Mayo Clinic/ RPS Consensus Report on Classification, Diagnosis, and Reporting of Glomerulonephritis

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Disclosure

Relevant Financial Relationships

None

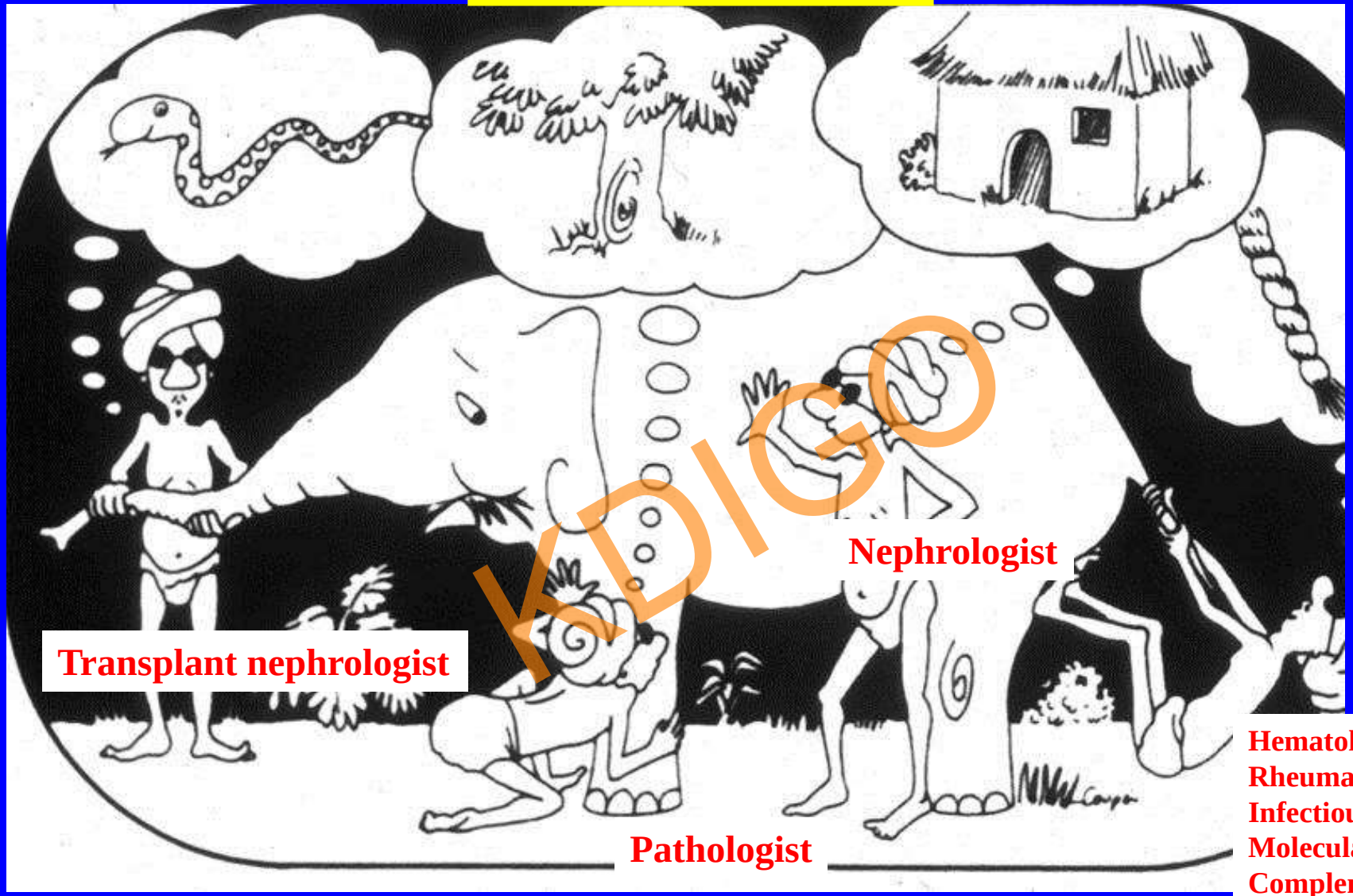
Off-Label/Investigational Uses

None

Learning Objectives

- Medical Knowledge
- Patient Care
- Practice-Based Learning and Improvement

Glomerulonephritis



The elephant that is Glomerulonephritis

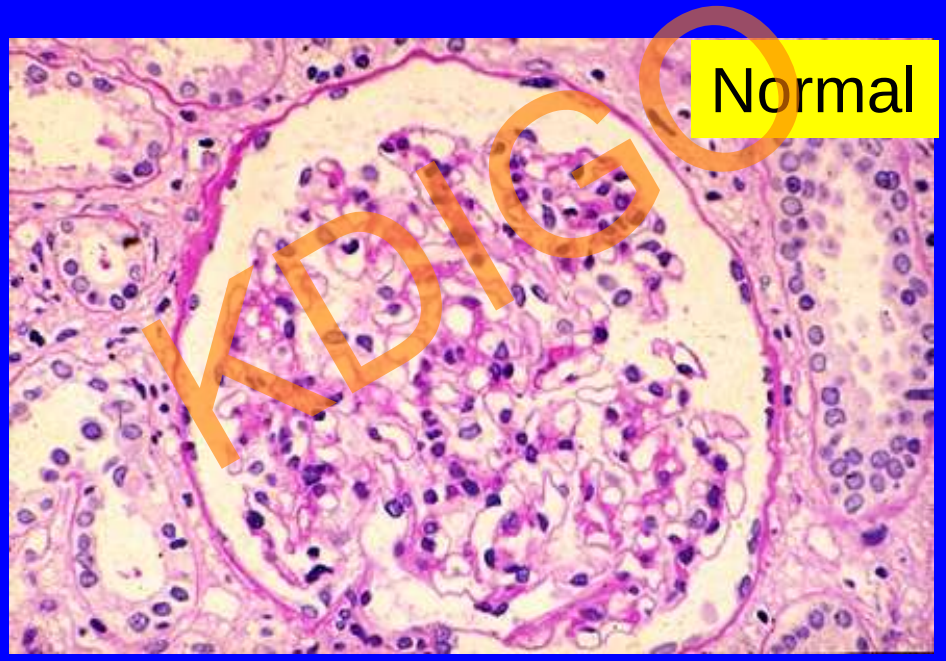
By-Dr. D. Cattran, Toronto

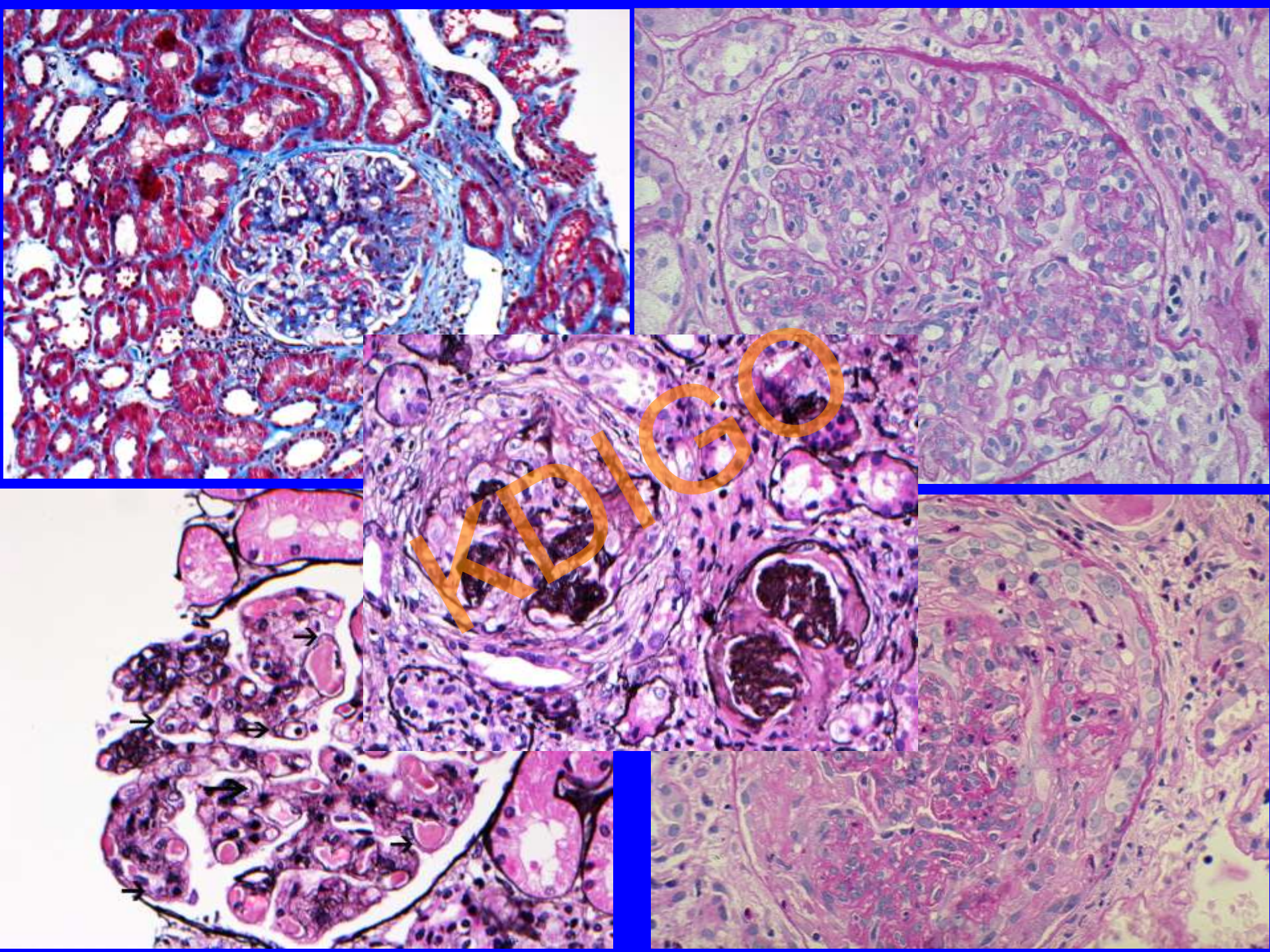
What happens in glomerulonephritis (GN)

- Deposition of *injurious elements* along the glomerular capillary walls……Ig, complement, fibrin…
- Leads to inflammation- proliferative changes
- Followed by healing/resolving- leads to remodeling of the capillary walls, sclerosis, scarring……end stage kidney disease

Inflammation leads to patterns of injury: pathologist view point is very “pattern-centric”

- Mesangial proliferative glomerulonephritis
- Diffuse (exudative or endocapillary) proliferative glomerulonephritis
- Crescentic and necrotizing glomerulonephritis
- Membranoproliferative glomerulonephritis
- Sclerosing glomerulonephritis.


Normal
KDIGO


KDIGO

Glomerulonephritis

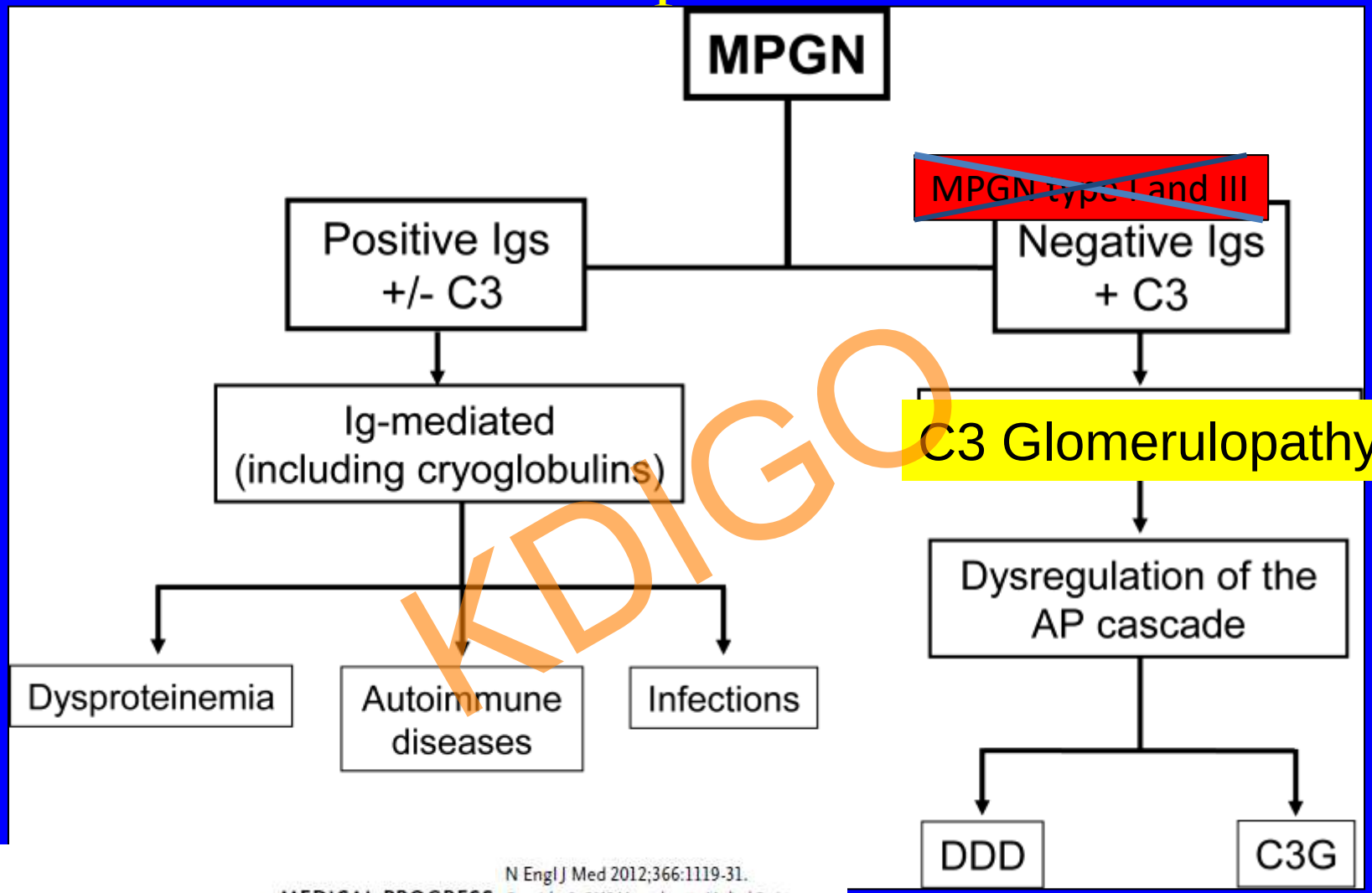
- Over the last 10-15 years we have made remarkable progress in understanding the etiology and pathophysiology of glomerulonephritis
- This is very relevant to the evaluation, management and prognosis of glomerulonephritis
- Sometimes, this progress and understanding does not spill over into the kidney biopsy pathology report
- There was a *need to come up with a basic consensus document to address this issue*

Two simple questions

- We need to address the basic classification of GN based on etiology/pathophysiology

- How do we incorporate this into the pathology report:
  - Logical
  - Sequential
  - Reproducible
  - And most importantly address the key clinical questions

MPGN – a simple classification



N Engl J Med 2012;366:1119-31.

Membranoproliferative Glomerulonephritis — A New Look at an Old Entity

Sanjeev Sethi, M.D., Ph.D., and Fernando C. Fervenza, M.D., Ph.D.

Sethi, Fervenza
Seminars of Nephrology, 2011

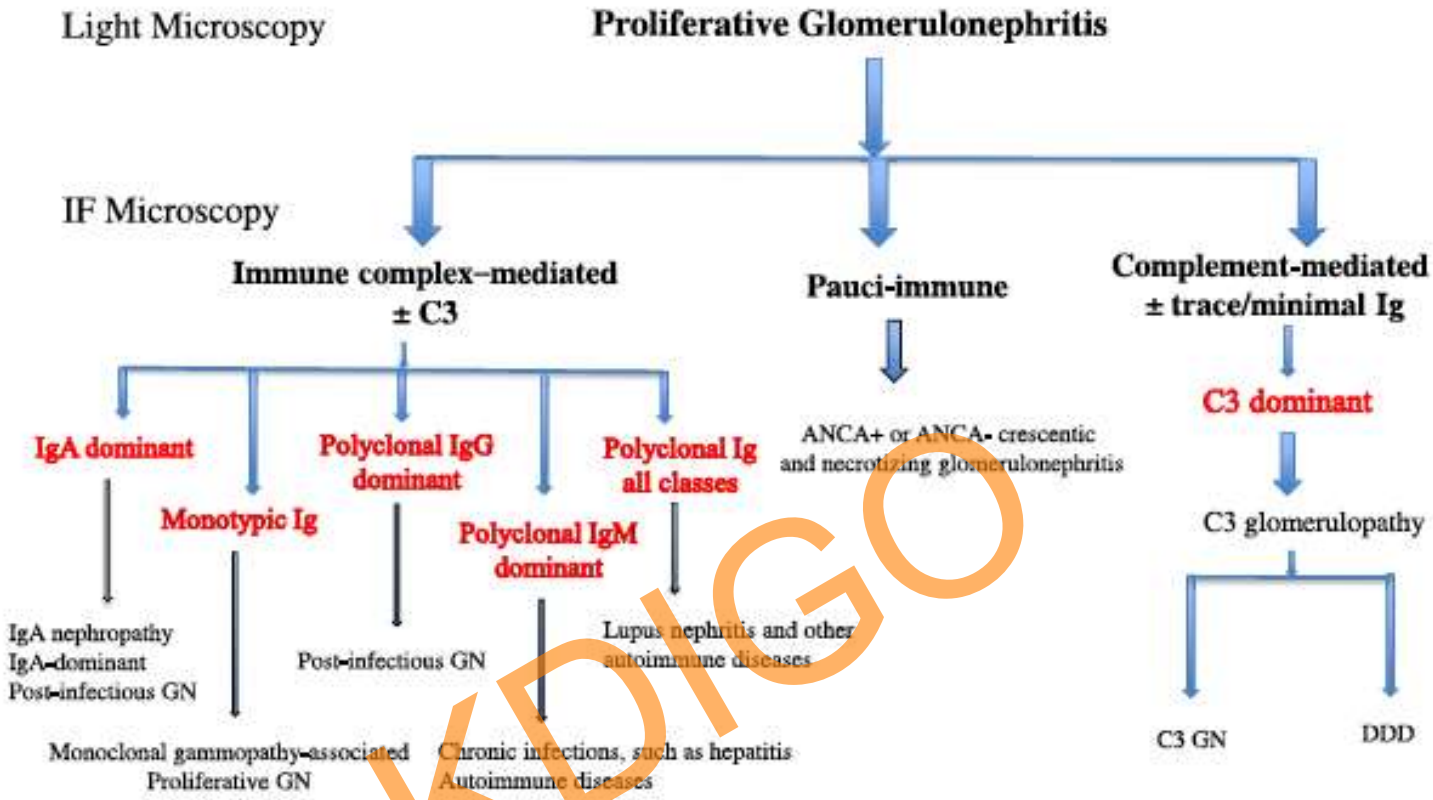


Figure 2. Schematic summary of proposed classification. Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; DDD, dense deposit disease; IF, immunofluorescence; Ig, immunoglobulin; GN, glomerulonephritis.

AJKD

Perspective

Etiology-Based Diagnostic Approach to Proliferative Glomerulonephritis

Sanjeev Sethi, MD, PhD

2013-14

- Thinking about it for 2-3 years, the more I travelled the more I felt the need but……
- Met with Lorraine Racusen and Mark Haas, Mysore, India, Aug 2014

- Came back and ran it by Fernando Fervenza. Basically asked him for the money.

November 2014, ASN, Philadelphia

- Called Helmut Rennke
- Lorraine Racusen and Michael Mengel- Lunch
- Sundaram Hariharan/Surya Seshan/Neeraja
- Terry Cook/Ian Roberts
- Tony Chang/Agnes Fogo/Ingeborg/Charlie Alpers
- Vivette D'Agati/Glen Markowitz
- Dick Glassock/Jai/Jerry/Dan Cattran
- The ones that got away-email-Charles Jennette, Pierre Ronco, Chris Winearls, Brad Rovin…….

Glomerulonephritis Consensus Meeting

February 19 and 20, 2015
Mayo Clinic | Rochester, Minnesota

Agenda

9:00 - 9:15 am	Welcome – Fernando C. Fervenza, MD, PhD
	Morning session chaired by Agnes Fogo, MD
9:15 - 9:45 am	What do the nephrologists want to see in the biopsy report Richard Glassock, MD
10:00 - 10:30 am	Introduction, purpose and basic proposal – Sanjeev Sethi, MD, PhD
10:30 - 11:00 am	Should we include well defined entities – Mark Haas, MD, PhD
11:00 - 11:30 am	Complement testing: Relevance and when and what to order – Richard Smith, MD
11:30 - 12 noon	The Banff experience – Michael Mengel, MD
Noon - 1:00 pm	Lunch
	Afternoon session chaired by Helmut Rennke, MD
1:00 - 3:00 pm	Small group discussion on guidelines/discussion: (60-90minutes discussion, followed by 10 minutes/report: total 120-150 minutes)

- Guidelines for immunofluorescence microscopy and reporting (Pathogenesis)(What is a positive IF, scoring system, false positive and negatives, Indeterminate/overlap/difficult to classify group)
- Guidelines for electron microscopy and reporting
- Guidelines for the final report (the content and order)
- Guidelines for the use of ancillary studies (lymphocyte marker studies, in situ hybridization, spectrometry, special stains, antigen retrieval and unmasking, C4d, IgG subtypes, etc.)
- Guidelines on nomenclature: the pathogenesis/patterns of injury/ etiology/disease entities
- Guidelines on chronicity: Glomerulosclerosis, IFTA and vascular lesions
- Clinical aspects in report: guide to evaluation/treatment

KDIGO

3:00 - 3:30 pm	Tea break
3:30 - 4:30 pm	Open hour for discussion
4:30 - 5:00 pm	Summary Sanjeev Sethi, MD, PhD and Fernando C. Fervenza, MD, PhD

Glomerulonephritis Consensus Meeting

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Classification of Glomerulonephritis

Pathogenic type	Specific Disease entity	Pattern of injury: focal or diffuse	Scores or class
Immune-complex GN**	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN fibrillary GN with polyclonal Ig deposits	Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*	-Oxford/MEST scores for IgA nephropathy - ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, PR3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing or multiple*	Focal, crescentic, mixed or sclerosing class (Berden/ EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing or mixed*	
Monoclonal Ig GN**	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits	Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*	
C3 glomerulopathy	C3 glomerulonephritis, dense deposit disease	Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*	

Primary diagnosis

- Disease entity/pathogenic type
- Pattern of injury
- Scores/class/grade
- Additional features:
    - Clinical modifiers
    - Extent of chronic changes: glomerulosclerosis/IFTA/arteriosclerosis

Secondary diagnosis- some examples

- Diabetic nephropathy
- Thin GBM
- ATN
- Interstitial nephritis

Table 2. Basic format of kidney biopsy report

(1) Specimen type: needle biopsy, wedge, *etc.*

(2) Diagnosis

- Primary diagnosis
  - Disease process/pathogenic type (*e.g.*, IgA nephropathy, lupus GN, ANCA GN, C3 GN)
  - Pattern of glomerular injury (*e.g.*, mesangial proliferative, membranoproliferative, necrotizing/crescentic, and focal and segmental sclerosing)
  - Histologic scores or grade (*e.g.*, Oxford/MEST for IgA nephropathy and ISN/RPS for lupus nephritis)
  - Additional features (*e.g.*, degree of global glomerulosclerosis, IFTA, vascular sclerosis, clinical modifiers, such as cryoglobulin/clinical HCV, bacterial endocarditis/clinical, staphylococcal cellulitis/clinical)
- Secondary diagnoses (list; *e.g.*, acute interstitial nephritis and diabetic glomerulosclerosis); these are not felt to be part of the primary disease

(3) Comment/narrative

- Can be used for summarizing/clarifying morphologic basis of primary and/or secondary diagnoses or clinicopathologic correlations, providing prognostic information, discussing differential diagnosis, and providing appropriate references

(4) Summary of clinical data

(5) Gross description

(6) LM description

(7) IF/IHC

(8) EM

(9) Addendum for special studies

MEST, mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy; ISN/RPS, International Society of Nephrology/Renal Pathology Society; EUVAS, European vasculitis study group; HCV, hepatitis C virus.

Table 5. Guidelines for LM

- Glomeruli
  - No. of glomeruli, including no. of globally and segmentally sclerosed and ischemic glomeruli
  - Focal versus diffuse and segmental versus global findings
  - Hypercellularity: mesangial, endocapillary, or exudative
  - Crescents: no./percentage, type (cellular, fibrocellular, or fibrous), and size (segmental or circumferential)
  - Fibrinoid necrosis and karyorrhexis
  - Wire loops, pseudo-(hyaline) microthrombi, and fibrin thrombi
  - Mesangial matrix expansion and presence of mesangiolysis
  - GBM thickening/thinning, double-contour formation, and other GBM abnormalities (*e.g.*, spikes)
  - Disruption of GBM
  - Disruption of Bowman's capsule
- Tubules and interstitium
  - Interstitial inflammation: type of infiltrate and location
  - Casts, crystals, and cysts
  - Acute tubular injury
  - Tubular basement abnormalities
  - IFTA: absent, mild, moderate, or severe
- Vessels
  - Arteritis, emboli, and thrombosis
  - Arteriosclerosis and arteriolosclerosis: absent, mild, moderate, or severe

Table 6. Guidelines for IF

- No. of glomeruli, including no. of globally sclerosed glomeruli or with other evident lesions
- Intensity of staining: negative, ±, 1+, 2+, and 3+
- Staining pattern: granular, linear, semilinear, smudgy, and linear accentuation
- Location: focal or diffuse; segmental or global; and mesangial, glomerular capillary wall, or both
- Interstitial and tubular basement membrane staining: if present
- Segmental trapping of C3 and IgM is common in areas of segmental sclerosis or scarring: segmental glomerular tuft or coarse segmental staining
- Internal controls: albumin along TBM and GBM, C3 in vessels, and polyclonal IgA casts in tubules

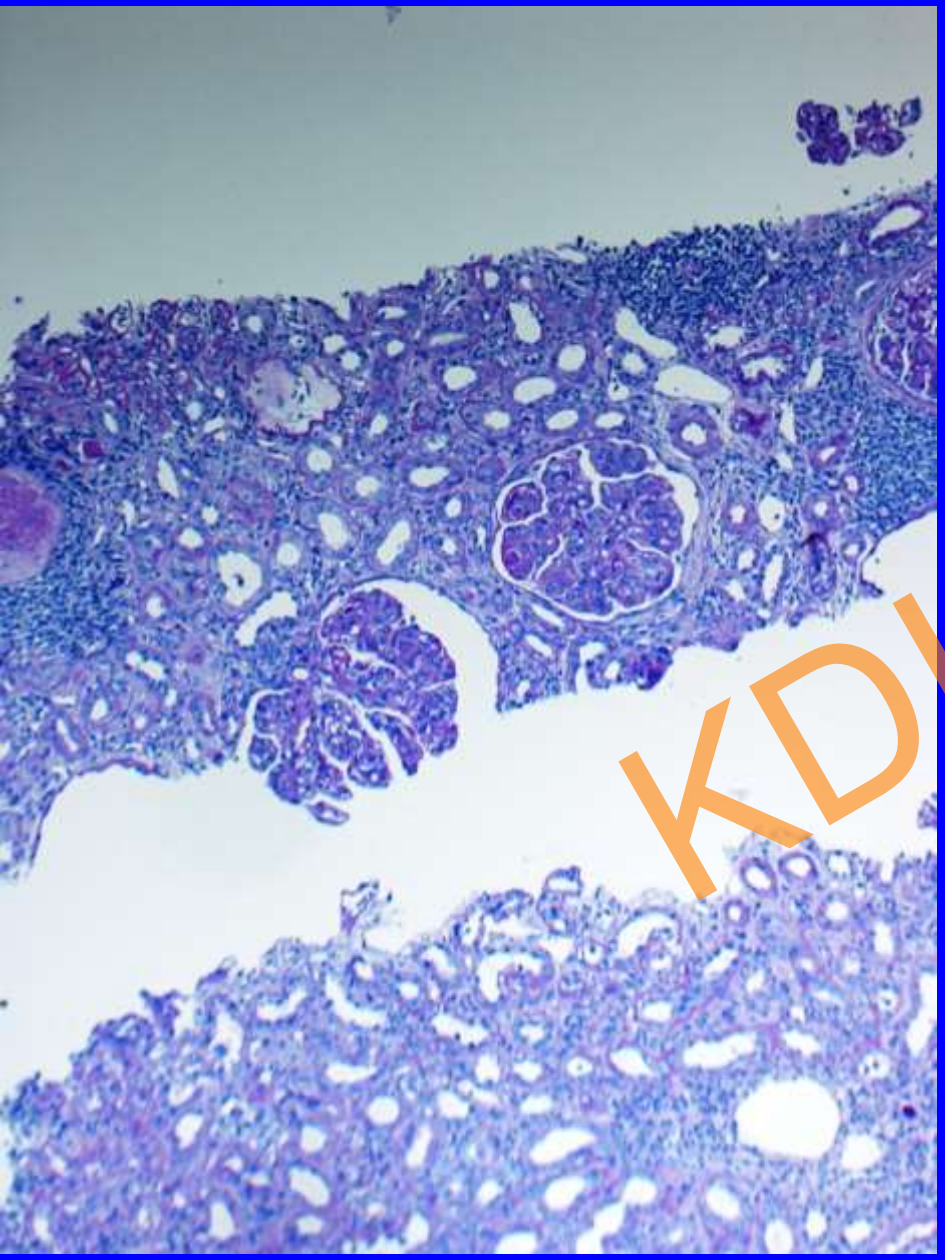
TBM, tubular basement membrane.

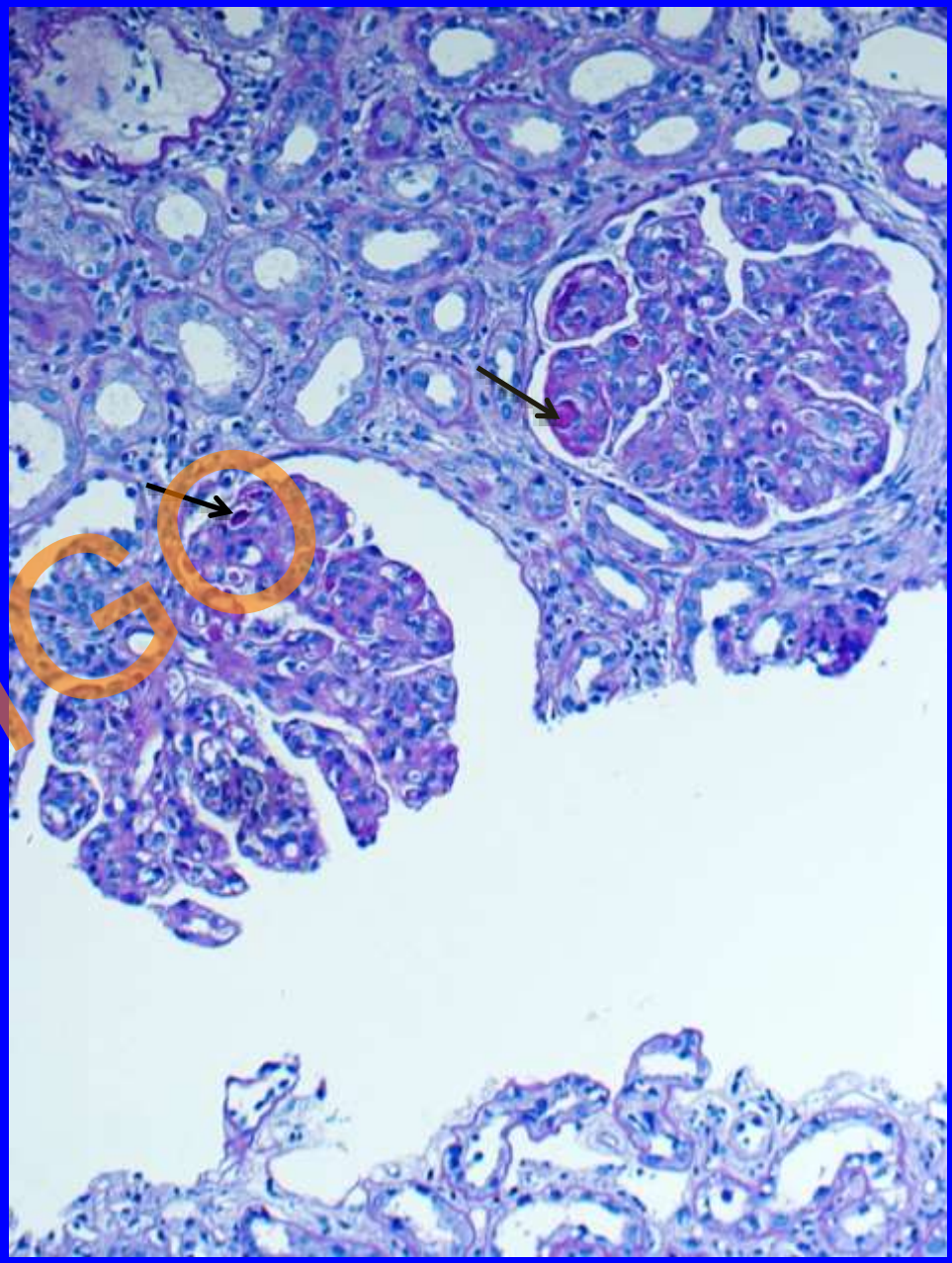
Table 7. Guidelines for EM

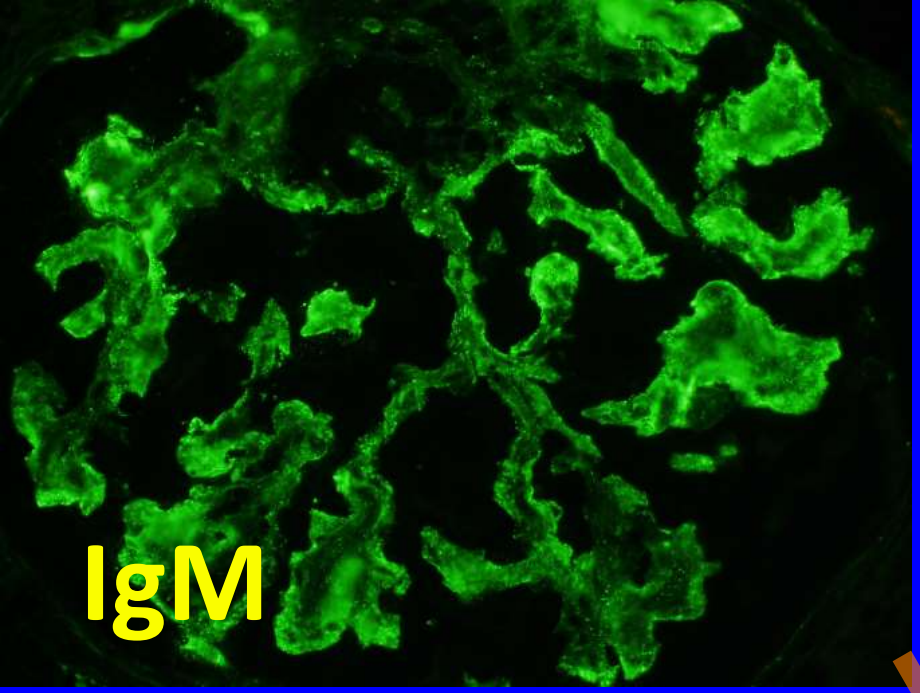
- No. of glomeruli studied by EM, including no. globally sclerosed or with other evident lesions
- Glomerular deposits: location, type, quantity, size, and substructure
- GBM: architecture, thin/thick, duplication, ischemic changes, and rupture
- Endothelium: fenestrations, swelling, and presence of tubuloreticular inclusions
- Mesangial matrix: normal/increased and mesangiolysis
- Mesangial cellularity: normal/increased
- Podocytes: preserved or effaced (%), protein reabsorption granules, and microvillus change
- Leukocytes/platelets/fibrin in capillary lumen/Bowman's space
- Tubular epithelial and basement membrane abnormalities when present

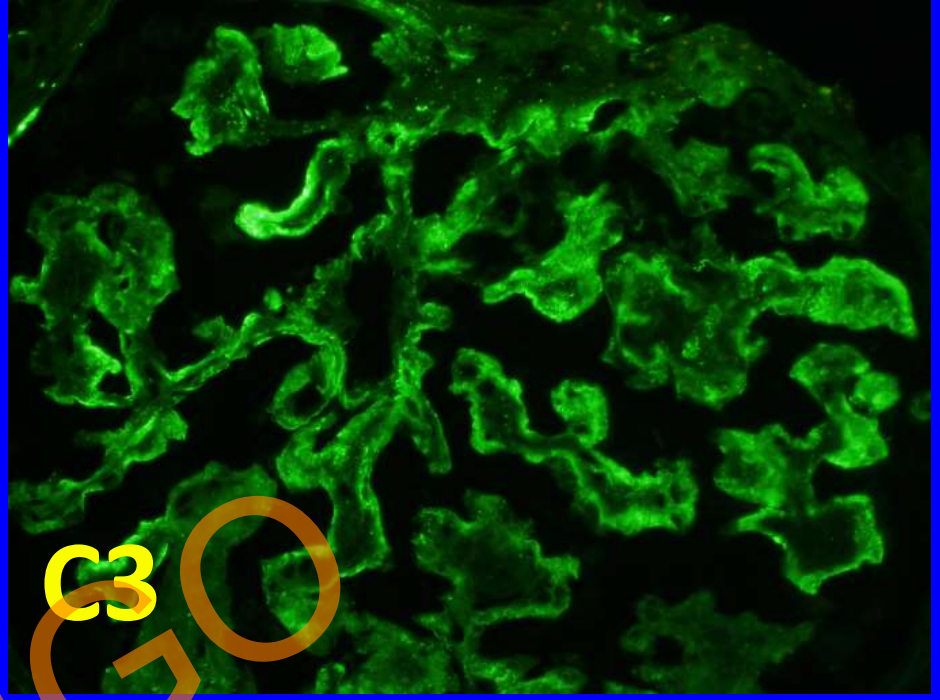
Some examples….Patient # 1

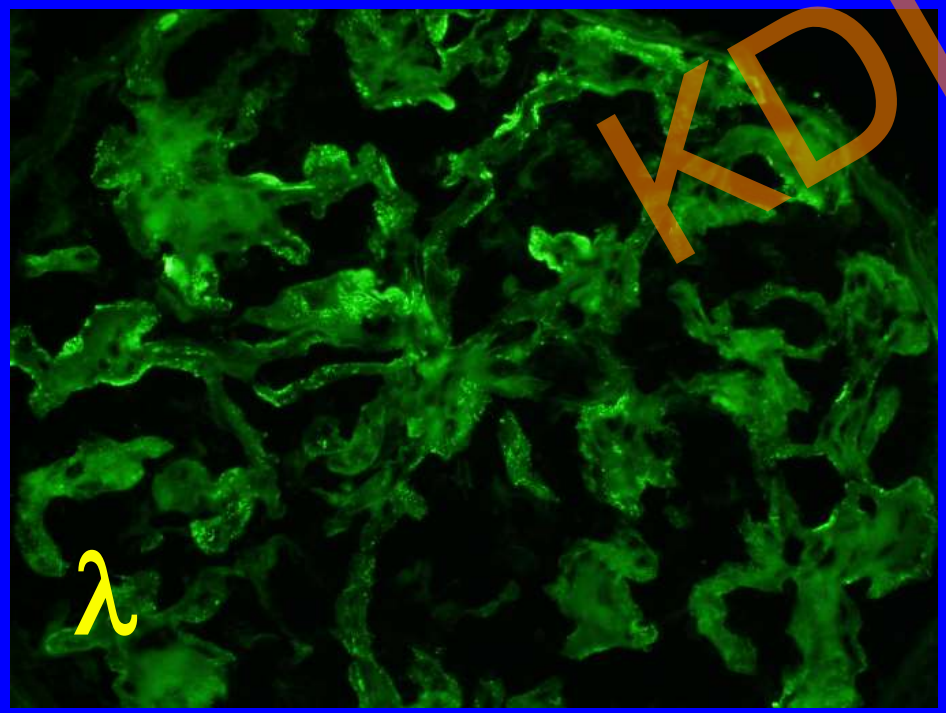
- Mr. GS is a 47-yr old man with proteinuria, hematuria and renal failure
- Serum creatinine 2.7 mg/dl, creatinine clearance 34 ml/min, urinary protein 2 gms/24 hours. Urinalysis- RBCs and few RBC casts
- History of hepatitis C, low complement titers

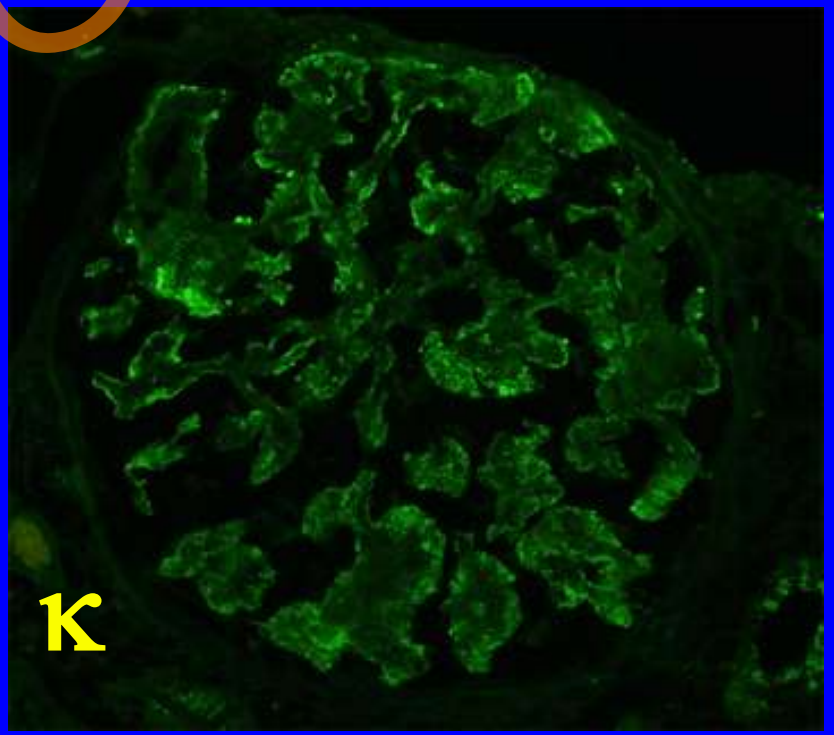


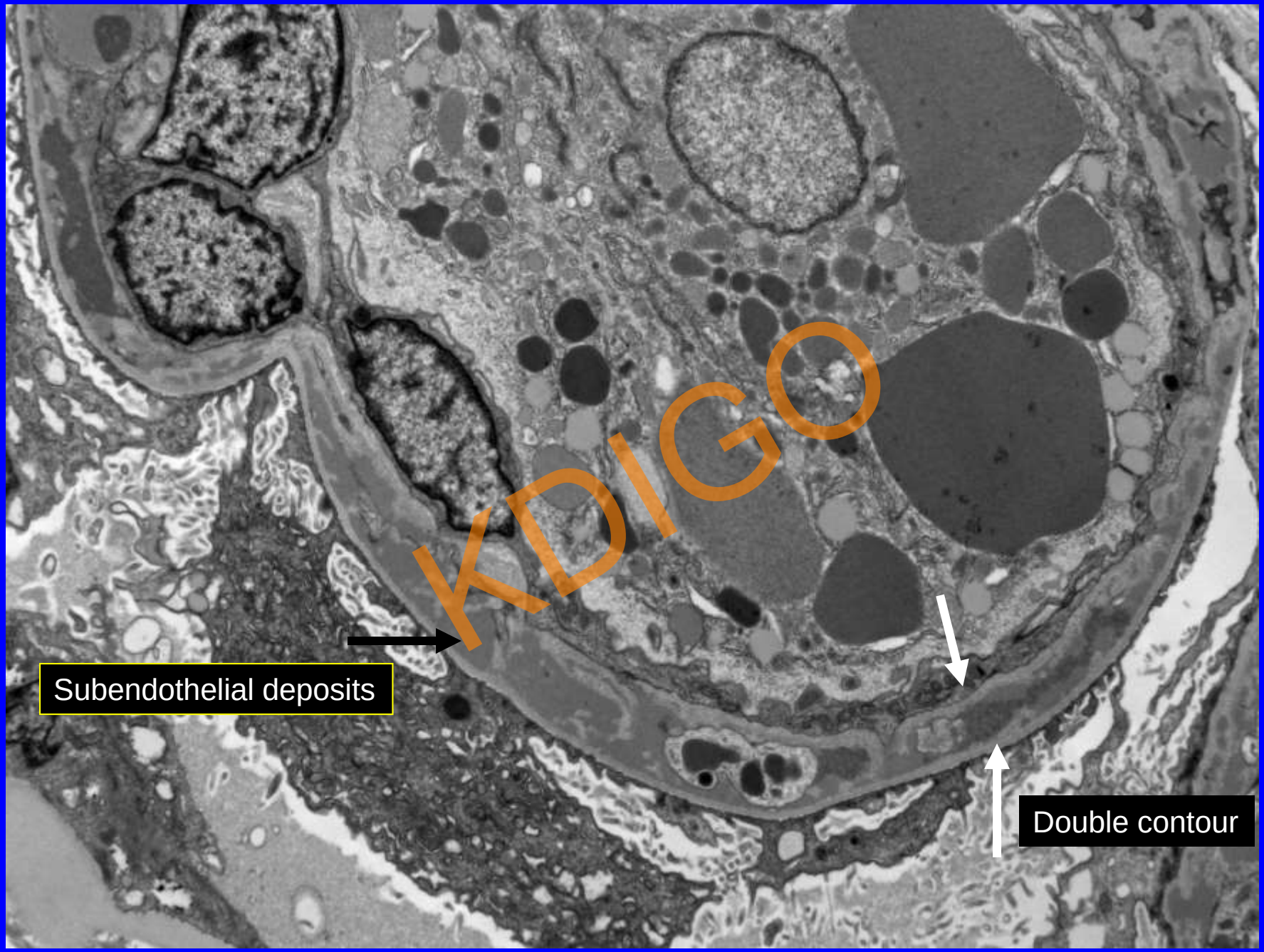











KDIGO
Subendothelial deposits
Double contour

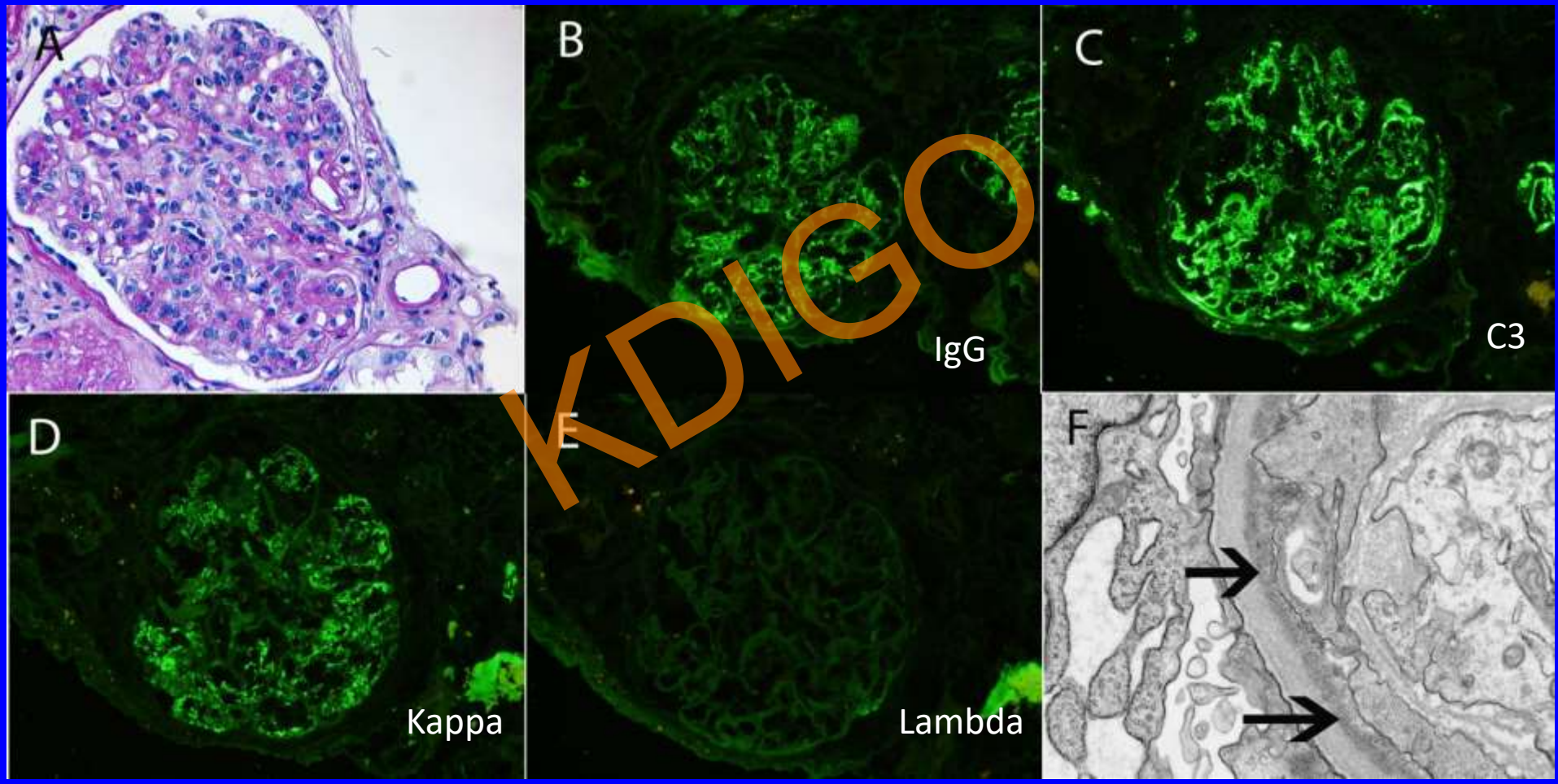
Diagnosis

- Primary diagnosis: Immune-complex glomerulonephritis (hepatitis C/clinical)
- Pattern of injury: Membranoproliferative glomerulonephritis
- Additional features:
  - with features of cryoglobulinemic glomerulonephritis (hepatitis C/clinical),
  - focal (20%) global glomerulosclerosis , moderate (30%) tubular atrophy and interstitial fibrosis
  - moderate arteriosclerosis and moderate hyaline arteriolosclerosis

Patient #2

- 58-year old man with nephrotic syndrome, hypertension, hyperlipidemia and edema.
- Serum creatinine 1.6 mg/dL
- UA- 30-50 RBC/HPF, with RBC casts
- Urine IFE kappa light chains

Kidney Biopsy



Diagnosis

- Primary diagnosis: Proliferative glomerulonephritis with monoclonal Ig deposits
- Pattern of injury: Membranoproliferative glomerulonephritis
- Additional features:
  - focal global glomerulosclerosis (30%), moderate (40%) tubular atrophy and interstitial fibrosis,
  - moderate arteriosclerosis and moderate hyaline arteriolosclerosis

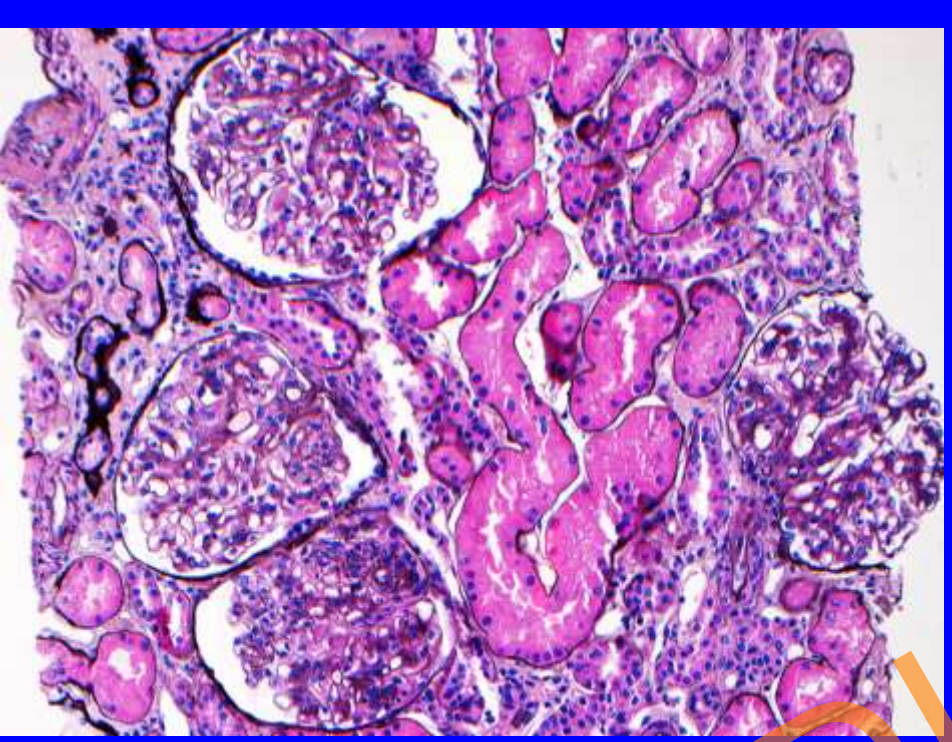
Ancillary study: IgG subtyping reveals IgG3 subclass, negative for IgG1, IgG2 and IgG4

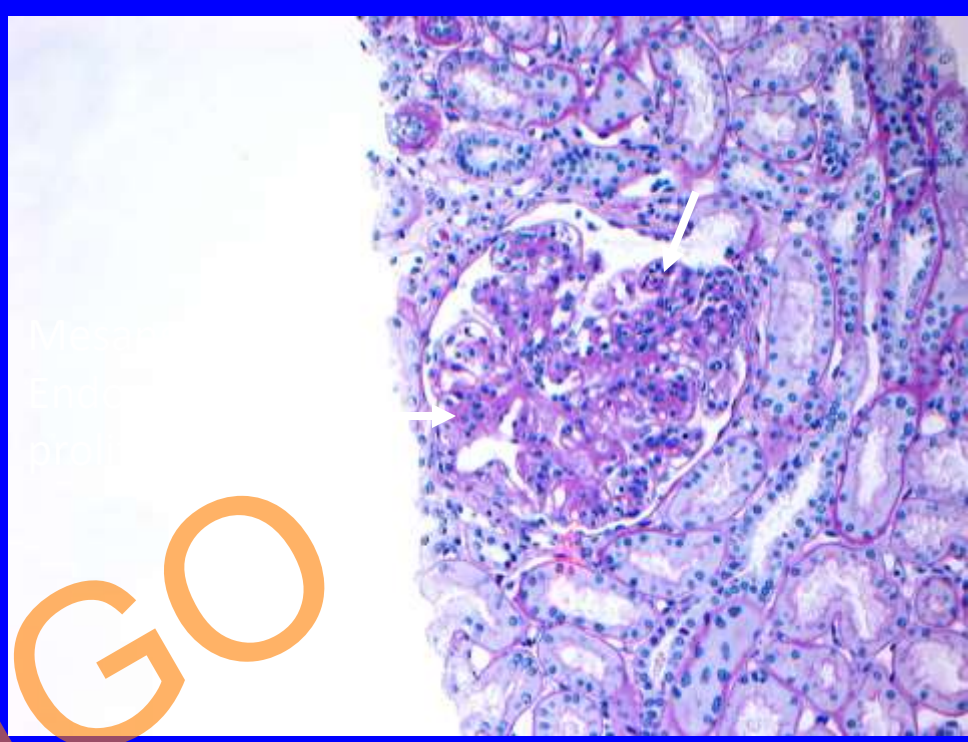
Patient # 3

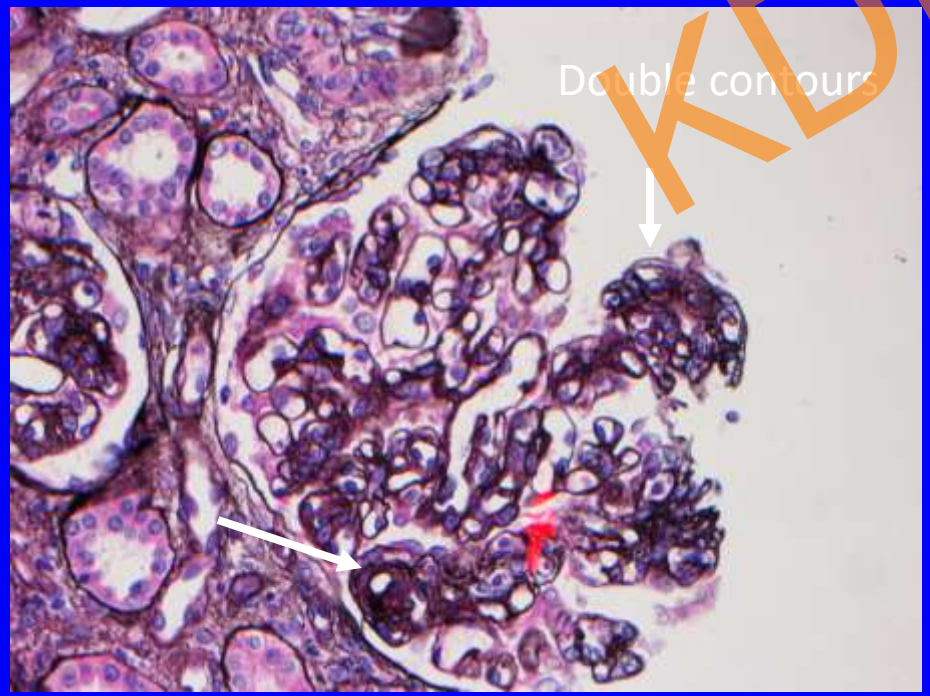
- 61-year old man with monoclonal gammopathy (IgG kappa protein with M spikes ranging from 0.5 to 0.9 g/dL over time), low complement titers (low C3 normal C4), and gross hematuria, few RBC casts. Serum creatinine 1.3 mg/dL

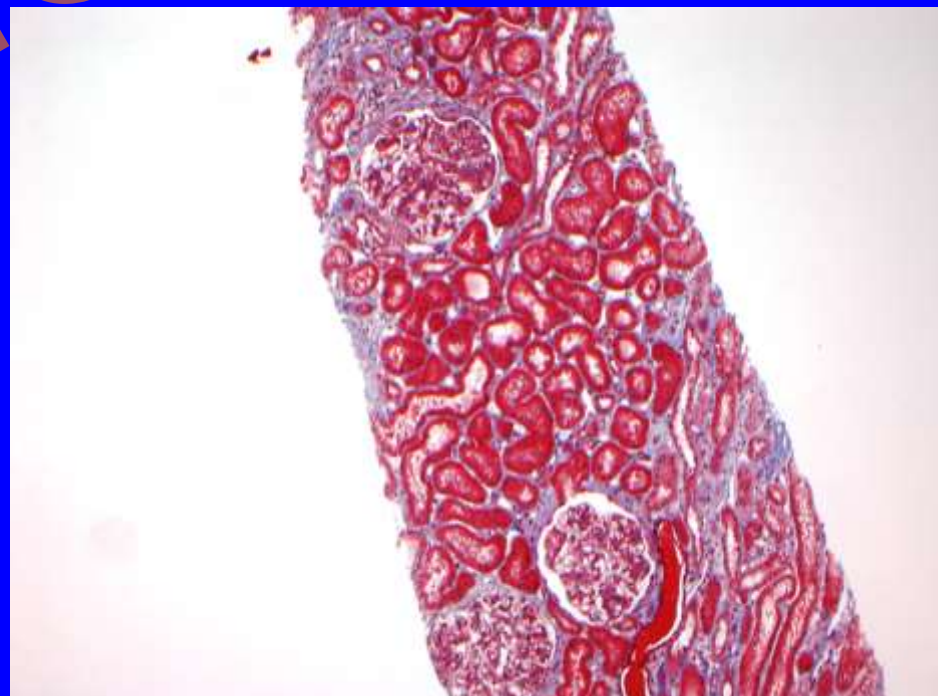
- Bone marrow 8% plasma cells: MGUS

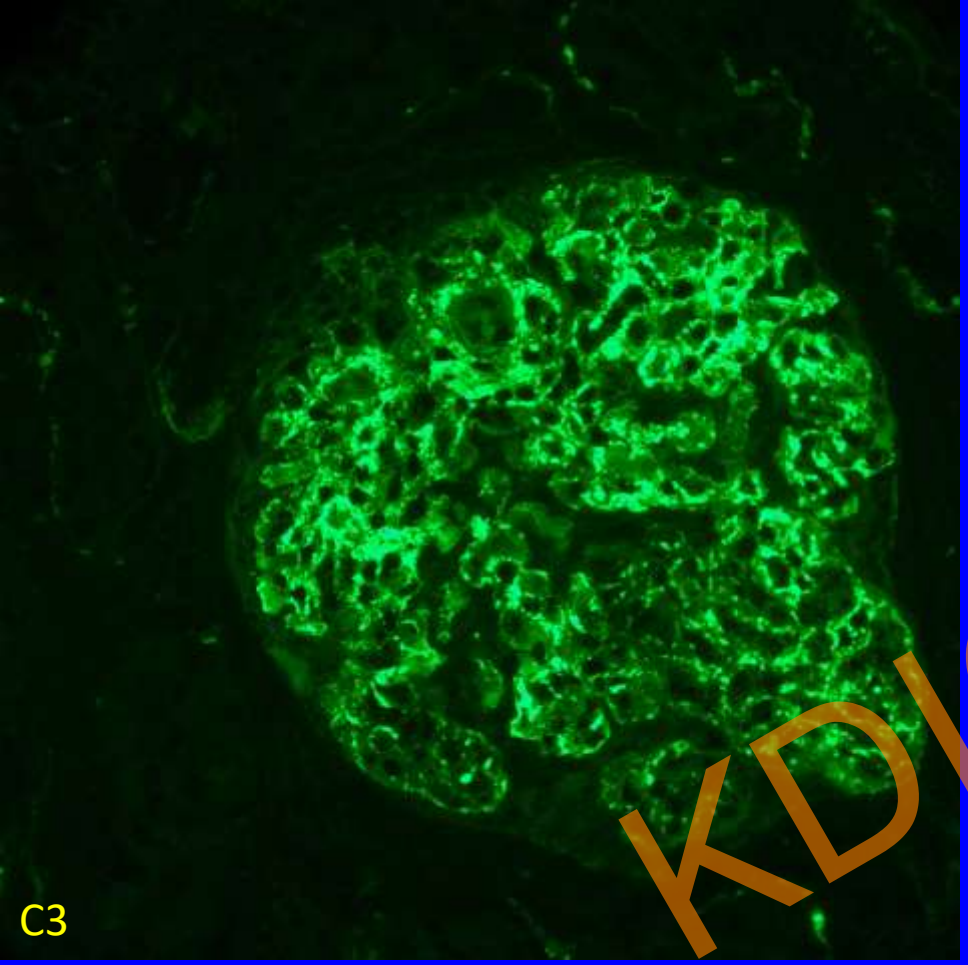
- Biopsied in 07 and 09

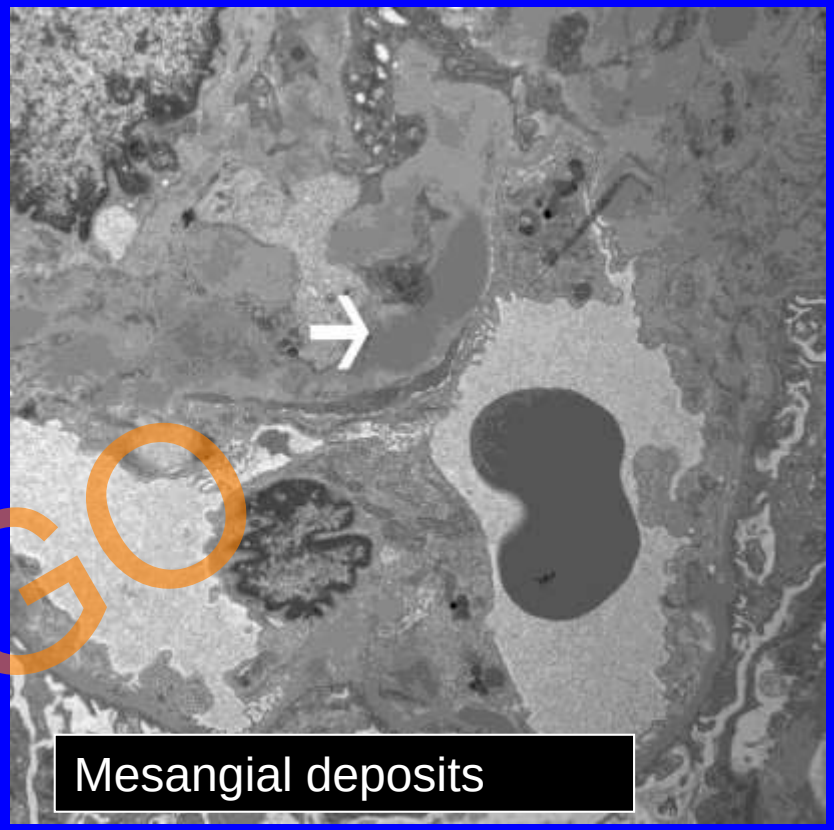




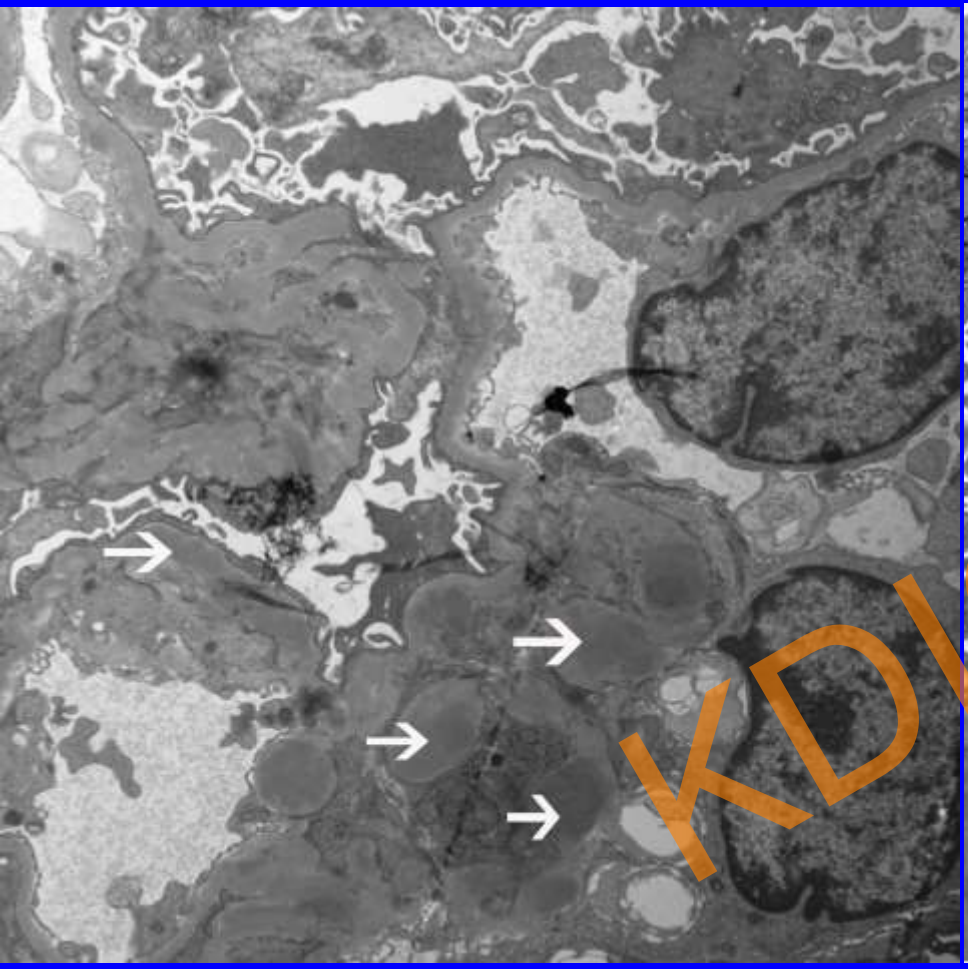




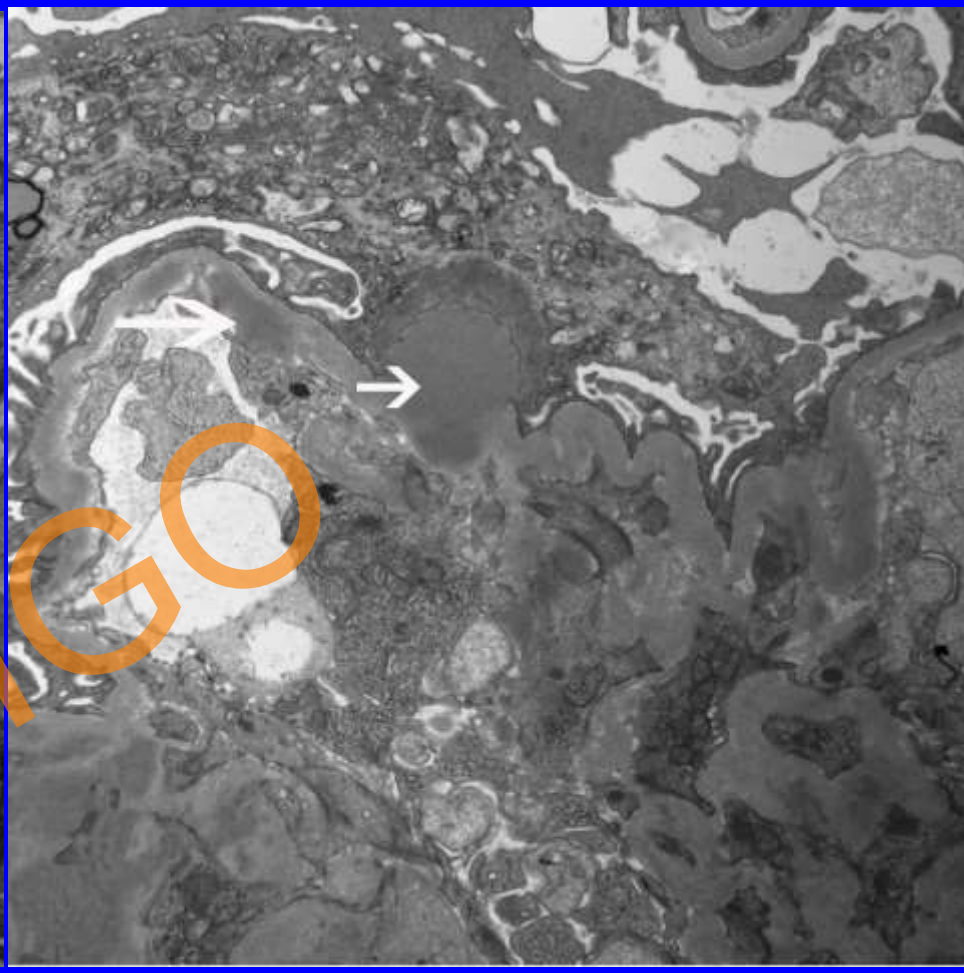




Negative IgG, IgM, IgA, C1q, kappa and lambda



Mesangial deposits



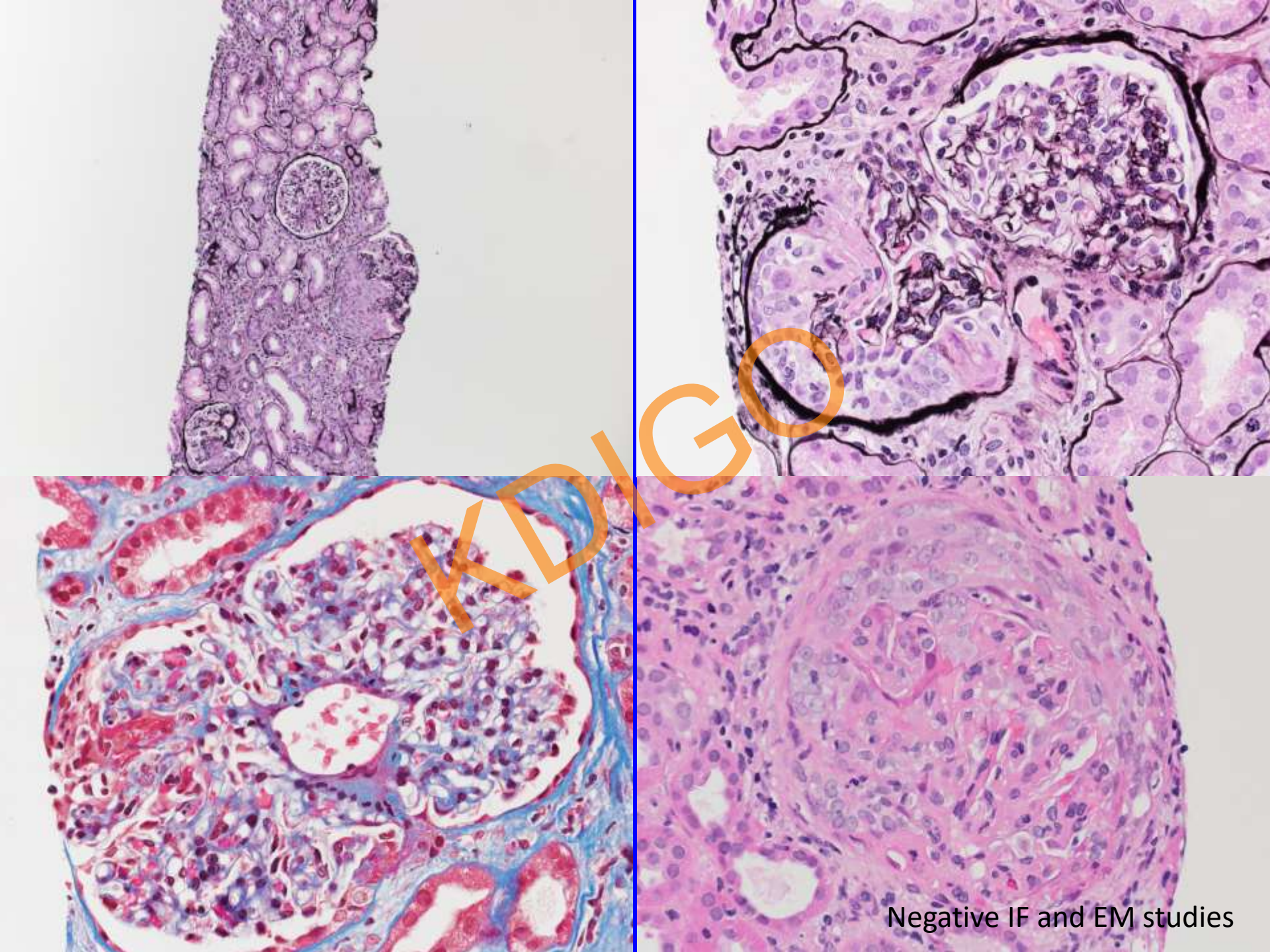
Capillary wall deposits: subendothelial and subepithelial deposits

Diagnosis

- Primary diagnosis: C3 glomerulonephritis
- Pattern of injury: Membranoproliferative glomerulonephritis
- Additional features:
  - Focal (20%) global glomerulosclerosis , mild (20%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis and moderate hyaline arteriolosclerosis

Patient # 4

- A 68-year-old woman presents with acute renal failure, hematuria, proteinuria, and pulmonary infiltrates.
- Serum creatinine of 3.8 mg/dL. Hemoglobin is low at 5.8.
- The patient has positive MPO/pANCA and ANA titers. Remaining serological evaluation is negative
- Urine analysis shows numerous red blood cells and few RBC casts


KDIGO
Negative IF and EM studies

ANCA GN

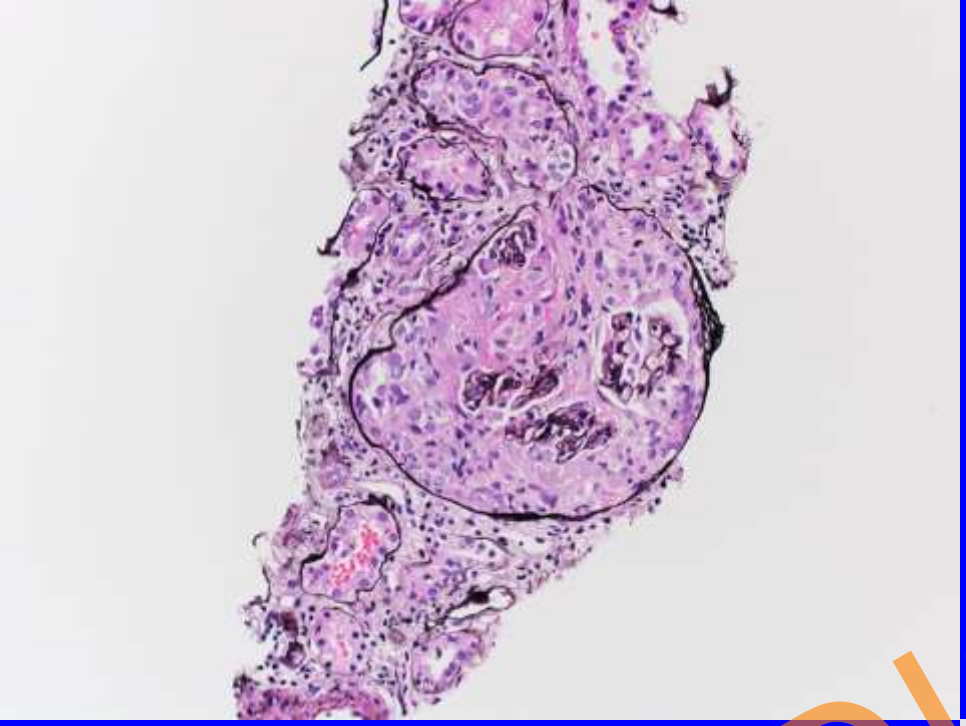
Kidney, needle biopsy:

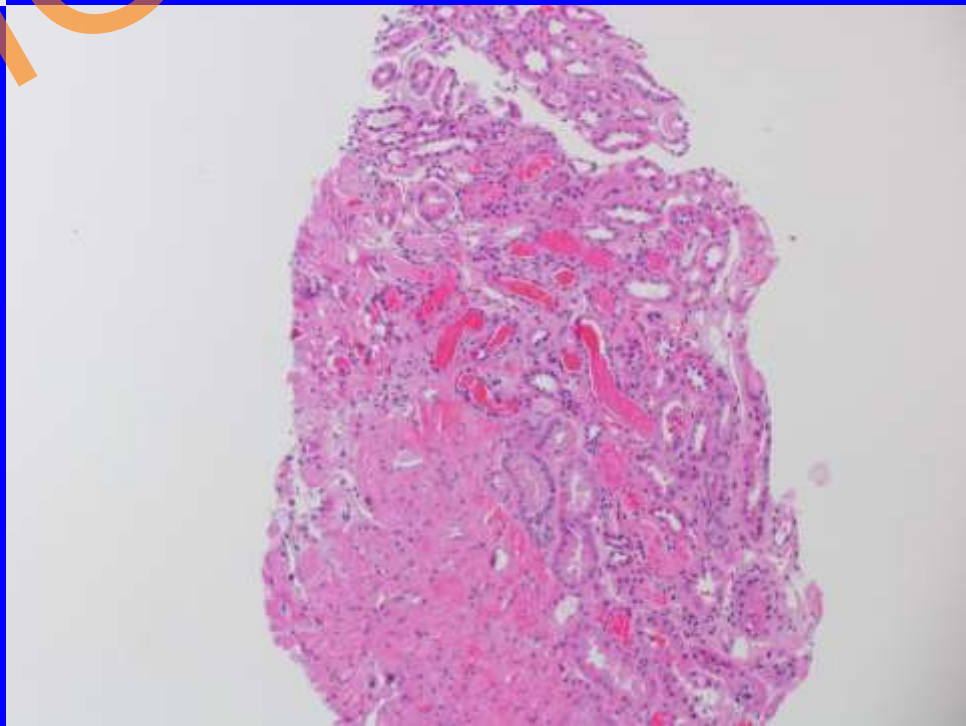
Primary diagnosis: MPO-ANCA glomerulonephritis (MPO/clinical)

- Pattern of injury: necrotizing and crescentic glomerulonephritis
- Prognostic class: Focal (≥50% normal glomeruli)
- Additional features: Focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), mild arteriosclerosis and moderate hyaline arteriolosclerosis

Patient #5

- 63-year old woman with subacute rise in serum creatinine from 1.8 to 3.7 mg/dL over the last 3 weeks.
- UA- 2+ protein 3+ blood, 100-200 RBC/HPF
- PR3+ cANCA +
- Remaining serology negative





Negative IF and EM studies

Kidney, needle biopsy:

Primary diagnosis: PR3-ANCA glomerulonephritis (PR3/clinical)

- Pattern of injury: necrotizing and crescentic glomerulonephritis
- Prognostic class: Mixed (<50% normal glomeruli)
- Additional features: Severe ATN, Focal global glomerulosclerosis (33%), moderate tubular atrophy and interstitial fibrosis (30%), mild arteriosclerosis and moderate hyaline arteriolosclerosis

Other examples: IgA nephropathy

Primary diagnosis: IgA nephropathy

Pattern of injury: Mesangial proliferative and sclerosing glomerulonephritis

Score/Grade: Oxford classification: M1 E0 S1 T1

Additional features: Focal (20%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis and severe hyaline arteriolosclerosis

Secondary diagnoses: Diabetic nephropathy, early

Lupus nephritis

- Primary diagnosis Lupus nephritis
- Pattern of injury: Diffuse proliferative and sclerosing glomerulonephritis, with focal (10%) cellular crescents
- Score/grade: ISN/RPS class IV-G (A/C)
- Additional features:
  - Glomerular and arteriolar fibrin thrombi (anti-phospholipid antibodies/clinical)
  - focal global glomerulosclerosis (20%), mild tubular atrophy and interstitial fibrosis (20%), moderate arteriosclerosis and moderate hyaline arteriolosclerosis

Anti-GBM glomerulonephritis

- Primary diagnosis: Anti-GBM glomerulonephritis
- Pattern of injury: Necrotizing and crescentic glomerulonephritis, severe
- Additional features:
  - Clinicopathologic features of Goodpasture syndrome (anti-GBM antibody/clinical),
  - focal global glomerulosclerosis (40%), moderate tubular atrophy and interstitial fibrosis (40%), mild arteriosclerosis and moderate hyaline arteriolosclerosis

Summary

- The main aim and purpose of consensus meeting was to classify glomerulonephritis *based on the underlying pathophysiology and etiology.*

- Based on the current knowledge there are *five basic classes of GN*:
  - immune–complex GN
  - pauci-immune GN
  - anti-GBM GN
  - monoclonal Ig GN
  - C3 glomerulopathy

  - Specific entities exist within each group

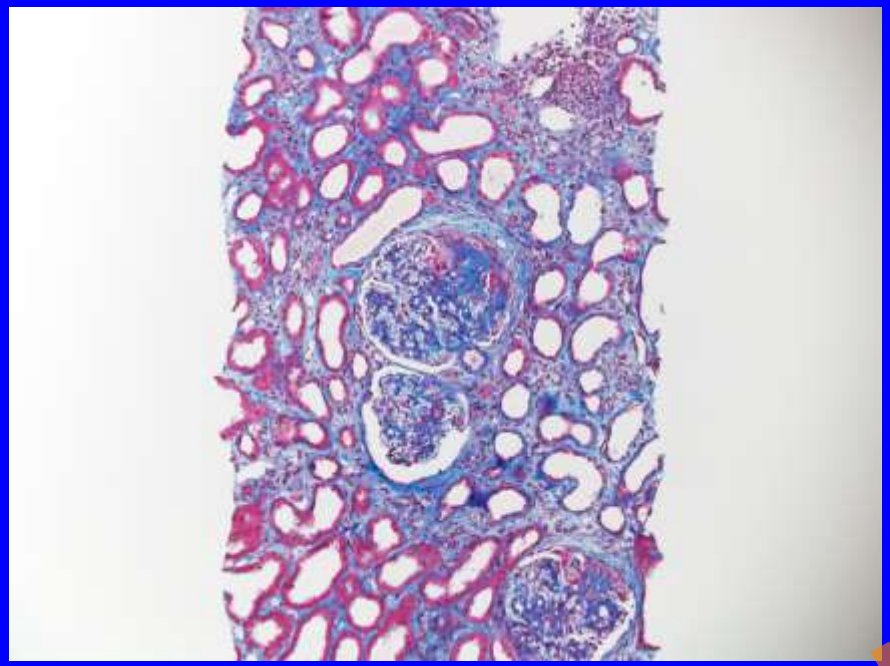
- The consensus document provides guidelines for the *kidney biopsy report* on glomerulonephritis

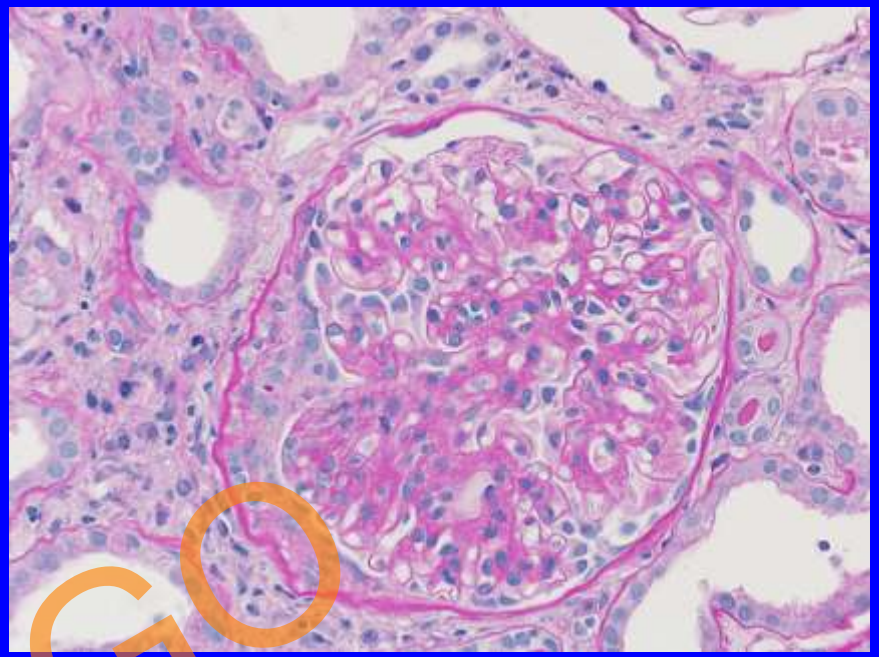
Shortcomings and limitations/needs further work

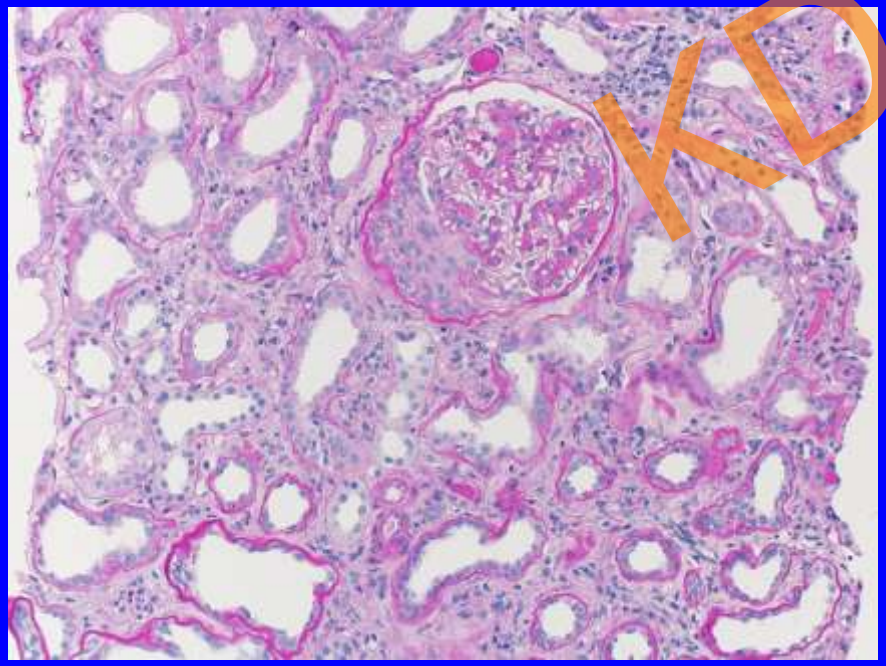
- Difficult cases- the diagnosis is not clear cut
- Limited biopsy sample
- Multiple diagnoses-GN + non GN diagnosis
- New disease entities
- Far from complete, work in progress, future modifications

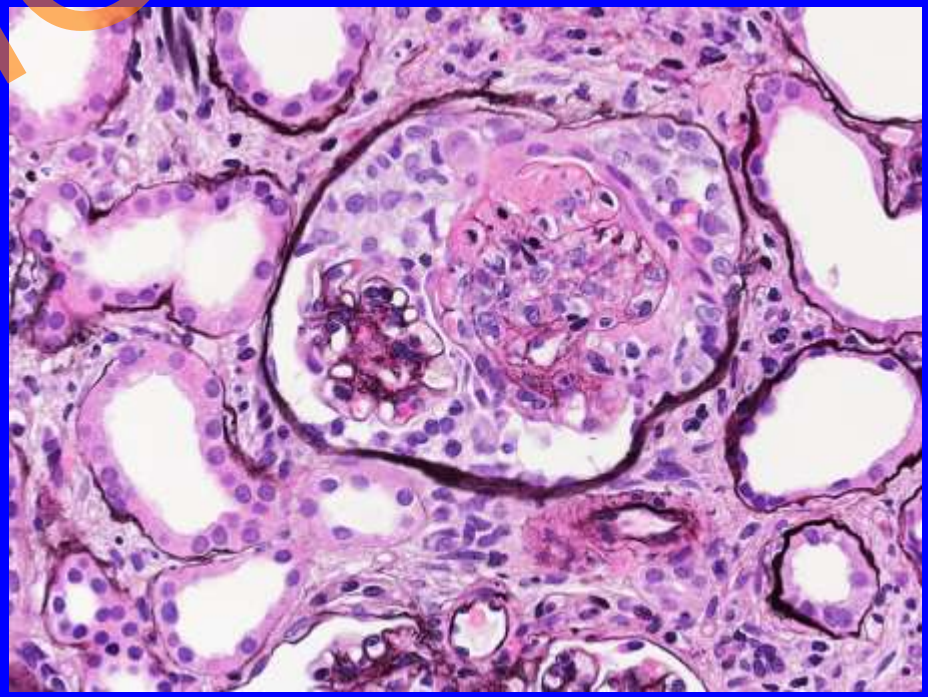
Example

- A 72 year old woman with hypertension and diabetes presented with acute on chronic kidney disease.
- Serum creatinine up from baseline of 1.5 to 2.1 mg/dL
- UA shows 3+ blood and 2+ protein
- Tobacco use









Final Diagnosis

Kidney, needle biopsy:

Primary diagnosis: 1) Pauci-immune glomerulonephritis.
2) Diffuse and nodular diabetic glomerulosclerosis, moderately advanced.

Pattern of injury: 1) Necrotizing and crescentic glomerulonephritis. 2) Diffuse and nodular glomerulosclerosis.

Score: Mixed class.

Additional findings: Focal (27%) global glomerulosclerosis , moderate (30%) tubular atrophy and interstitial fibrosis, moderate arterial sclerosis.

Glomerulonephritis Consensus Meeting

February 19 and 20, 2015
Mayo Clinic | Rochester, Minnesota

MAYO CLINIC

SPECIAL ARTICLE www.jasn.org

Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN

Sanjeev Sethi, Mark Haas, Glen S. Markowitz, Vivette D. D'Agati, Helmut G. Rennke, J. Charles Jennette, Ingeborg M. Bajema, Charles E. Alpers, Anthony Chang, Lynn D. Cornell, Fernando G. Cosio, Agnes B. Fogo, Richard J. Glassock, Sundaram Hariharan, Neeraja Kambham, Donna J. Lager, Nelson Leung, Michael Mengel, Karl A. Nath, Ian S. Roberts, Brad H. Rovin, Surya V. Seshan, Richard J.H. Smith, Patrick D. Walker, Christopher G. Winearls, Gerald B. Appel, Mariam P. Alexander, Daniel C. Cattran, Carmen Avila Casado, H. Terence Cook, An S. De Vriese, Jai Radhakrishnan, Lorraine C. Racusen, Pierre Ronco, and Fernando C. Fervenza

*Mayo Clinic, Rochester, Minnesota

EDITORIAL www.jasn.org

A Systematic Method for Categorizing GN

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