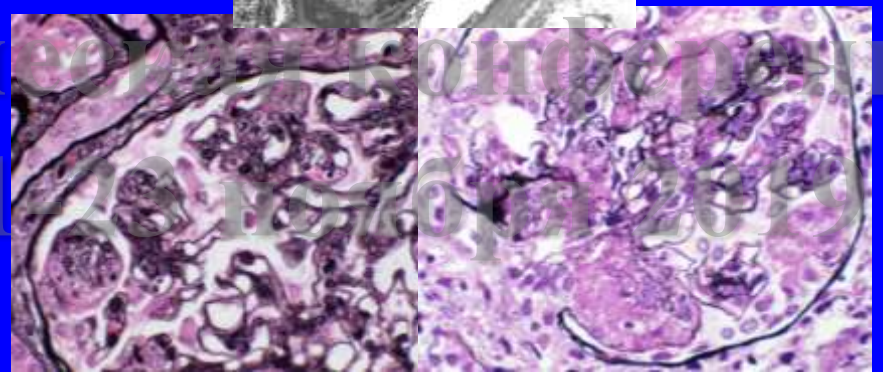
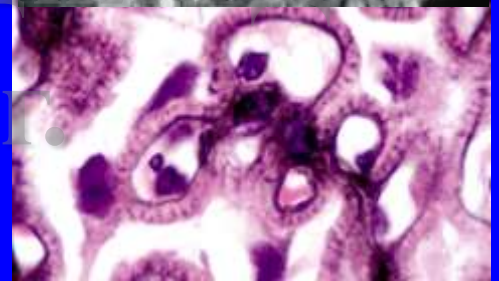


Pictures drawn by
Charles Jennette

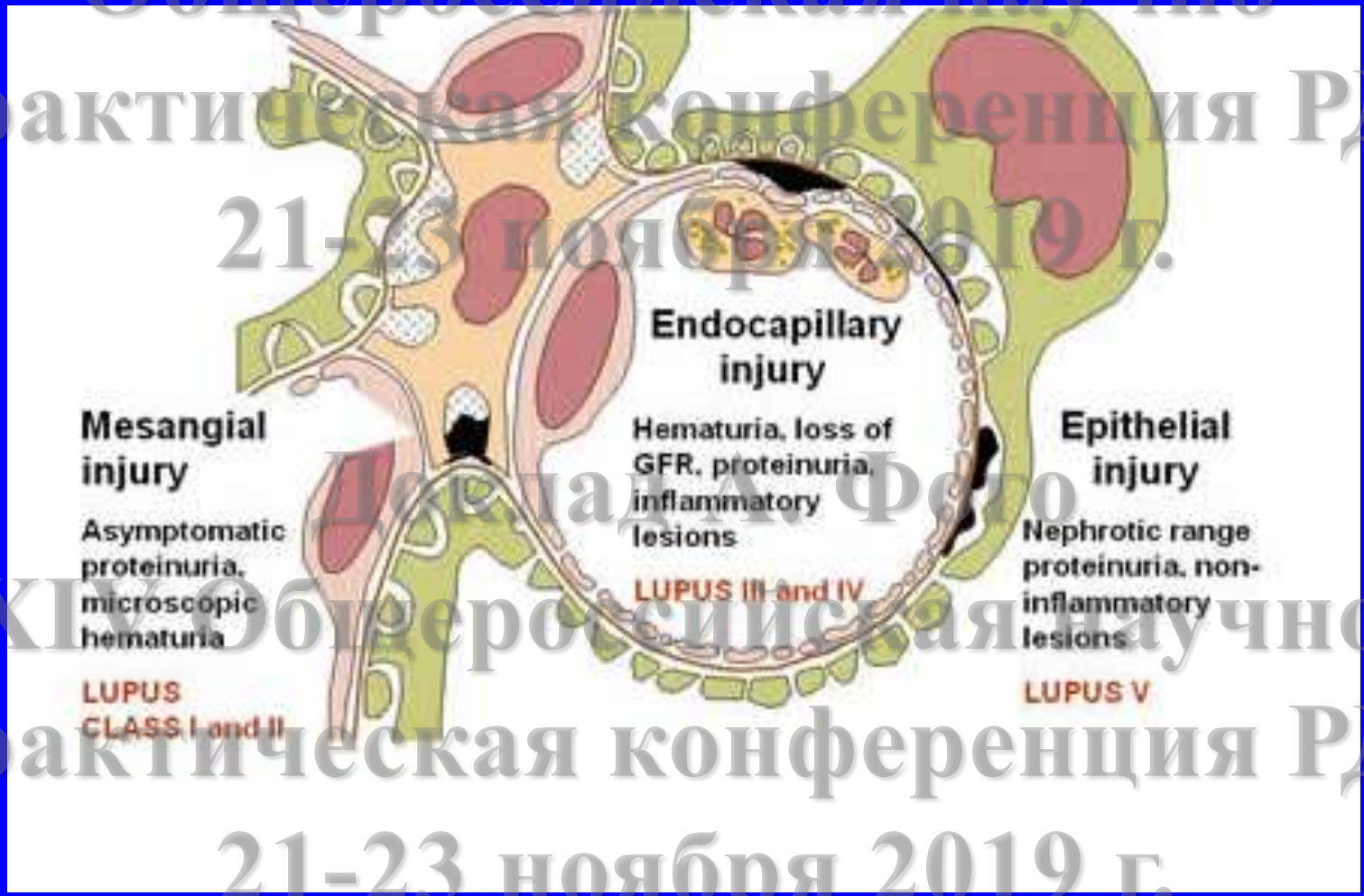
Mesangial LN (class I/II) "Proliferative" LN (class III/IV) Membranous LN (class V)



Clinical Correlates Of Varying Patterns of Injury



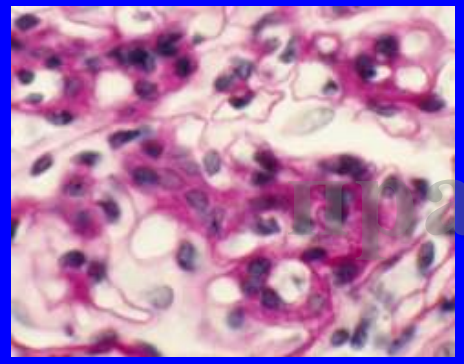
Courtesy Ingeborg Bajema

Presenting Features of Different LN Classes

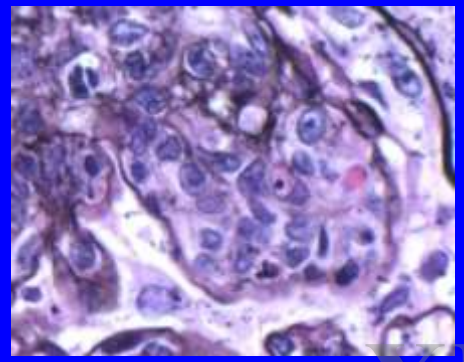
Clinical Feature	I n=5	II n=54	III n=107	IV-G n=111	IV-S n=87	V n=159	VI n=18
Asymptomatic hematuria	40	19	22	4	6	5	0
Asymptomatic proteinuria	40	42	25	7	6	13	0
Nephrotic syndrome	20	15	17	40	38	65	11
Nephritic syndrome	0	20	34	27	26	7	0
Acute kidney injury	0	4	2	18	16	2	0
Chronic kidney disease	0	0	0	4	8	8	89
	100 %	100 %	100 %	100 %	100 %	100 %	100 %

Seshan S, Jennette JC. Arch Pathol Lab Med 2009;133:233-48.

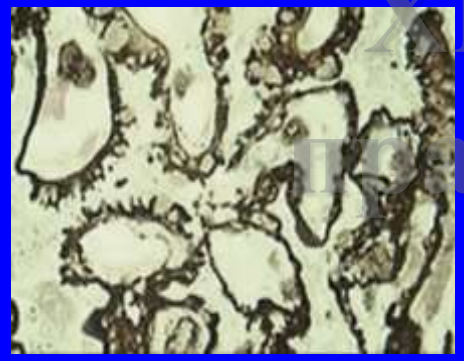
Simplified Approach to Lupus Nephritis Patterns



‘mesangial’



‘proliferative’



‘membranous’

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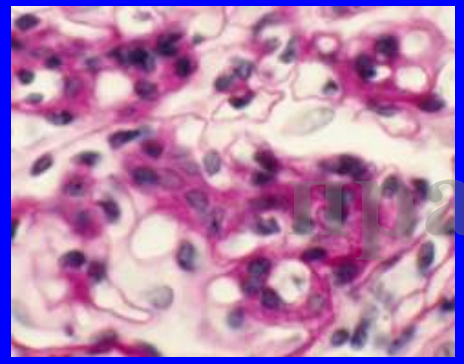
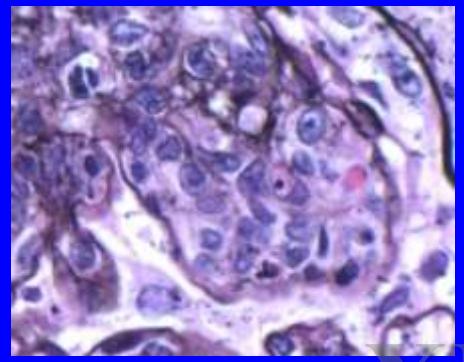
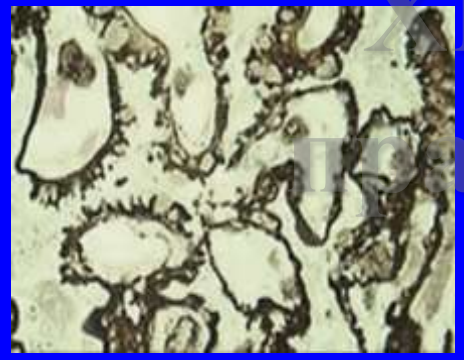
Simplified Approach to Lupus Nephritis Patterns







Present in < 50% of glomeruli

Active or Chronic?

Present in ≥ 50% of glomeruli

Active or Chronic? Segmental / Global?

The Final Result of Experts' Work Over Long Time…

Table 3. International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

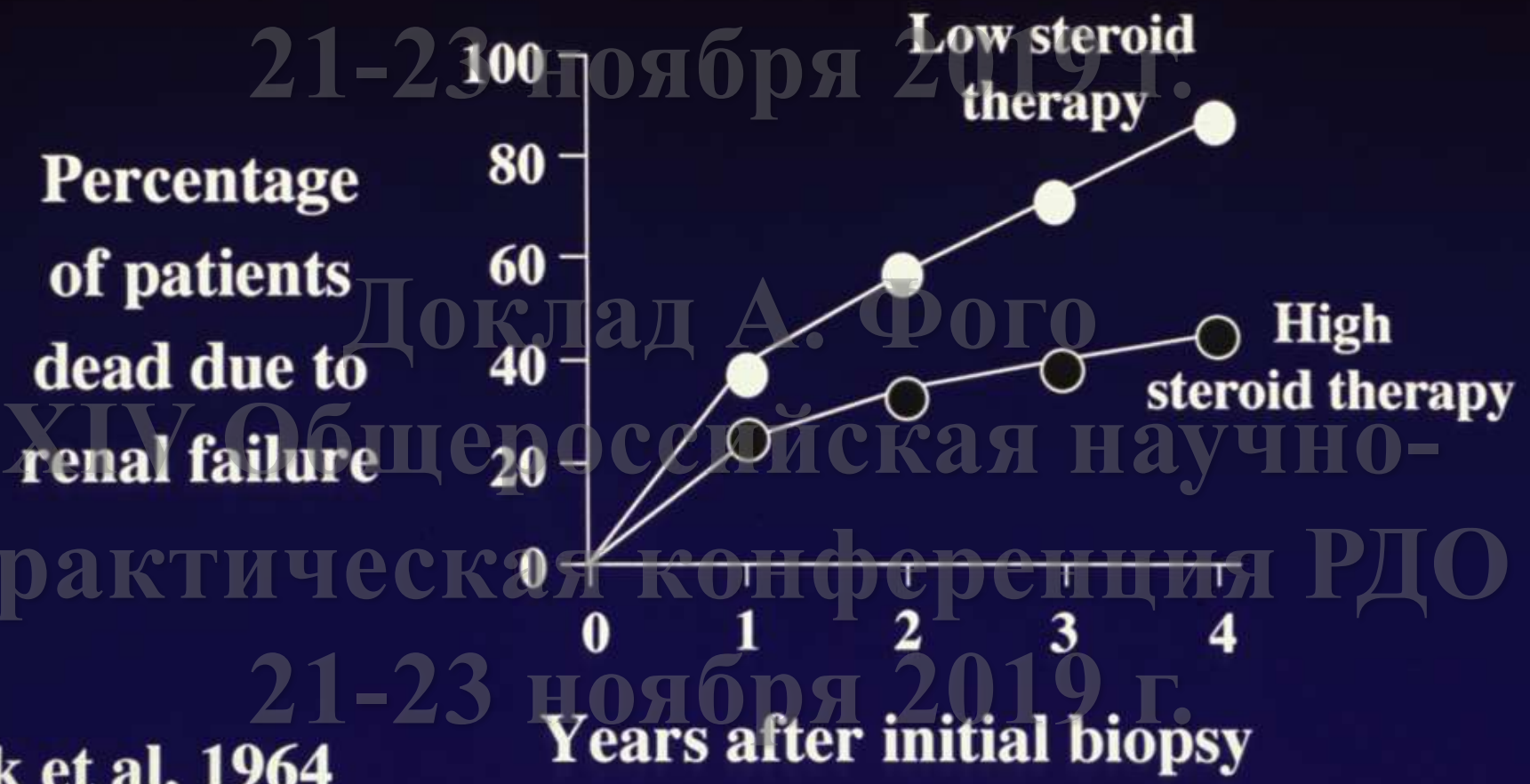
Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

The Natural History of the Renal Manifestations of Systemic Lupus Erythematosus

- Serial biopsy study in 87 SLE patients
- Poor prognosis of “active lupus nephritis”
- Response to steroids
- Rare transformation

Pollak, Pirani and Schwartz, J Lab Clin Med 1964

Renal Failure Death in SLE



Pollak et al, 1964

Challenges Remain with the ISN/RPS LN Classification

- Lack of precise differentiation of types of cells in hypercellular lesions
- How many cells are too many?
- How helpful is A+C?
- Can we be more granular in describing lesions, and thus classifying?
- Interobserver variability

- Outcome-
- Level 1- Current recommendations
- Level 2- Gather unbiased data to determine significance of varying lesions

Interobserver Variability

RPS Survey on LN

Does this glomerulus contain a lesion which would put the biopsy in class III or IV? ☐ Yes ☐ No

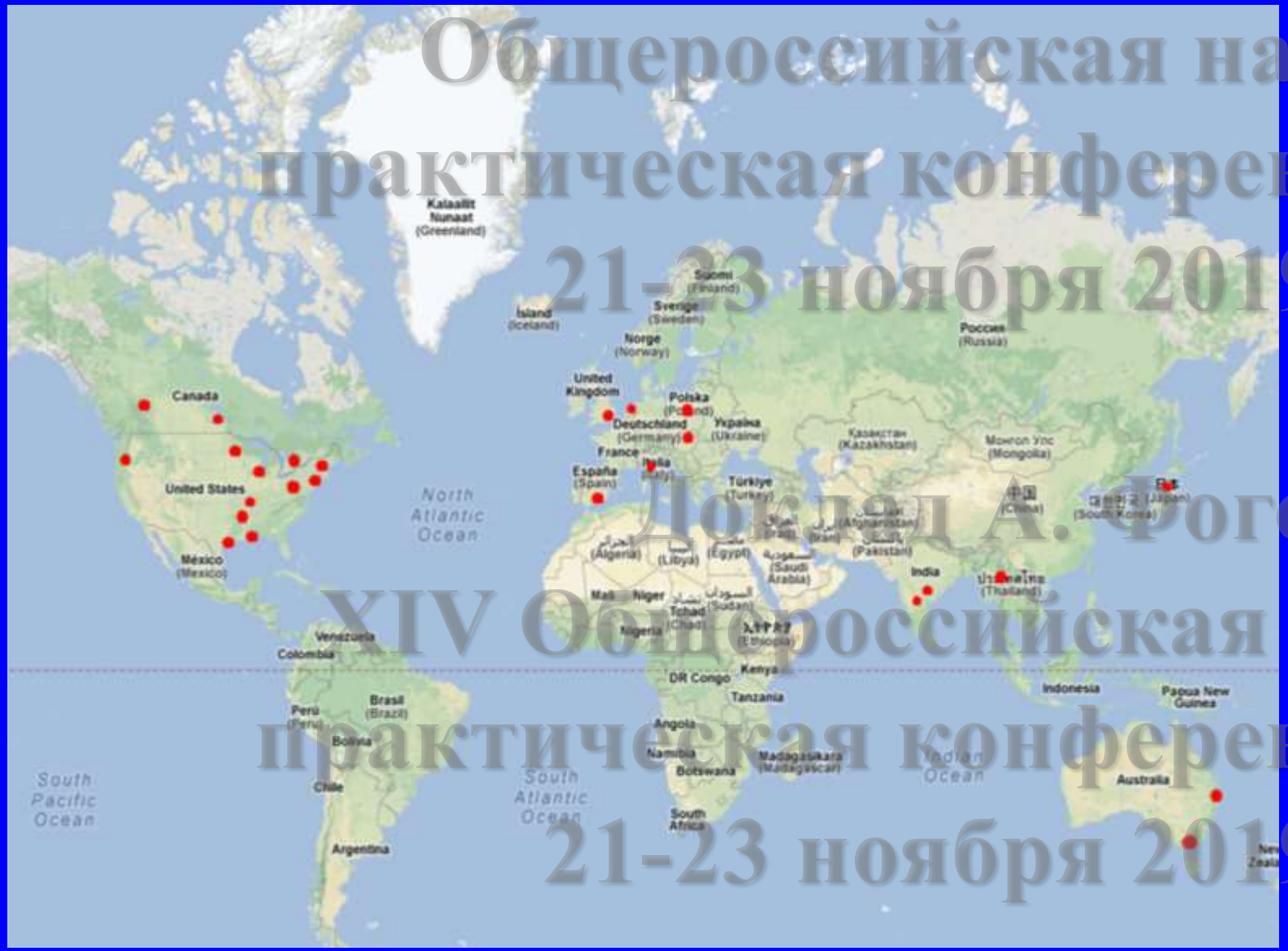
If so, please also indicate

Active and/or chronic	☐ Active	☐ Chronic	☐ Active/chronic
Segmental or global	☐ Segmental	☐ Global	
Endocapillary proliferation	☐ Present	☐ Absent	
Influx of inflammatory cells	☐ Present	☐ Absent	
Swelling of endothelial cells	☐ Present	☐ Absent	
Extracapillary proliferation	☐ Present	☐ Absent	
If present	☐ Cellular	☐ Fibrocellular	☐ Fibrous
Wire loops	☐ Present	☐ Absent	
Fibrinoid necrosis	☐ Present	☐ Absent	
Karyorrhexis	☐ Present	☐ Absent	

Other lesions? ☐ Yes ☐ No If yes, please describe

Comments

RPS Survey on LN



Sent to 360 members:

34 participants
12 countries

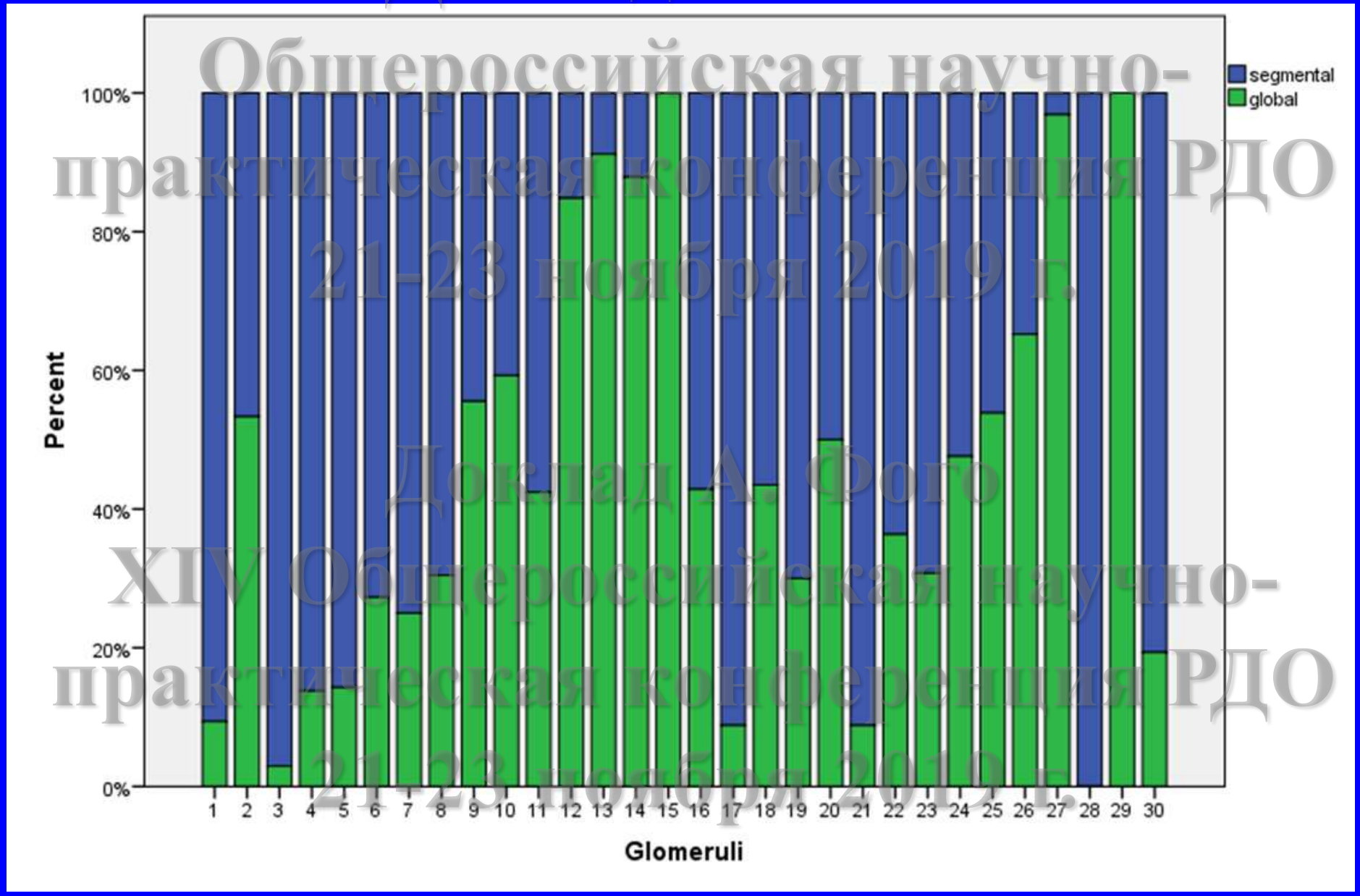
Interobserver (dis)agreement

Parameter	Statistical method	Outcome*
Class III/IV	ICC	0,39
Active and/or chronic	kappa	0,35
Segmental or global	kappa	0,39
Endocapillary proliferation	ICC	0,46
Influx of inflammatory cells	ICC	0,32
Swelling of endothelial cells	ICC	0,46
Extracapillary proliferation	ICC	0,57
Type of crescent	kappa	0,45
Wire loops	ICC	0,35
Karyorrhexis	ICC	0,29

*>0,8 excellent; 0,6 – 0,8 good; 0,4 – 0,6 moderate; <0,4 poor

No statistically significant effect of level of experience on outcome

Segmental or Global?



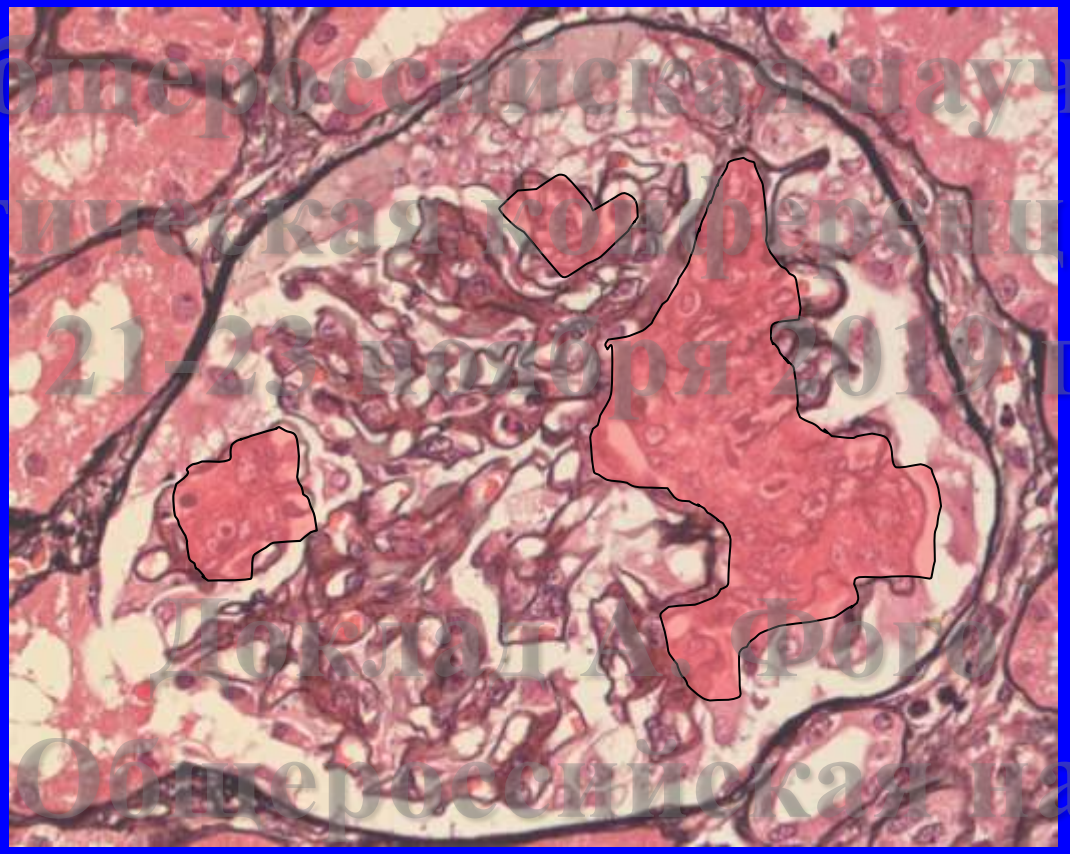
Why do we disagree?

- We observe different things
- We use different definitions

- We do not know what we are doing….

Why do we disagree?

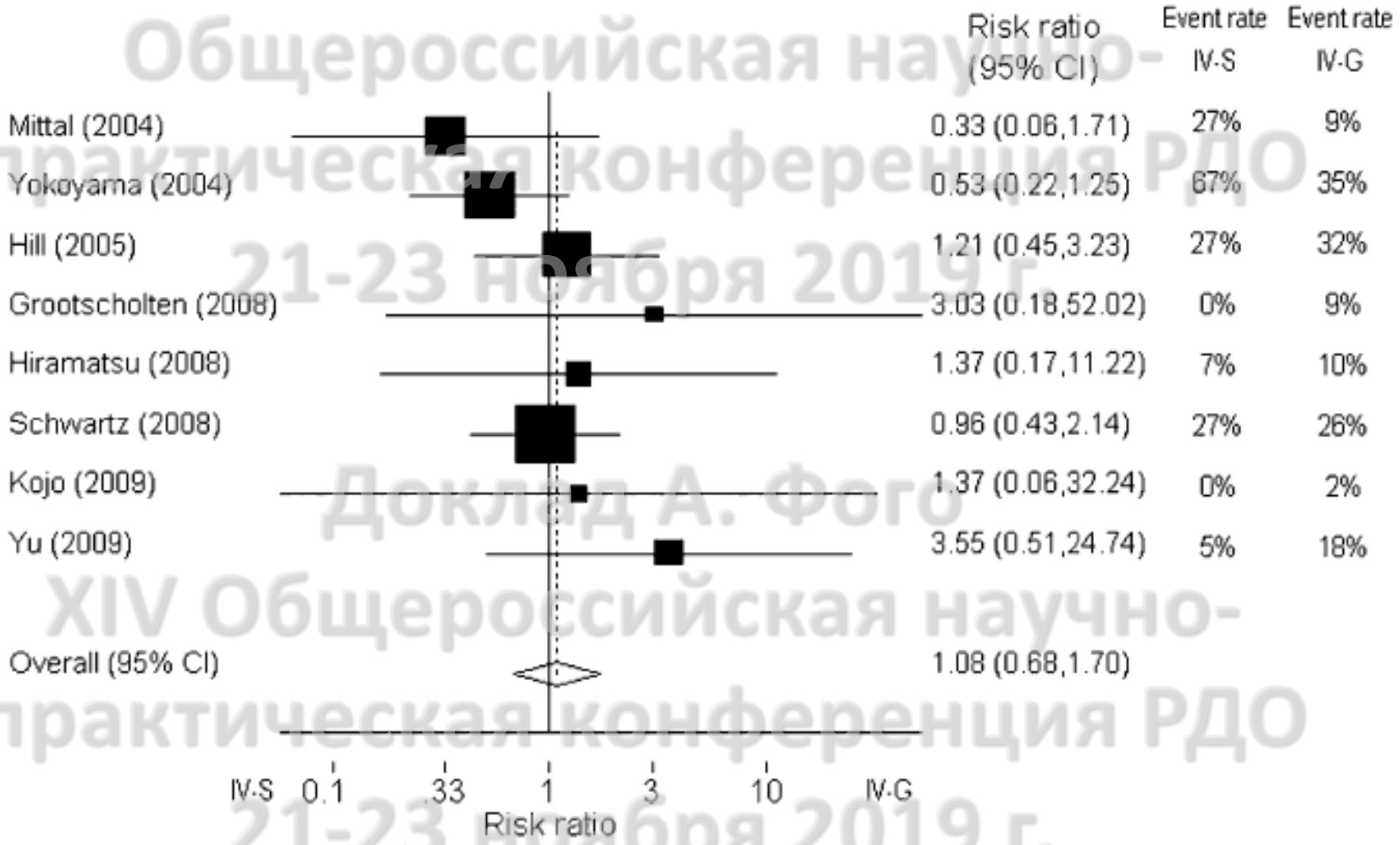
Segmental or Global?



Global: A lesion involving more than half of the glomerular tuft

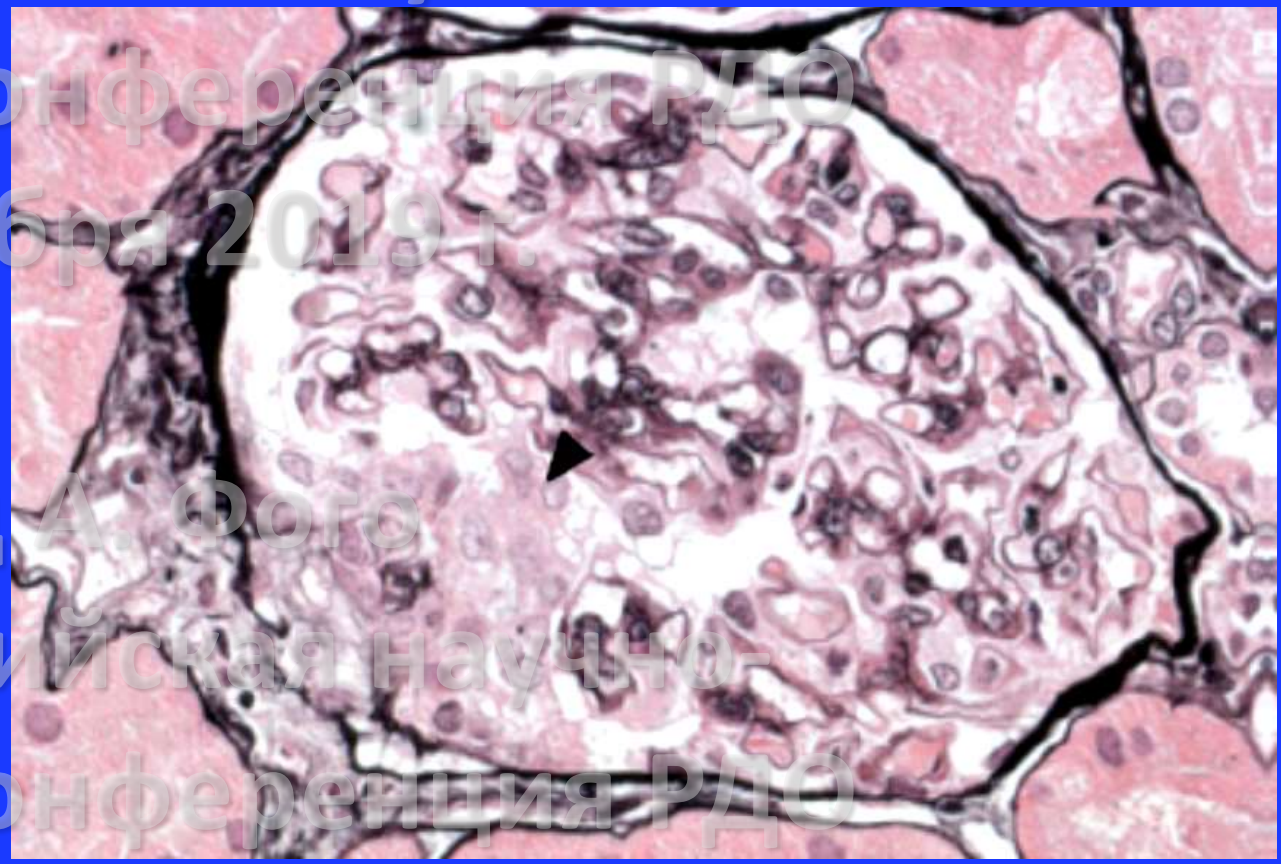
Segmental: A lesion involving less than half of the glomerular tuft (i.e., at least half of the glomerular tuft is spared)

Clinical Significance of Segmental vs Global?



Haring et al. JASN 2012

Definitions Matter



And this is not a crescent

Leiden Lupus Nephritis Meeting May 2016

Aim:

To improve problematic definitions that form the basis of the LN classification and thereby increase interobserver agreement between nephropathologists worldwide who apply these definitions to classify lupus nephritis

Ingeborg Bajema, Suzanne Wilhelmus, Charles E. Alpers, Jan A. Bruijn, Robert B. Colvin, Terry Cook, Vivette D'Agati, Franco Ferrario, Mark Haas, J. Charles Jennette, Kensuke Joh, Cynthia C. Nast, Laure-Hélène Noël, Emilie Rijnink, Ian S.D. Roberts, Surya V. Seshan, Sanjeev Sethi, Agnes B. Fogo

Leiden lupus nephritis meeting, May 2016

Aim:

To improve the lupus nephritis classification using an evidence-based approach.

First step:

Refining the existing definitions-

because they form the essential elements on which the classification is based.

Two-level Approach to Improving LN Classification

Level 1:

Adjust definitions for inconsistencies, vagueness, omissions.
Minor changes to thresholds if evidence to do so already exists; clarifying details;
providing useful examples that illustrate difficult issues.

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21-23 ноября 2019 г.

Level 2:

Evidence-based multi-center study, involving scoring of separate parameters, relation to outcome.
Results used to guide possible modifications of the existing classification system.

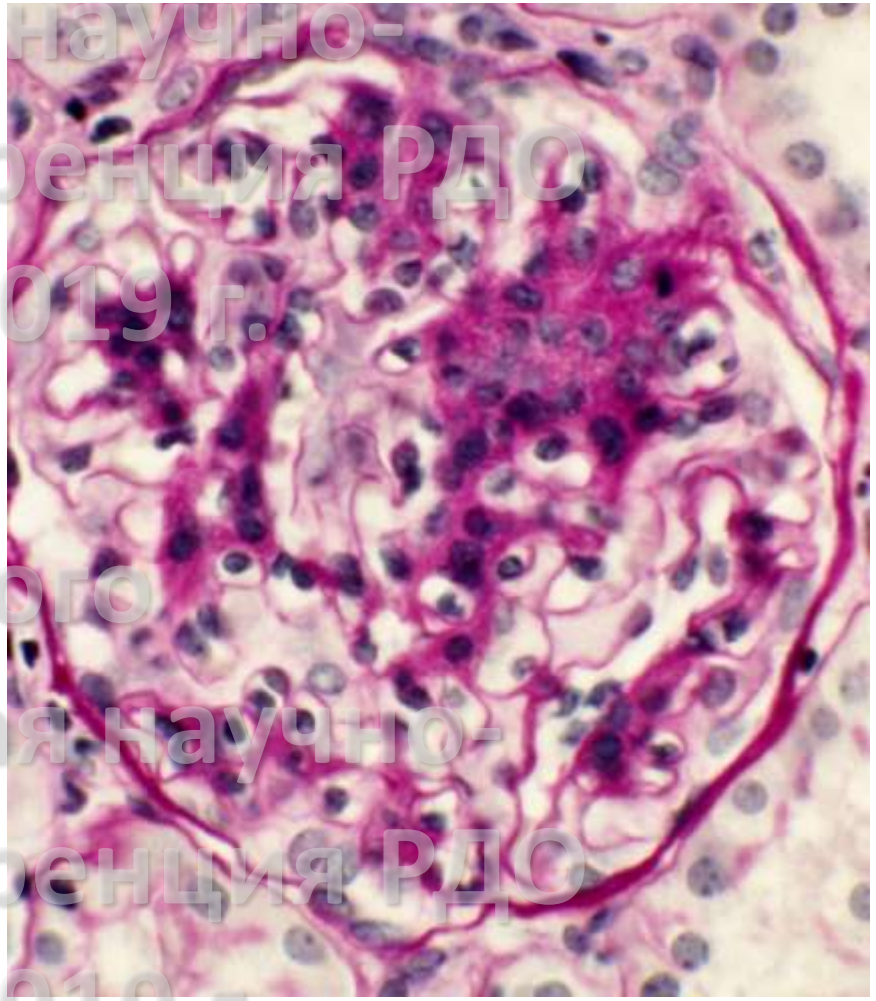
Conundrums of the mesangium in LN

How much hypercellularity in how many glomeruli?

How many cells, and how to combine with matrix expansion (cut-off)?

If only mesangial cells: ***hyperplasia.***

If not only mesangial cells: ***endocapillary hypercellularity?***



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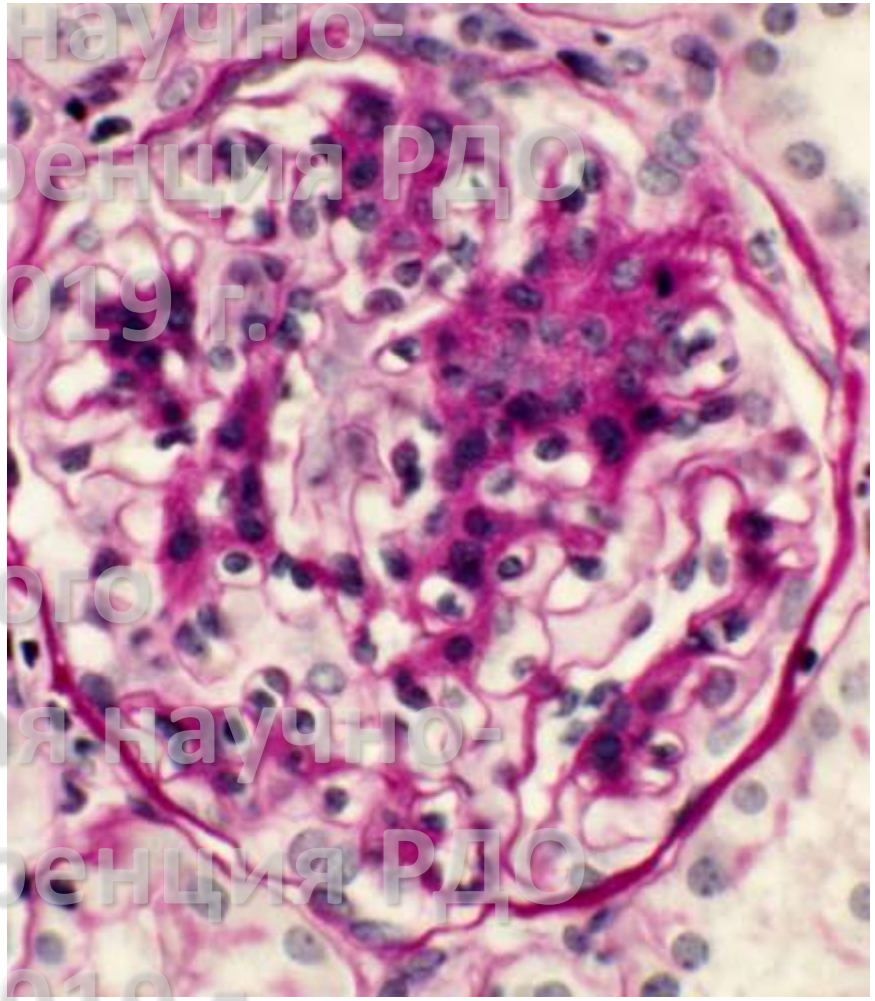
Considerations of the mesangium in LN

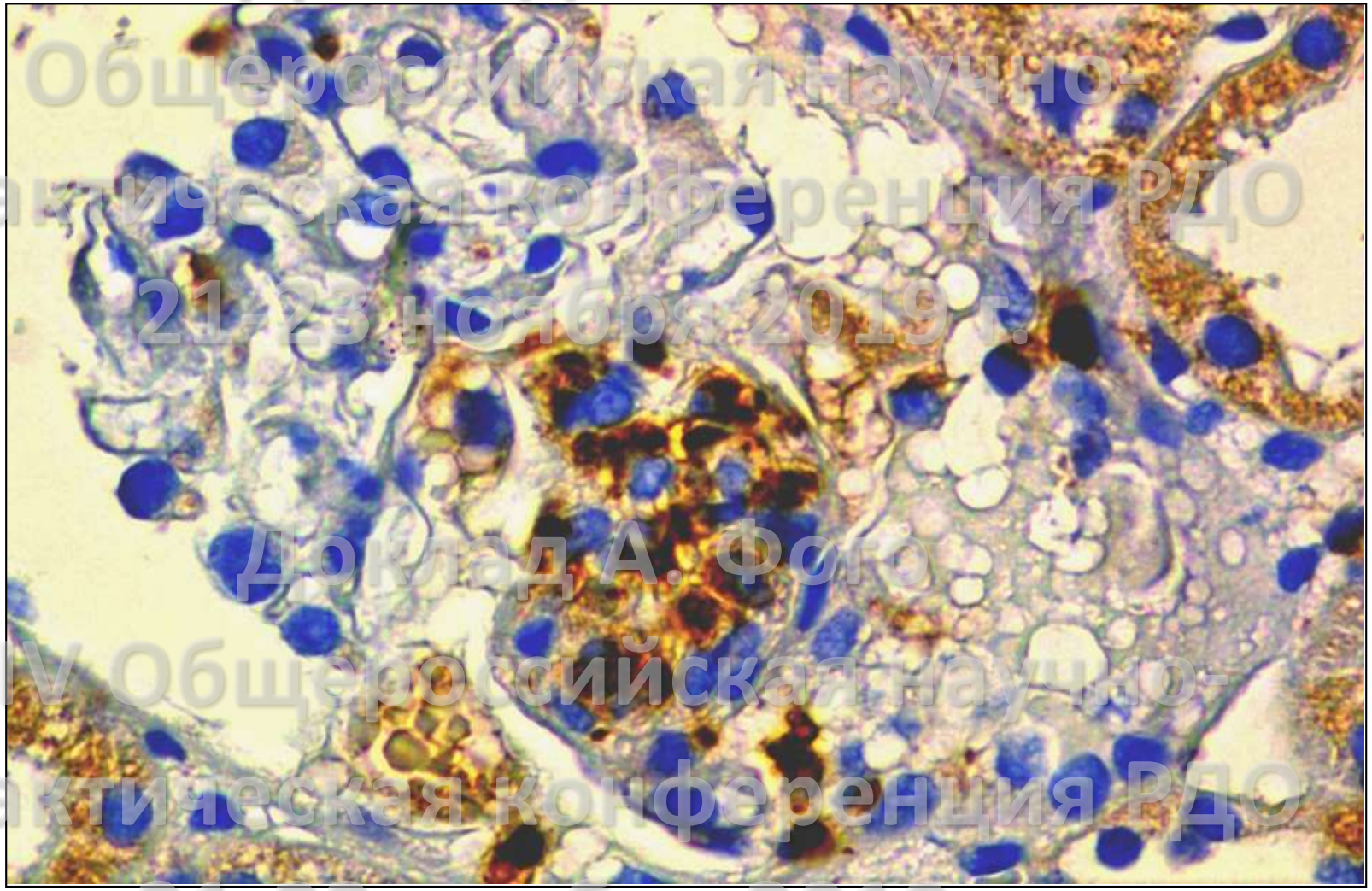
Level 1:
Increase threshold of mesangial hypercellularity from 3 to 4 cells/mesangial area (congruent with IgAN)

Level 2 tasks:
-Determine cut-off to distinguish Class I vs II.
(BUT- hypercellularity in only one area in one glomerulus seems a rather low threshold.)

-Role of inflammatory cells in mesangium.



CD68 staining in LN



From Dr. Franco Ferrario

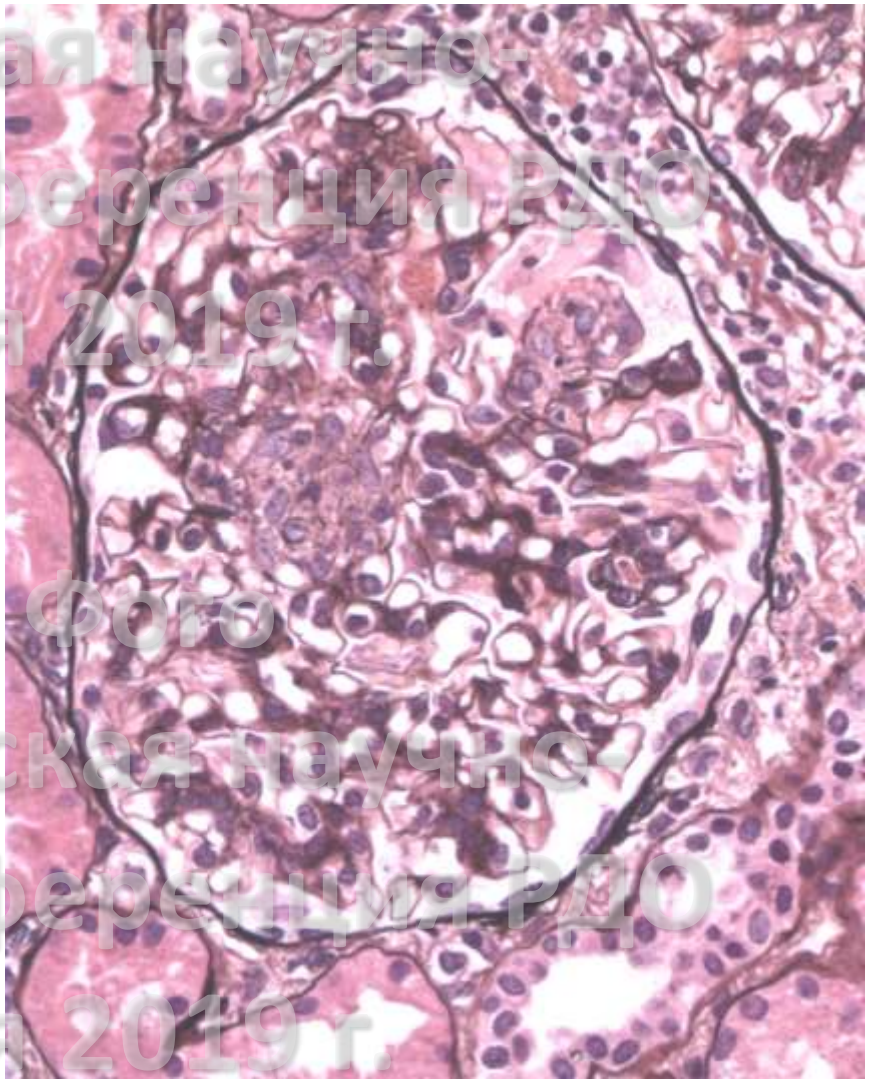
Conundrums of endocapillary lesions

Endocapillary ‘proliferation’

Types and numbers of cells involved: unclear

Amount of lumen reduction: unclear

Role of endothelial cells: unclear

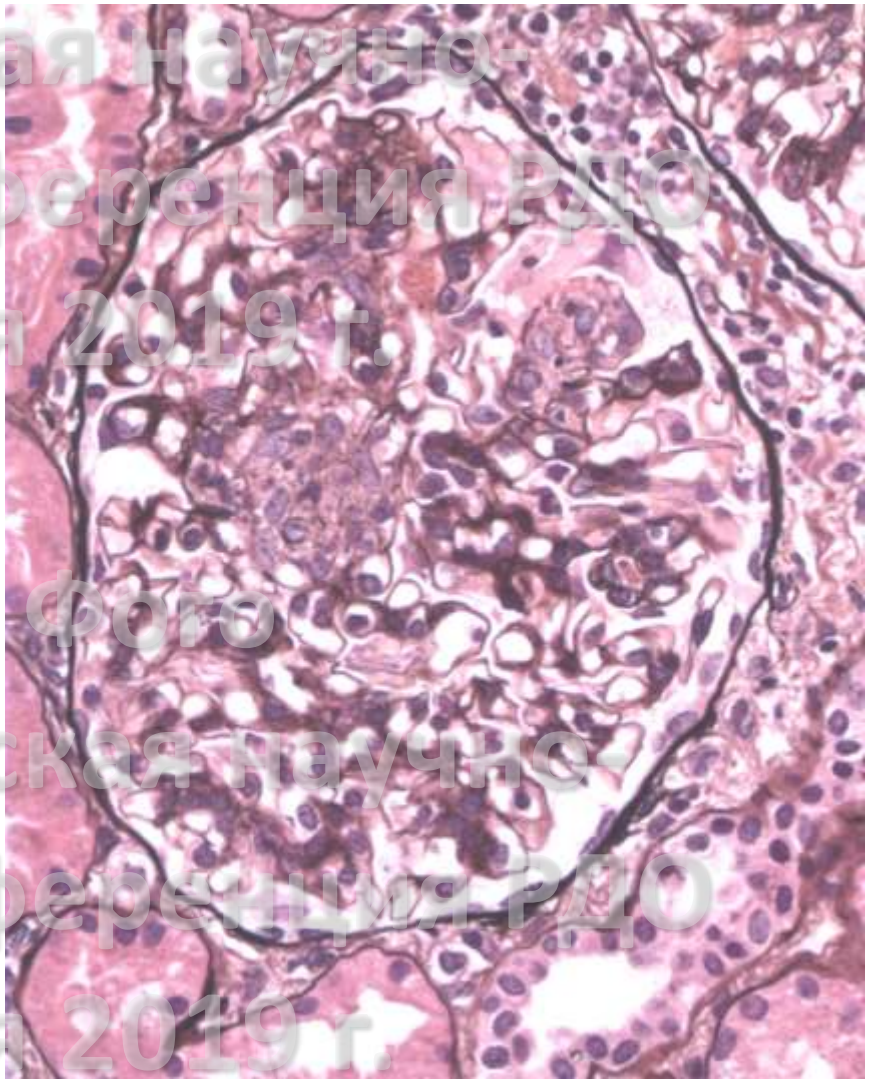


Considerations of endocapillary lesions

Level 1:
Replace the term
endocapillary proliferation
by
endocapillary hypercellularity

Level 2 tasks:
Determine cut-off levels for:

- **number of inflammatory cells**
- **extent of capillary luminal narrowing**
- **role of endothelial cell swelling**



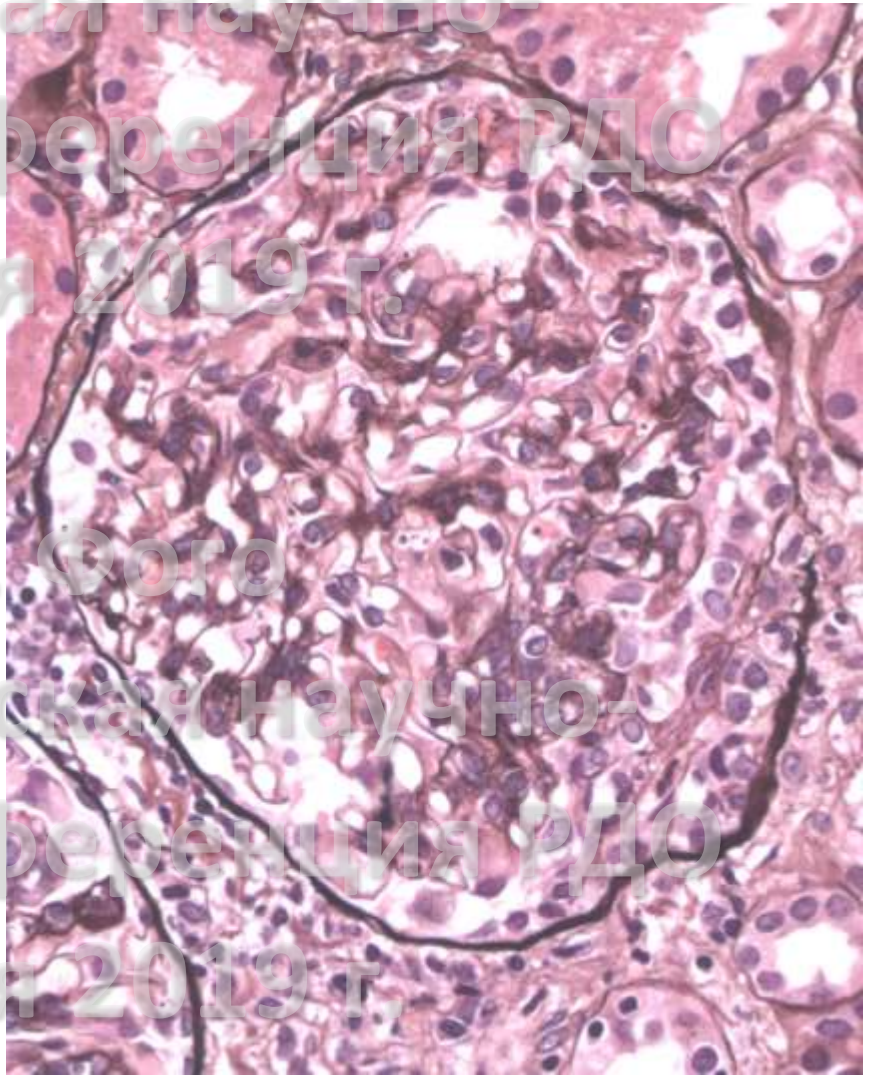
Conundrums of extracapillary lesions

Composition

Fibrous / Cellular

Involving ≥25% of Bowman's capsule

What to do with a glomerulus with 2 types of crescents?



Considerations of extracapillary lesions

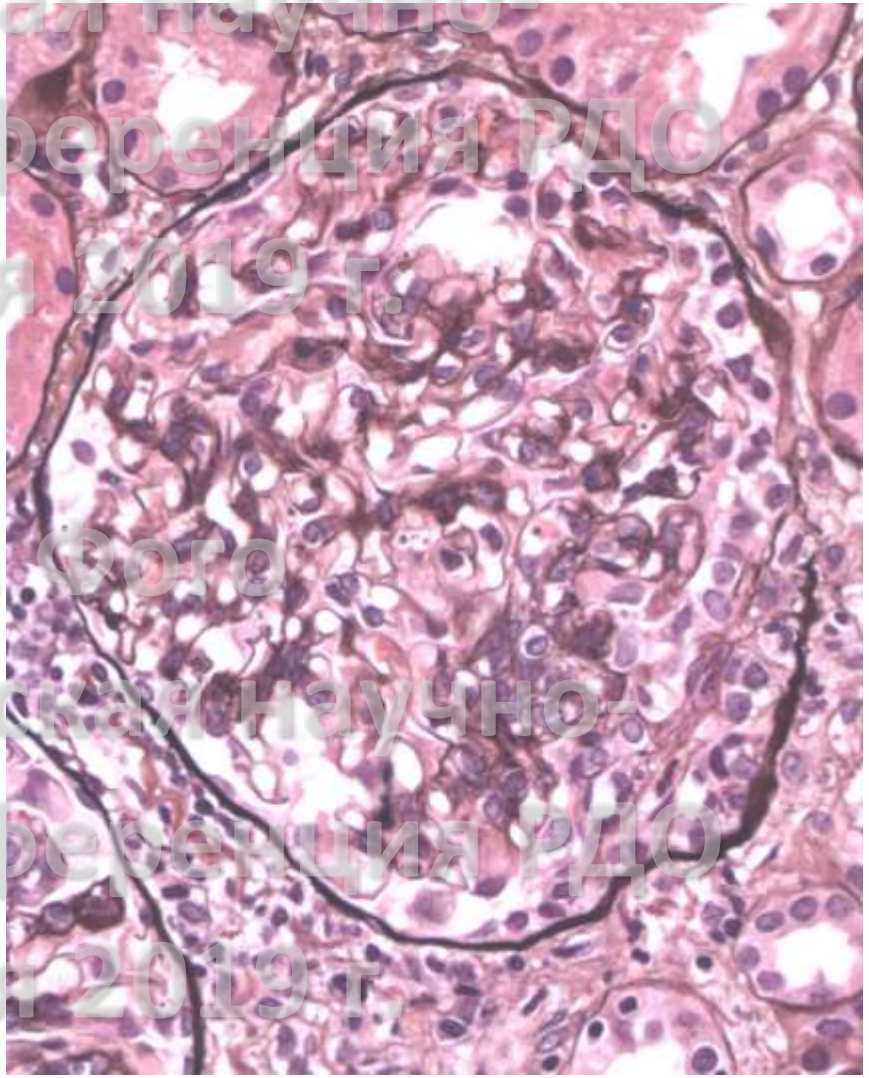
Nomenclature: a variable mixture of cells

Composition may vary from predominantly:
- **epithelial cells**

OR
- **monocytes/macrophages**

Fibrous / Cellular

Level 1:
Threshold to diagnose a crescent changed:
from 25% of circumference involved to 10%



Conundrums of segmental/global lesions

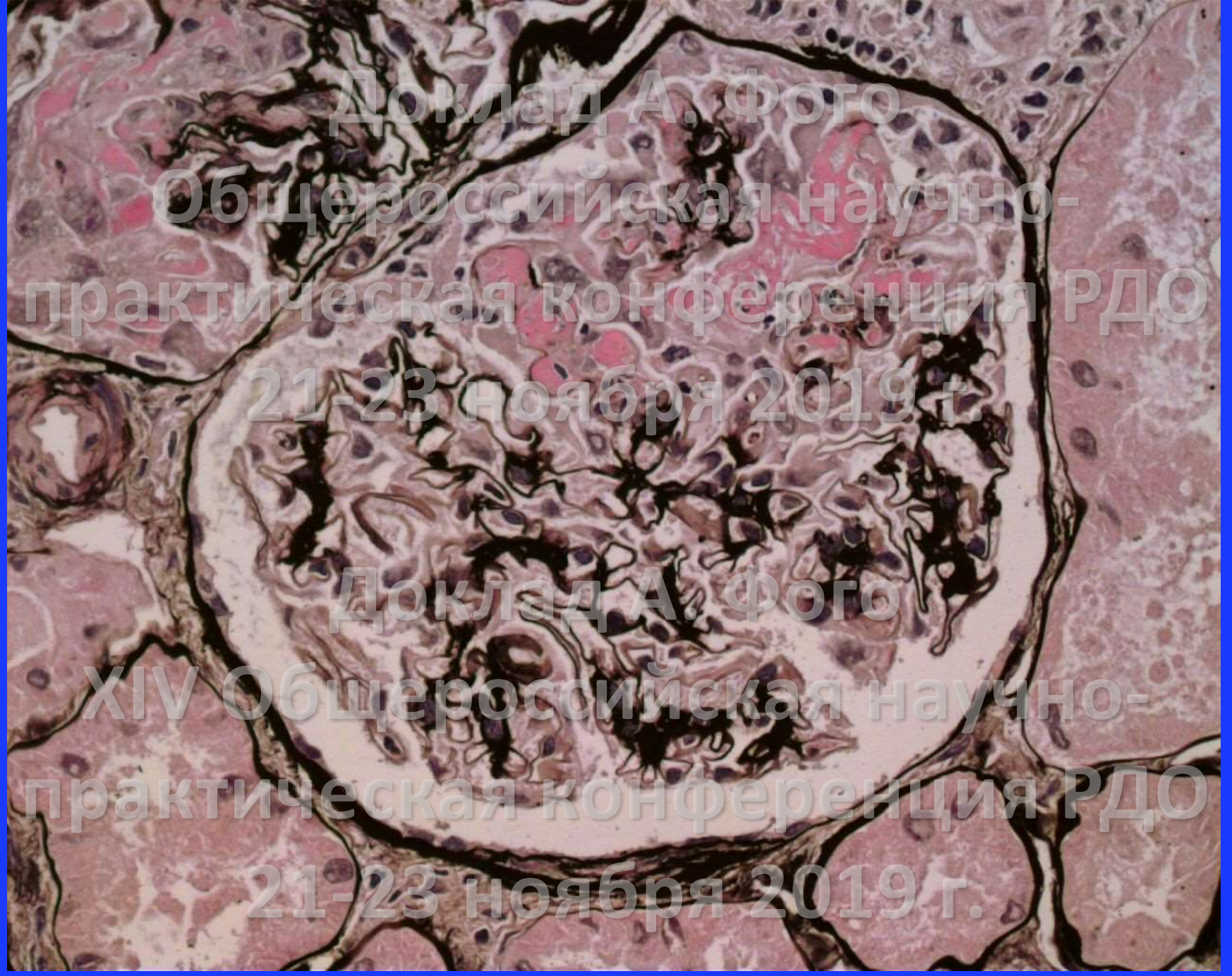
Clinical significance: questioned

Interobserver variation: large

Uncertain how to combine endocapillary lesions and extracapillary lesions into the segmental / global distinction

Part of the original discussion to indicate ‘vasculitic-like’ lesions lost

Consideration: remove segmental/global connotations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Clinical and Histopathologic Characteristics Associated with Renal Outcomes in Lupus Nephritis

n = 105

Biopsy-proven Lupus nephritis (1997-2011)

9.9 years

PREDICTORS

RENAL FLARE

n = 47

Fibrinoid necrosis
1.04 (1.00-1.07)
Non-white race
2.23 (1.23-4.04)

ESRD

n = 21

Fibrinoid necrosis
1.08 (1.02-1.13)
Fibrous crescents
1.09 (1.02-1.17)
IF/TA ≥ 25%
3.89 (1.25-12.14)
Baseline eGFR
0.98 (0.97-1.00)
Non-white race
7.16 (2.34-21.91)

*HR (95% CI)**

CONCLUSION

In the assessment of the risk of progressive renal dysfunction, the LN classification should include an index of evidence-based predictors in conjunction with clinical findings.

E Rijnink et al., 2017 CJASN

Non-immune Complex Lesions

- Podocytopathies
- Vascular
- TBM deposits

- Biopsy essential for specific dx

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Vascular lesions in SLE

- **No impact on prognosis:**
  - Uncomplicated vascular deposits
- **Poor prognosis:**
  - Thrombotic microangiopathy
  - Lupus vasculopathy

  (noninflammatory necrotizing lesions with variable immune deposits)
  - Lupus vasculitis

  (necrotizing and inflammatory vasculitis with transmural infiltration of the vessel wall)

TMA and APL and SLE

- TMA occurs in any class of LN, +/- APL
- APL Ab in 25-50% of SLE pts- not all with TMA
- Renal: TMA thromboses in large arteries cortical necrosis

Hill G et al

Conundrums of activity/chronicity

A, C and A/C are insufficient discriminators

Consideration:

Move back to the NIH Activity/Chronicity Indices

Original NIH Activity/Chronicity Assessments

Table 13-4

ACTIVITY AND CHRONICITY INDICES[a]

Index of Activity (0-24)	
Endocapillary hypercellularity	(0-3+)
Leukocyte infiltration	(0-3+)
Subendothelial hyaline deposits	(0-3+)
Fibrinoid necrosis/karyorrhexis	(0-3+) x 2
Cellular crescents	(0-3+) x 2
Interstitial inflammation	(0-3+)
Index of Chronicity (0-12)	
Glomerular sclerosis	(0-3+)
Fibrous crescents	(0-3+)
Tubular atrophy	(0-3+)
Interstitial fibrosis	(0-3+)

Varying Views on A and C

Activity index (graded on a scale of 0 to 3+ for each); total of 24

1. Endocapillary proliferation,
2. Glomerular leukocyte infiltration,
3. Wire loop deposits,
4. Fibrinoid necrosis and karyorrhexis (X2),
5. Cellular crescents (X2)
6. Interstitial inflammation

Activity *
Glomeruli
Hypercellularity
Karyorrhesis or fibrinoid necrosis
Cellular crescents **
Wire loops **
Leukocyte infiltration
Tubule/Interstitium
Mononuclear cell infiltration

- Endocapillary hypercellularity with or without leucocyte infiltration ; luminal reduction
- Karyorrhexis
- Fibrinoid necrosis
- Rupture of GBM
- Cellular or Fibrocellular Crescents
- Subendothelial deposits on LM
- Intraluminal Immune aggregates

Activity index
Cellular proliferation
Leukocyte infiltration
Fibrinoid necrosis
Cellular crescents
Hyaline thrombi
Mononuclear infiltration
Activity index risk group†

A vs C, and All in Between

Will Await Level 2 EVIDENCE!

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27 yo man with SLE

- Previous bx 2009:
  - Membranous class V and diffuse LN class IV
- One glomerulus with collapse
- Remission in response to aggressive RX

- Now marked NS, increased Screat
- Renal biopsy is essential

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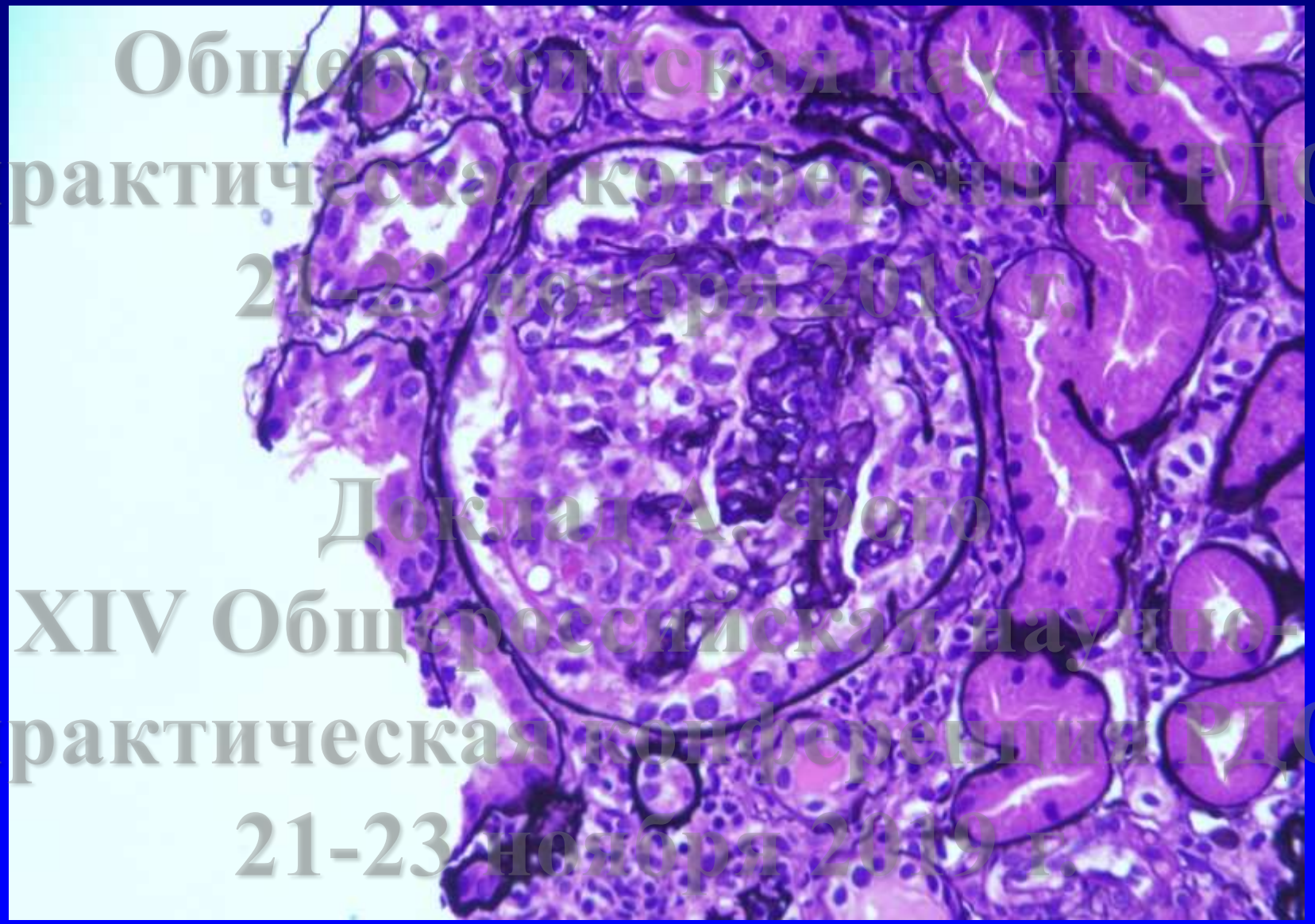
Collapsing GP and LN



Final Diagnosis

- Membranous lupus nephritis, Class V
- Focal lupus nephritis (A+C)

- Collapsing GP

- More collapse, less activity of endocapillary proliferative lesions

- This severe injury is NOT captured by ISN/RPS classification

Areas for Ongoing Consideration- Level 2 work to be done

- Classification of non-glomerular lesions
- Further dissection of varied pathogeneses and importance of varied glomerular lesions-
- Add “Risk predictor score” from evidence-based study, define those responsive to specific Rx or not
- Possible role of AI?

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