

# Glomerular Diseases Part II

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BUMC INTERNAL MEDICINE RESIDENT LECTURE

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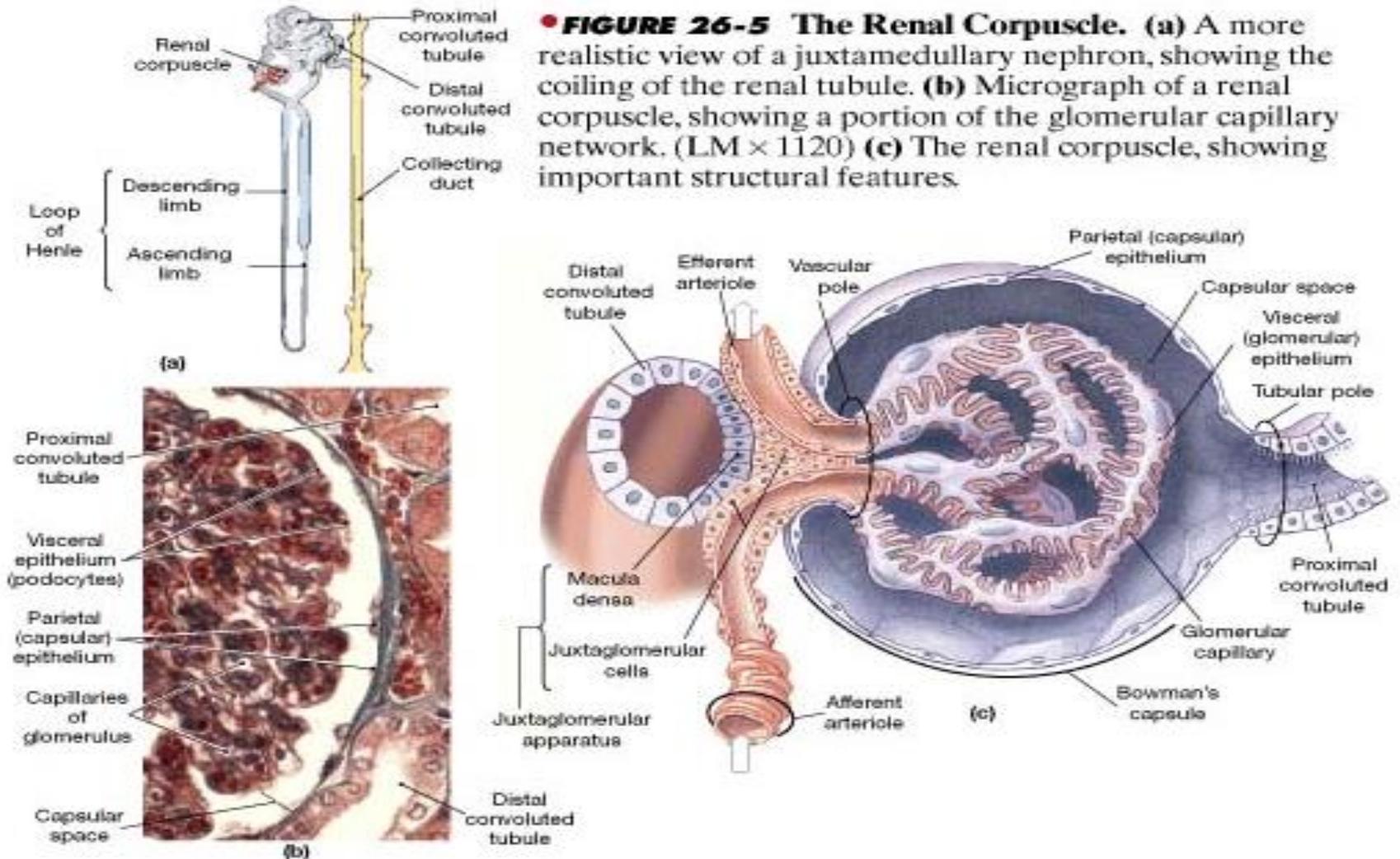
# Learning Objectives

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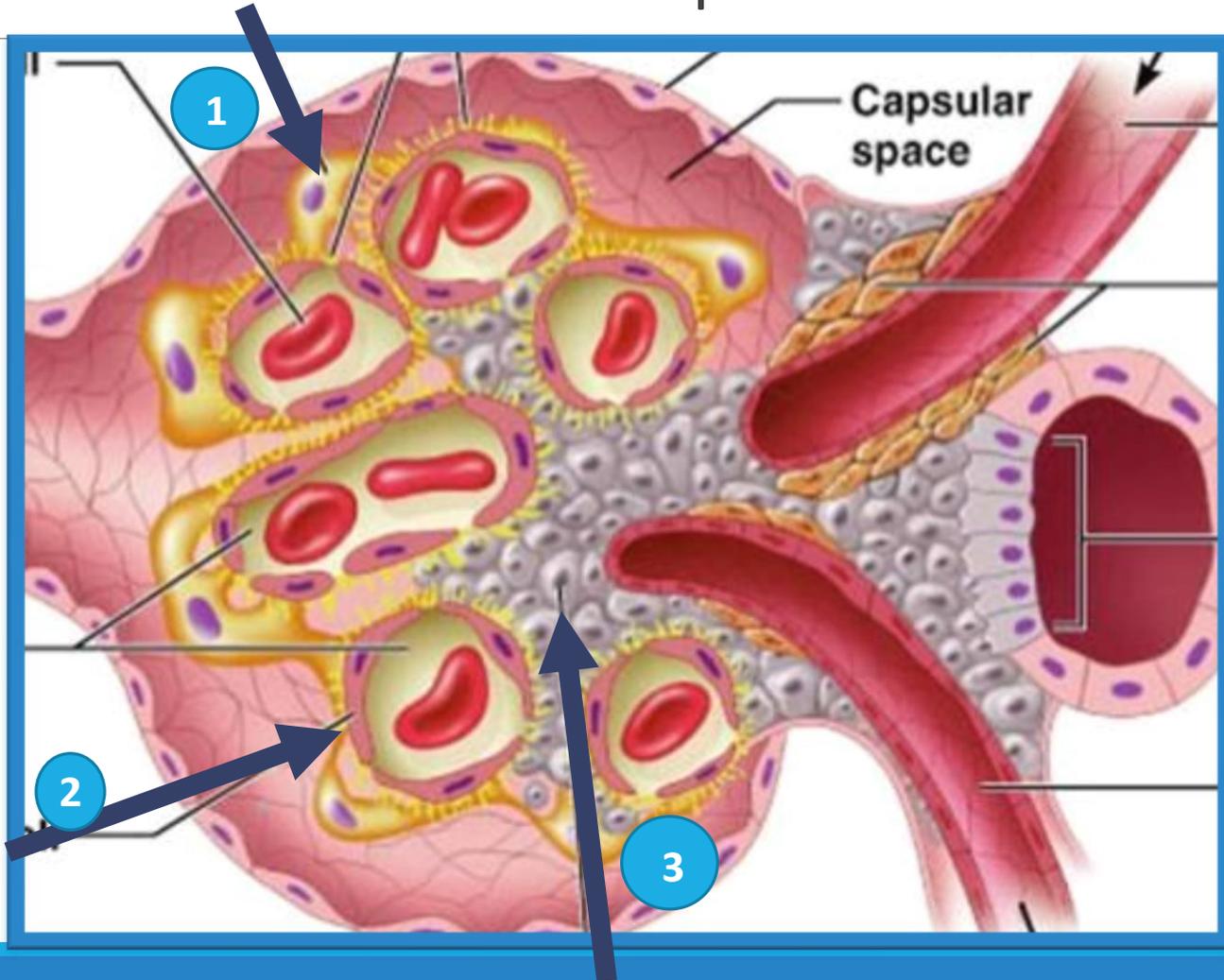
1. Diagram the classic clinical presentations, laboratory findings, and associated systemic diseases (if any) of the following syndromes:
  - Immune-Complex GN (Subcategorize diagnoses within the category of Immune-complex GN)
  - Anti-Glomerular Basement Membrane (GBM) Disease
  - Pauci-Immune Glomerulonephritis (ANCA positive)
  - Minimal Change Disease
  - Focal Segmental Glomerulosclerosis
  - Membranous Glomerulonephropathy
  - Diabetic nephropathy
  - Lupus nephritis
2. Subcategorize which GNs present with hypocomplementemia and distinguish which complement (C3 versus C4) is low in each.
3. Describe the clinical presentation of rapidly progressive glomerulonephritis (RPGN) and formulate a probable diagnosis based on the clinical and pathology findings seen.

# The Renal Corpuscle

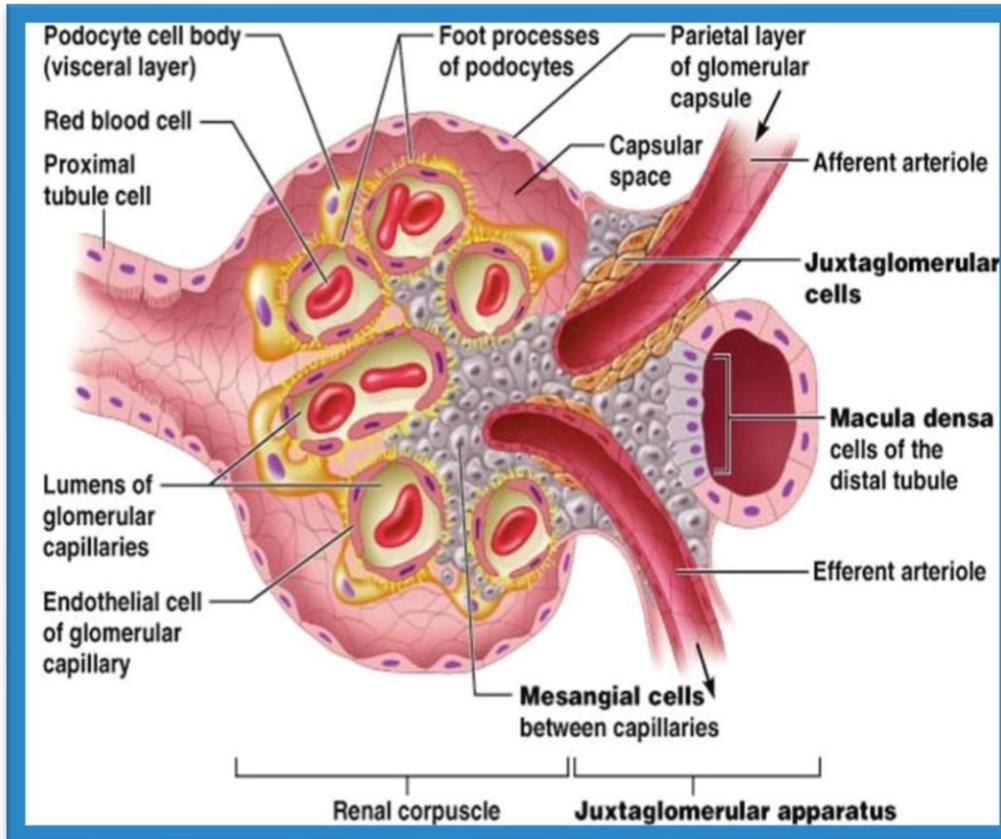
• **FIGURE 26-5 The Renal Corpuscle.** (a) A more realistic view of a juxtamedullary nephron, showing the coiling of the renal tubule. (b) Micrograph of a renal corpuscle, showing a portion of the glomerular capillary network. (LM  $\times 1120$ ) (c) The renal corpuscle, showing important structural features.



Question: Name the 3 different cell types shown in the renal corpuscle below



# Answer



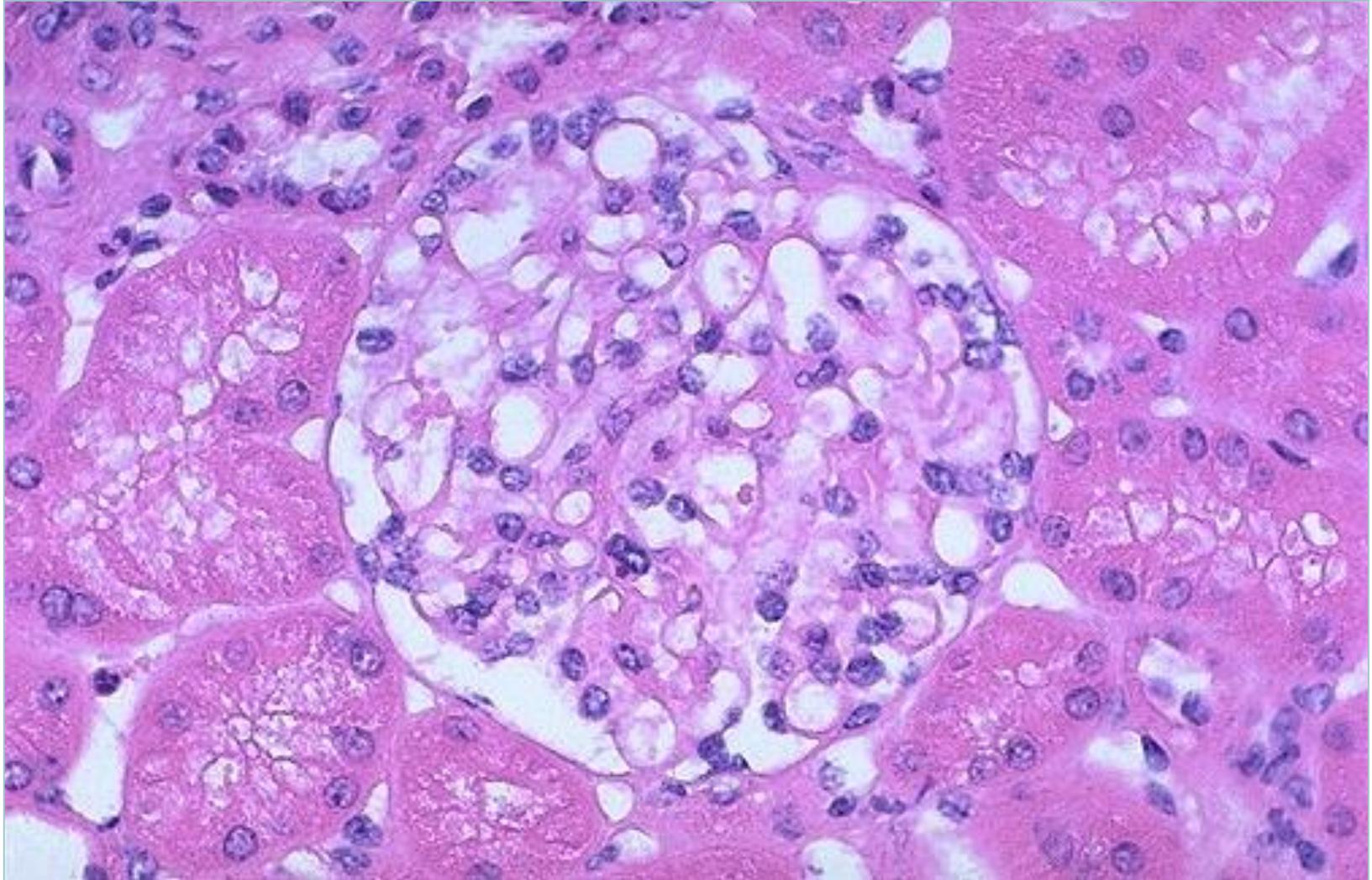
- 1) Podocyte (VEC)
- 2) Endothelial Cell
- 3) Mesangial Cell

# Glomerulus: Capillary network latin *“little ball of yarn”*

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# Normal Glomerulus: LM



# Glomerular Histology

- **Glomerular capillary wall**

- **GBM**

- Made of Type IV collagen and laminin

- 3 layers on EM

- **Podocyte = VEC**

- Cytoplasmic foot processes wrap around GBM

- Gap b/t podocytes form slit pores

- Key proteins: nephrin, CD2AP, podocin

- **Endothelial cell**

- Initial barrier b/t capillary lumen & Bowman space

- VEGF receptors

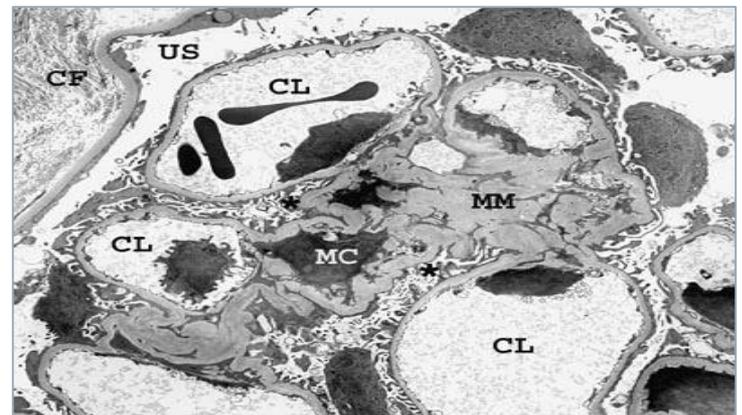
- Synthesize NO & Endothelin-1

- **Mesangium = matrix + mesangial cells**

- ~1-3 cells per capillary

- Support, phagocyte properties

- Contractile, role in GFR regulation



# Which of the following would indicate a non-glomerular source of hematuria?

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- A. Hypertension
- B. Proteinuria of 2000 mg on 24 hour urine
- C. Bright red blood at the end of urinary stream
- D. Negative urological workup
- E. RBC casts

# Answer

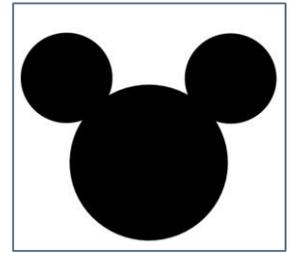
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C. Bright red blood at the end of urinary stream

# Glomerular Hematuria

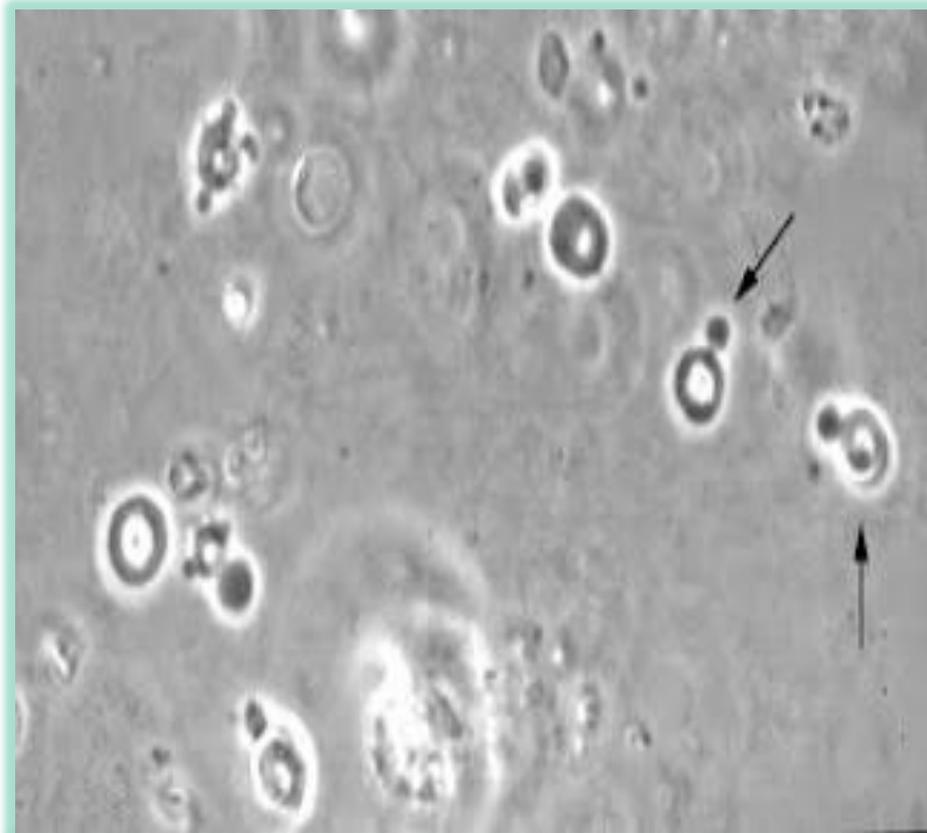
- RBC > 3 per HPF on 2 or more separate urinalyses
- Dysmorphic RBCs
- RBC casts
- Proteinuria > 500mg
- Decline in GFR
- Hypertension
- Negative urological workup
- Absence of clots, terminal hematuria





# Dysmorphic RBCs

Normal erythrocytes	Glomular erythrocytes
Fresh erythrocytes, no double contour	simple ring shape
Fresh erythrocytes, with double contour	curly ring shape
thorn apple shape	curly ring shape slitted
shadow of erythrocyte without margin	ring shape with surface protrusion
shadow of erythrocyte with margin remnants +/- spikes	ring shape with surface protrusion
deformed shadow of erythrocyte	ring shape with internal bleb
deformed erythrocyte curly double contour	ring shape with internal bleb



deformed erythrocyte with curly double contour	ring shape with internal bleb
deformed shadow of erythrocyte	ring shape with internal bleb

# RBC Cast

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# Diagnostic Evaluation: Glomerular Disease

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- Spin urine and look under microscope
- Quantify proteinuria
- Perform Serological workup
  - Primary vs Secondary (systemic)
- Renal ultrasound for morphology
- Renal biopsy

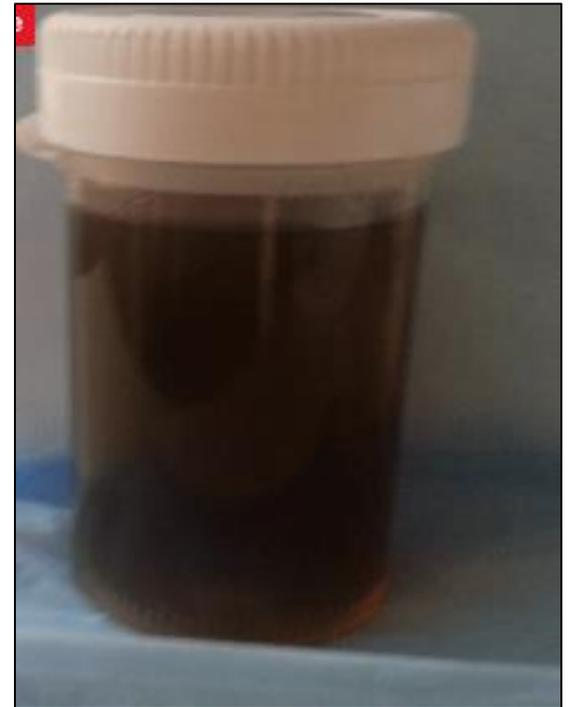
## Serological Evaluation

- C3, C4, CH50
- Hepatitis B, C panel
- ANA with reflex
- ANCA
- Anti-GBM Ab
- SPEP/UPEP
- Streptozyme, blood cultures

# Sub-nephrotic Glomerulonephritis: “Nephritic Syndrome”

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- Sub-nephrotic proteinuria < 3.5 grams
- Glomerular hematuria
  - Micro
  - Macro – dark urine, gross hematuria
  - Active urinary sediment
- Hypertension
- Elevated BUN/Creatinine



# Causes of Sub-nephrotic Glomerulonephritis (GN)

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- Immune-complex GNs
- Lupus Nephritis
- Hereditary Nephritis (Alport's)
  - Hereditary defect of type IV collagen
- Anti-GBM Antibody (Ab) Disease
  - Autoimmune disease, antibodies against alpha-3 chain of type IV collagen
- Pauci-immune GNs / Small vessel vasculitis
  - Granulomatosis with polyangiitis (GPA) - 80% +ANCA
  - Microscopic polyangiitis (MPA) – 90% +ANCA
  - Negative immunofluorescence on pathology

Others: HUS, HSP, EGPA – 40% +ANCA

# Immune-Complex GNs

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- IgA Nephropathy

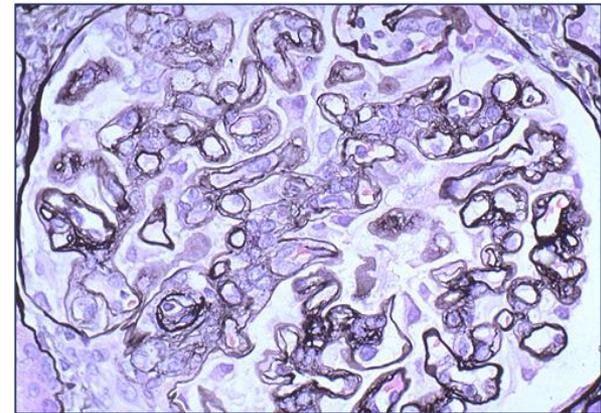
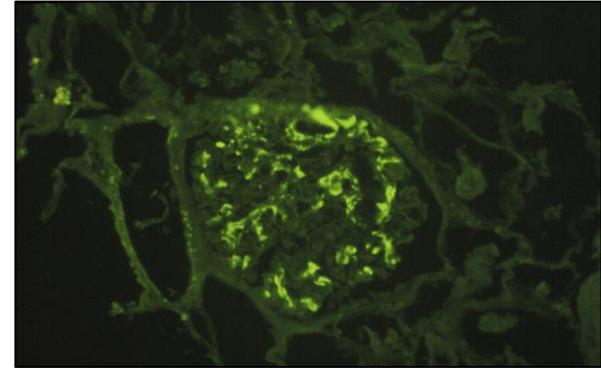
- Most common GN worldwide
- IgA immune-complex deposition in glomerular mesangial cells with mesangial proliferation

- Membranoproliferative Glomerulonephritis

- Immune-complex and/or complement protein deposition in the mesangium and **subendothelium** of the capillaries with GBM double contouring and “tram-track” appearance
- Cryoglobulinemia
- C3 glomerulopathy

- Infection-related/Post-strep GN

- Cryoglobulinemia



Which of the following is NOT associated with IgA nephropathy?

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- A. Crohns disease
- B. Liver disease
- C. Celiac disease
- D. Rheumatoid arthritis
- E. Celiac disease

# Answer

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D. Rheumatoid arthritis

# IgA Nephropathy

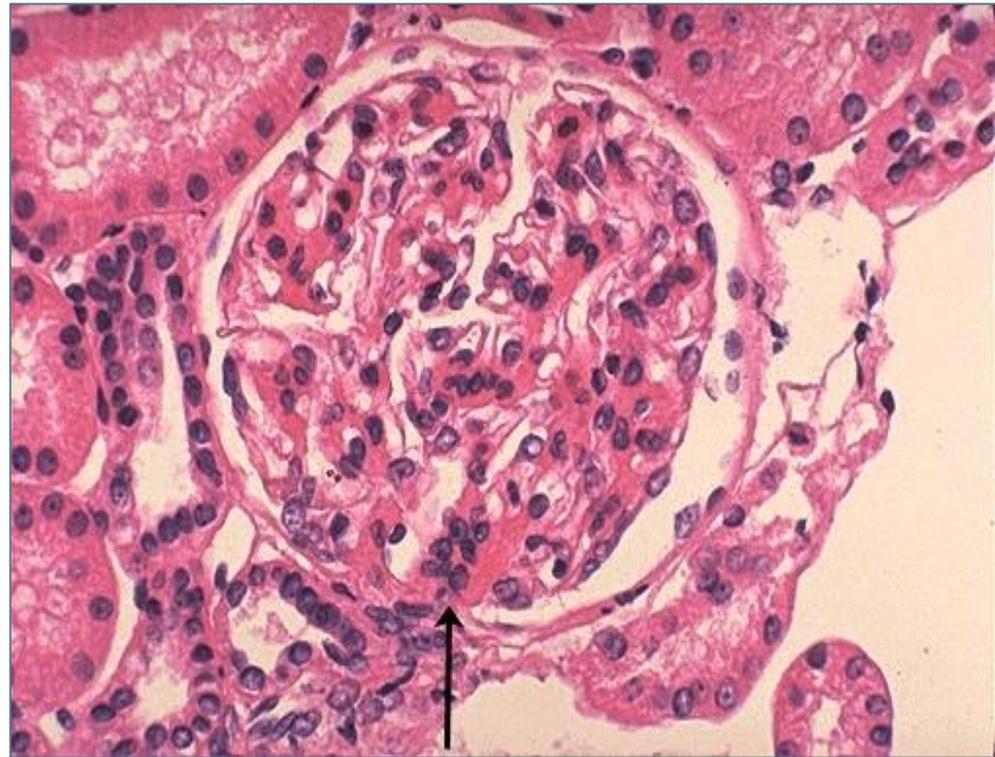
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- Most common GN **in the world**
- Male > female, 2<sup>nd</sup> to 3<sup>rd</sup> decade of life
- Clinical presentations are varied and progression typically slow.
  - Temporal relationship with URI/tonsillitis
  - 50 % Macrohematuria
- Associations / Secondary Causes
  - Liver disease
  - Celiac disease
  - Crohn's disease
  - Reiter syndrome, Ankylosing spondylitis
  - HSP = systemic vasculitis + IgA, children
- Treatment limited to ACE/ARB

# IgA Nephropathy Pathology

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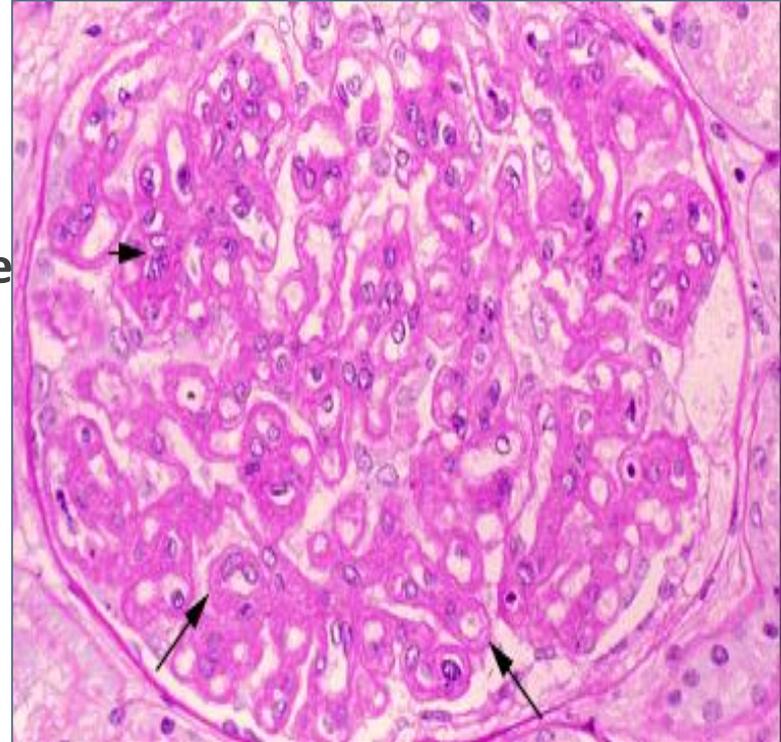
- Defect in IgA1-producing cells, leading to galactose deficient IgA1
- Antibodies form against galactose-deficient IgA1 (Gd-IgA1) → immune complexes which accumulate in glomerular mesangium
- Mesangial proliferation and matrix expansion on LM
- Deposits of IgA (often accompanied by C3 and IgG) in the mesangium on IF



# The Membranoproliferative Pattern of Injury

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- AKA MPGN or Mesangiocapillary GN
- Describes a general pattern of injury of variety of diseases that share common pathogenetic mechanism
- Typical LM features mesangial hypercellularity, endocapillary proliferation & **capillary wall double contours, ie “tram tracks”**
- Deposition of immunoglobulins, complement or both in mesangium & capillary walls



# Membranoproliferative GN (MPGN)

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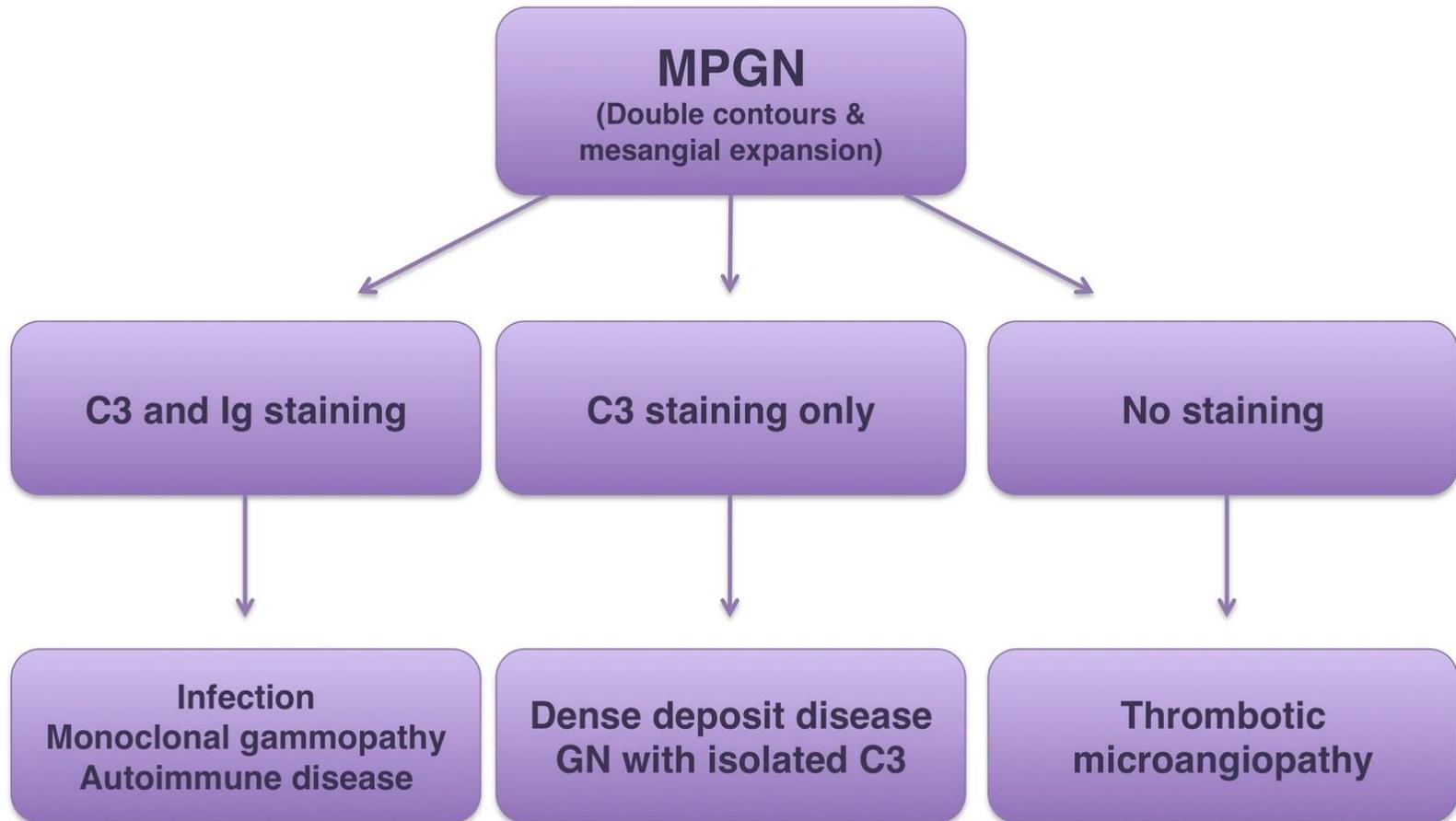
Clinical: **sub-nephrotic** > nephrotic

**Low serum C3**

Causes

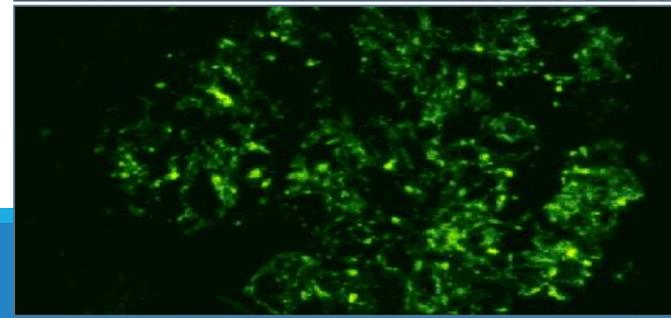
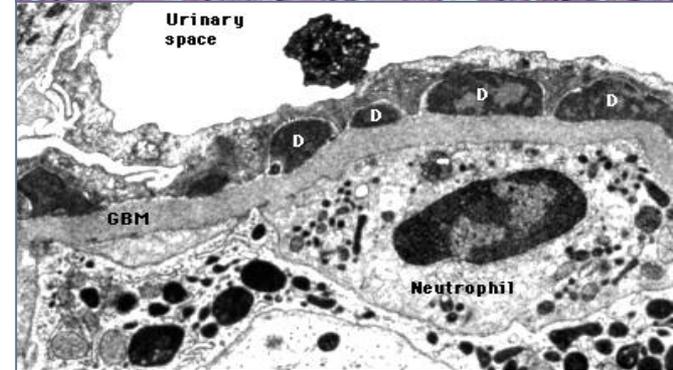
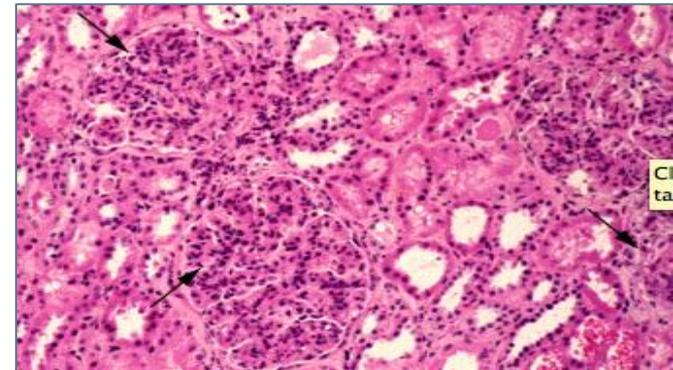
- Infections: HBV, HCV, infectious endocarditis, chronic bacterial or parasitic infections
- Auto-immune disease: SLE, Sjogrens, RA
- Dysproteinemias, inherited mutations in complement-regulating proteins

# MPGN Classification



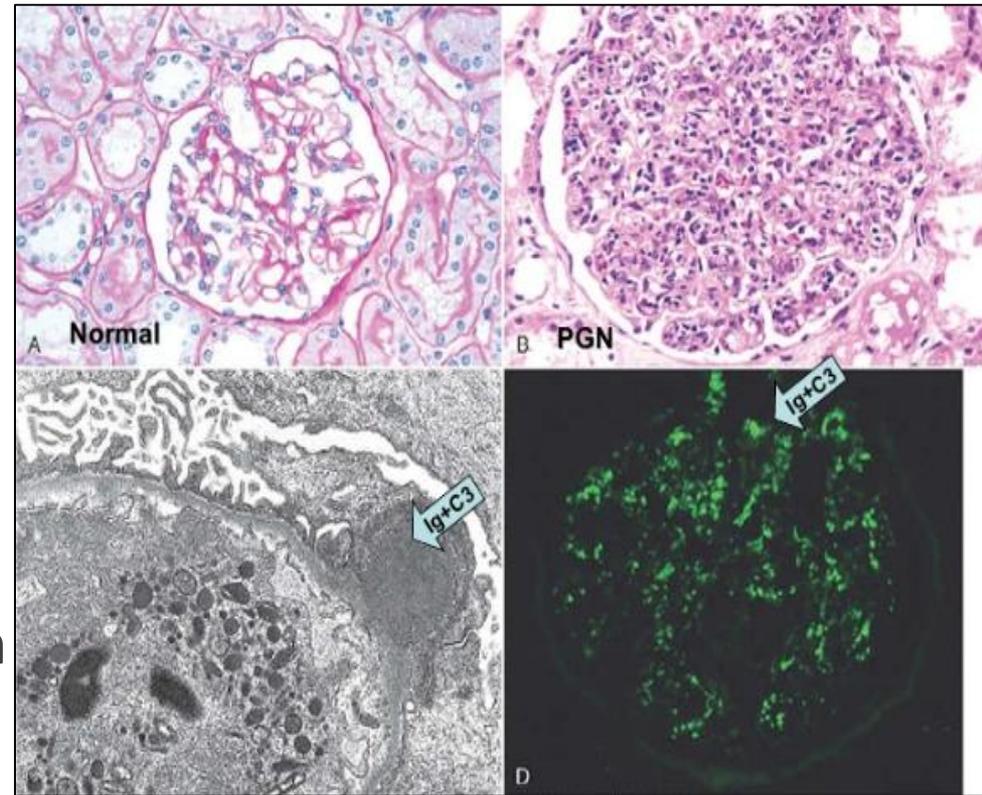
# Infection-Related / PSGN

- PSGN on decline in developed countries
  - 97 % cases occur in regions of the world with poor socioeconomic status
  - In developed countries, no longer a strong association with pharyngitis, rather skin-related
  - Mainly affects children, seasonal pattern
  - 1-8 weeks POST-infection
- Staph, gram (-) bact, viral infections more common in adults → GN develops DURING active infection
- **Low C3**



# Infection-Related / Post-Strep Glomerulonephritis Pathology

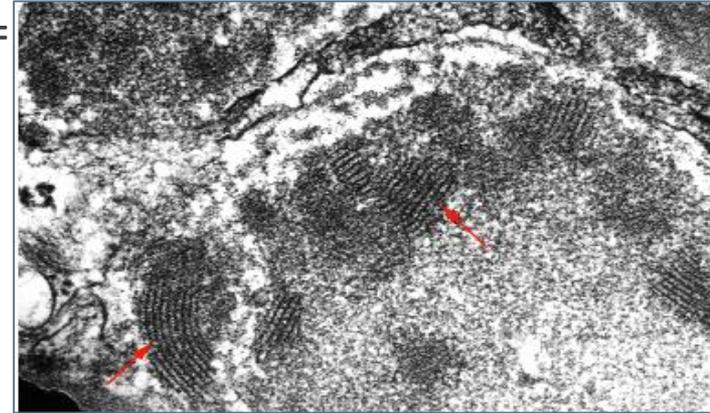
- Circulating immune complexes
- LM: Hypercellular glomeruli, intracapillary WBC/neutrophils
- EM: Electron-dense, glomerular **subepithelial** immune-complex deposits ("humps")
- IF: + IgG, C3 epithelial w/coarse granular glom wall/mesangial deposits AKA "starry sky" pattern



# Mixed Cryoglobulinemia

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- Production of circulating IG that precipitate on cooling
- IG complexes deposit in glomeruli + arterioles → bind complement → proliferative response
  - Sub-endothelial deposits on electron microscopy= “fingerprinting”
- Renal disease occurs in ~ 40 %
- **Low serum C4 > C3** and (+) RF
- Associations
  - Type I: Myeloma, Waldenstrom macroglobulinemia
  - Type II: Infections such as HCV, HBV
  - Type III: Collagen-vascular diseases, lymphoproliferative diseases, HCV



# Lupus Nephritis (LN)

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- Renal disease results from deposition of circulating immune complexes → complement cascade activation → comp-mediated damage, leukocyte infiltration, cytokine release
- Anti-dsDNA correlates best with renal disease
- **Low C4 > C3**

# ISN / Renal Pathology Society Classification of Lupus Nephritis (2004)

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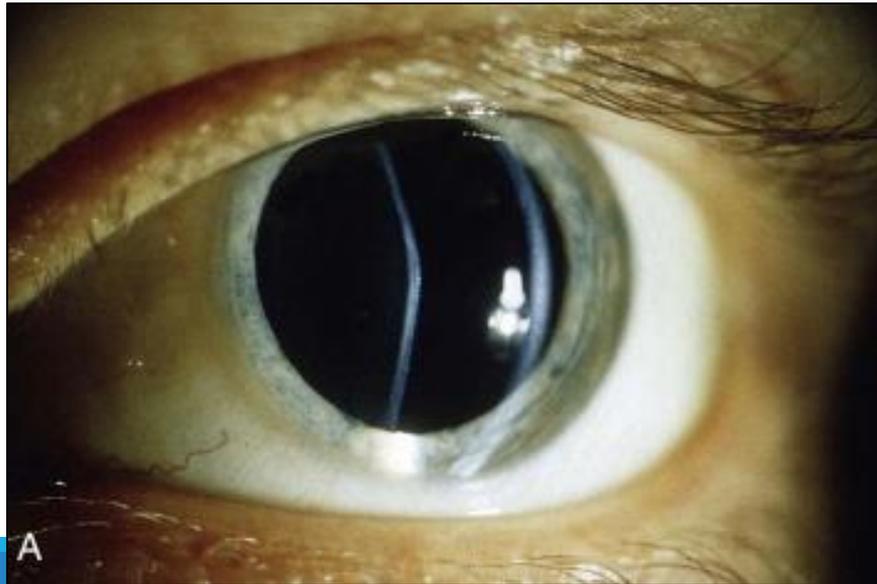
Class	Renal Pathology
I	Minimal mesangial LN
II	Mesangial proliferative LN
III	Focal LN (< 50 % glomeruli)
IV	Diffuse LN ( $\geq$ 50 % glomeruli)
V	Membranous LN
VI	Advanced sclerosing LN ( $\geq$ 90% globally sclerosed glomeruli)

# Question

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You are seeing a 26 year-old healthy man for pre-employment physical. He has no complaints. On ROS, he admits to a few episodes of gross hematuria for which he did not seek medical attention.

On physical examination, his BP is 159/88. His BMI is 21. He appears well except for a conical protrusion of the lens noted on ophthalmic exam pictured below.



# Question Continued

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What is the most likely diagnosis?

- A. Anti-GBM antibody disease
- B. IgA Nephropathy
- C. Hereditary nephritis
- D. HSP

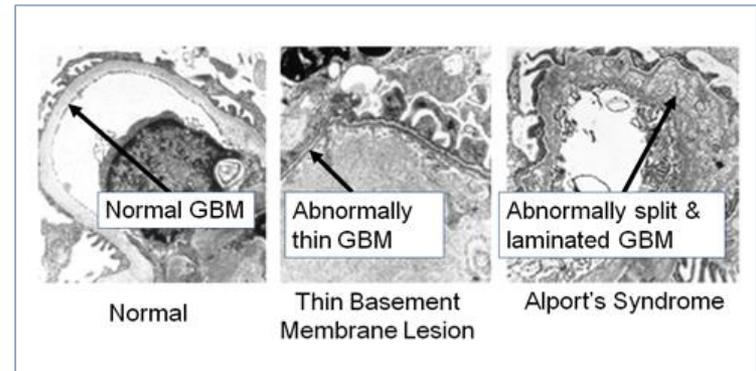
# Answer

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C. Hereditary nephritis

# Hereditary Nephritis: “Alport’s Syndrome”

- X-linked, either AR or AD
- Mutation in COL4A5 gene on X chromosome encoding  $\alpha$ -5 chain of type IV collagen found in GBM
- Clinical presentation: young man with asymptomatic persistent microhematuria
- Progression to ESRD typically by age 35



## Other Clinical Characteristics

- Sensorineural deafness
- Anterior lenticonus
- Retinopathy
- Leiomyomatosis

# Anti-GBM Disease

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Circulating antibodies to GBM with IgG deposits

Renal disease + pulmonary hemorrhage = Goodpasture Syndrome (30-40% pts)

Age/Gender predilection

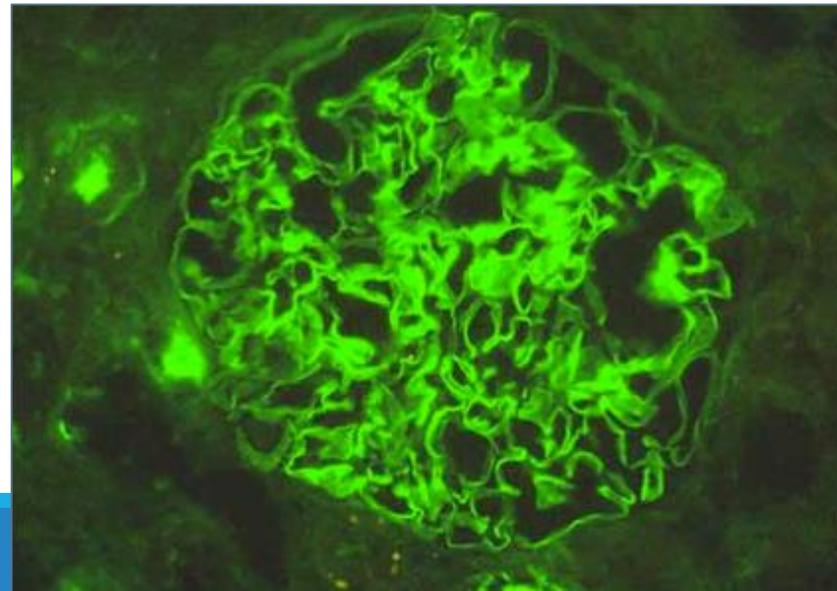
- 20-30 yo men > women
- 60-70 yo women > men

Diagnosis

- Renal bx: Linear IgG staining on IF
- (+) Anti-GBM Ab

Treatment

- Plasmapheresis, steroids, Cytoxan



# Pauci-Immune GN

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- Misnomer – classic renal autoimmune disease
- Most common cause of RPGN
- Usually a component of systemic small-vessel vasculitis
- Distinct histological pattern on IF
  - < 2+ glomerular Ig and complement staining
  - 1 year mortality ~ 80% without treatment
- ANCA (+) vasculitis ~ 90 %
  - Granulomatosis with Polyangiitis (GPA)
  - Microscopic Polyangiitis (MPA)
  - Renal-limited ANCA (+) vasculitis – 80% are MPO-ANCA (+)
  - Eosinophilic Granulomatosis with Polyangiitis (EGPA or Churg-Strauss)
- ANCA (-) vasculitis ~ 10 %

# Match the most common ANCA staining with the pauci-immune GN.

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- A. Granulomatosis with Polyangiitis (GPA)
  - B. Microscopic Polyangiitis (MPA)
  - C. Renal-limited ANCA (+) vasculitis
  - D. Eosinophilic Granulomatosis with Polyangiitis
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- p-ANCA (MPO Ab)
  - c-ANCA (PR3 Ab)

# Answer

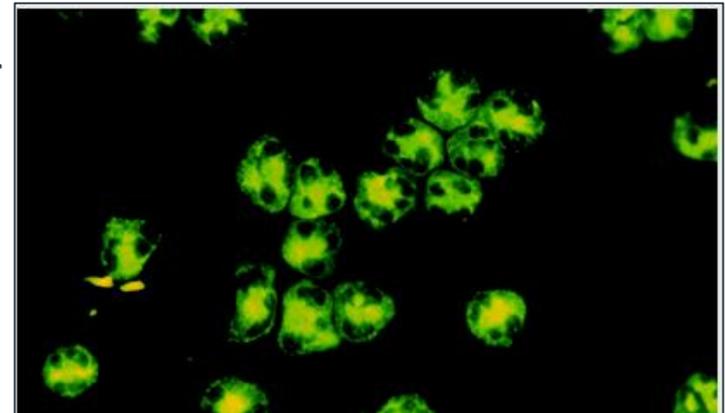
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- A. Granulomatosis with Polyangiitis (GPA) - c-ANCA
- B. Microscopic Polyangiitis (MPA) - p-ANCA
- C. Renal-limited ANCA (+) vasculitis - p-ANCA
- D. Eosinophilic Granulomatosis with Polyangiitis - p-ANCA > c-ANCA

# Granulomatosis with Polyangiitis (GPA)

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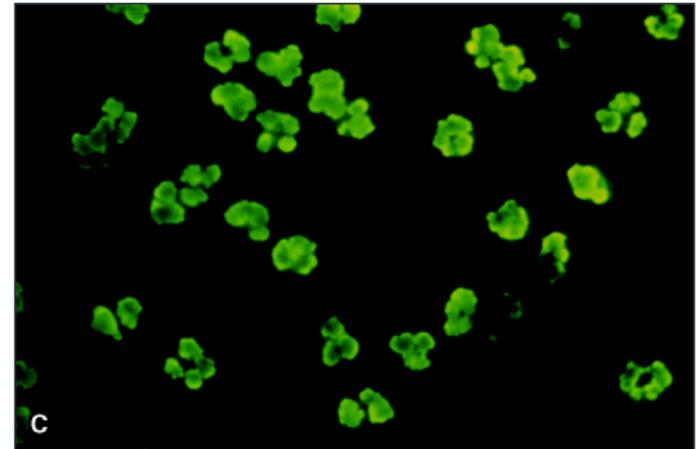
- cANCA cytoplasm staining for PR3 antibodies → neutrophil activation → release of ROS and lytic enzymes + alternative complement path activation
- Granulomatous inflammation and extensive extra-renal involvement → upper respiratory tract, ENT, & lung (oral ulcers, nasal discharge, uveitis, sinusitis, pulm infiltrates)
- Higher relapse rate than pANCA phenotype
- Microbial factors implicated – + *S aureus* nares
- ? Genetic factors – more common in whites, older



# Microscopic Polyangiitis (MPA)

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- pANCA perinuclear staining for MPO-antibodies
- Worse renal prognosis than cANCA phenotype
- Similar clinical picture to GPA but without significant respiratory tract involvement
- Non-specific sx fatigue, fever, anorexia, weight loss
- ~ 50% patients: Leukocytoclastic angiitis  
urticaria, livedo reticularis & other skin lesions



# Eosinophilic Granulomatosis with Polyangiitis

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- AKA “Churg-Strauss”
- pANCA (+) > cANCA
- Eosinophilia, asthma, and atopy
  - +/- elevated serum IgE levels
- Episodic cough and and pulm infiltrates years prior to syst
- Tender subcutaneous nodules (granulomas) on the extensor surfaces of the arm (50-67%)
- Peripheral neuropathy, usually mononeuritis multiplex (75%)
- Milder than GPA and MPA



# ANCA Vasculitis: Treatment

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- Steroids
- Cyclophosphamide
- Rituxan
- Plasmapheresis in severe / dialysis-dependent AKI

# Rapidly Progressive GN (RPGN)

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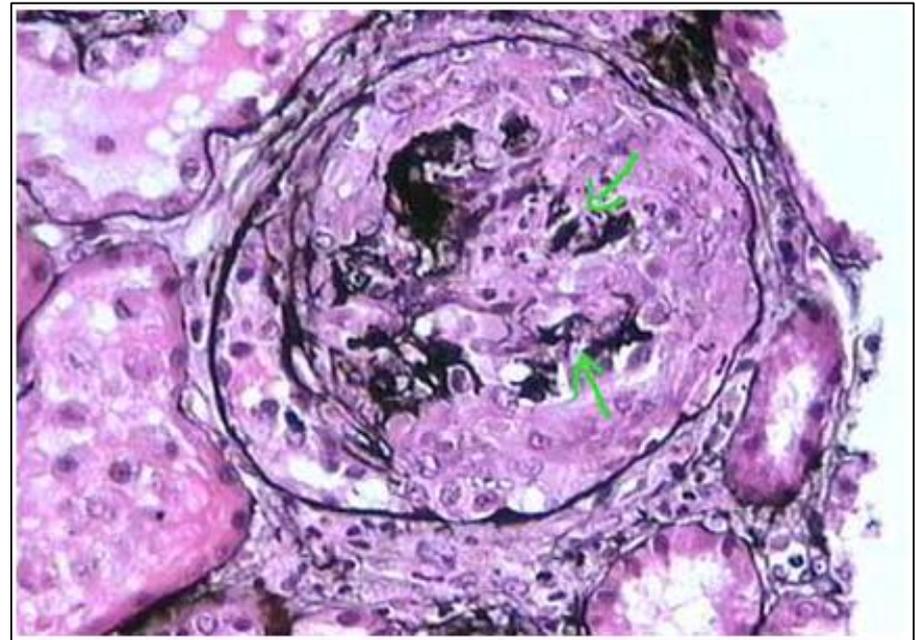
- NOT a specific disease
  - Clinical & histological entity indicating severe glomerular damage
- Clinical definition: rapidly progressive renal failure (weeks to months) secondary to acute glomerulonephritis
- Pathological definition: glomerular extracapillary proliferation
  - Hallmark: “Crescents” typically  $\geq 50\%$  gloms
  - AKA “Crescentic GN”

# Glomerular Crescent

Either partially or completely filling up Bowman's space

Composed of proliferating parietal epithelial cells, podocytes, macrophages, and fibroblasts

Stimulated by entry of fibrin and other plasma proteins from the capillary lumens following the rupture of the GBM



**Extracapillary proliferation within a glomerulus**

# Which of the following is NOT a cause of RPGN?

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- A. Pauci-immune GN
- B. IgA nephropathy
- C. Anti-GBM Ab disease
- D. Renal amyloid

# Answer

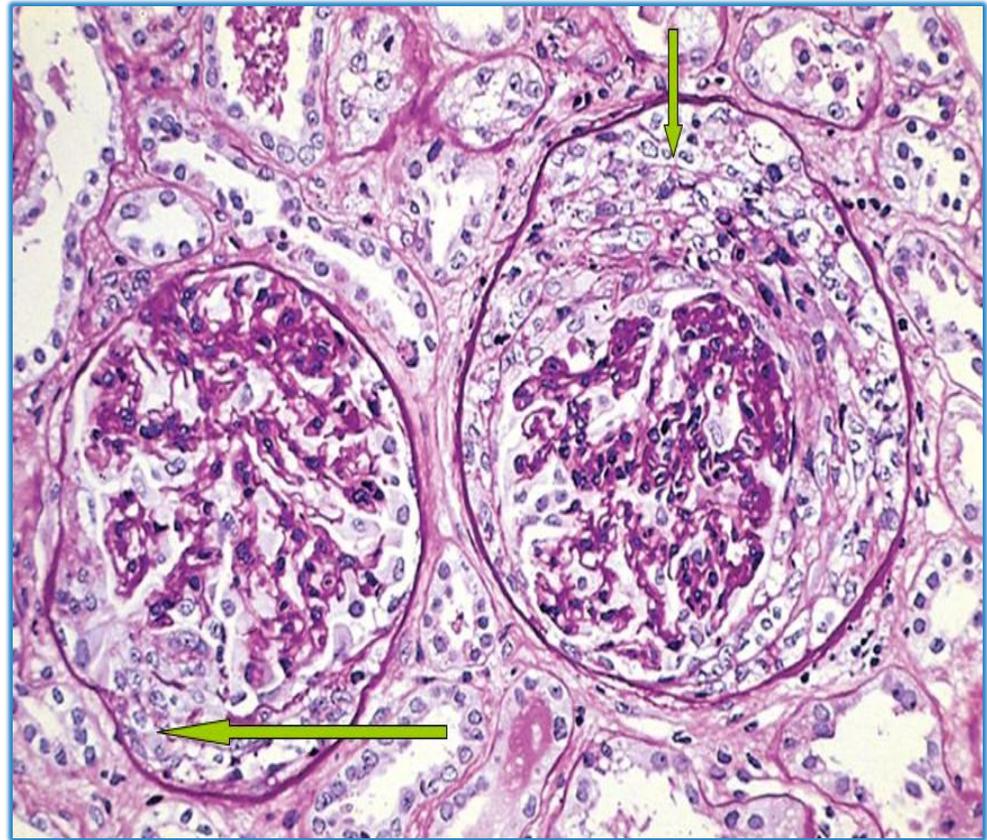
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D. Renal amyloid

# RPGN Causes

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- Pauci-immune GN (80%) = #1 Cause
  - 96 % are ANCA (+)
- Anti-GBM Ab disease
- Immune-complex GNs



# Questions?

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# References

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