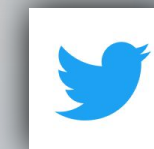


XXI CORSO NAZIONALE DI ULTRASONOLOGIA  
VASCOLARE

20-22 Aprile 2023

# Le arteriopatie infiammatorie... la valutazione nefrologica

*Carlo Alfieri*



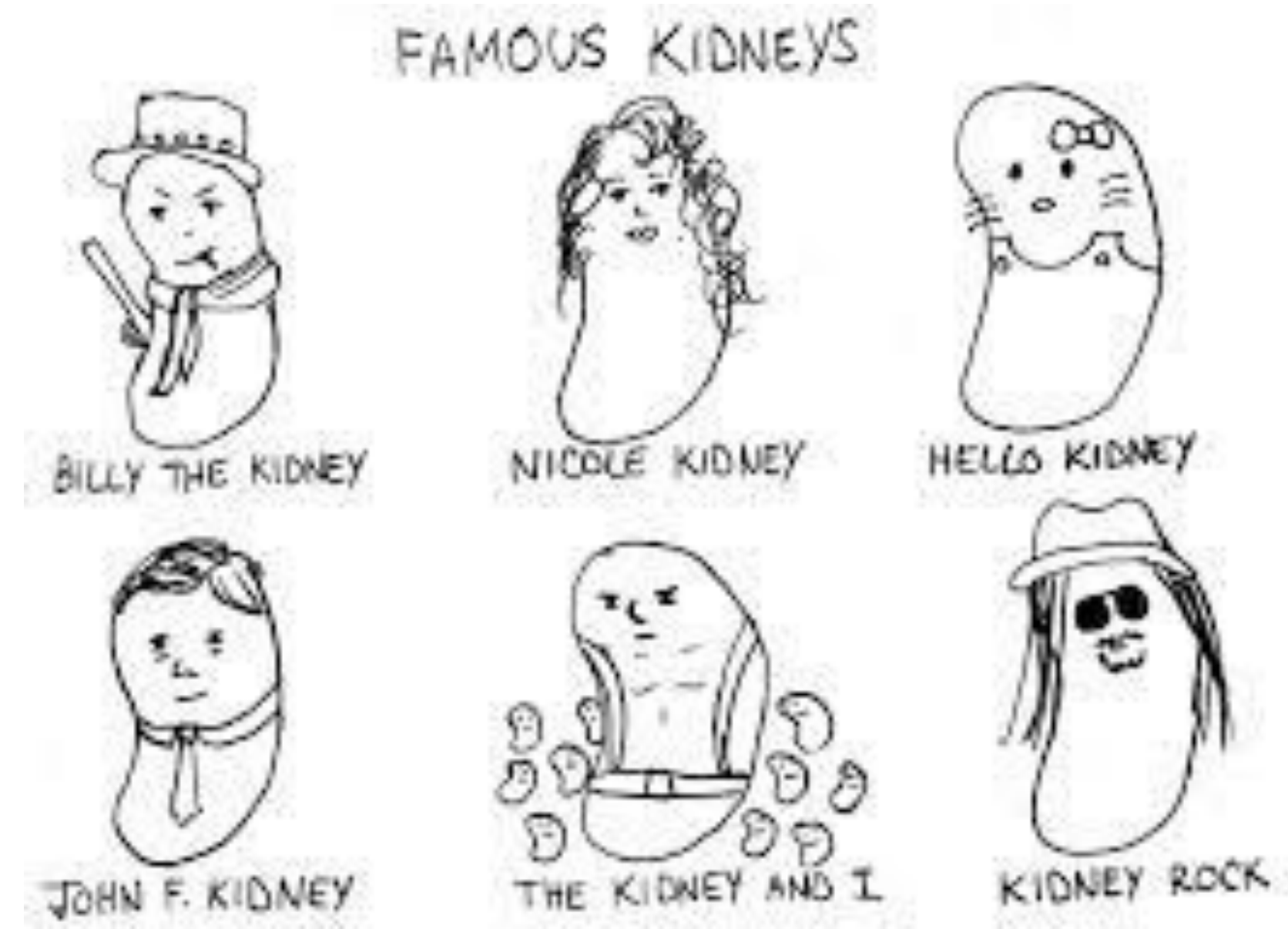
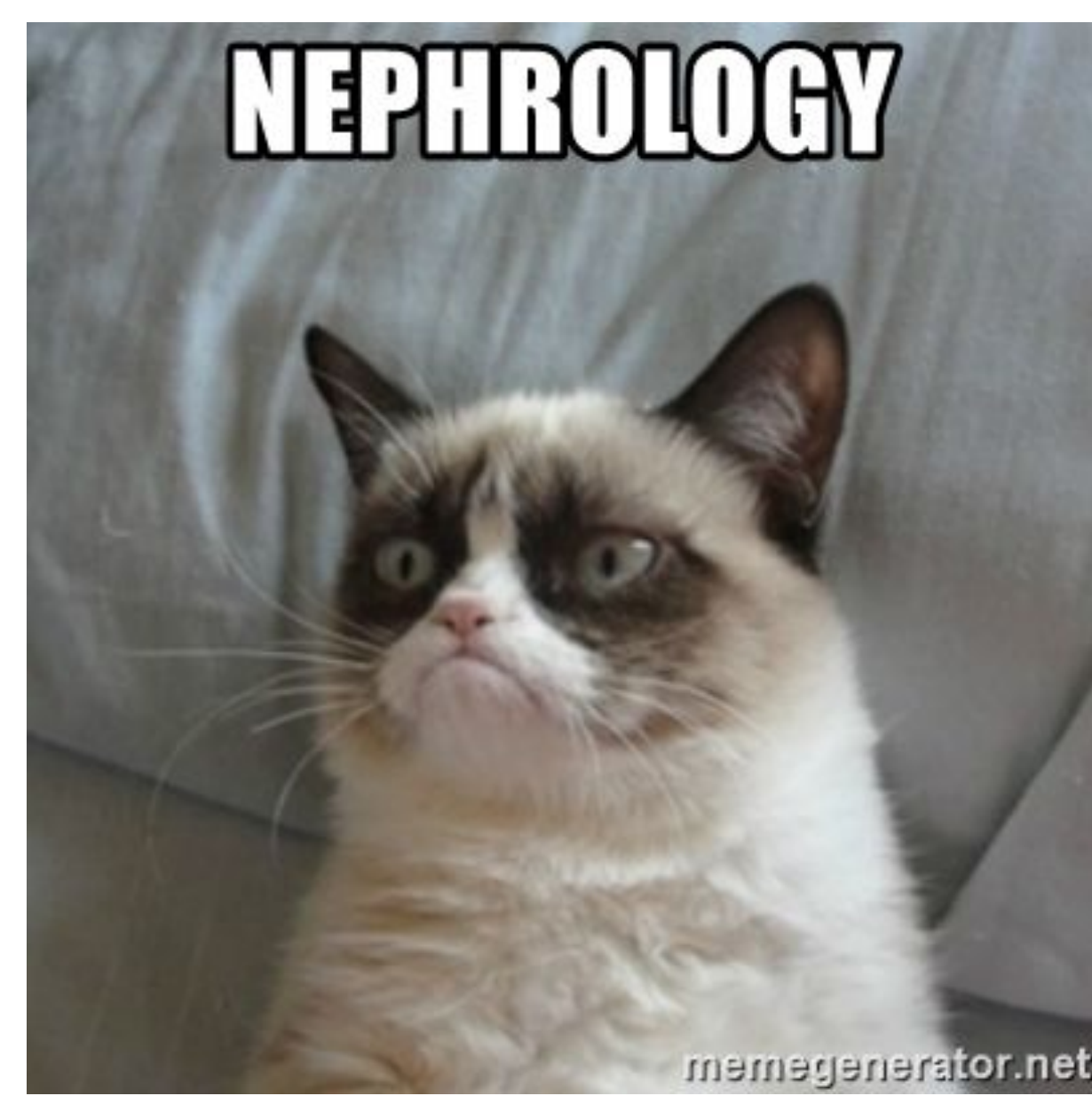
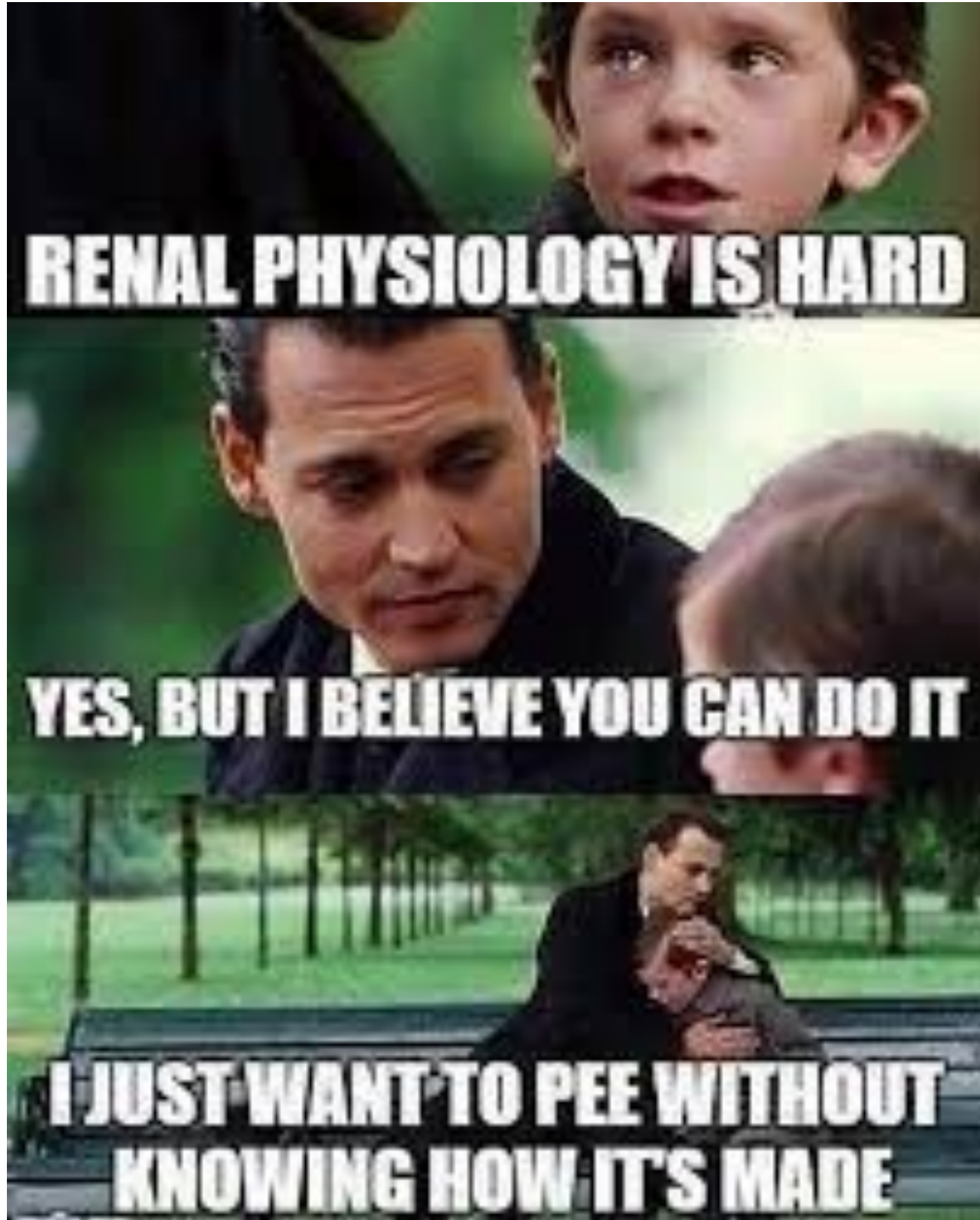
@CARLO\_ALFIERI

*Nephrology, dialysis and renal transplantation*

*Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan*

*Department of Clinical Sciences and Community Health  
University of Milan*





# Definition

Inflammatory



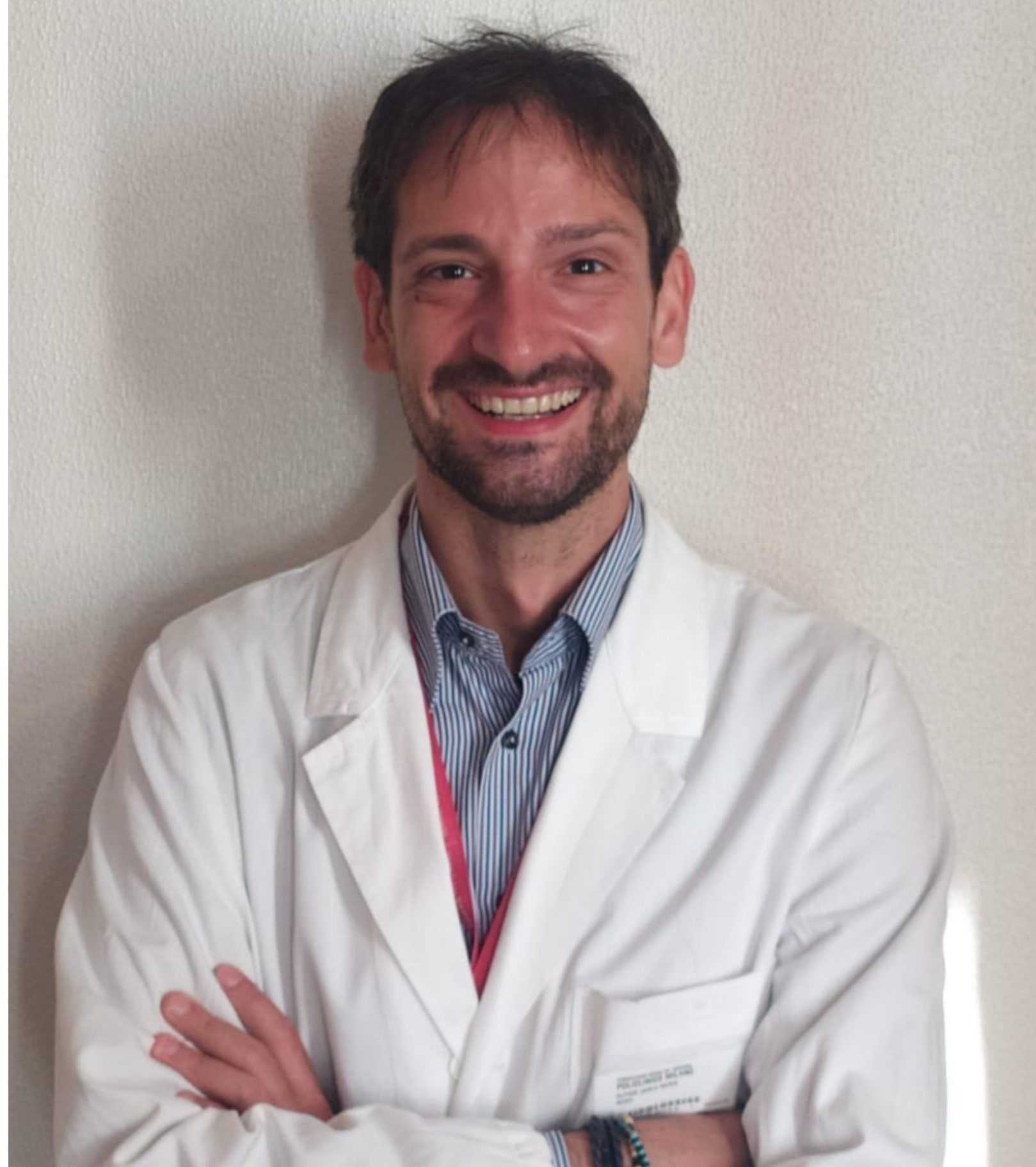
Pertaining to, characterized by, causing, resulting from, or becoming affected by inflammation

Arteriopath

y

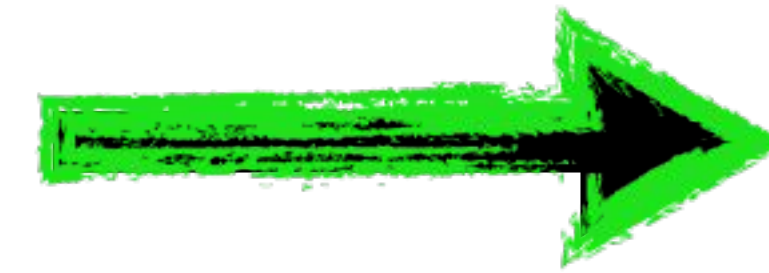


Any disease of an artery



# Agenda

Nephrologic evaluation: from the  
beginning to deep points



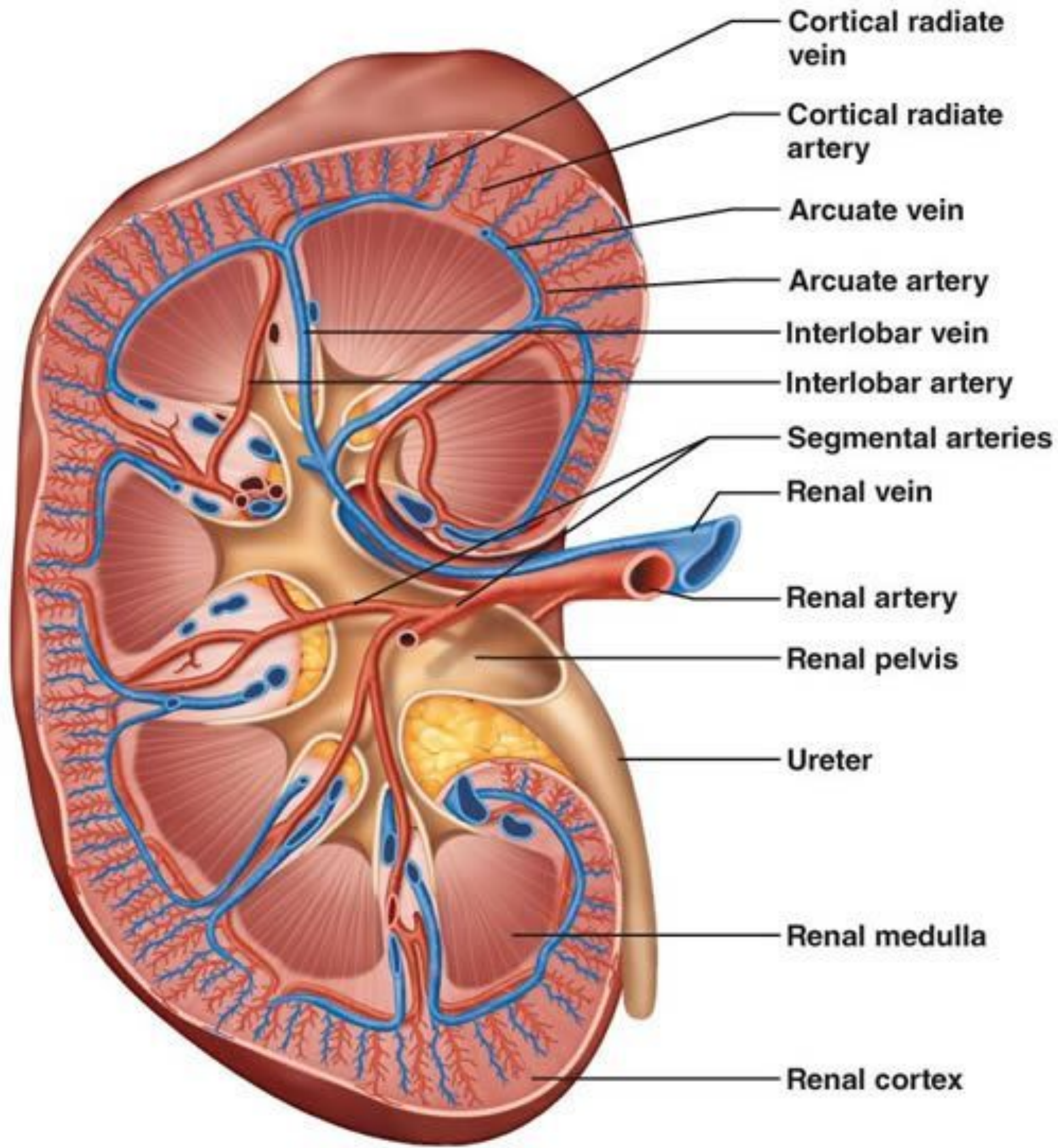
IgA Vasculitis



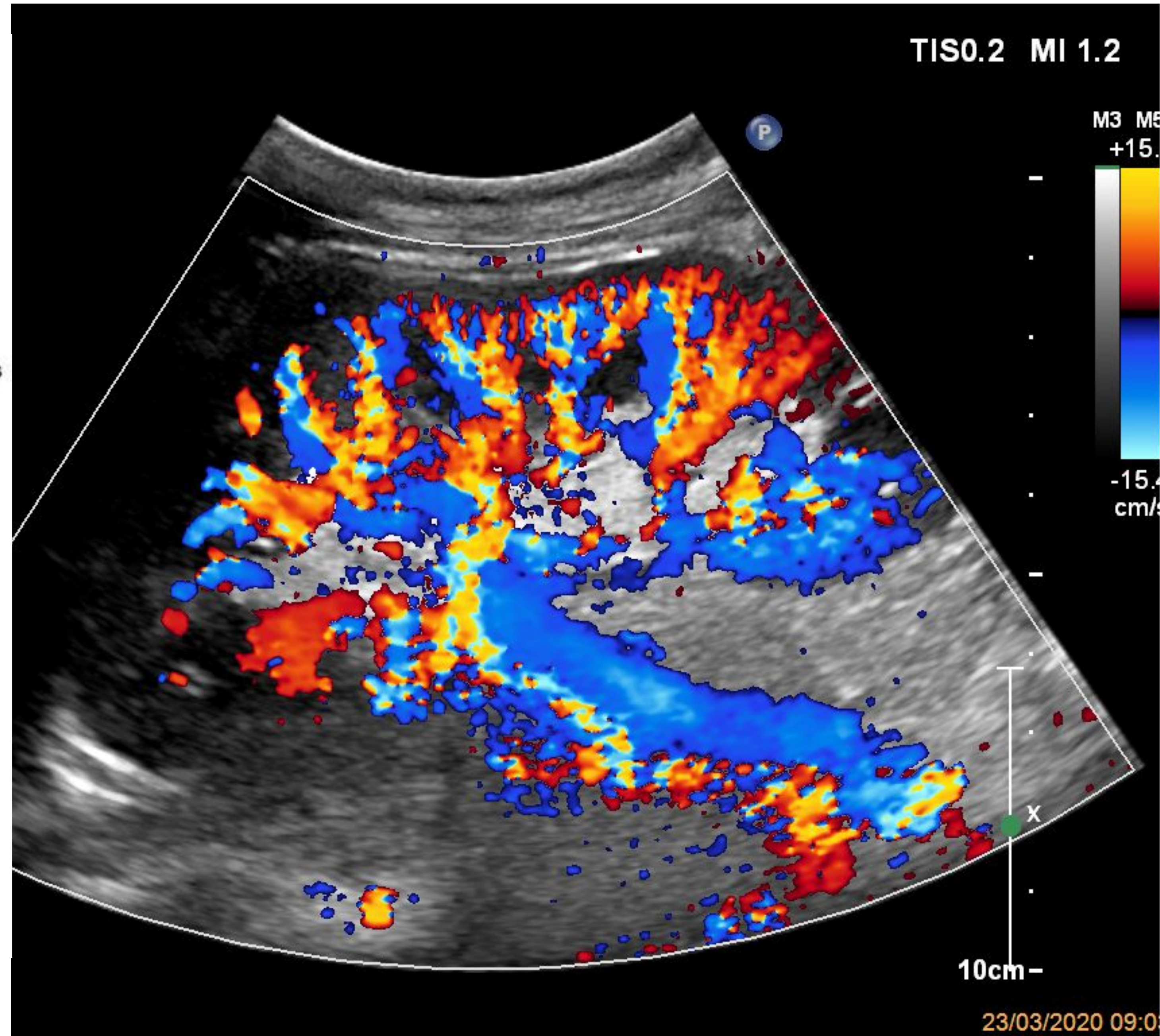
Lupus Nephritis

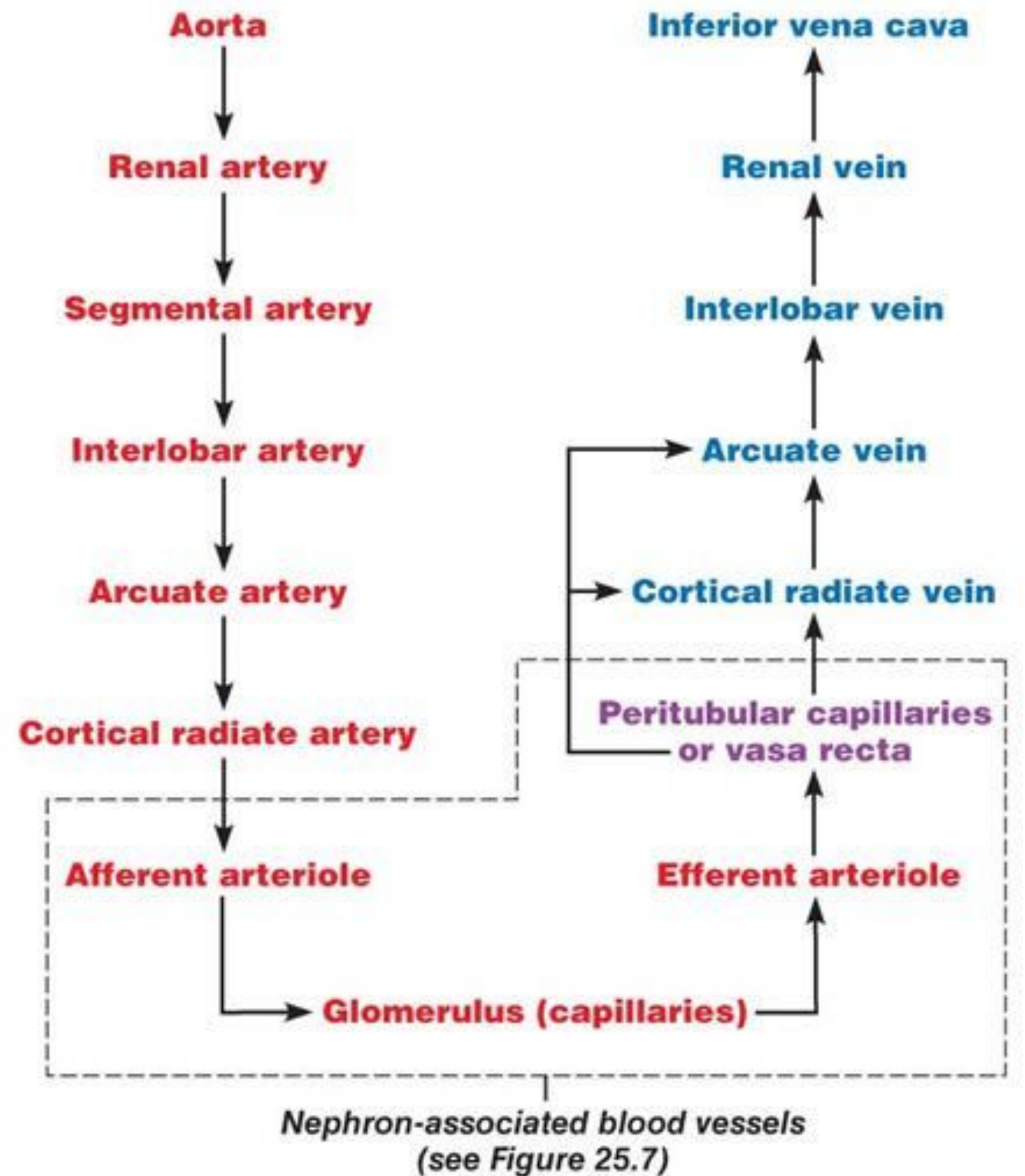
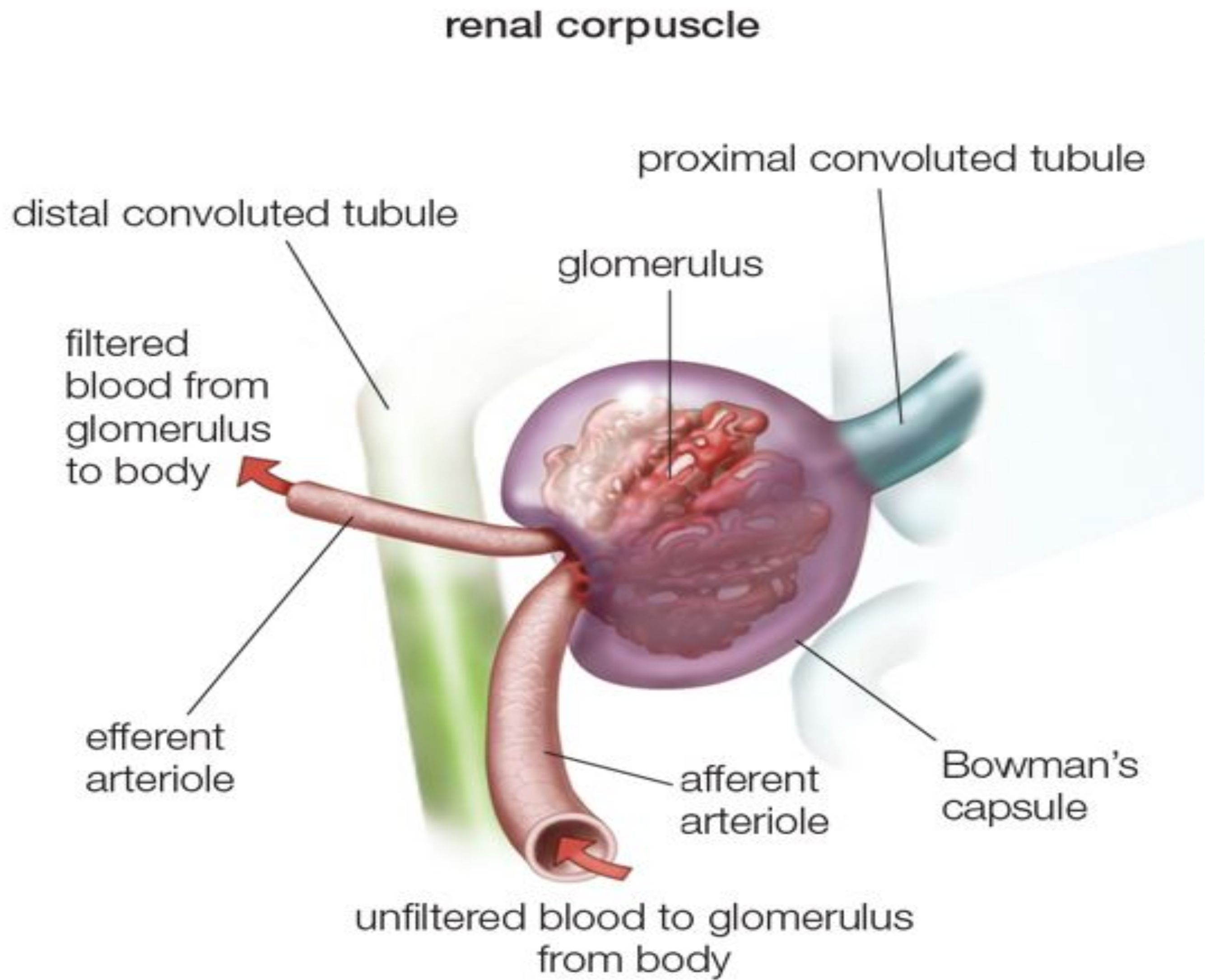


ANCA  
related  
glomerulonephritis



**(a) Frontal section illustrating major blood vessels**





**(b) Path of blood flow through renal blood vessels**

# Inflammatory artheriopathies

- Definition and classification
- Pathogenic mechanisms
- Clinical aspects
  - Symptoms
  - Diagnosis
  - progression
- Therapy



Renal disease characterized by

**inflammatory processes**

involving **primarily** the glomerulus, but often also other renal compartments  
(tubules, interstitium, vessels)



# Inflammatory artheriopathies

- Definition and classification
- Pathogenic mechanisms
- Clinical aspects
  - Symptoms
  - Diagnosis
  - progression
- Therapy



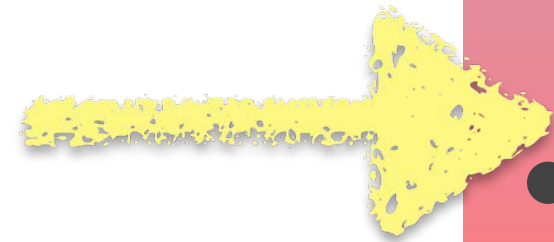
# Symptoms

Specific of the  
renal  
involvement

Symptoms  
associated to  
the systemic  
disease

# Inflammatory artheriopathies

- Definition and classification
- Pathogenic mechanisms
- Clinical aspects
  - Symptoms
  - Diagnosis
  - progression
- Therapy



# Methods for assessing renal function

## Glomerular function

- Quantitative evaluation
- Qualitative evaluation

## Tubular function

## Endocrine functions

## Morphological evaluation

- Microscopic evaluation
- Macroscopic evaluation



# The assessment of glomerular function

- Quantitative evaluation
  - Creatinine??...better Glomerular filtration rate!
- Qualitative evaluation
  - Proteinuria
  - Urine analysis

# Proteinuria

## Albuminuria

■ Urinary-Albumin  $\geq 30$  mg/day

Mild 30 mg - 300mg/ day

Moderate-severe  $> 300$  mg/day

## Albuminuria/Creatininuria

Albuminuria categories in CKD		
Category	ACR (mg/g)	Terms
A1	$< 30$	Normal to mildly increased
A2	30-300	Moderately increased*
A3	$> 300$	Severely increased**

\*Relative to young adult level. ACR 30-300 mg/g for  $> 3$  months indicates CKD.  
\*\*Including nephrotic syndrome (albumin excretion ACR  $> 2220$  mg/g)

## Proteinuria:

2018 National Kidney Foundation

■  $> 0.200$  g/day

Low 0.200- 1.0 g/day

Mild 1.0-3.5 g/day

Severe (nephrotic)  $>3.5$  g/day

## DIFFERENT TYPES OF PROTEINURIA

Transient proteinuria



Occurs with dehydration, stress, heavy exercise, fever & subsides on its own

Orthostatic proteinuria



Loses protein via urine only while standing & never while sleeping

Persistent proteinuria



Consistent presence of proteins in urine from kidney disease, diabetes & high BP

## HOW DO YOU TEST FOR PROTEINURIA

Have your urine sample tested at a lab via dipstick test, protein electrophoresis, microscopic & visual examinations

Undergo blood tests that tell you about kidney function

Get the kidneys scanned to detect stones, tumors & more

Do kidney biopsy if doubtful of tumors & growths



iCliniq  
The Virtual Hospital

# Urine analysis

*Urinalysis is one of the key tests to evaluate kidney and urinary tract disease*

*The use of an early morning urine sample is suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, especially for the measurement of albumin*

## General and microscopic characteristics

- Colour: depending on the concentration of the urochrome. Abnormal changes in color can be caused by pathologic conditions, drugs, or foods.
  - Appearance: normally transparent and odorless
  - Specific gravity: weight of a volume of urine compared with the weight of the same volume of distilled water: depends on the mass and number of the dissolved particles
  - pH: reflects the presence of hydrogen ions (H<sup>+</sup>)
  
  - Proteinuria
  
  - Sediment
    - RC
    - WC
    - Casts
    - crystals
- } Urine sediment examination is an integral part of urinalysis!!



# Urinary microscopic evaluation

Red blood cells

# Urinary microscopic evaluation

Urinary erythrocytes have a mean diameter of approximately 6  $\mu\text{m}$ :

- isomorphic, with regular shapes and contours, derived from the urinary excretory system;
- dysmorphic, with irregular shapes and contours, which are of glomerular origin

- Hematuria

- Microscopic:  $> 3\text{-}4$  RBC x field
- Macroscopic
- Continuous
- Episodic/sporadic

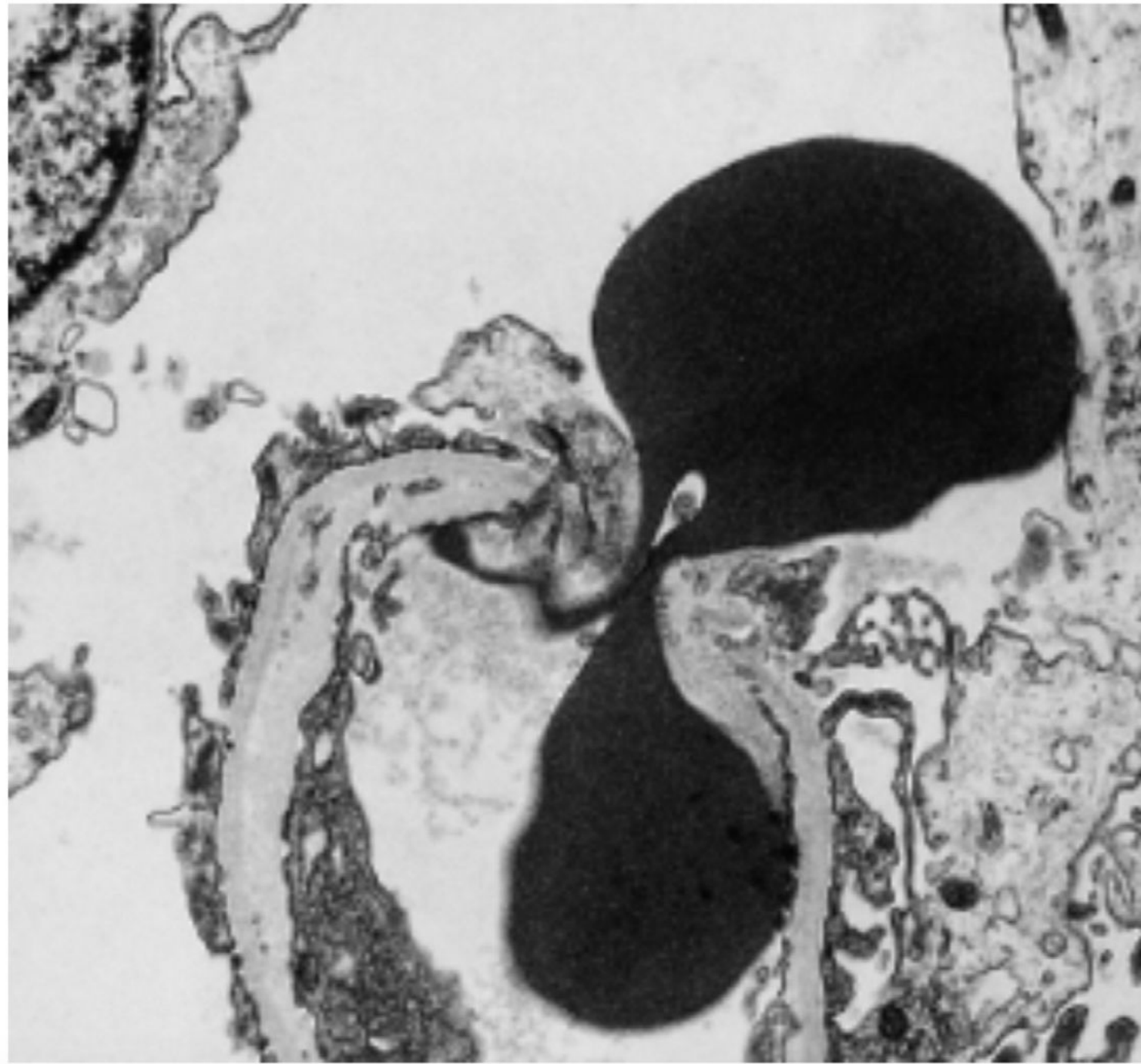


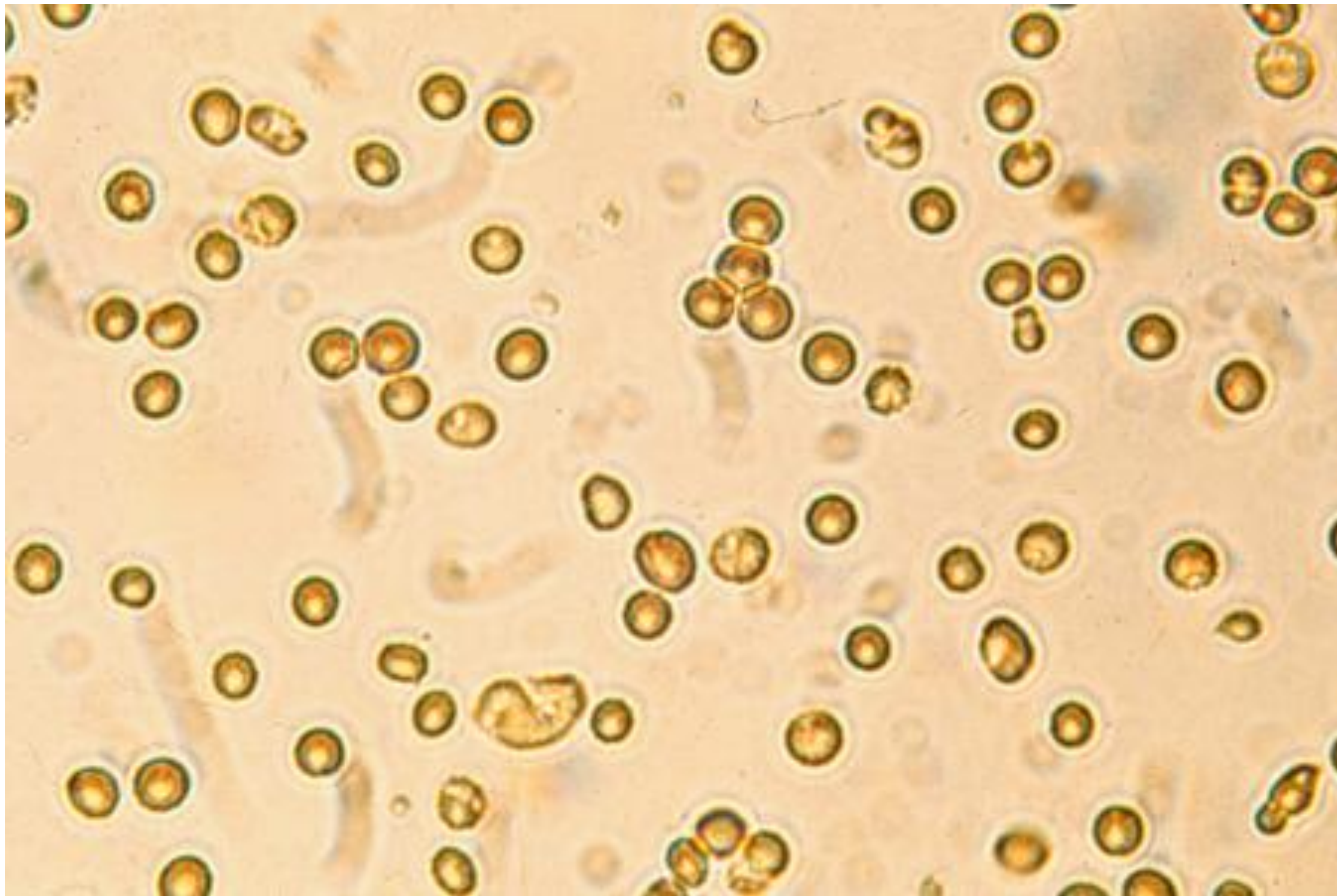
# Why dysmorphic erythrocytes ?

The average diameter of an erythrocyte is 6-8  $\mu\text{m}$ , which is about 100 times the size of the endothelial fenestration (60-80 nm) in the glomerulus

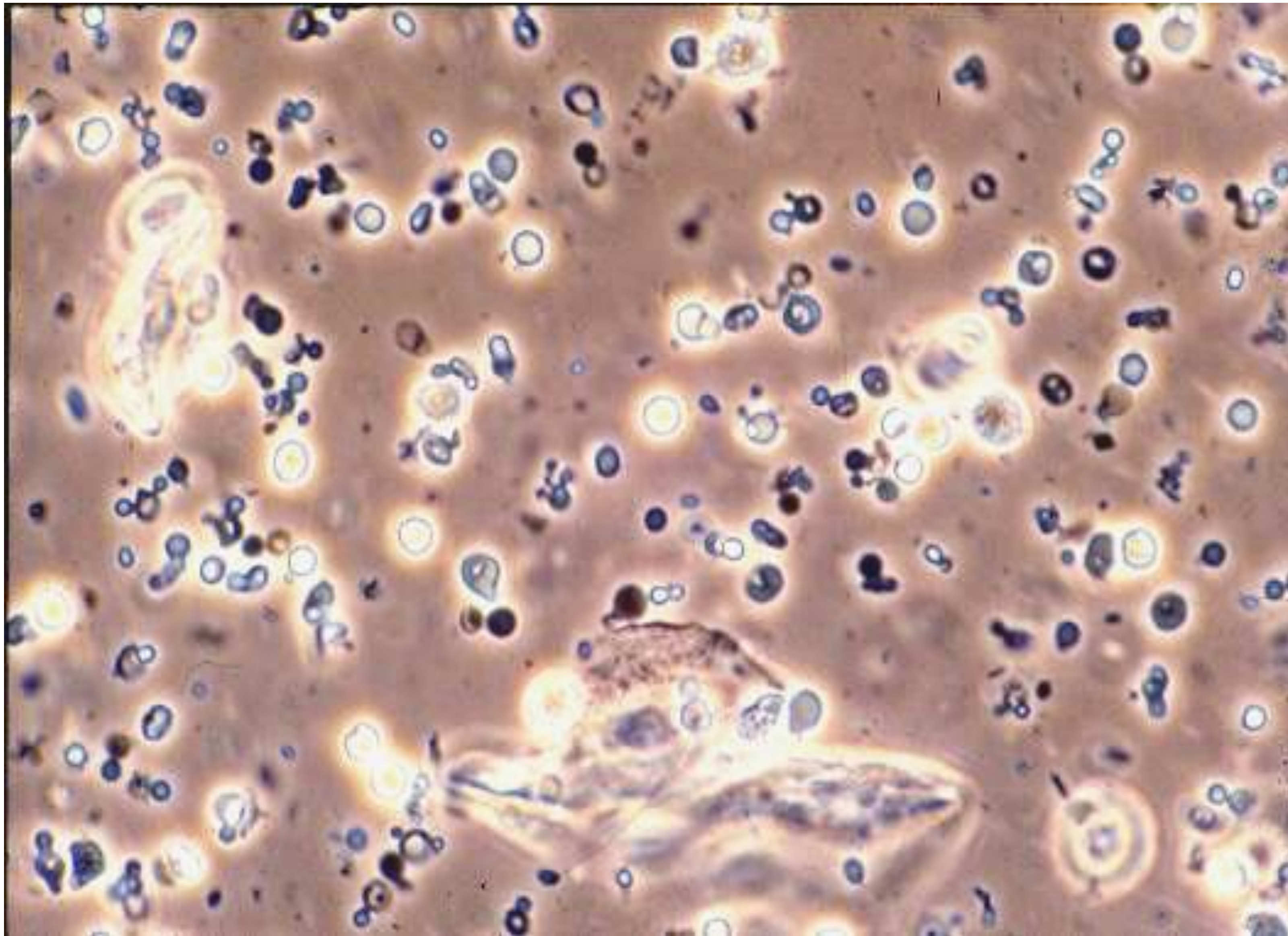
In immune-complex glomerulonephritis (GN), without cellular crescents, hematuria may result from small ruptures in GBM that may occur due to lysosomal digestion around deposited immune complexes

Passage of RBCs through a disrupted GBM might be sufficient for dysmorphism, but further membrane alteration and fragmentation occur due to differential pH and osmotic forces in tubular fluid, resulting in loss of hemoglobin and forming hypochromic dysmorphic RBC.

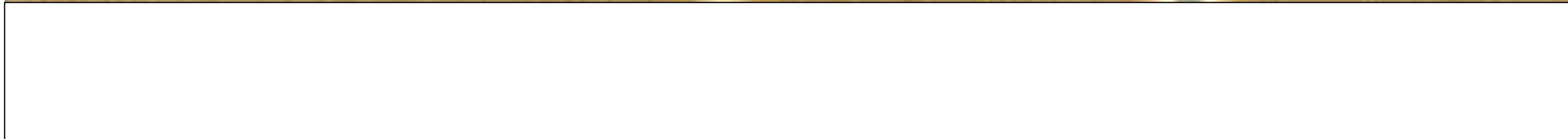
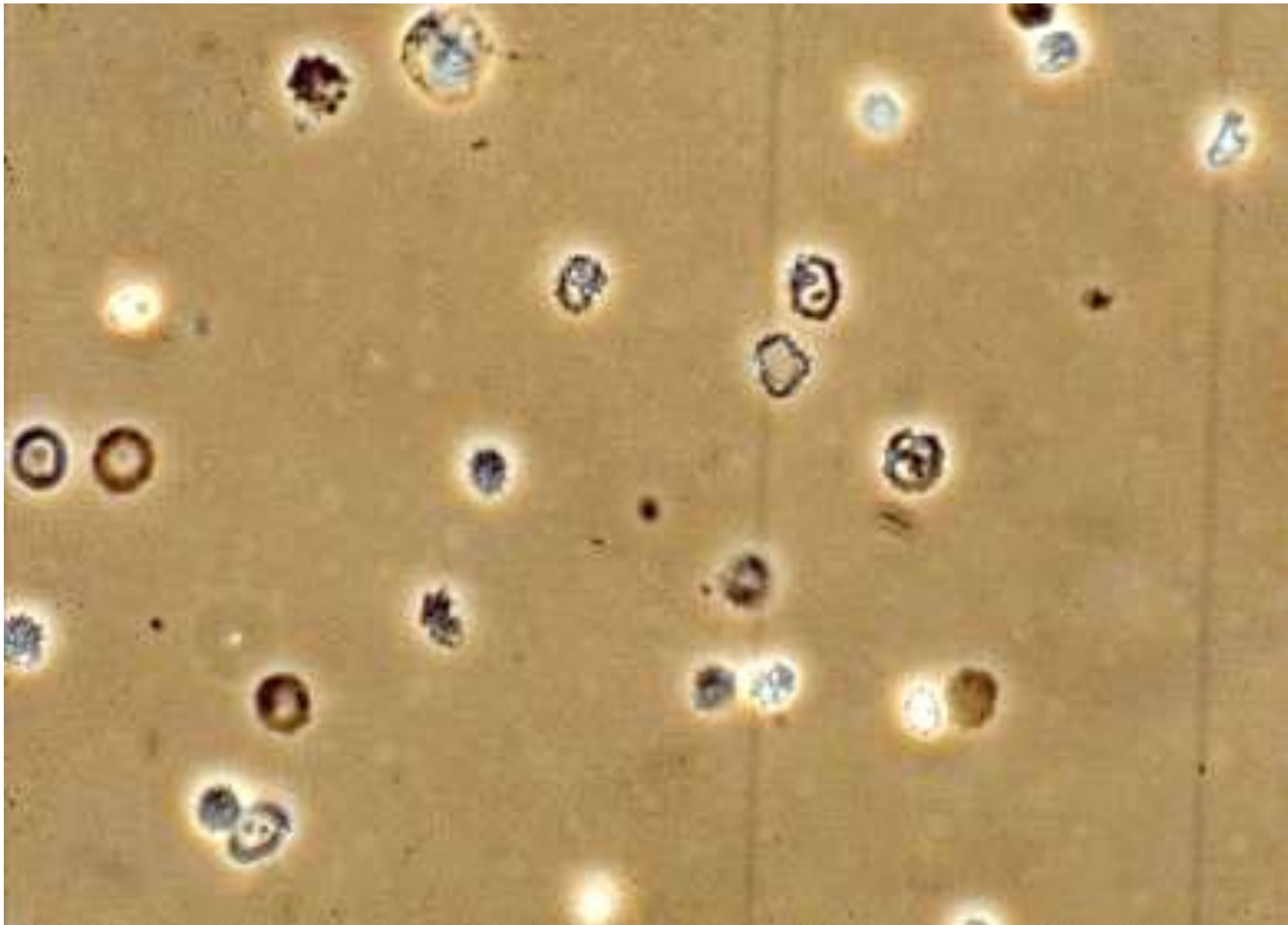


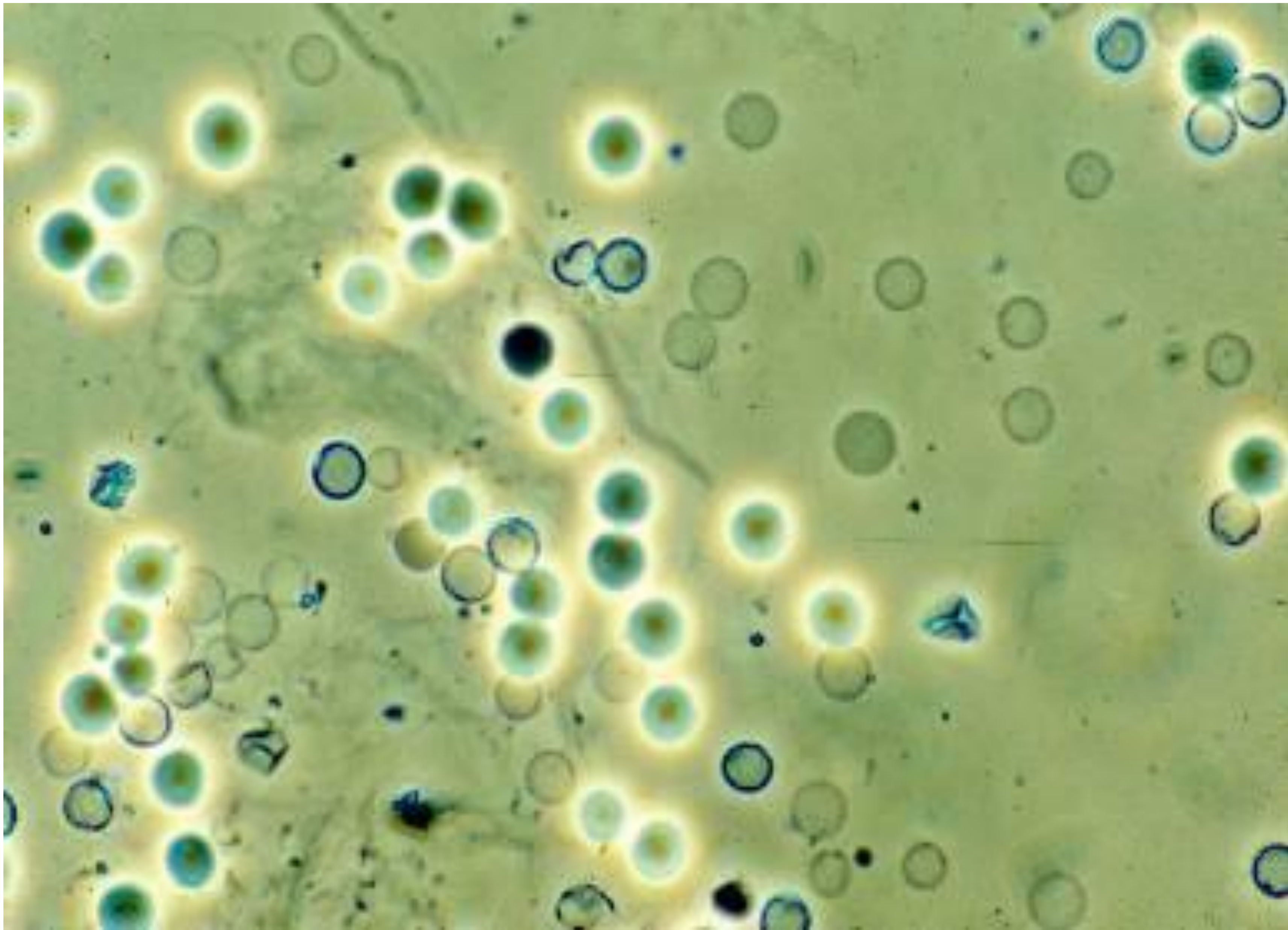


Ballon-shaped red cells, all of similar appearance  
(calculi in the renal pelvis) (400x)



Hematuria: the cells are clearly abnormal (glomerulonephritis). Findings of this kind indicate the red cells have almost certainly come from the glomerulus (400x)





# Urinary Casts

<b>Cast</b>	<b>Main Clinical Associations</b>
Hyaline	Normal individual; renal disease
Hyaline-granular	Normal individual; renal disease
Granular	Renal disease; acute tubular necrosis
Waxy	Renal disease with possible functional impairment
Fatty	Proteinuria; nephrotic syndrome
Erythrocyte	Glomerular hematuria; proliferative/necrotizing GN; acute interstitial nephritis
Leukocyte	Acute interstitial nephritis; acute pyelonephritis; proliferative GN
Renal tubular epithelial cell (so-called epithelial casts)	Acute tubular necrosis; acute interstitial nephritis; proliferative GN; nephrotic syndrome
Hemoglobin	Same as for erythrocyte cast; hemoglobinuria caused by intravascular hemolysis
Myoglobin	Rhabdomyolysis
Bilirubin	Jaundice caused by increased direct bilirubin
Bacterial, fungal	Bacterial or fungal infection in the kidney
Containing crystals	Renal stone disease; crystalline nephropathies
Mixed	According to components present in the cast

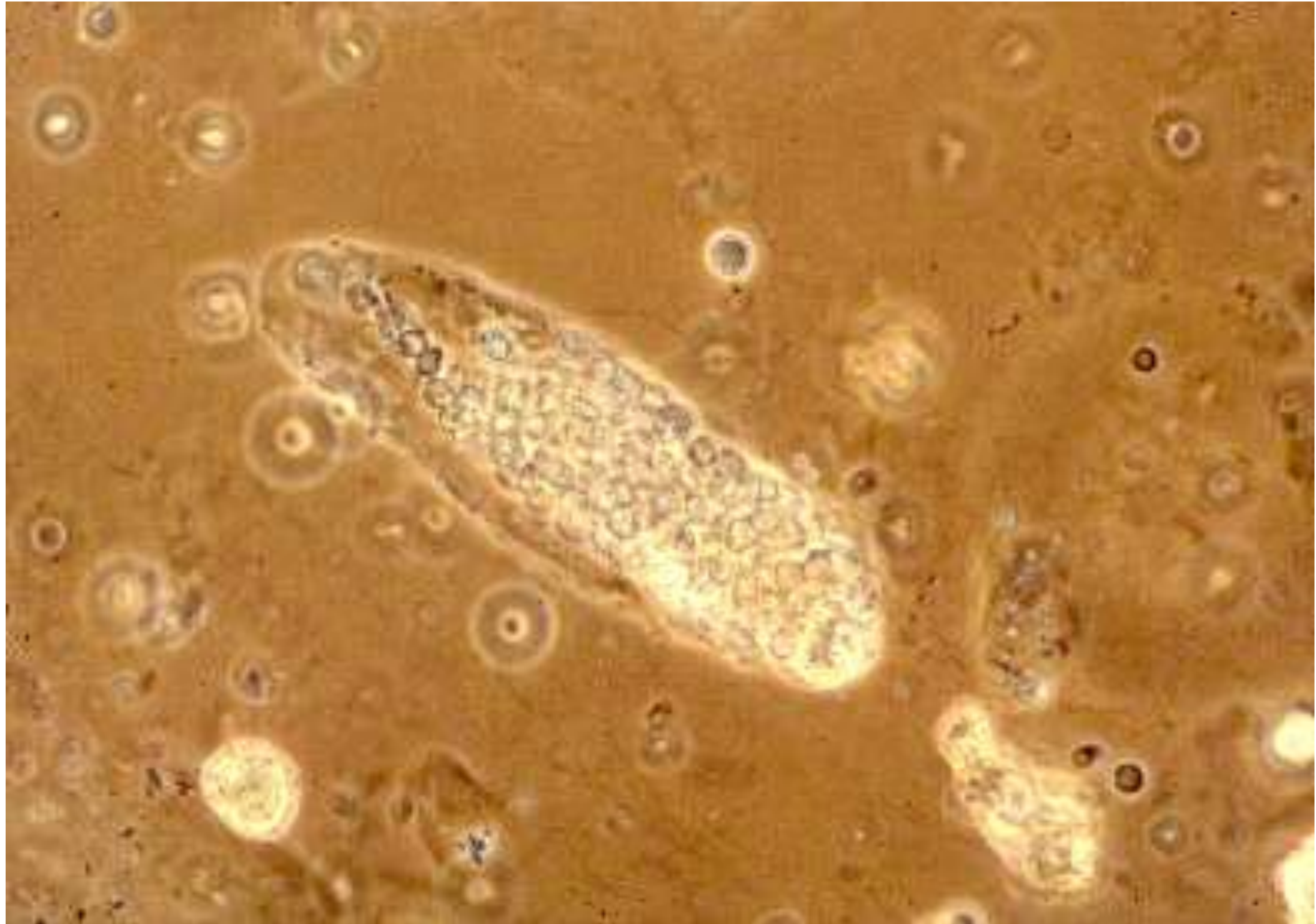
Cylindrical elements of variable diameter and length which form mostly in the distal tubules and collecting ducts of the kidneys





*RBC cast - brightfield, unstained -  
from patient with acute presentation  
of Granulomatosis with polyangiitis*

**Usually considered a marker of  
glomerular bleeding**



**ERYTHROCYTE CAST** usually considered a marker of glomerular bleeding

# Urinary sediment as...liquid biopsy??

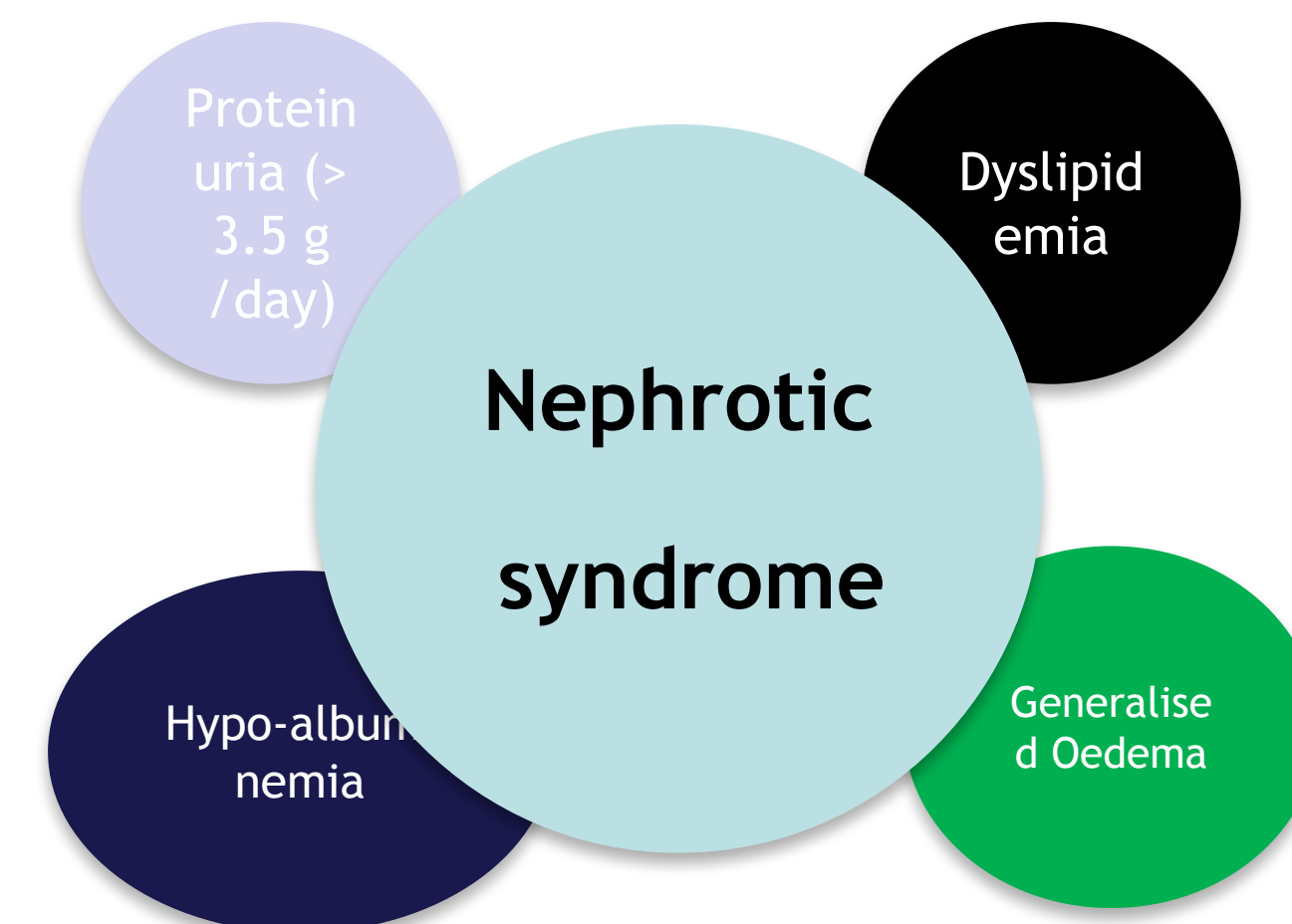
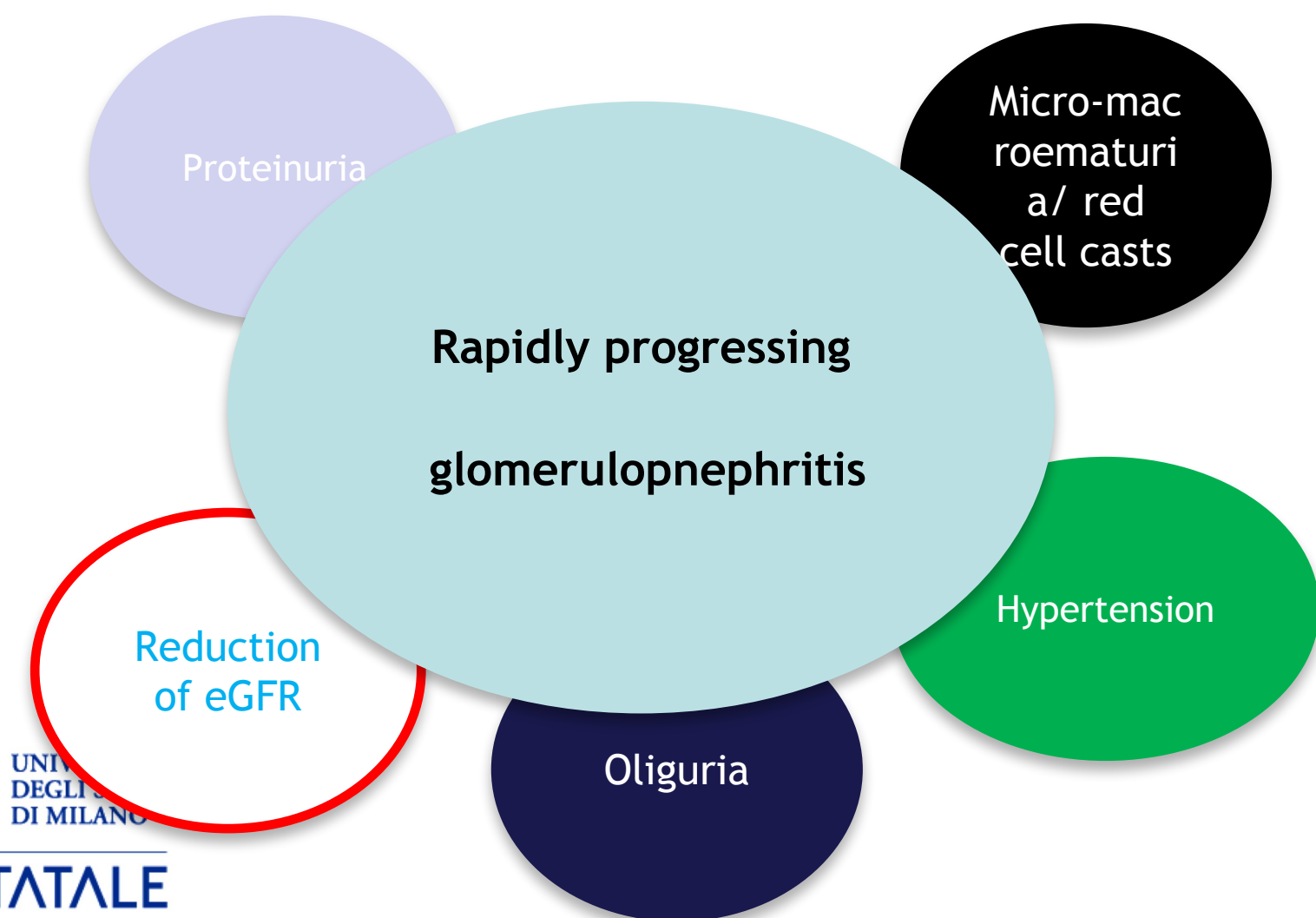
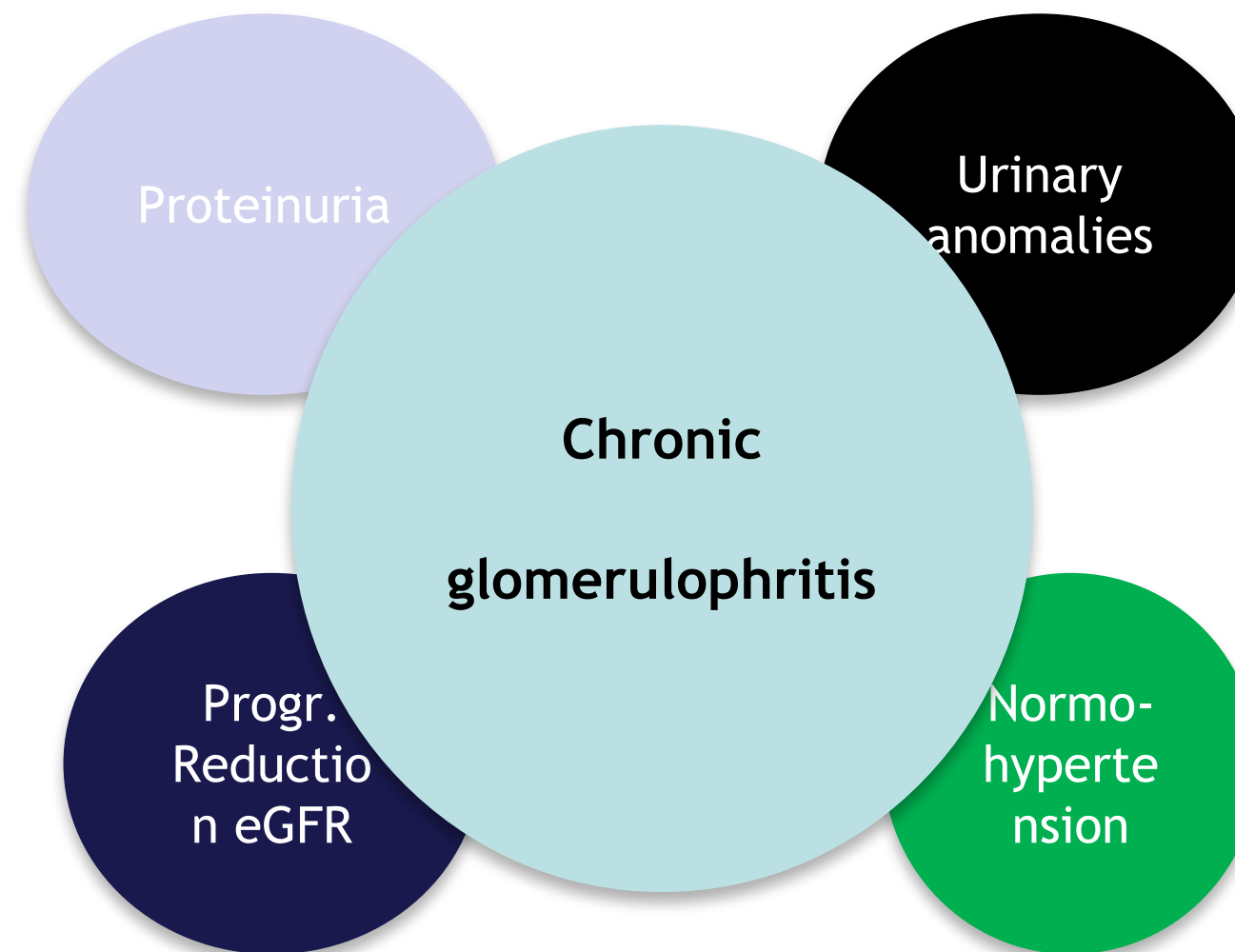
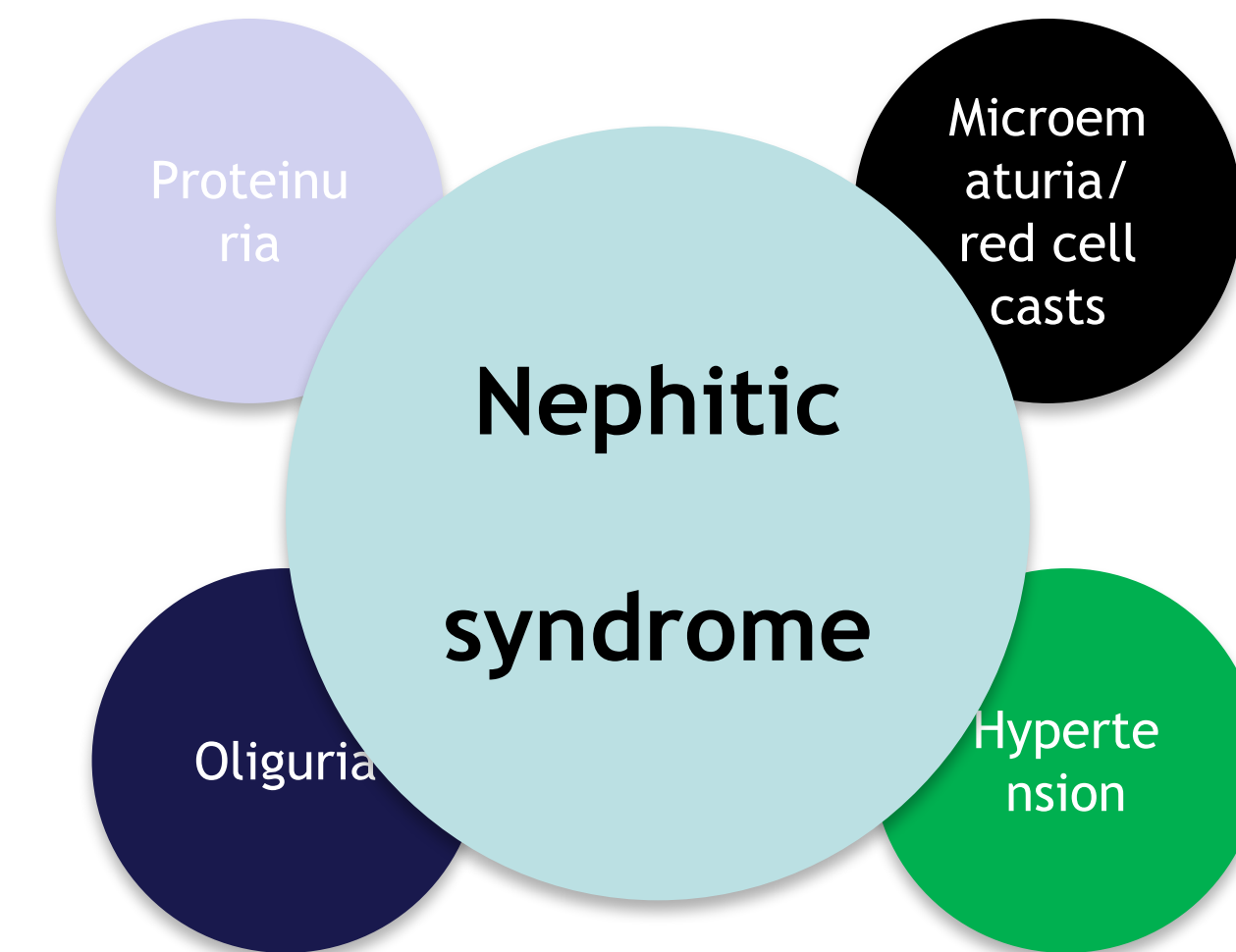
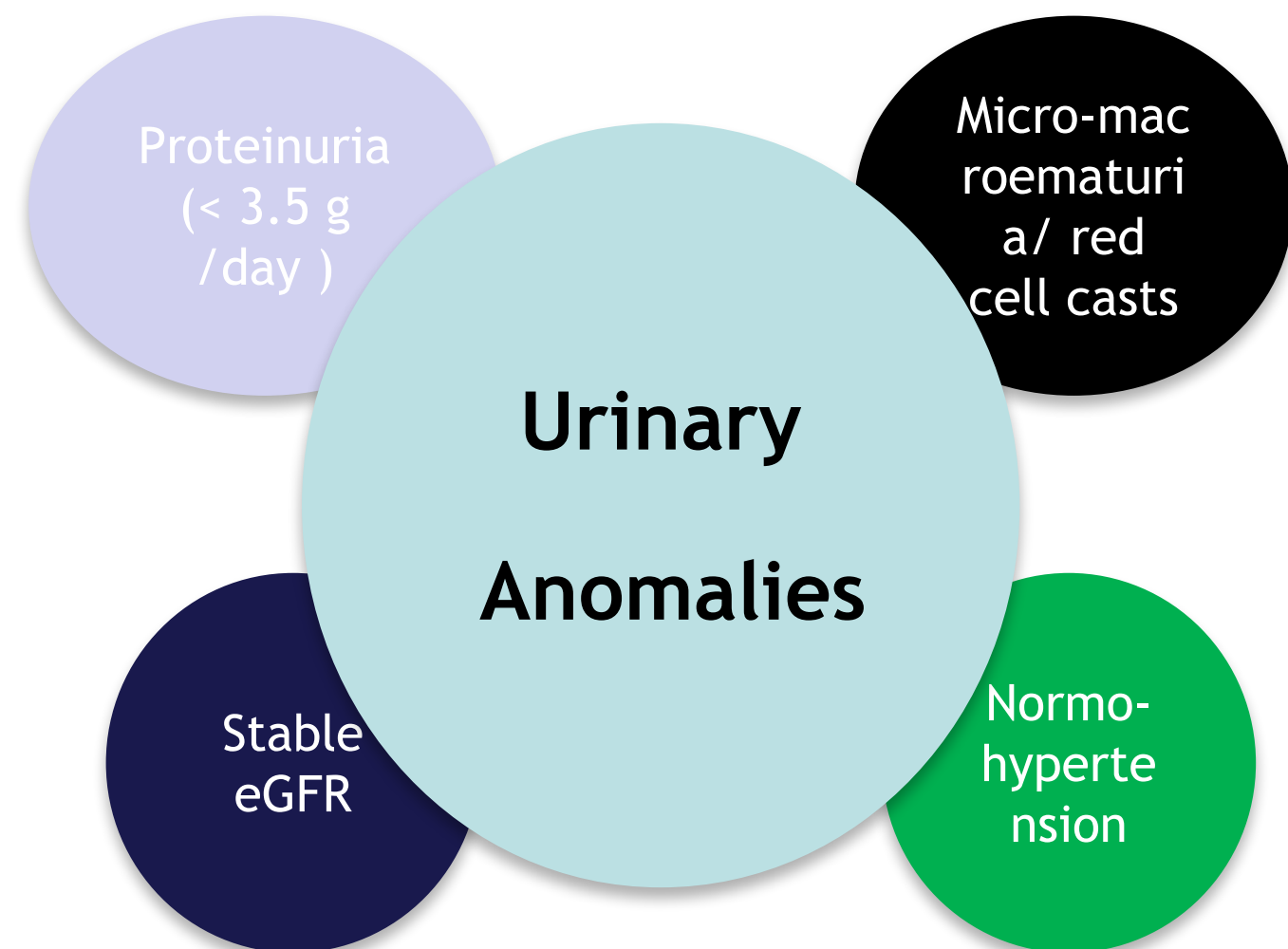
Renal Disease	Hallmark	Associated Findings
Nephrotic syndrome (proteinuria: +++++)	Fatty particles	Renal tubular epithelial cells (RTECs) RTEC casts Erythrocytes (absent to moderate number)
Nephritic syndrome (proteinuria: + → +++++)	Erythrocytes (moderate to high number) Erythrocyte/hemoglobin casts	Leukocytes (low to moderate number) RTECs (low number) RTEC casts Waxy casts
AKI with ATN (proteinuria: absent to +)	RTECs RTEC casts Granular casts	variable according to cause of ATN (e.g., myoglobin casts in rhabdomyolysis, uric acid crystals in acute urate nephropathy, erythrocytes in proliferative/active glomerulonephritis)
Urinary tract infection (proteinuria: absent)	Bacteria Leukocytes	Isomorphic erythrocytes Superficial transitional epithelial cells Struvite crystals (for infections caused by urease-producing bacteria) Leukocyte casts (in renal infection)
Polyomavirus BK infection (proteinuria: absent)	Decoy cells	Decoy cell casts (in BK virus nephropathy)
Urologic diseases (proteinuria: absent)	Isomorphic erythrocytes (low to high number) Leukocytes	Transitional cells (deep, superficial, atypical)

*Few importance to the evaluation of urine analysis and of urinary sediment*

**BUT**

*Few expertise in the reading of urinary sediment*

*Automatized reading*



# Methods for assessing renal function

## Glomerular function

- Quantitative evaluation
- Qualitative evaluation

## Tubular function

## Endocrine functions

## Morphological evaluation

- Microscopic evaluation
- Macroscopic evaluation



# Methods for assessing renal function

## □ Glomerular function

- Quantitative evaluation
- Qualitative evaluation

## □ Tubular function

## □ Endocrine functions

## □ Morphological evaluation

- Microscopic evaluation
- Macroscopic evaluation



# Indications for renal biopsy

- **Strong indications**

- Nephrotic syndrome
- Nephritic syndrome
- AKI of unknown cause
- Renal Graft dysfunction

- **Discretionary indications**

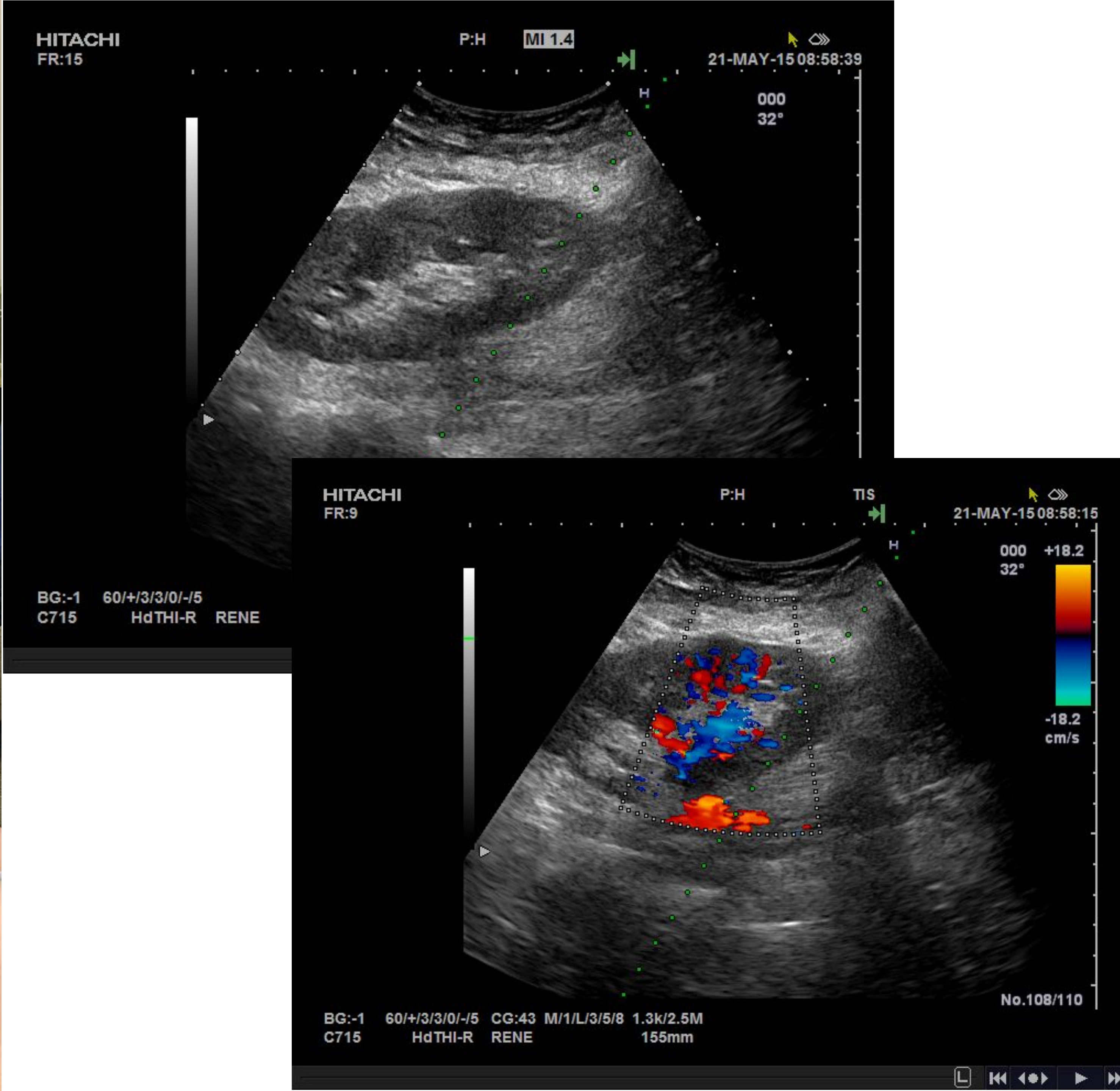
- Non nephrotic proteinuria
- Persistent hematuria
- CKD of unknown etiology (with renal parenchyma still conserved, at least in part)
- Persisting urine analysis alterations in systemic diseases with potential renal involvement

# Renal Biopsy



*Il prelievo viene effettuato utilizzando aghi del diametro di 14-16 Gauge, di tipo tracciante a ghigliottina o, meno frequentemente, aghi per aspirazione.*





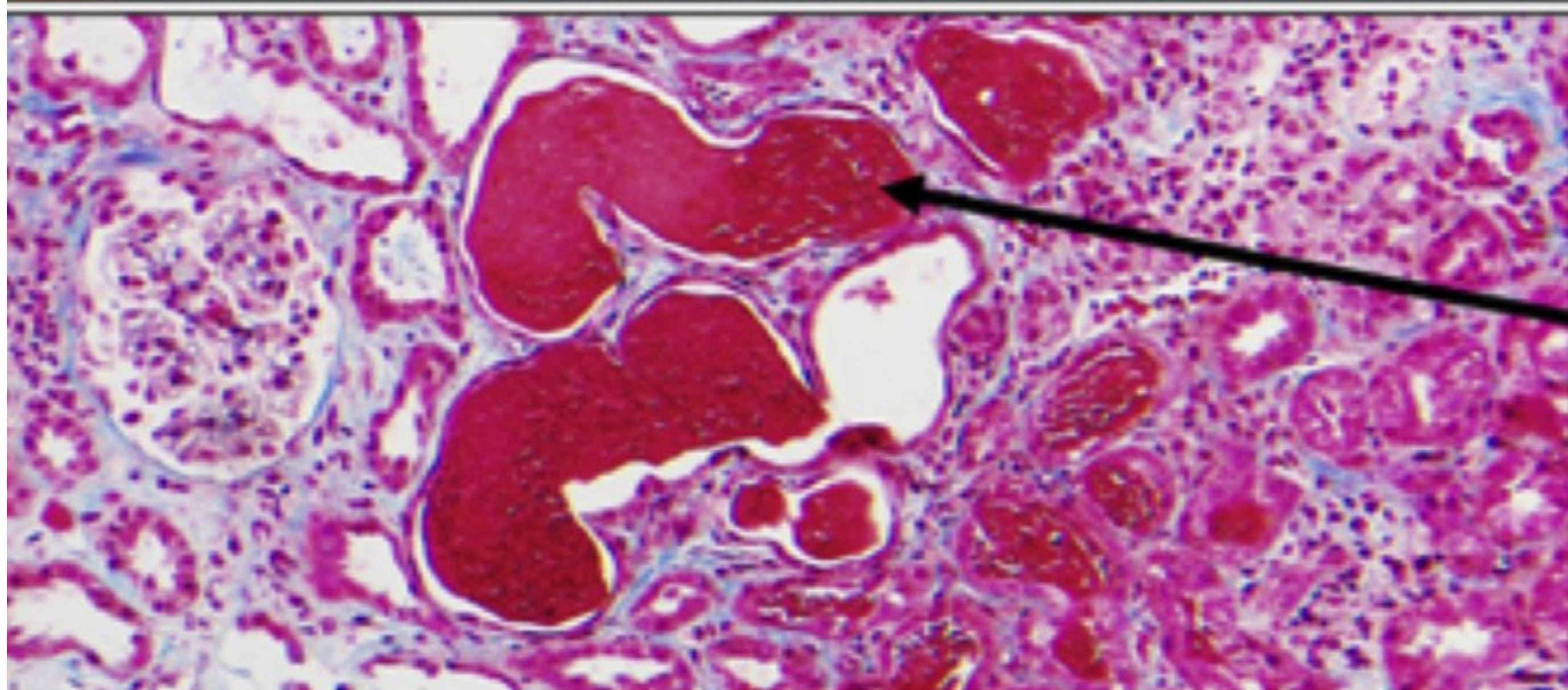
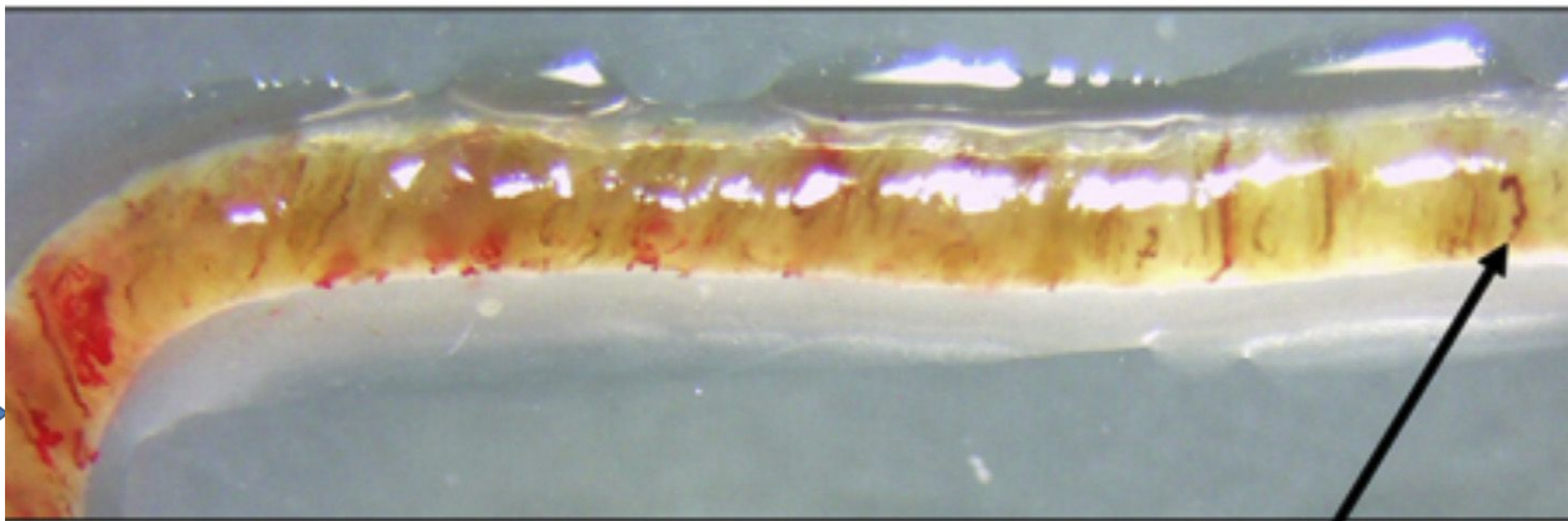


# Renal biopsy: procedure



Polo  
superiore

Polo inferiore



Blood in  
tubular  
lumens

Sample evaluation

# Anatomo-pathological classification of renal lesions

## □ Extent of the glomerular involvement

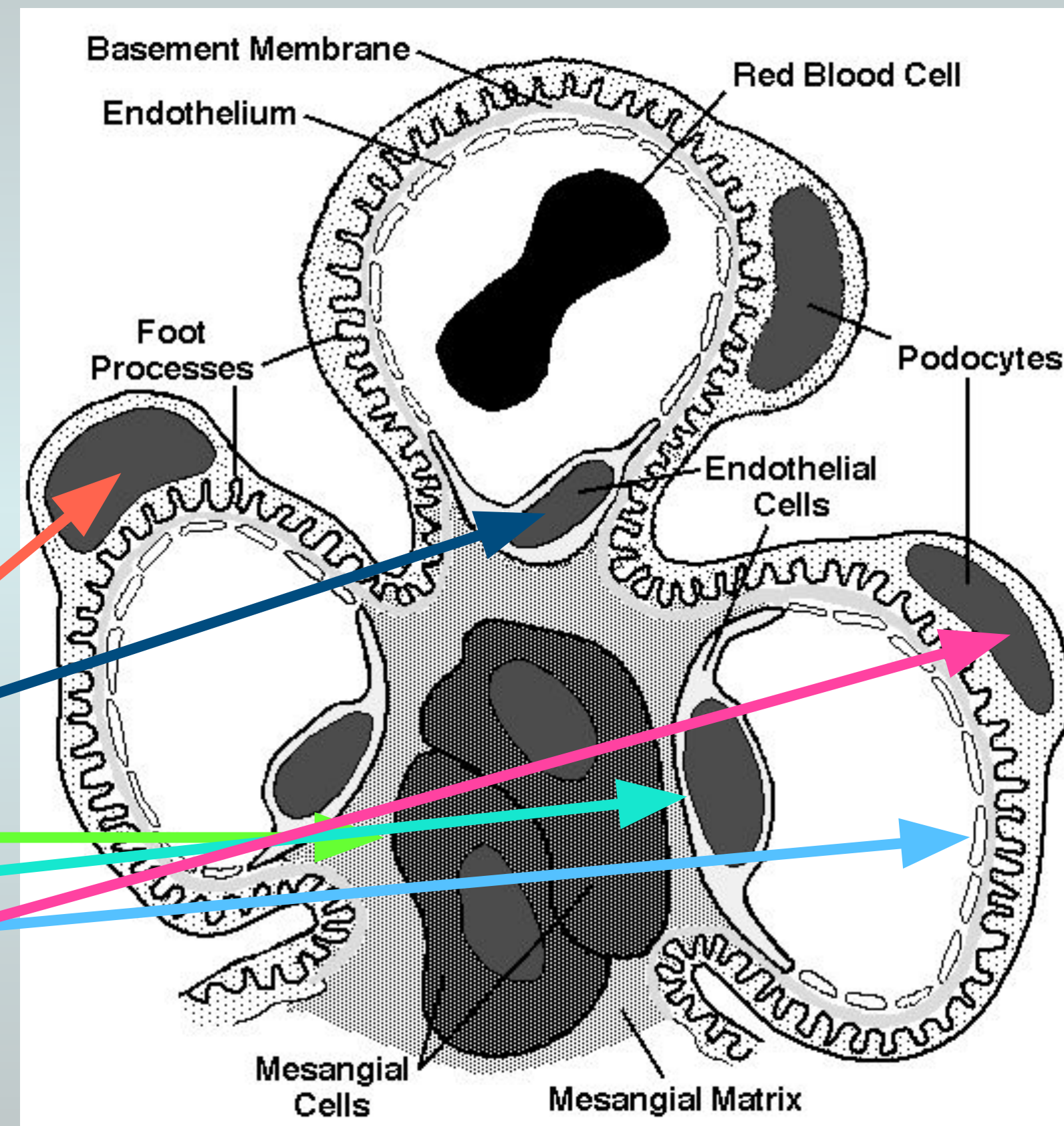
- Diffuse: all glomeruli
- Focal: some glomeruli
- Global: all the tuft involved
- Segmental: part of the tuft

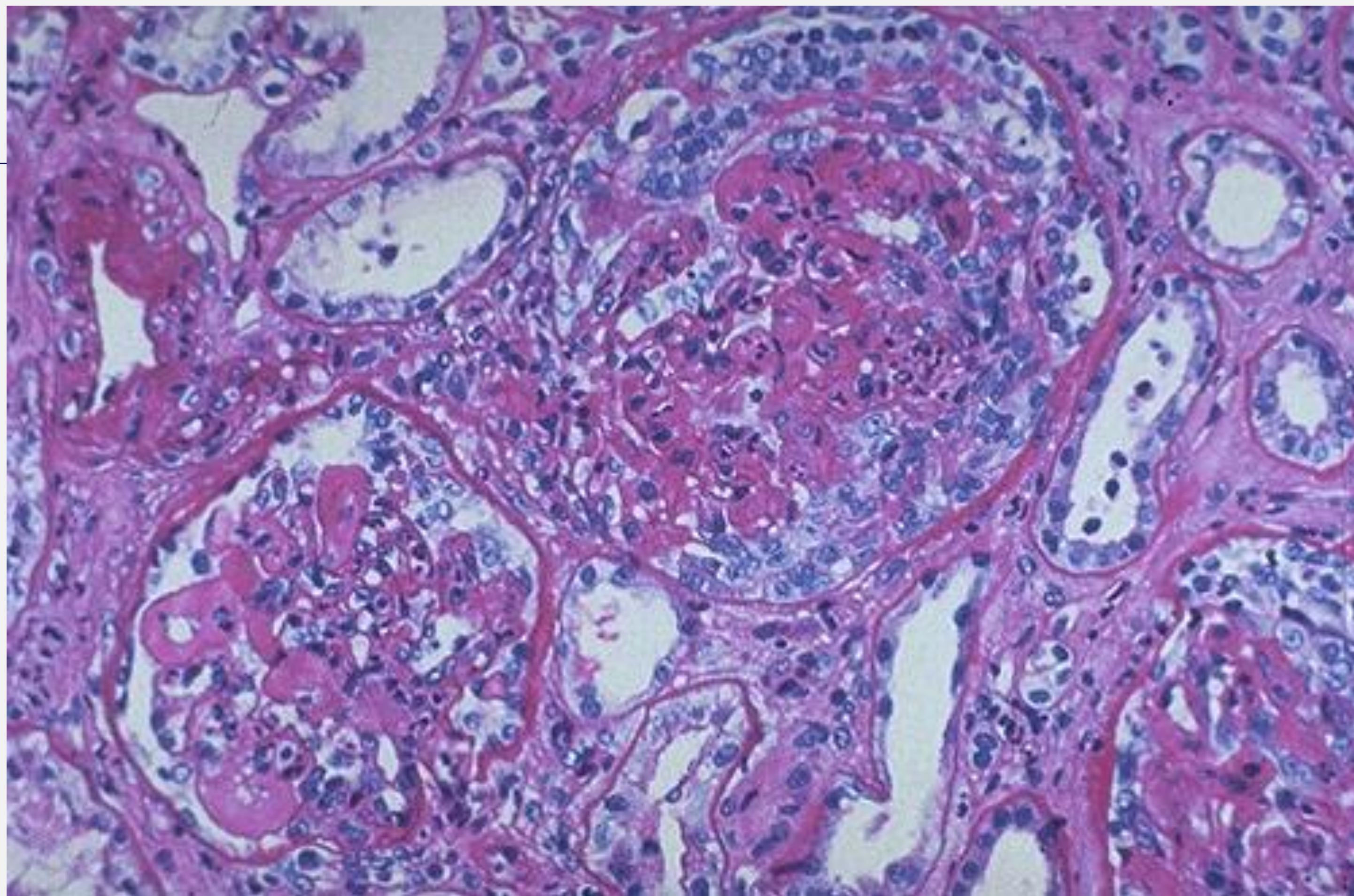
## □ Lesion characteristics

- Cell proliferation
- Cell Infiltration
- Hyalinosis/sclerosis/necrosis
- GBM changes
- Deposits
- Ultrastructural changes

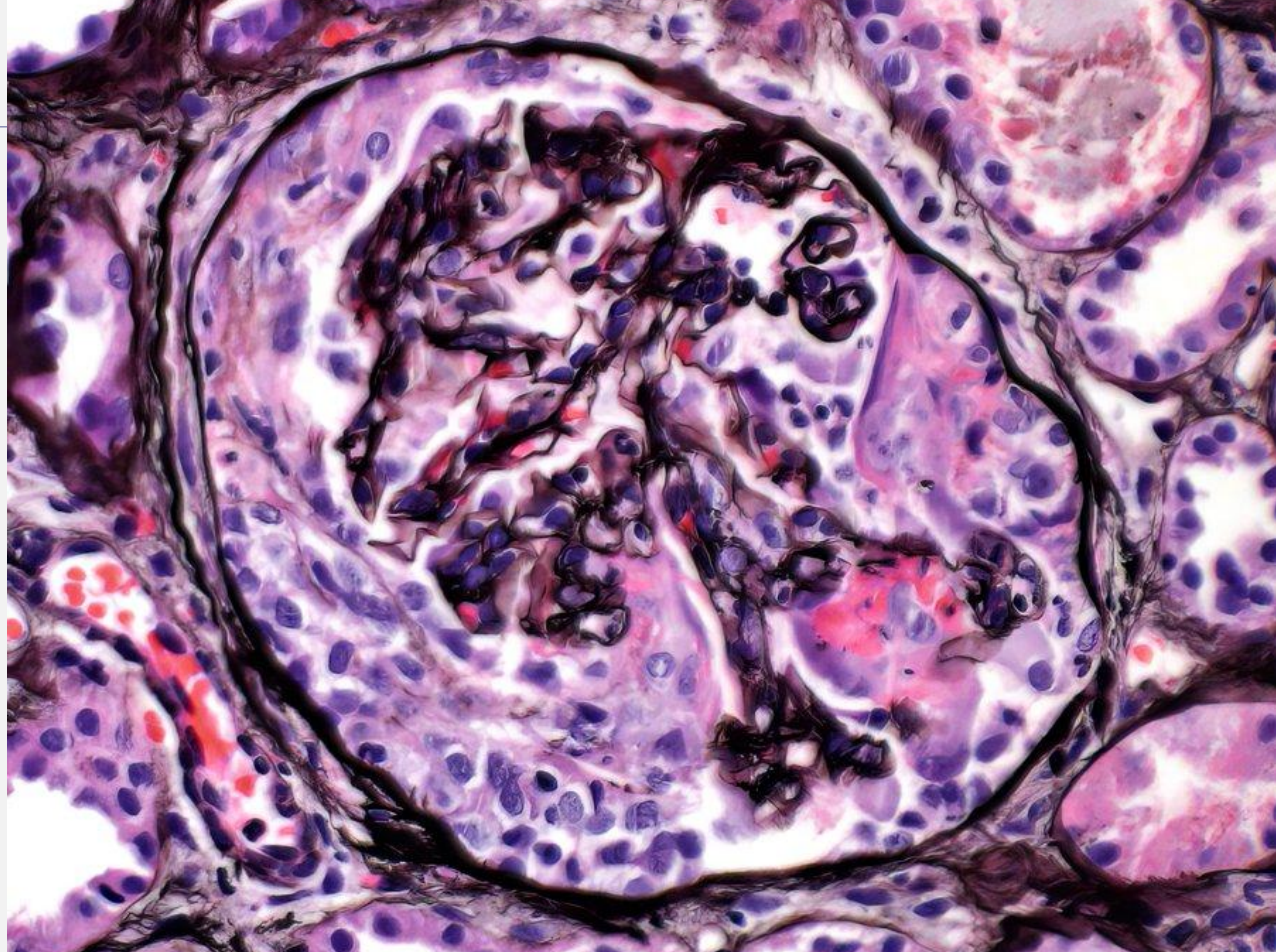
## □ Lesion localization

- mesangial
- Endothelial
- Membranous
- Extracapillary





**Seen here within the glomeruli are crescents composed of proliferating epithelial cells. Crescentic glomerulonephritis is known as rapidly progressive glomerulonephritis (RPGN) because this disease is very progressive. There are several causes, and in this case is due to SLE. Note in the lower left glomerulus that the capillary loops are markedly thickened (the so-called "wire loop" lesion of lupus nephritis).**



# Methods for assessing renal function

## Glomerular function

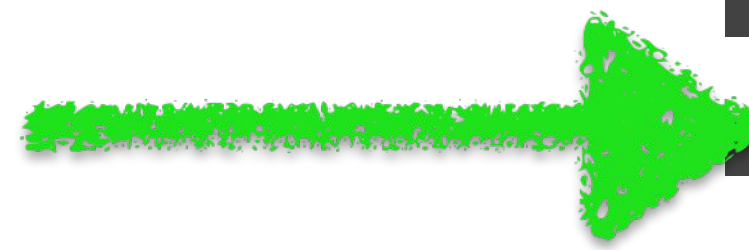
- Quantitative evaluation
- Qualitative evaluation

## Tubular function

## Endocrine functions

## Morphological evaluation

- Microscopic evaluation
- Macroscopic evaluation



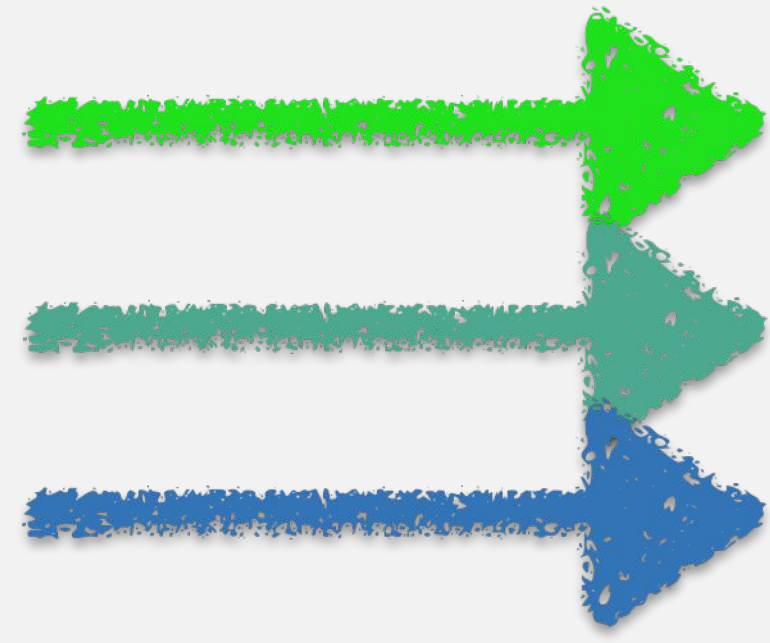


# ECHOGRAPHY AND KIDNEYS

---

Ultrasound is relatively inexpensive and provides a rapid way to assess renal location, contour, and size without radiation exposure

# Renal ultrasound in inflammatory arteriopathies



- Evaluation of renal size
- Evaluation of renal morphology
- Vascular supply (doppler)



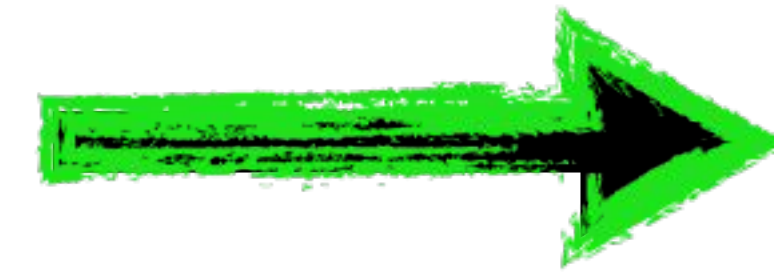
- Obstructive Nephropathy
- Cystic diseases
- Neoplasia
- Acute Kidney Injury (AKI)
- Chronic Kidney Diseases (CKD)
- Evaluation of Kidney Graft
- Renal Biopsy

*The cortex may appear hyper- or hypoechoic with globular hypoechoic pyramids due to interstitial edema*

*In inflammatory arteriopathies involving glomerular damage, RI significantly increases (> 0.75–0.80) because of the prevailing damage involves the microcirculation and for the reduced area of the vessels*

# Agenda

Nephrologic evaluation: from the  
beginning to deep points



IgA Vasculitis



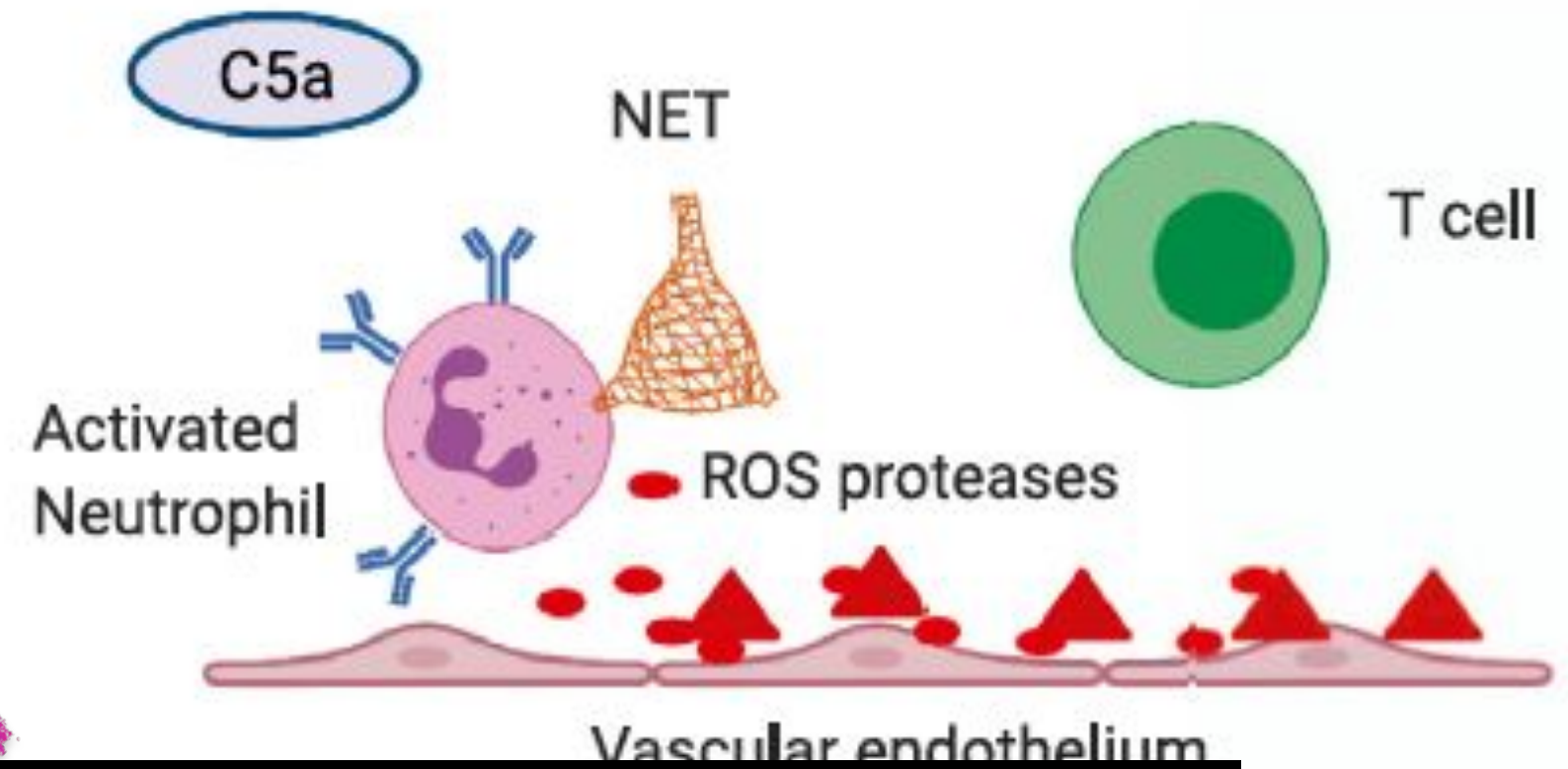
Lupus Nephritis



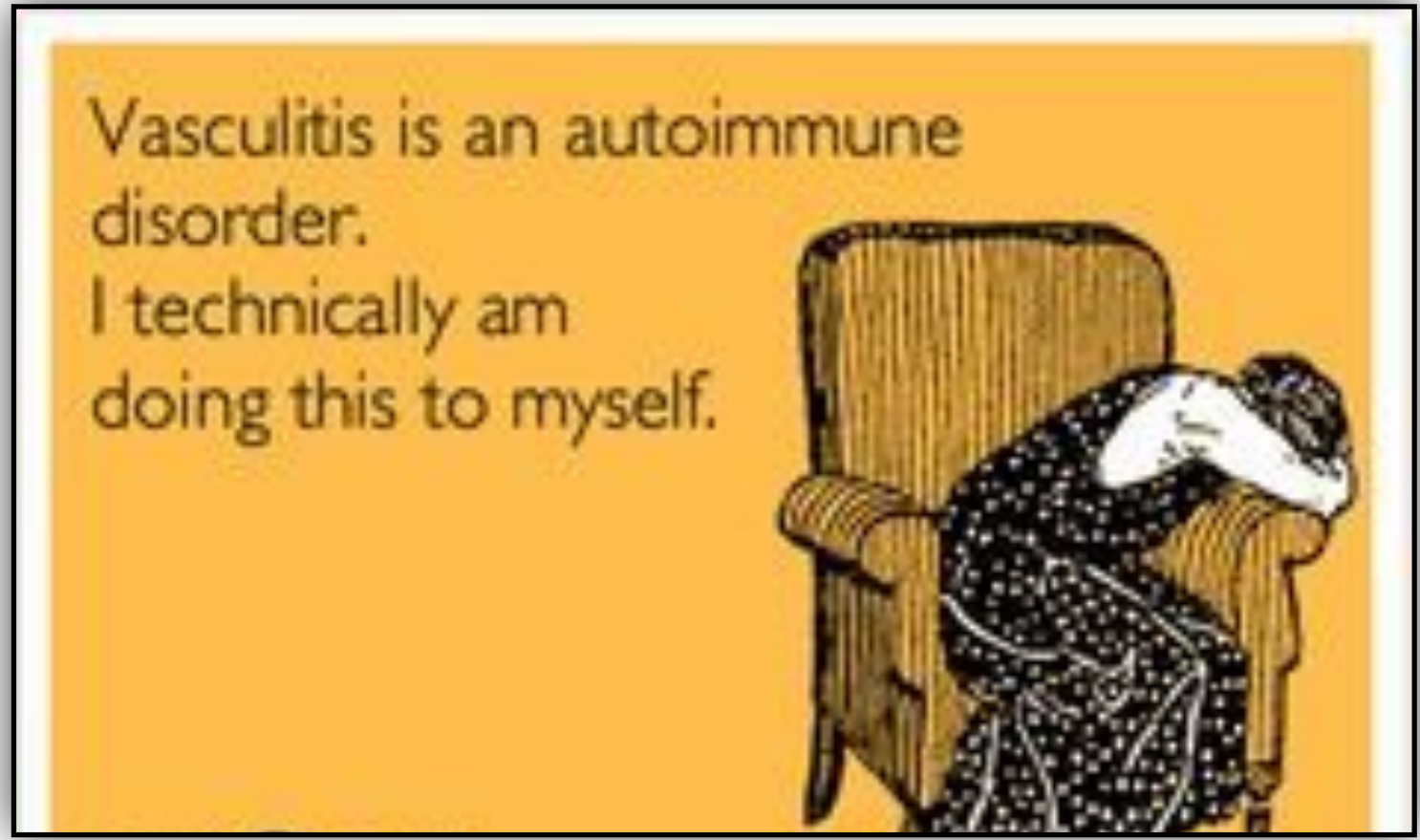
ANCA  
related  
glomerulonephritis

# Indirect immune-mediated kidney diseases

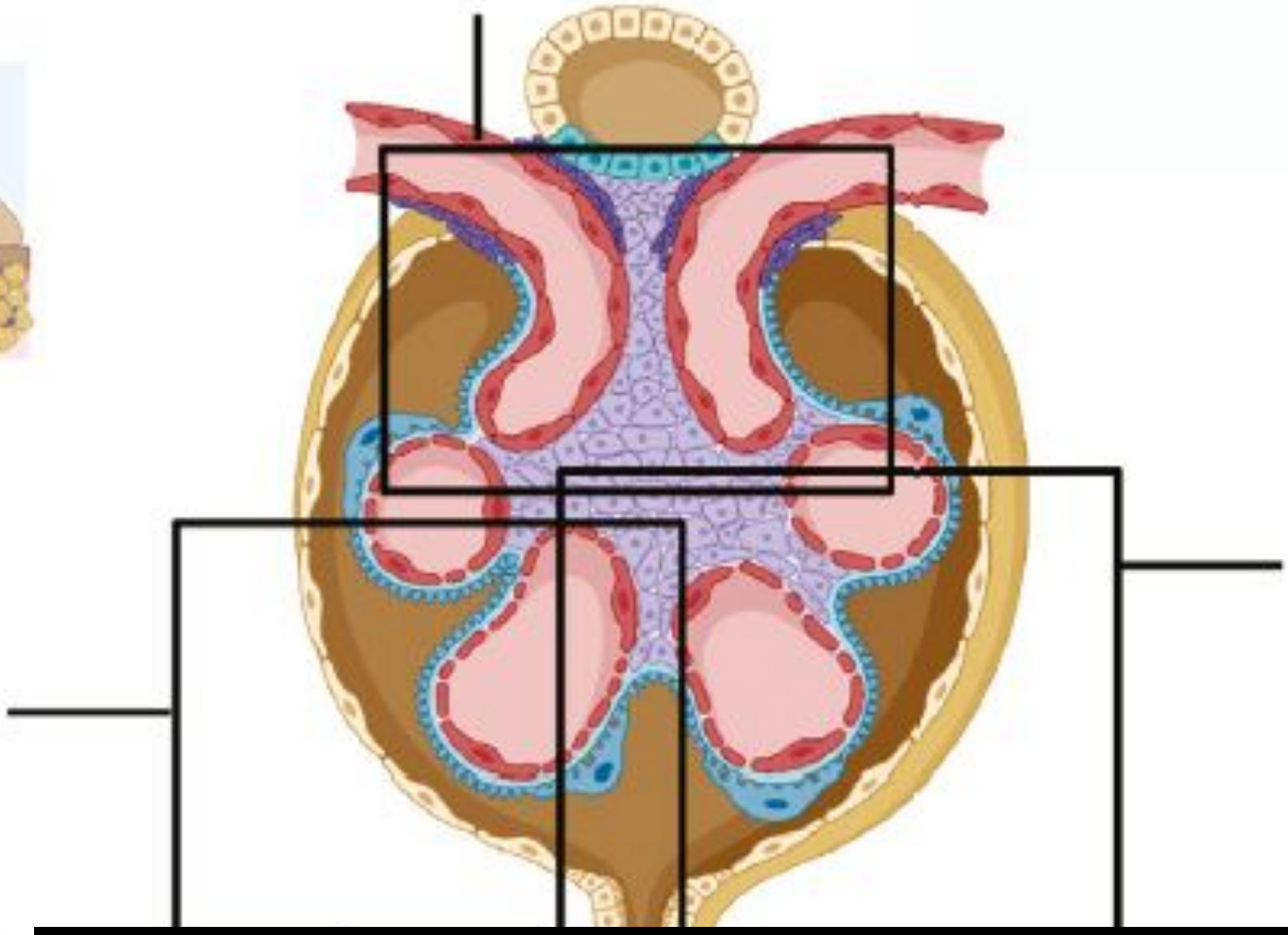
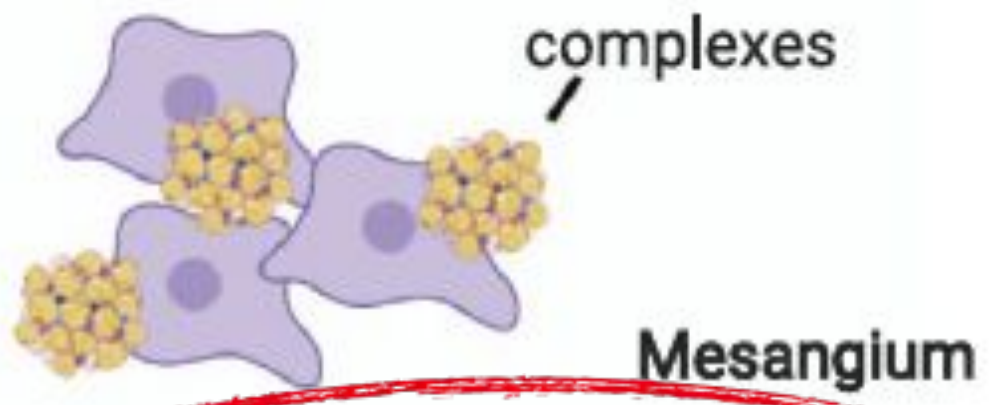
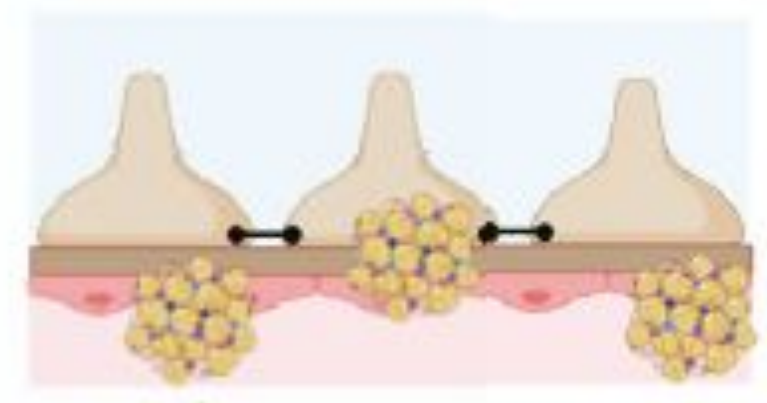
**Systemic antibody induced vascular damage: ANCA vasculitis**



*ANCA: excessive activation of neutrophils—> generation of inflammatory cytokines, reactive oxygen species, and lytic enzymes—> formation of neutrophil extracellular traps (NETs) and complement activation—>significant vascular damage.*



**Glomerular basement membrane**



**Immune complex deposition: SLE and IgA nephropathy**

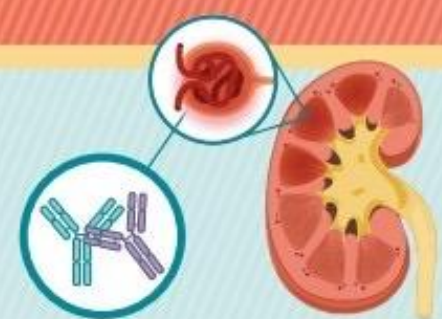
*SLE: genetic variants interfere with immune tolerance to nuclear autoantigens, leading to immune complex formation.  
IgA: The pathogenic immune complexes contains abnormally glycosylated polymeric IgA1, and its deposition triggers mesangial cell proliferation, extracellular matrix expansion, and cytokine release.*



# IgA Vasculitis

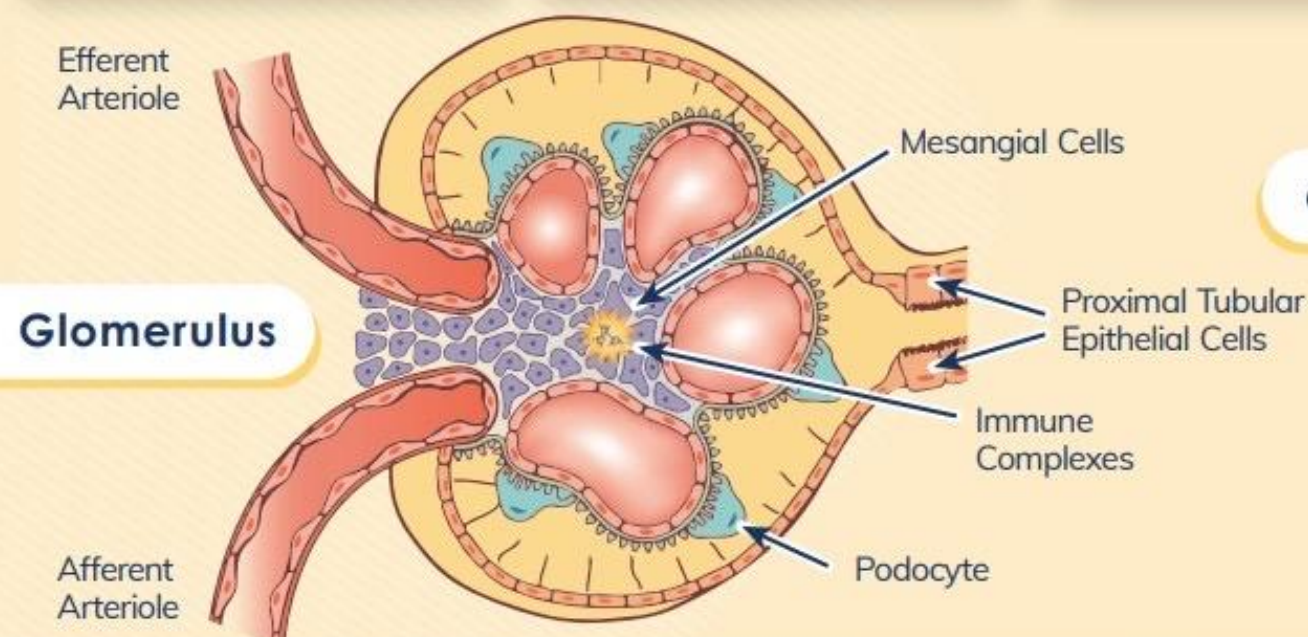
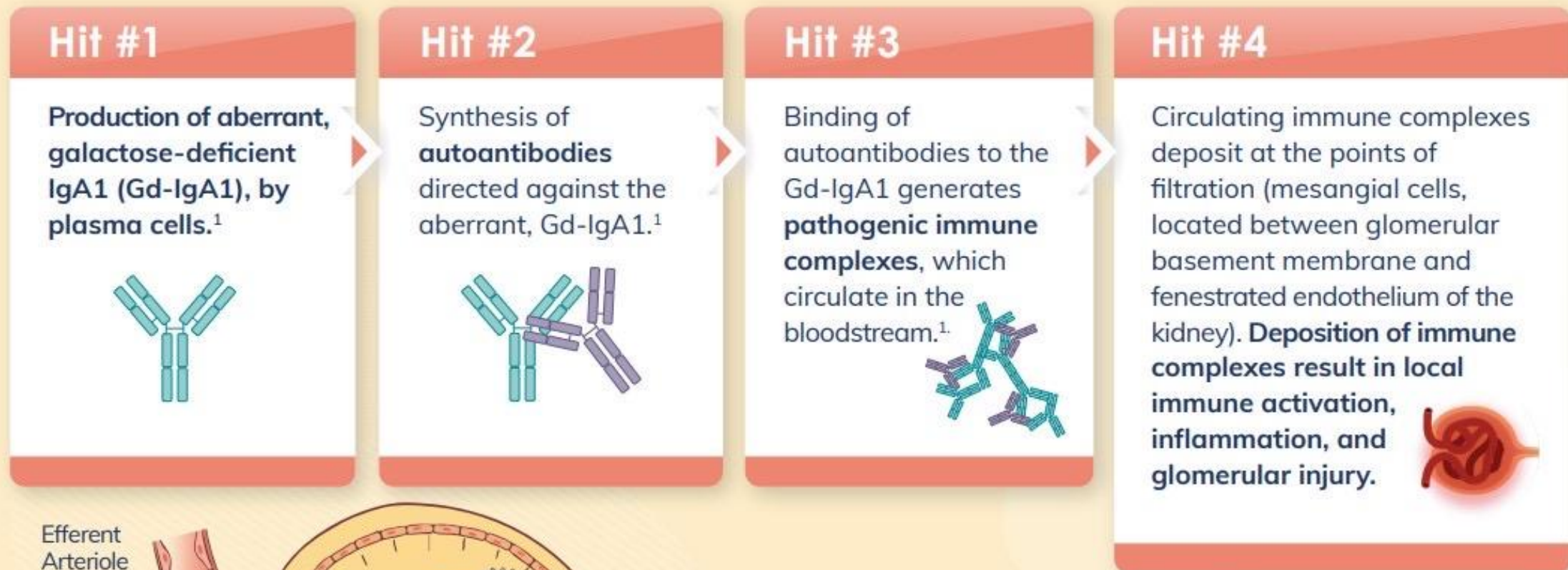
IgAN is the most common primary glomerular disease worldwide and often presents with persistent hematuria. Macroscopic hematuria coincident with an upper respiratory tract or gastrointestinal infection is frequently present

## The "Four Hit" IgA Nephropathy (IgAN) Pathogenesis Theory



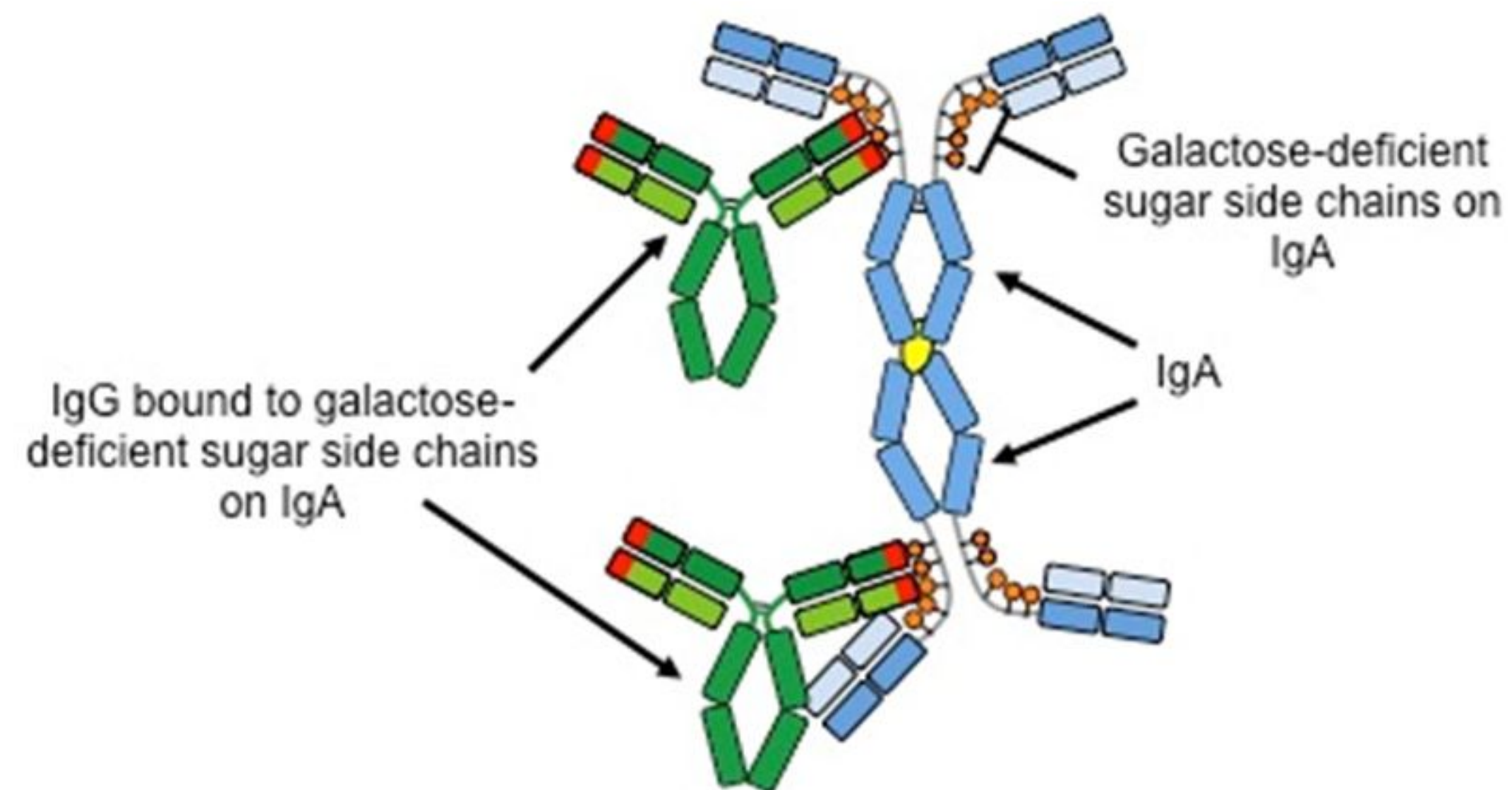
### Pathogenesis of IgA Nephropathy (IgAN)

Normally, immunoglobulin A (IgA) is produced on the body's mucosal surfaces as part of the innate immune response. However, in patients with IgAN a **galactose-deficient IgA (Gd-IgA1)** is produced leading to an autoimmune response, deposition of Gd-IgA1 containing immune complexes in the kidney tissue, and ultimately kidney injury. The current model of pathogenicity in IgAN involves four hits that drive disease development and progression.<sup>1</sup>



### Outcome Of The Four Hit Pathogenic Process:

- Injury to the podocytes and proximal tubular epithelial cells
- Worsening kidney function progressing to chronic kidney disease.
- Which left unaddressed, can lead to kidney failure and the need for renal replacement therapy, such as transplant or dialysis.<sup>1,4</sup>



## IgA Vasculitis

The presence of a skin rash is a prerequisite of the disease, and often self-limiting.

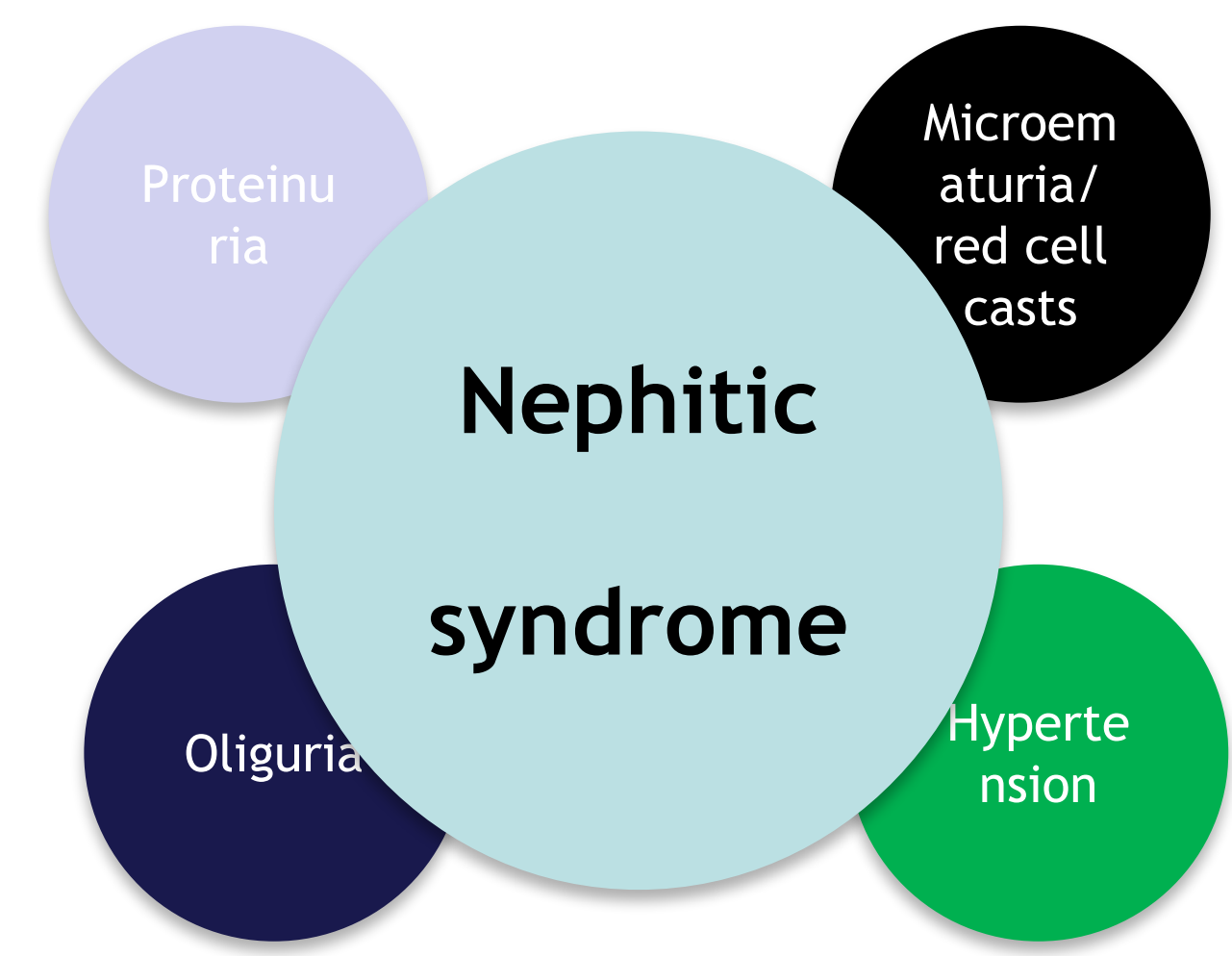
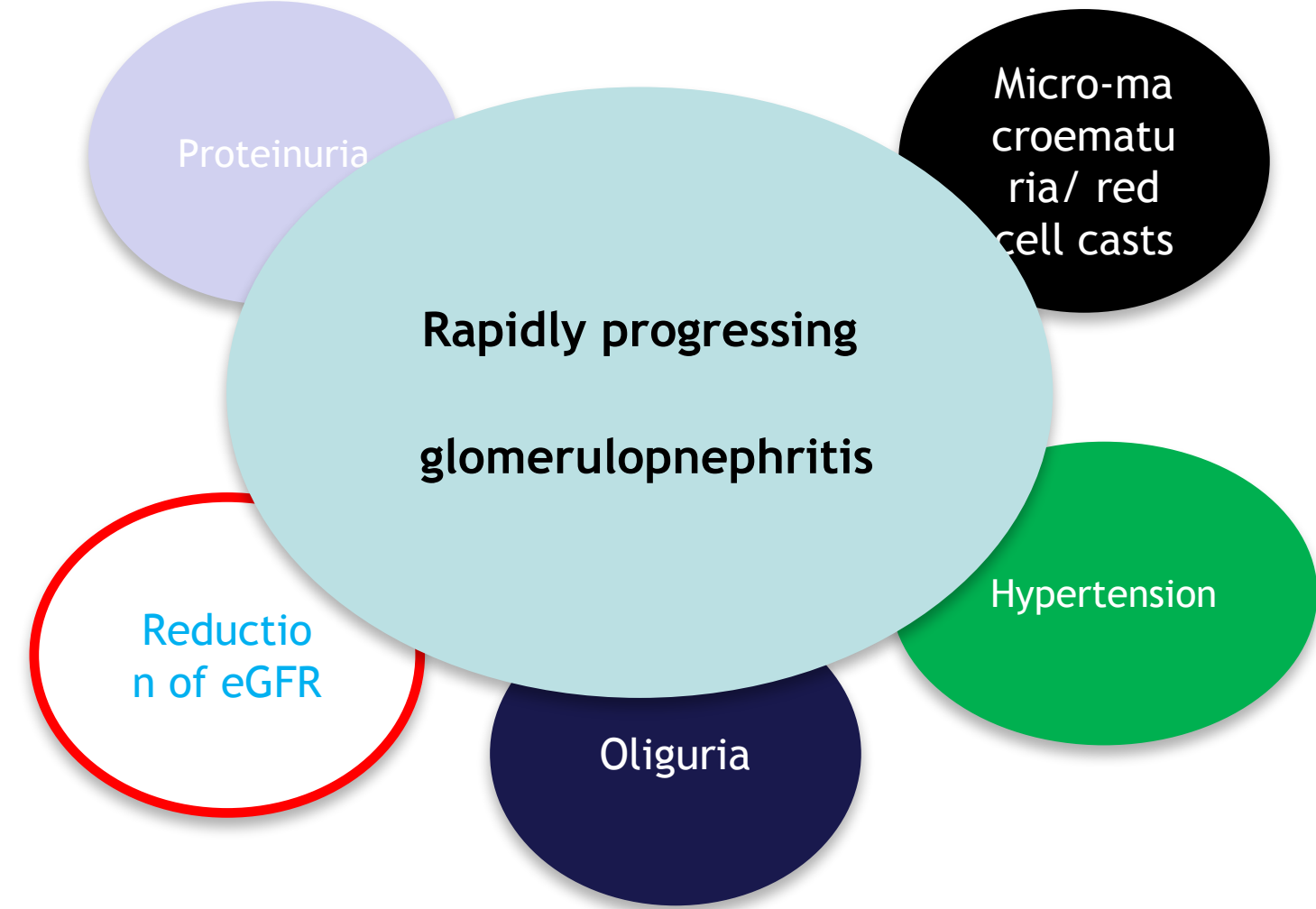
Renal involvement is considered an entity with IgA-dominant glomerulonephritis, very much similar to the more frequently occurring IgA nephropathy (IgAN).



In the skin, IgA deposits typically occur in foci with small vessel vasculitis.



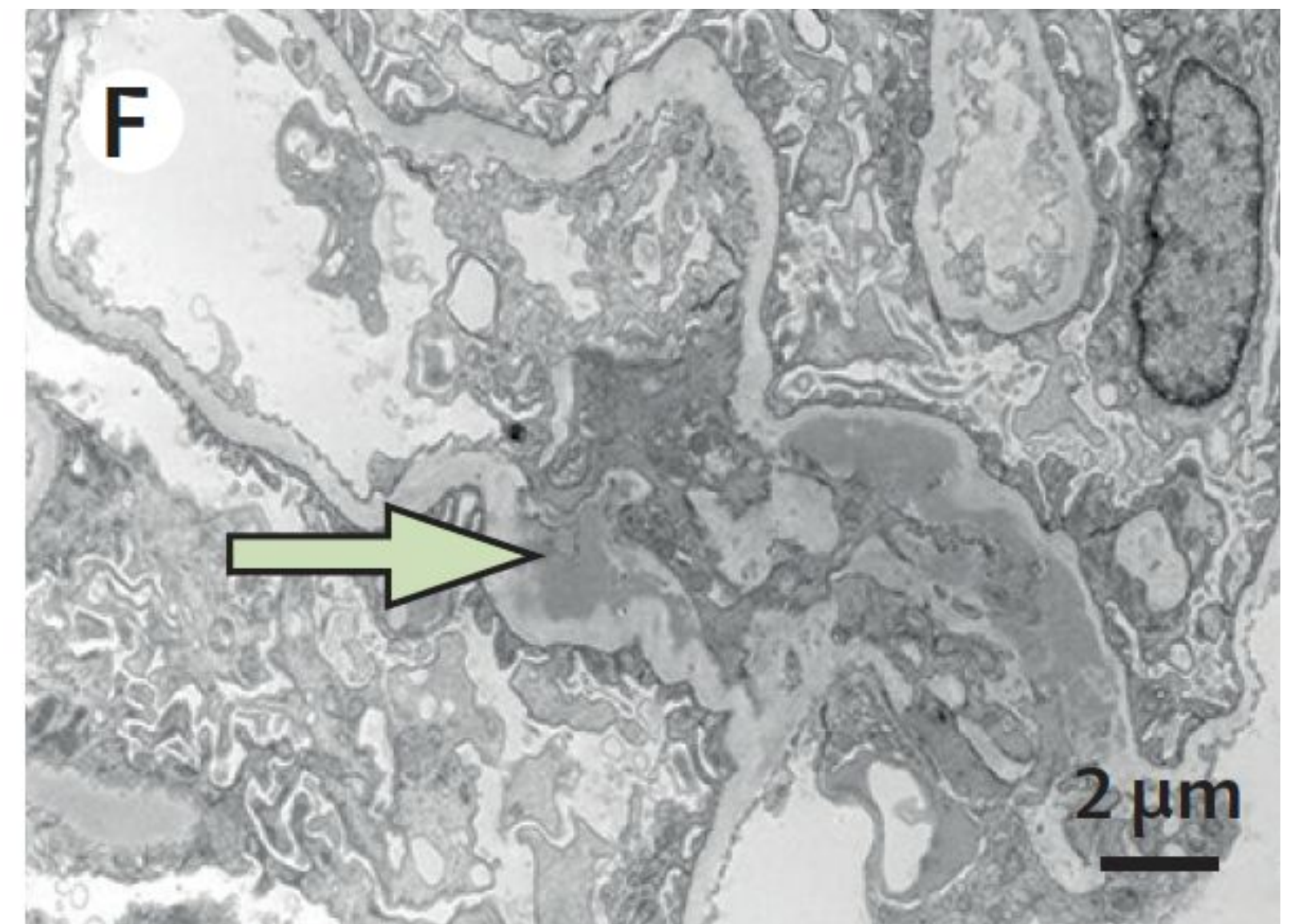
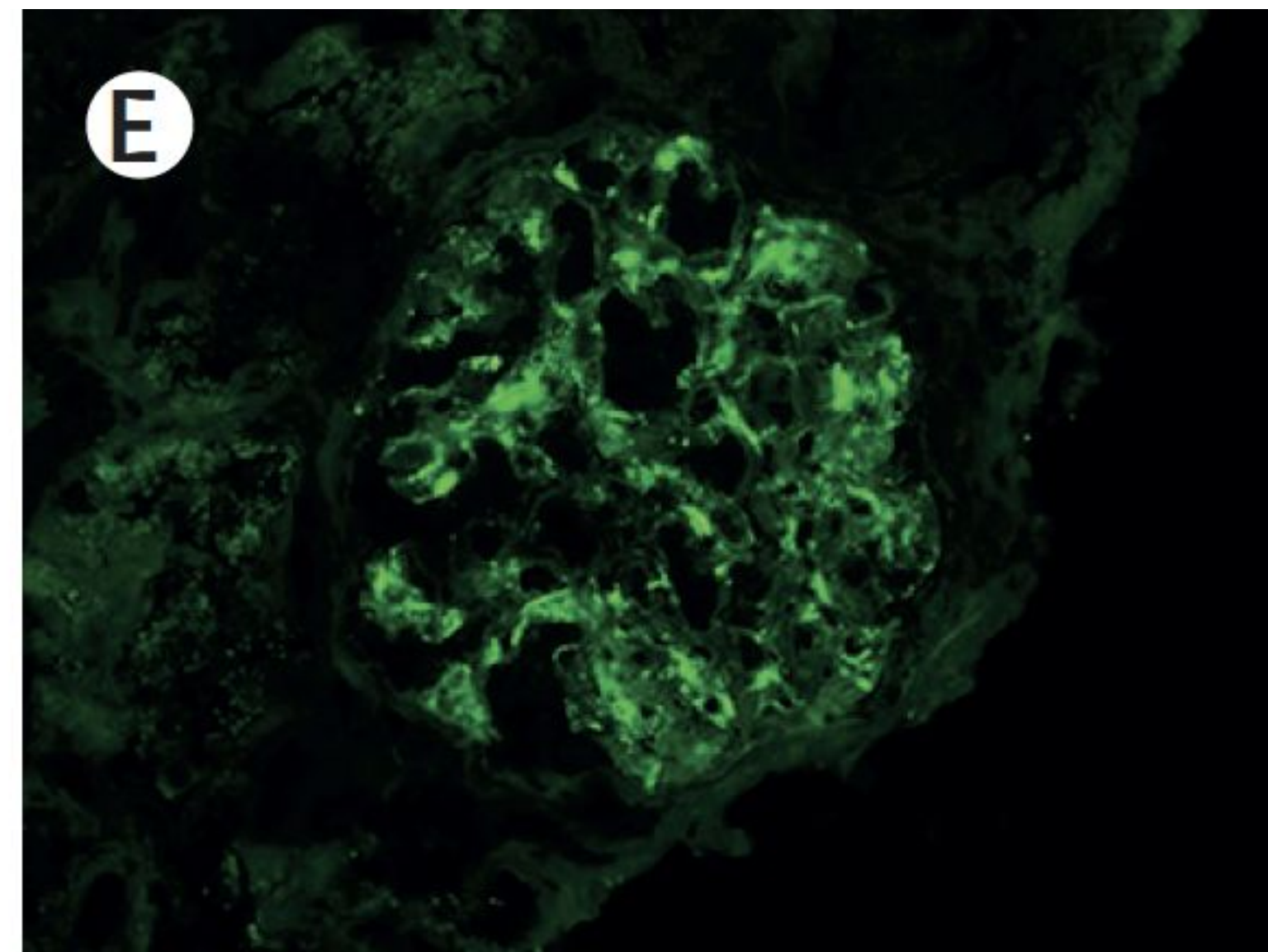
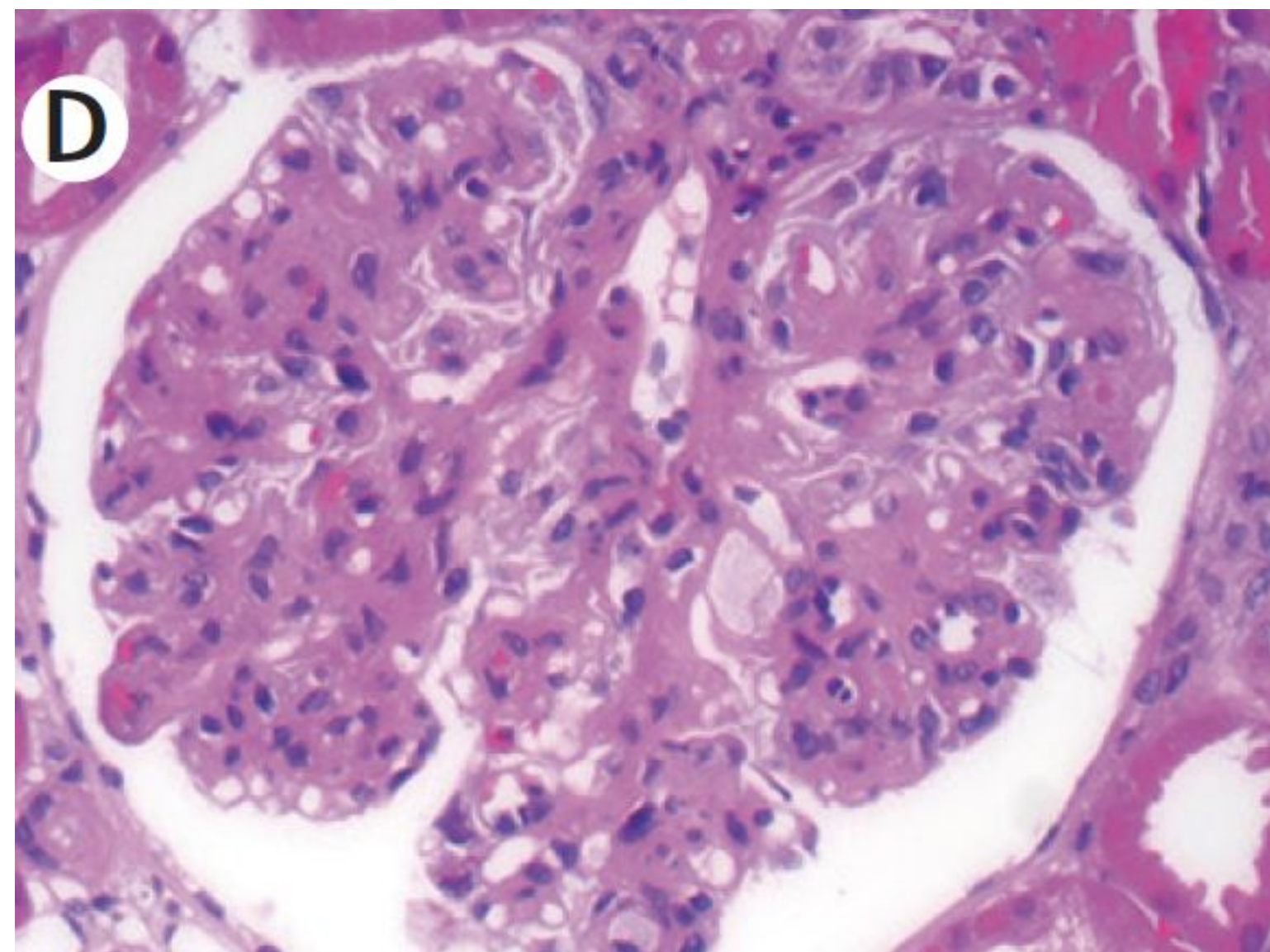
# IgA Vasculitis



(D) Light microscopy showing mesangial hypercellularity (haematoxylin and eosin stain, x40).

(E) Immunofluorescence microscopy showing bright mesangial IgA (x20).

(F) Electron microscopy showing many mesangial electron dense deposits (arrow; x4800).



IgA Vasculitis

# RENAL ULTRASOUND

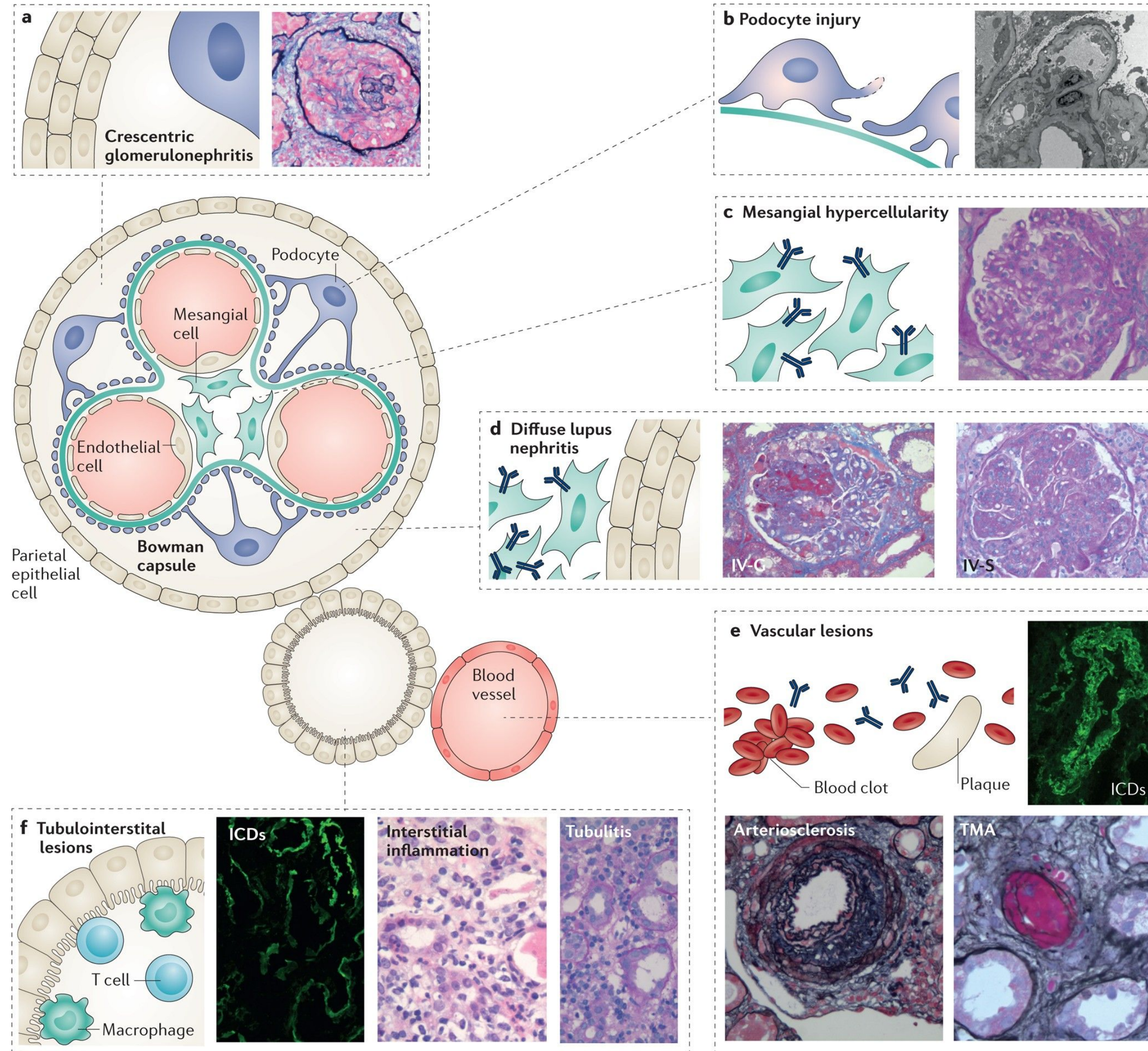




# Lupus Nephritis

50% of LES!

*Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs and tissues, of which the development of kidney disease is the most important predictor of morbidity and mortality.*



**Lupus Nephritis Class I/II**  
Mesangial injury

*Asymptomatic proteinuria, microscopic hematuria*

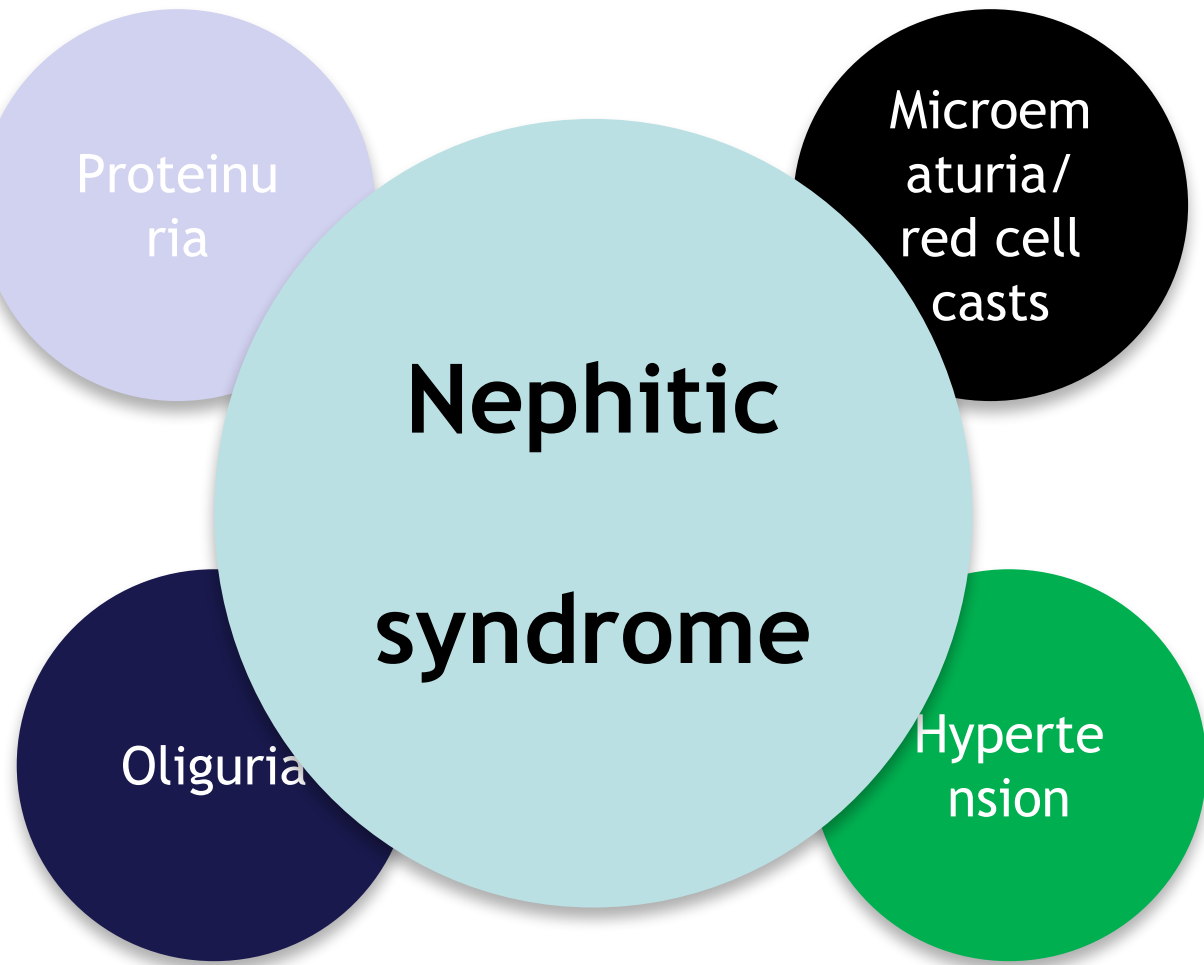


**Lupus Nephritis Class III/IV**  
Inflammation and endocapillary injury

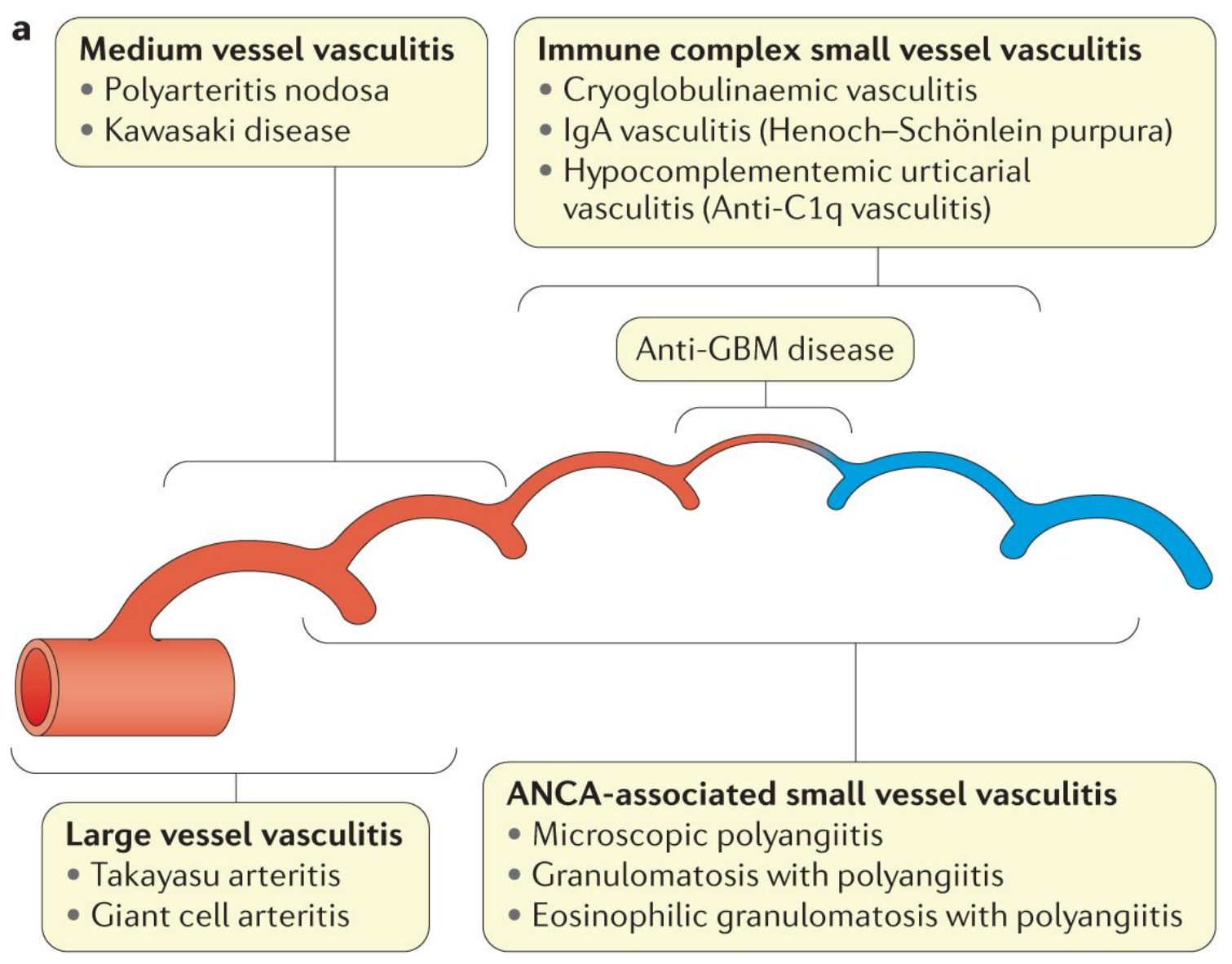
*Hematuria, proteinuria and reduced GFR*



**Lupus Nephritis Class V**  
Podocyte injury  
No inflammation  
*Nephrotic range proteinuria*

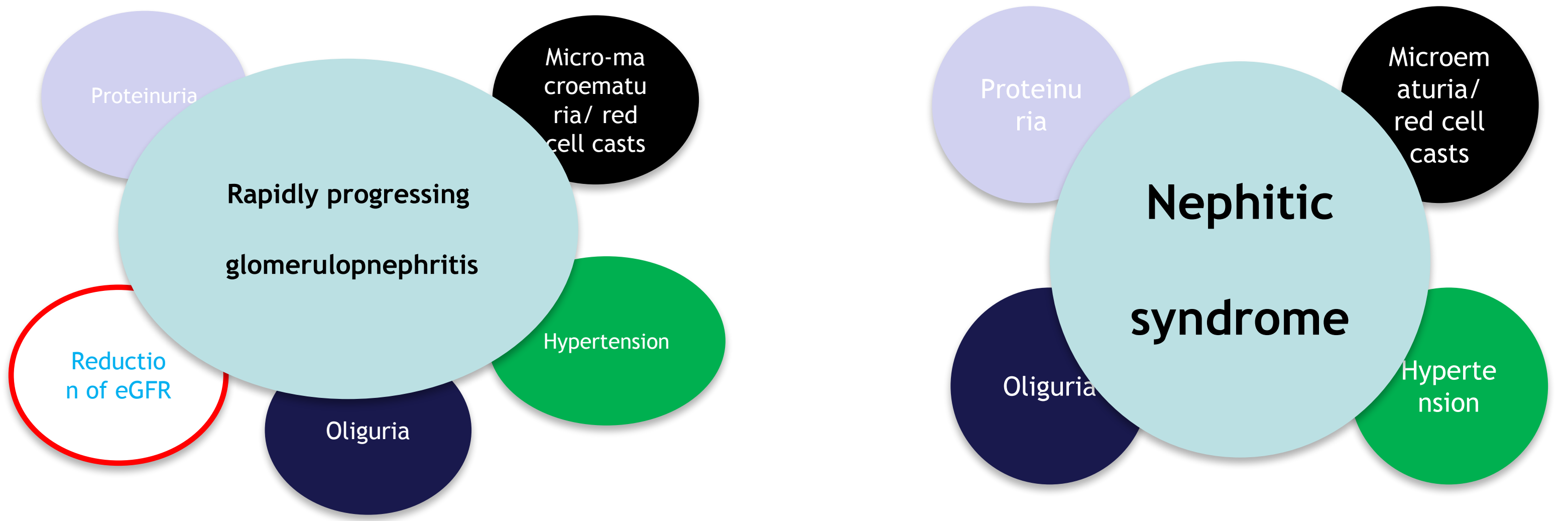


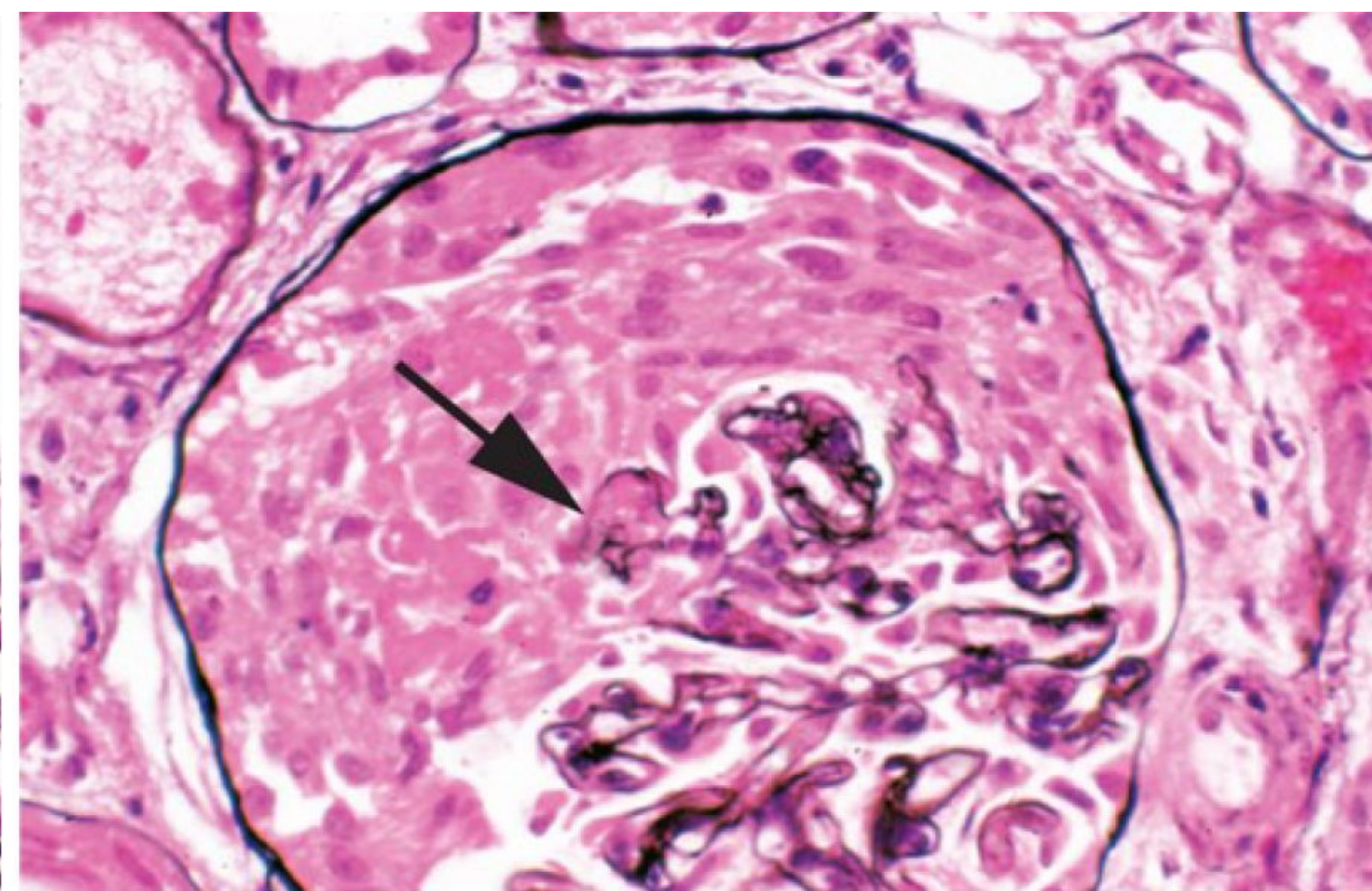
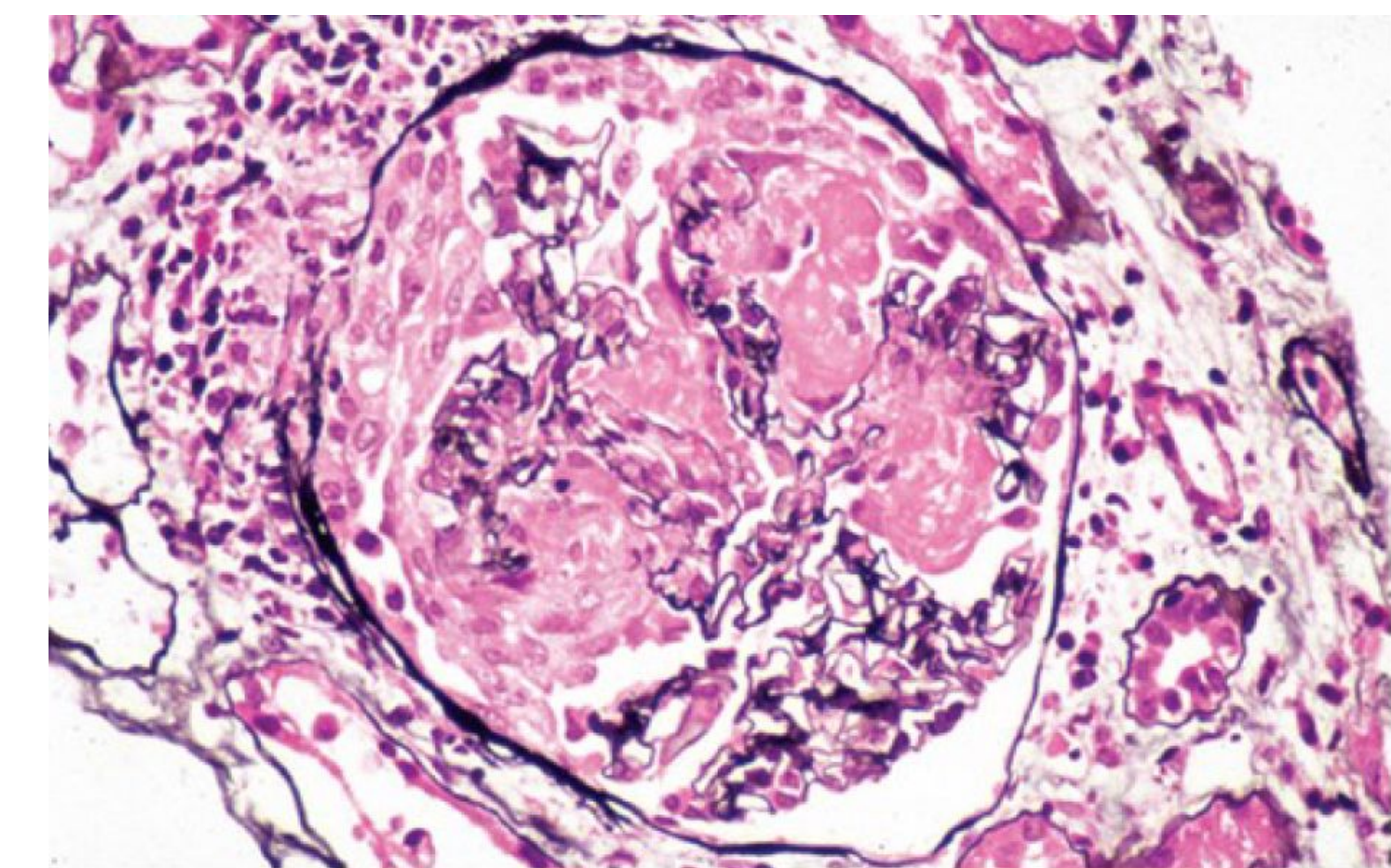
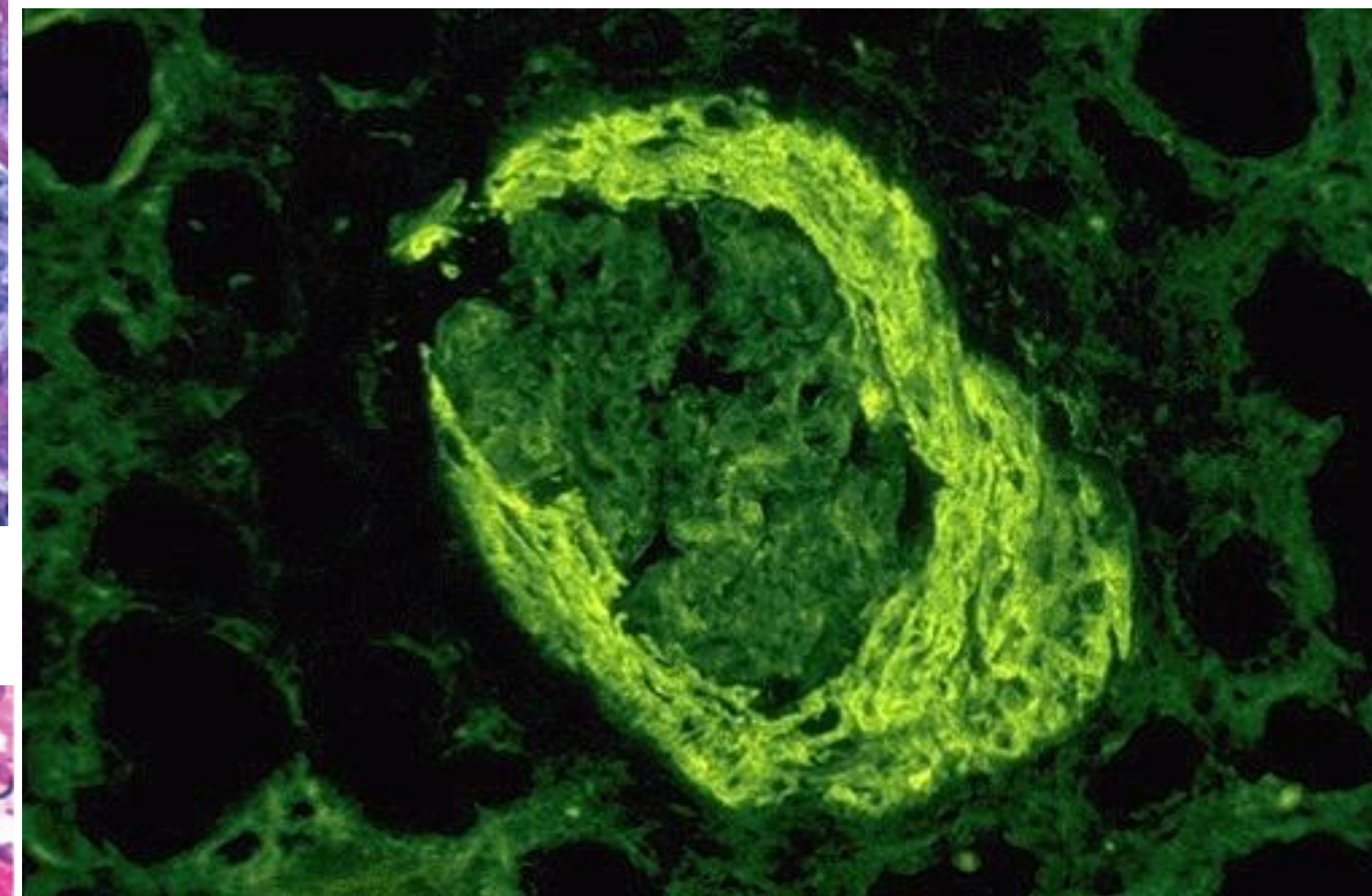
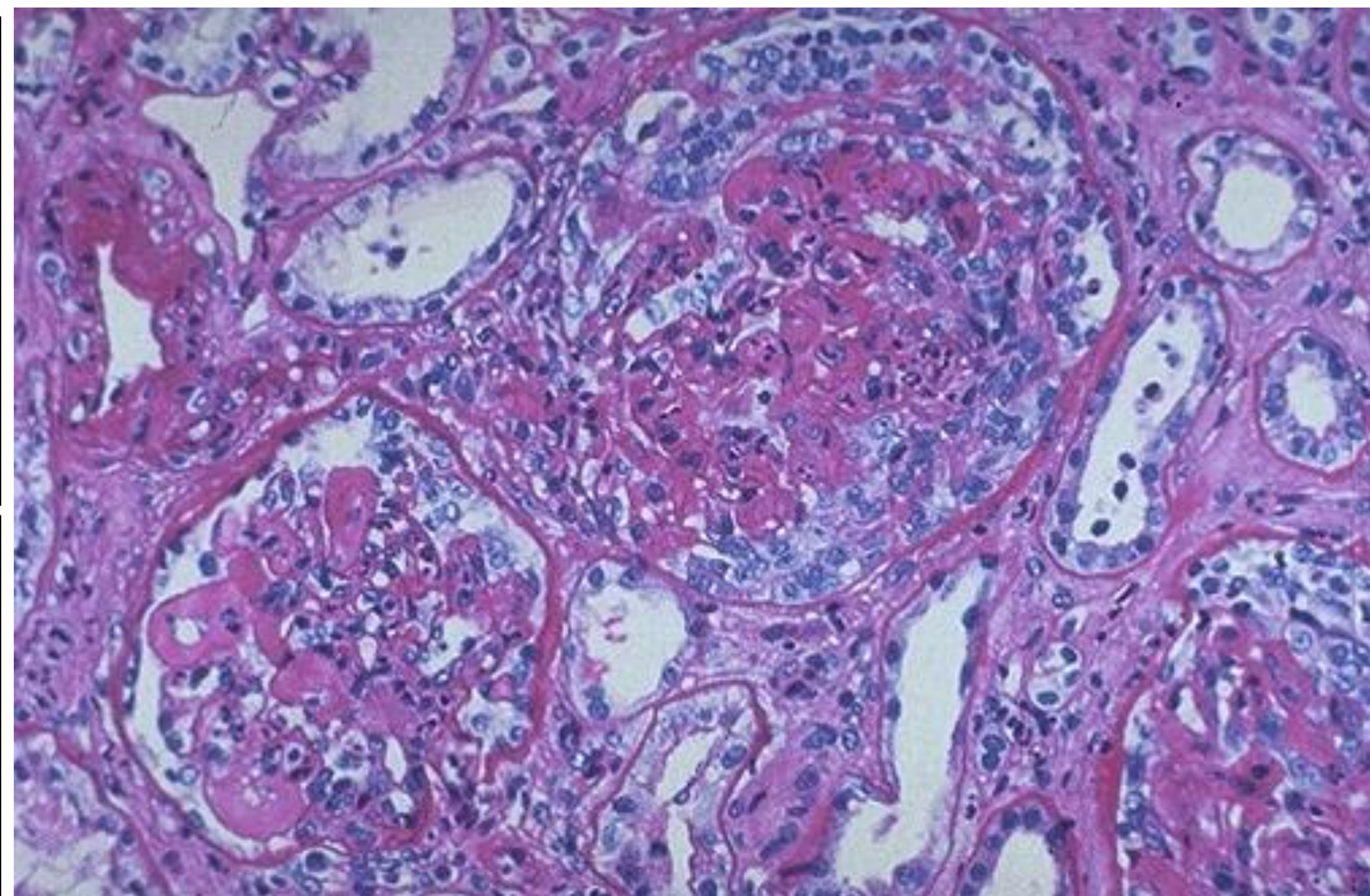
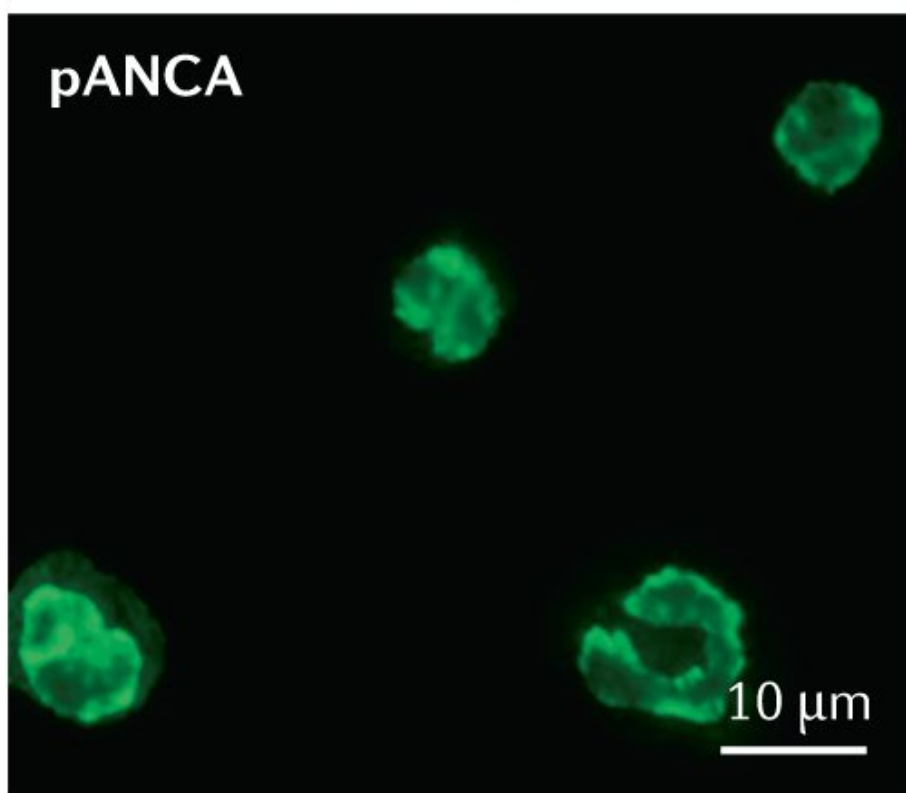
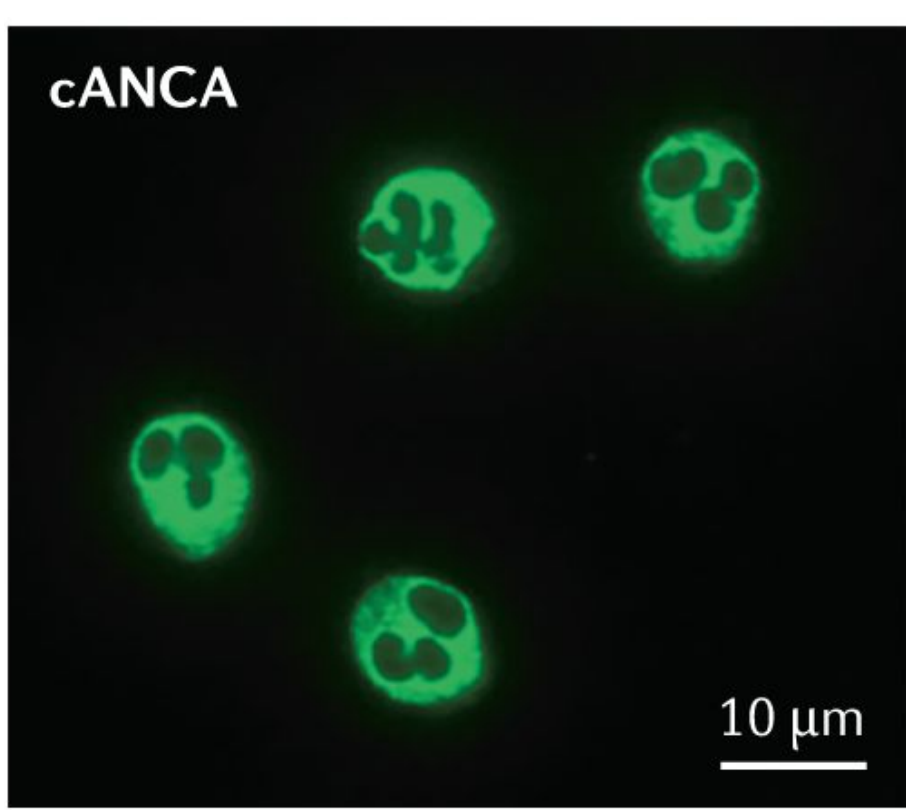
# ANCA related glomerulonephritis



In ANCA-associated vasculitis, kidney disease is most frequent in microscopic polyangiitis (>80%), while less frequent in granulomatosis with polyangiitis (around 60%) and in eosinophilic granulomatosis with polyangiitis (around 25%–30%).

ANCA bind to peripheral neutrophil epitopes, which through a complex interaction between triggered neutrophils and the endothelium

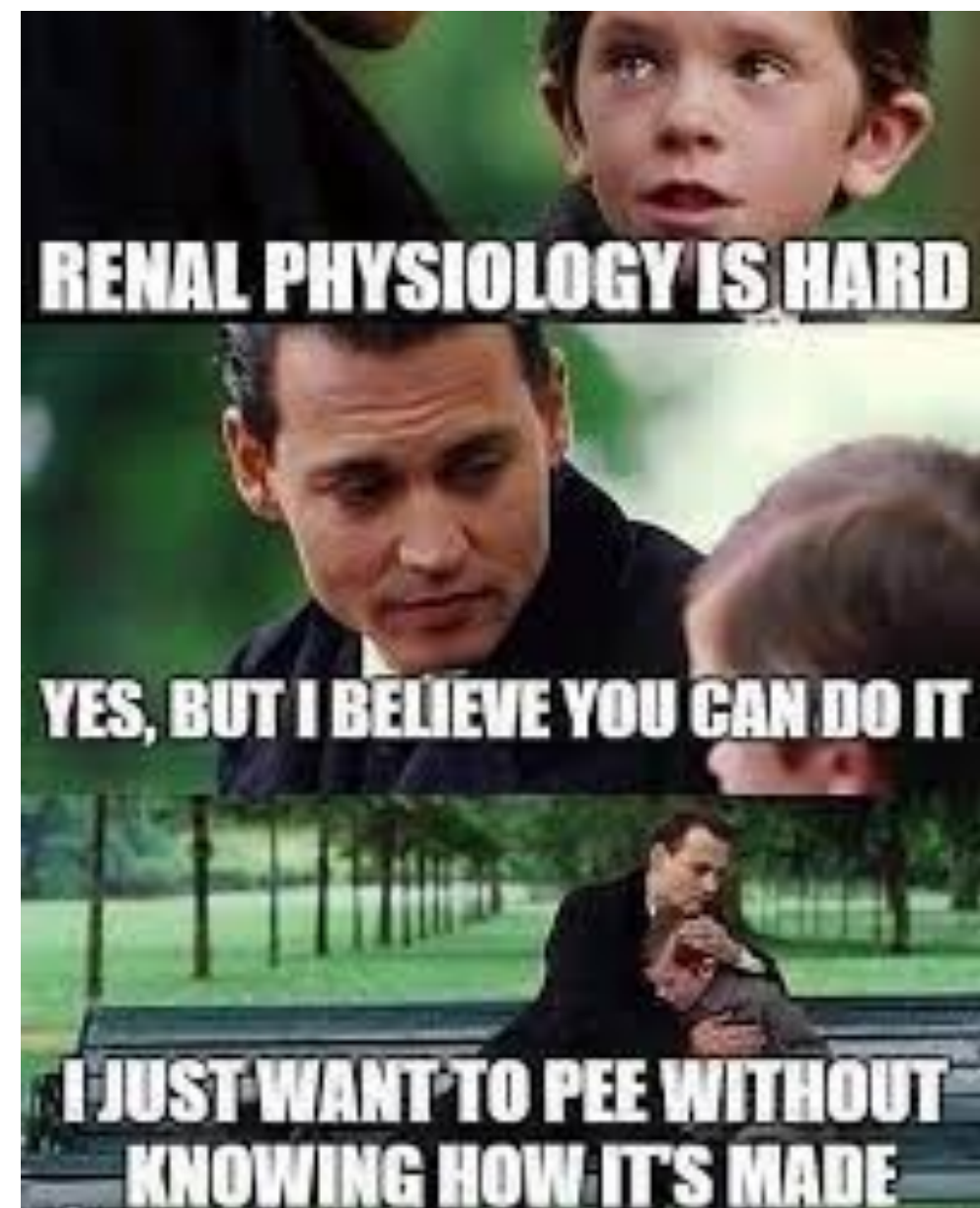




# Take home messages

Kidneys are frequently involved in inflammatory arteriopathies

General and specific renal function evaluation is mandatory for a correct management of these diseases



# I hanks for your attention!



**Carlo Alfieri**  
Email: [carlo.alfieri@unimi.it](mailto:carlo.alfieri@unimi.it)



@CARLO\_ALFIERI

*Passo del Maloja - Agosto 2021*