Thrombotic Microangiopathy

Clinicopathological Correlations

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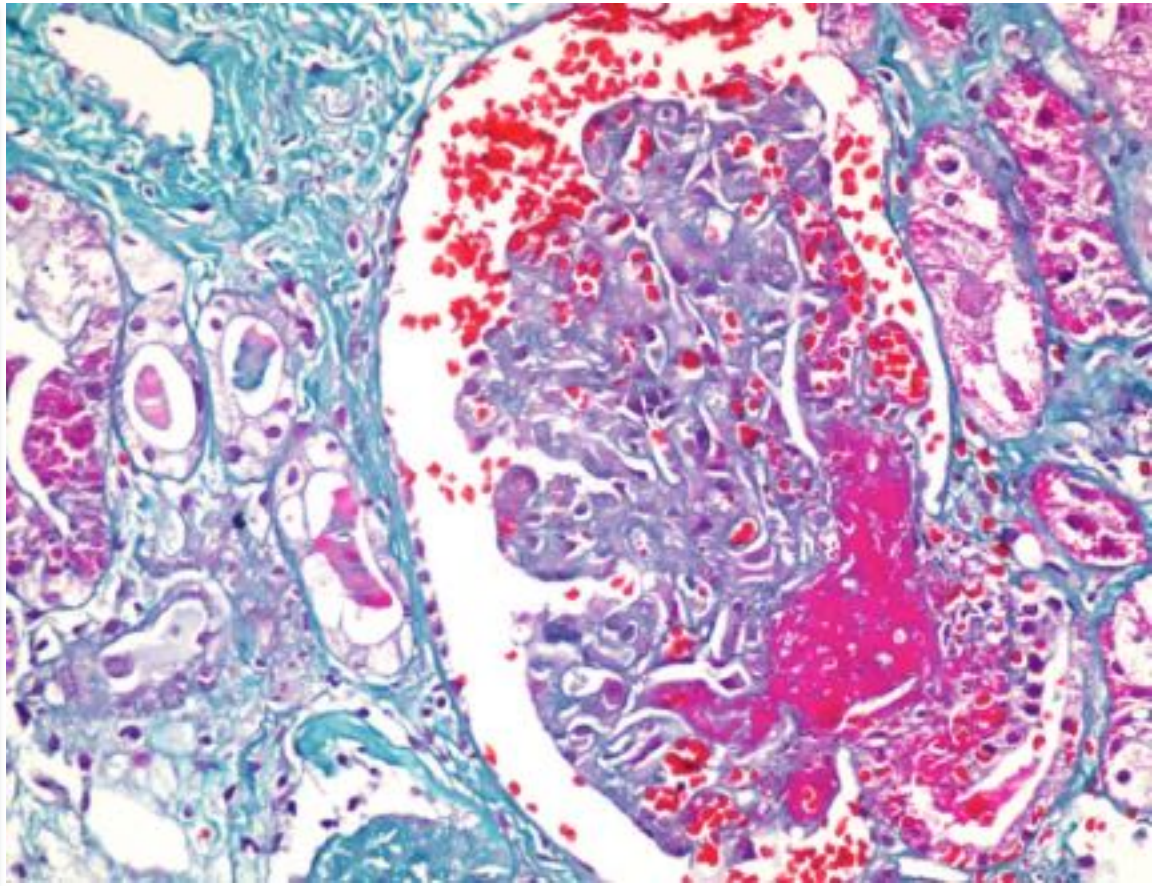
Thrombotic Microangiopathy

- A pathological lesion observed in a wide spectrum of diseases
- Triggered by endothelial injury and/or dysfunction
- The term thrombotic microangiopathy (TMA) was first introduced by Symmers in 1952, defining a lesion of :
  - ✓ vessel wall thickening (mainly arterioles or capillaries) with swelling or detachment of the endothelial cell from the basement membrane
  - ✓ accumulation of fluffy material in the subendothelial space
  - ✓ intraluminal platelet thrombosis
  - ✓ partial or complete obstruction of the vessel lumina

Thrombotic Microangiopathy

A histopathological (morpholgical) term that defines glomerular, arteriolar or interlobular artery lesions and is characterized by a patchy distribution

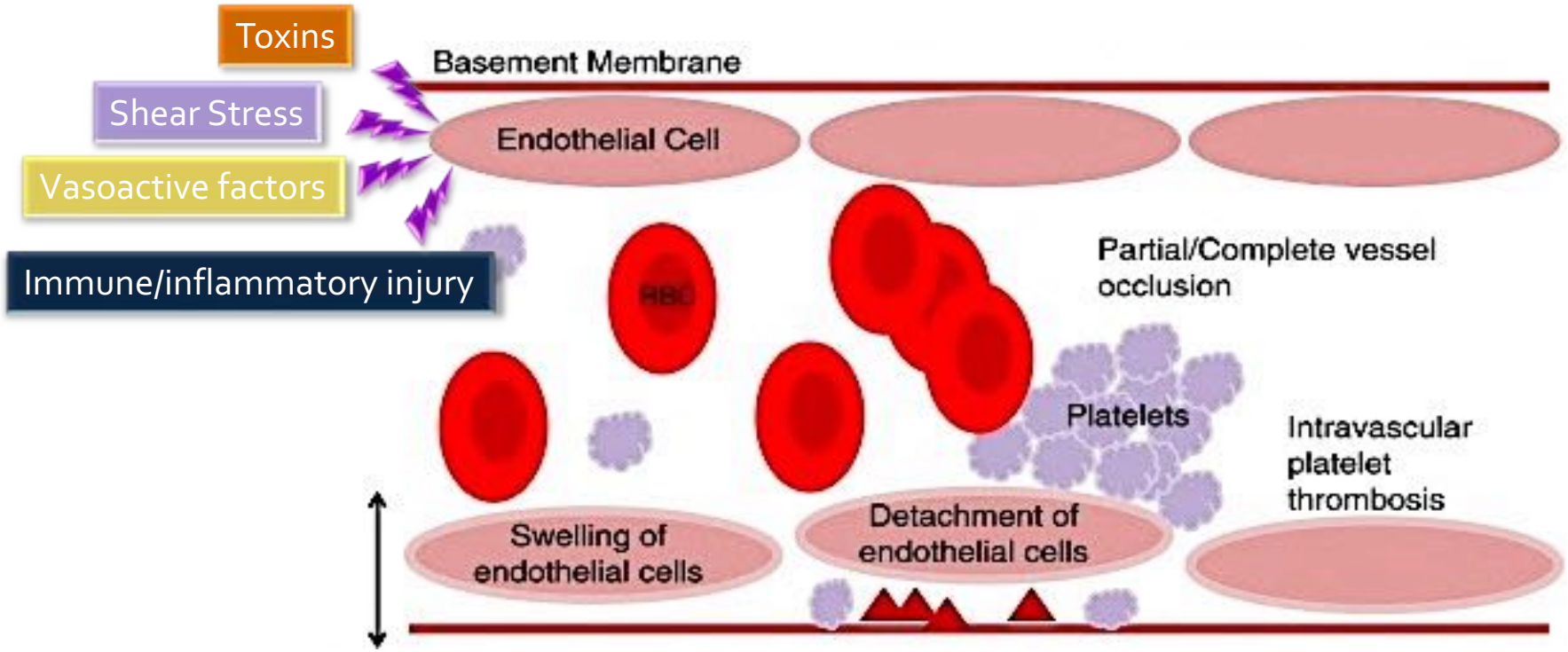


Box 1. Conditions Associated With TMA

- ADAMTS13-mediated TMA (TTP)
  - Congenital (cTTP)
  - Immune (iTTP)
- Complement-mediated TMA (aHUS)
  - Congenital
  - Immune
- Coagulation-mediated TMA (pathogenic variants in *PLG*, *THBD*, and *DGKε*)
- Metabolic (defects of cobalamin metabolism)
- Infection-associated TMA
  - Bacterial: Shiga toxin–producing *Escherichia coli*, *Streptococcus pneumoniae*, *Campylobacter jejuni*, *Klebsiella pneumoniae*
  - Viral: influenza, HIV, EBV, CMV, BK virus, parvovirus B19, SARS-CoV-2
  - Fungal: histoplasmosis
- Pregnancy-associated TMA
  - Preeclampsia
  - HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome
  - Trigger of TTP, aHUS, CAPS
- Drug-induced TMA
  - Immune mediated
    - Via drug-triggered antibodies against platelets/neutrophils: gemcitabine, oxaliplatin, trimethoprim-sulfamethoxazole, quinine, vancomycin
    - Via autoantibodies against ADAMTS13: ticlopidine
  - Non–immune mediated
    - Chemotherapy: alemtuzumab, gemcitabine, mitomycin C, vincristine, doxorubicin, pentostatin, VEGF inhibitors, tyrosine kinase inhibitors, proteasome, and checkpoint inhibitors
    - Immunosuppressive therapy: calcineurin inhibitor, sirolimus, interferon β
    - Antibiotics: ciprofloxacin, levofloxacin, metronidazole, nitrofurantoin, penicillin
    - Other: cocaine, ecstasy, estrogen/progesterone, anti-inflammatories, oxymorphone, simvastatin
- Transplant-associated TMA
  - Solid organ
  - Hematopoietic stem cell transplant
- Malignancy-associated TMA
  - Solid: breast, gastric, lung, ovarian, prostate, and urothelial cancers
  - Hematologic: Myelo and lymphoproliferative, monoclonal gammopathies (myeloma, smouldering myeloma, MGRS), and POEMS
- Autoimmune diseases
  - APS, including CAPS
  - SRC
  - SLE
  - Primary glomerulonephritis and vasculitis (observed on biopsy)
  - Sjögren syndrome, rheumatoid arthritis, dermatomyositis
- Hypertensive emergency
- Other: hemophagocytic lymphohistiocytosis, sickle cell disease, Castleman disease and variants

Pathogenesis

Direct Endothelial Damage



Modified from Keir L, Coward RJ - Pediatr. Nephrol. (2010)

Thrombotic Microangiopathy

Typically:

- Thrombocytopenia
- Microangiopathic hemolytic anemia (MAHA)
- Organ Injury , frequently AKI

The kidney is the most frequently injured organ, but other systems including the central nervous system, the cardiovascular and respiratory systems, and the gastrointestinal tract may also be affected

Depending on the organ primarily involved clinical symptoms may vary considerably from mild to severe

Associated with significant morbidity and mortality (early recognition)

Thrombotic Microangiopathy

Renal limited forms

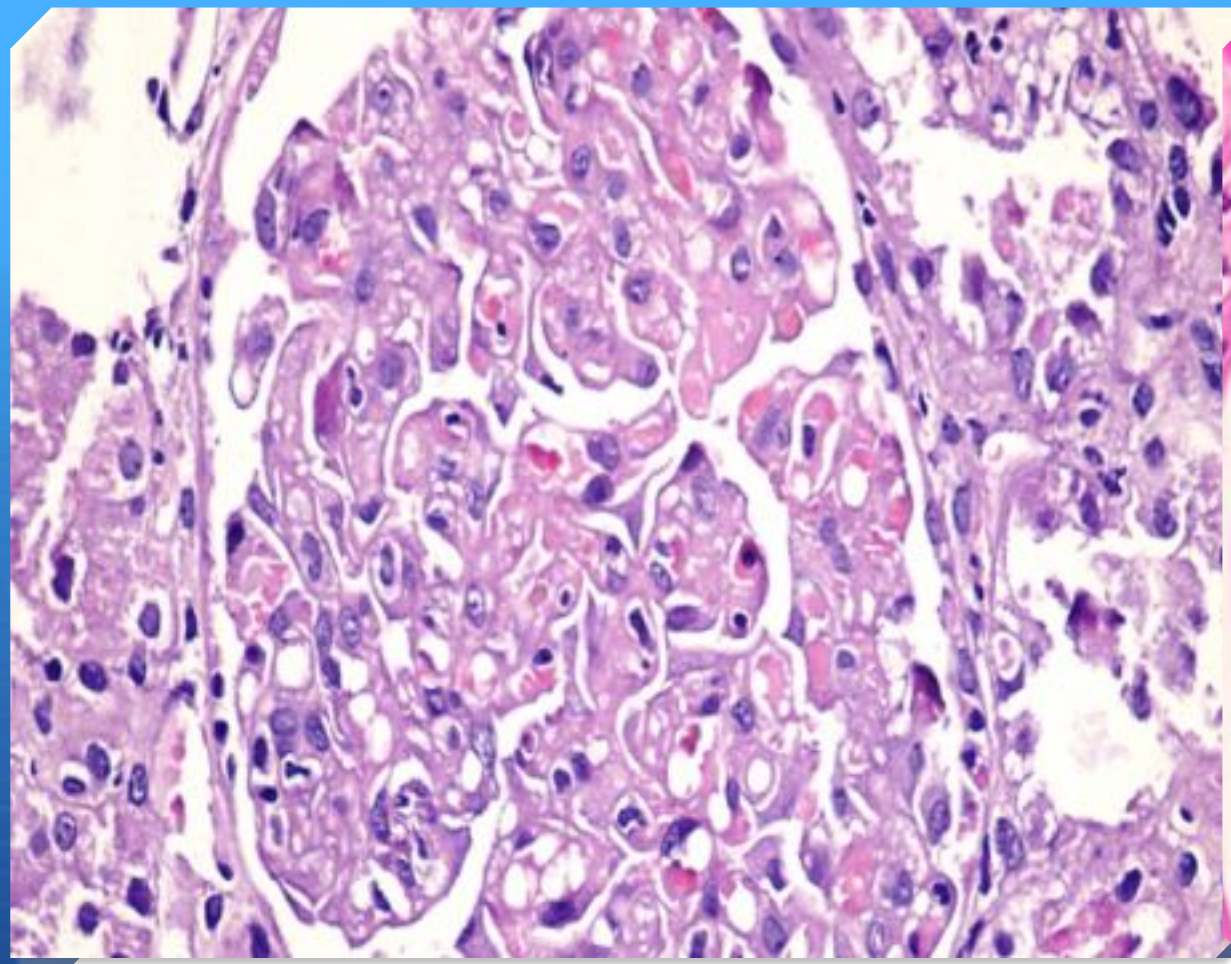
- Frequently encountered in clinical practice
- can be diagnostically challenging, often delaying the initiation of targeted therapy
- Observed more often in the setting of GN (ANCA-associated vasculitis, IgA nephropathy, MGN, FSGS) , solid organ transplantation and in drug-induced TMA

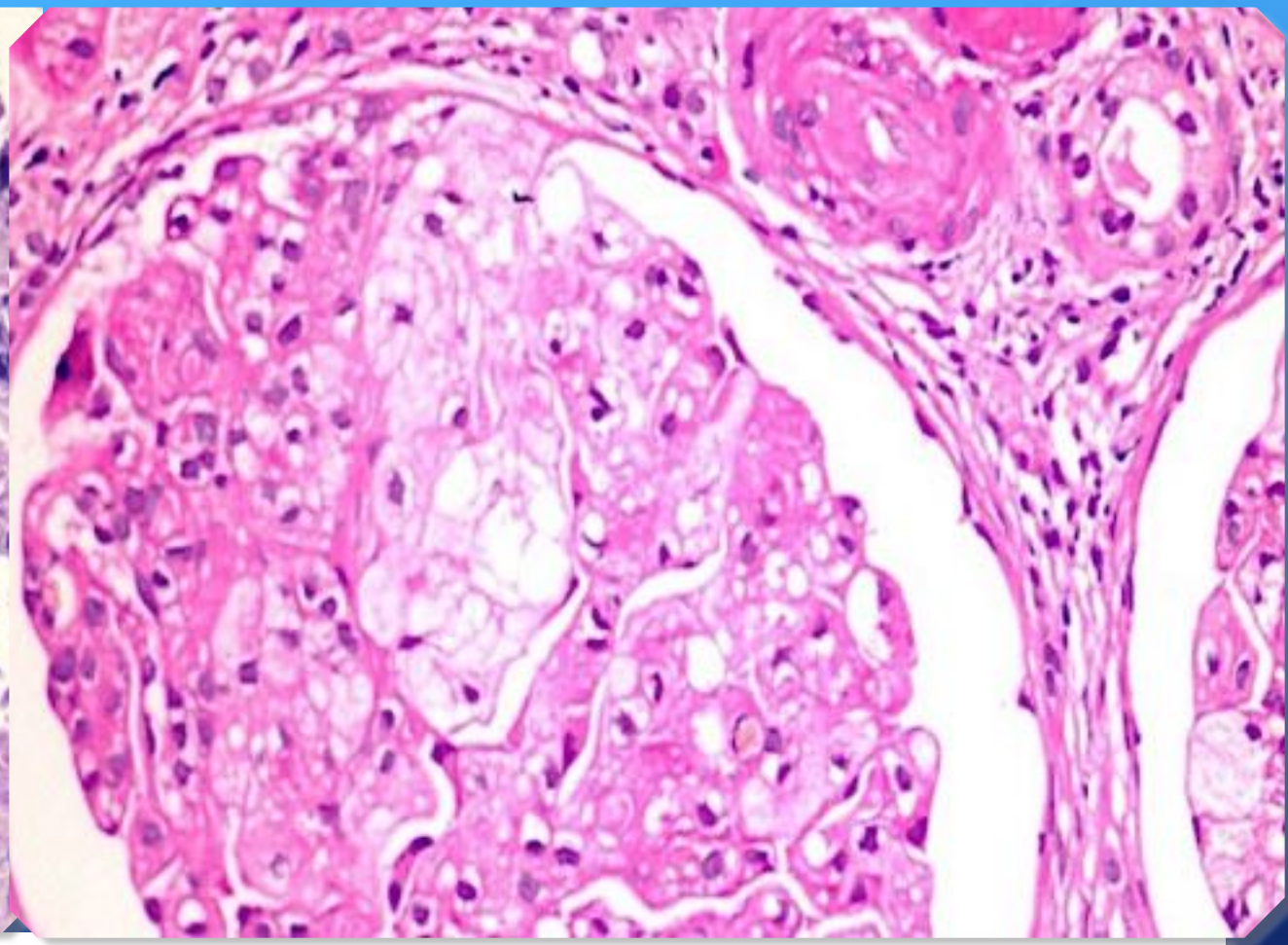
Pathological features in the Kidney

Depend upon type , degree and the stage of injury (early versus late)

- In the kidney (native and transplant) interlobular arteries, afferent arterioles and glomerular capillaries are typically affected
- Can be divided into acute and chronic lesions
- Glomerular, Arteriolar/Arterial dominant or Glomerular & arteriolar/arterial

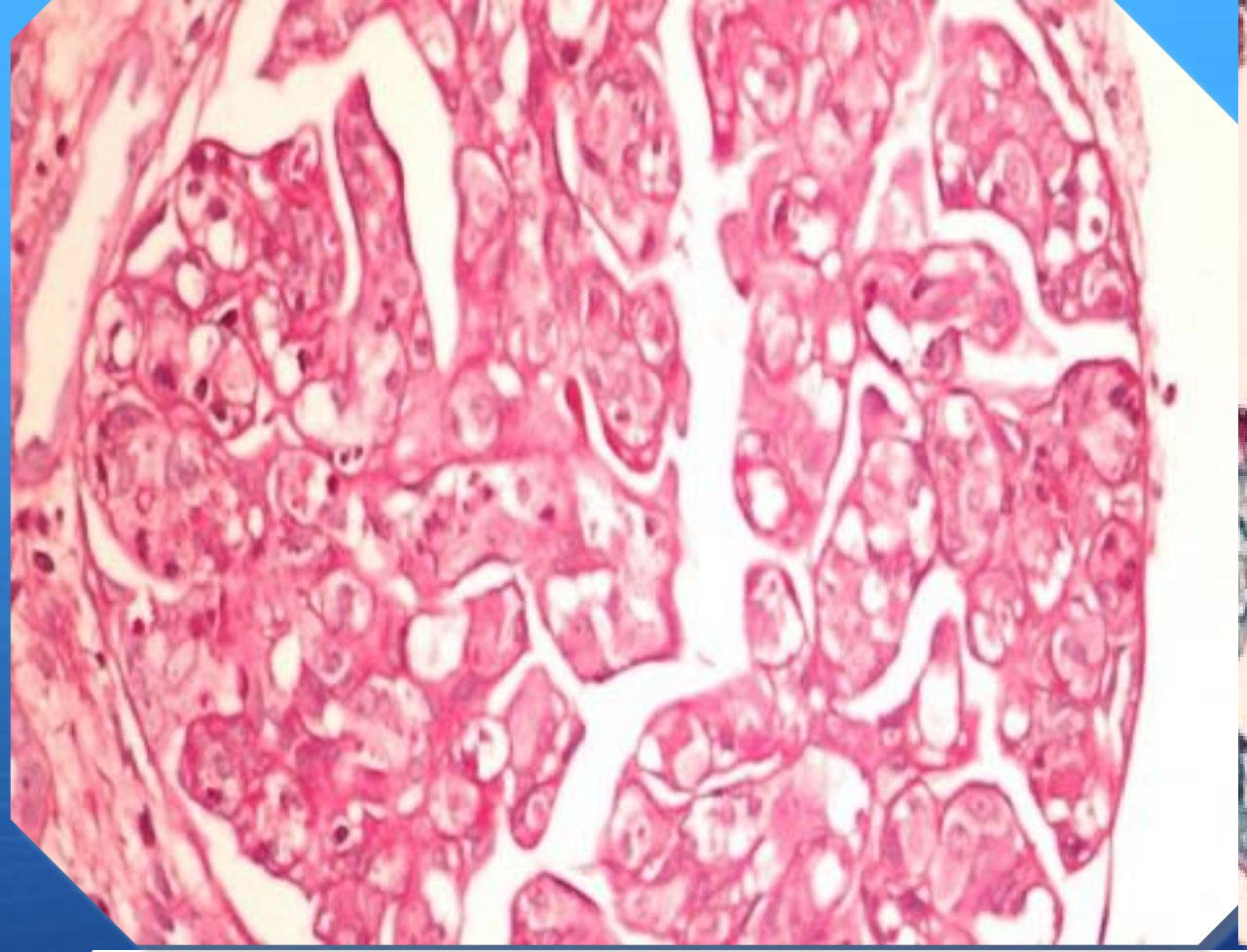
Do not distinguish between the multiple disease entities associated with TMA

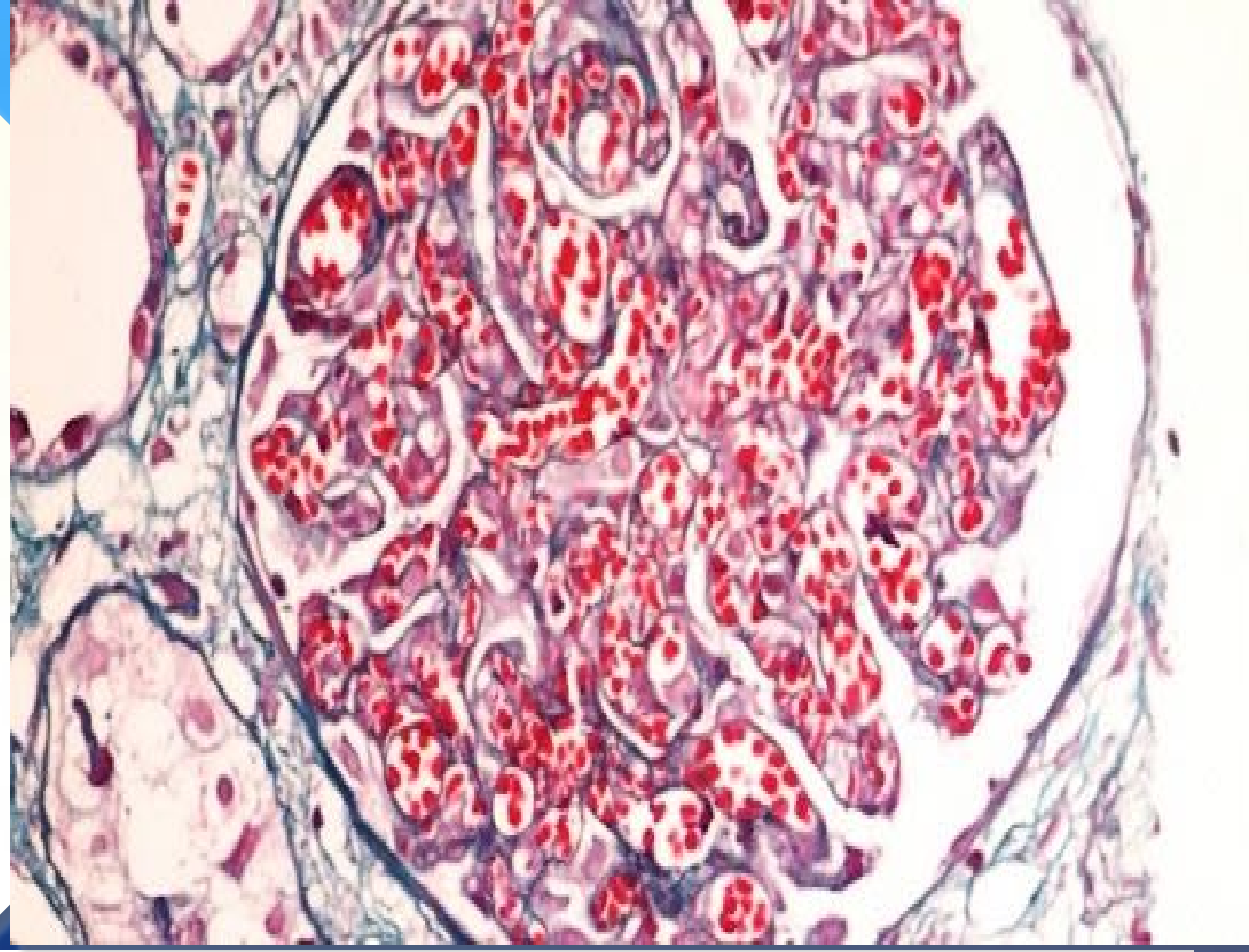




Glomerular (acute)

endothelial cell injury/endothelial swelling



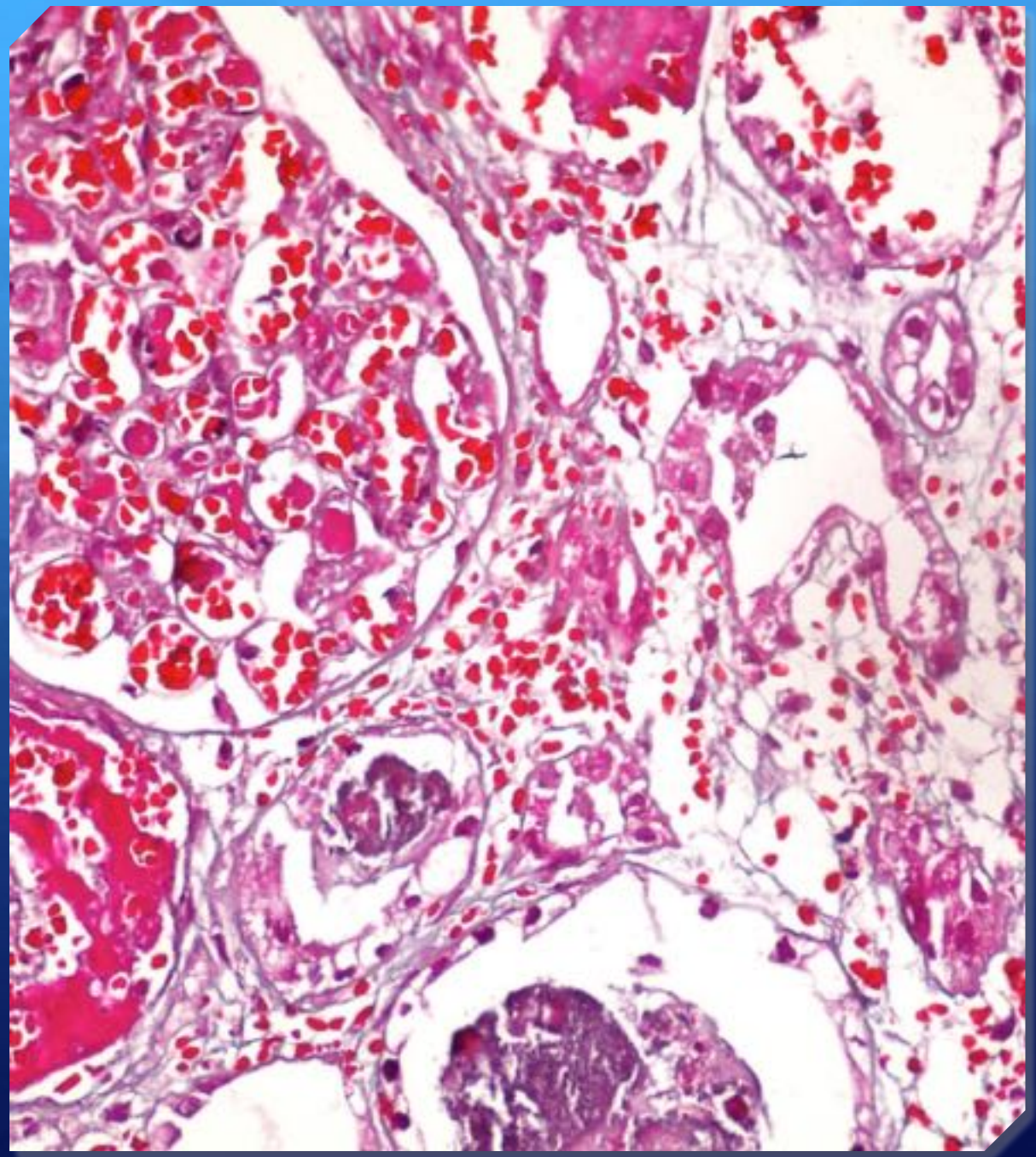


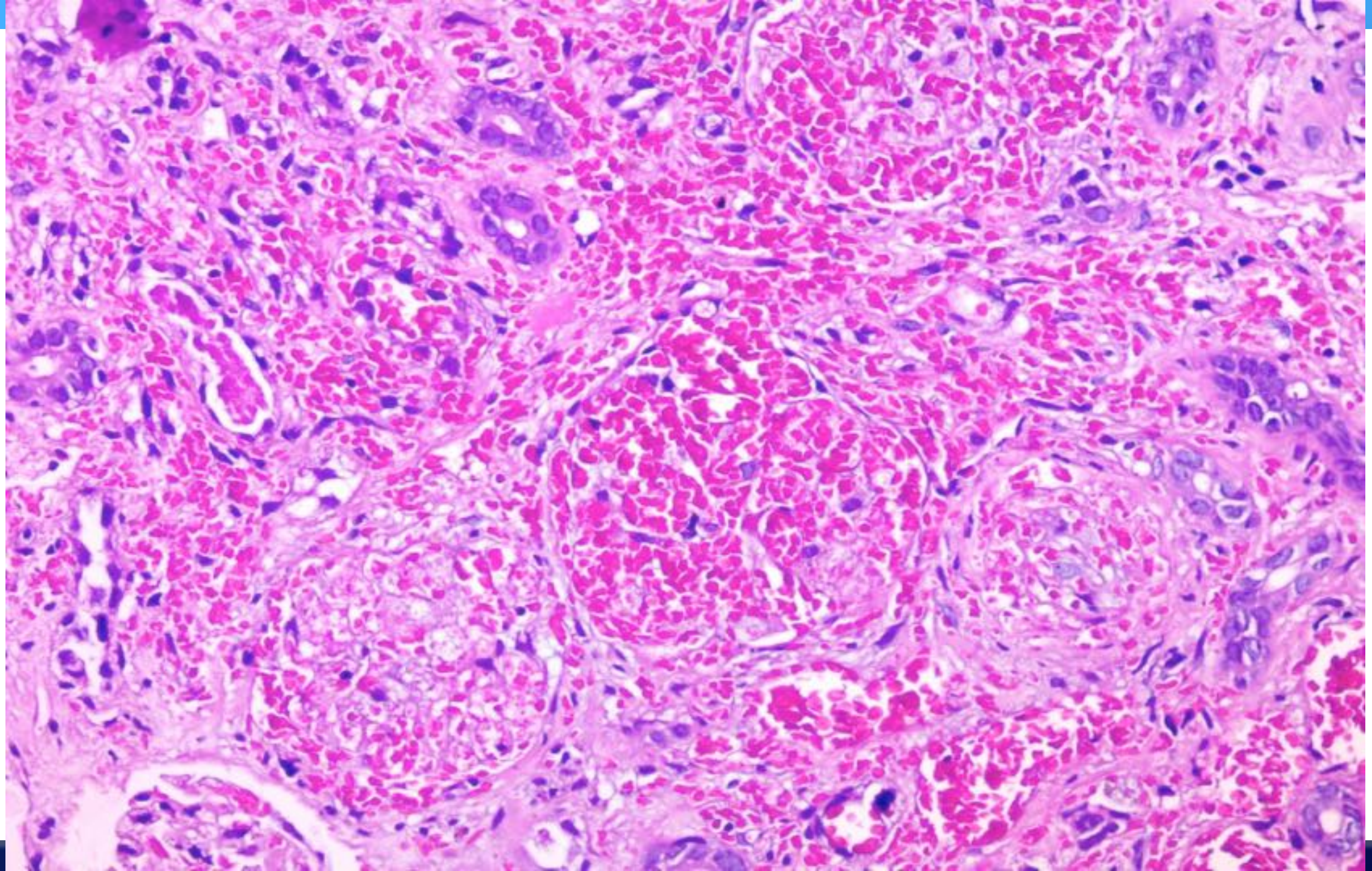
Glomerular (acute)

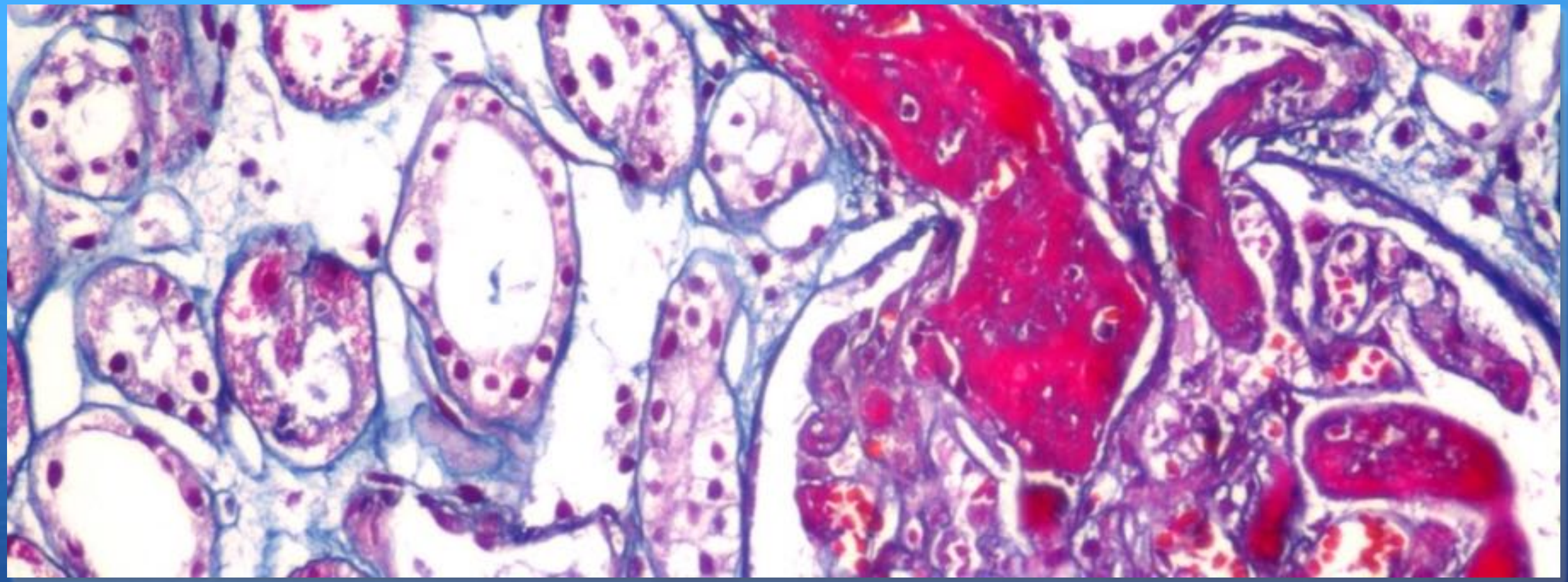
Inflammation, congestion

Glomerular (acute)

Intravascular congestion & red Cell fragmentation





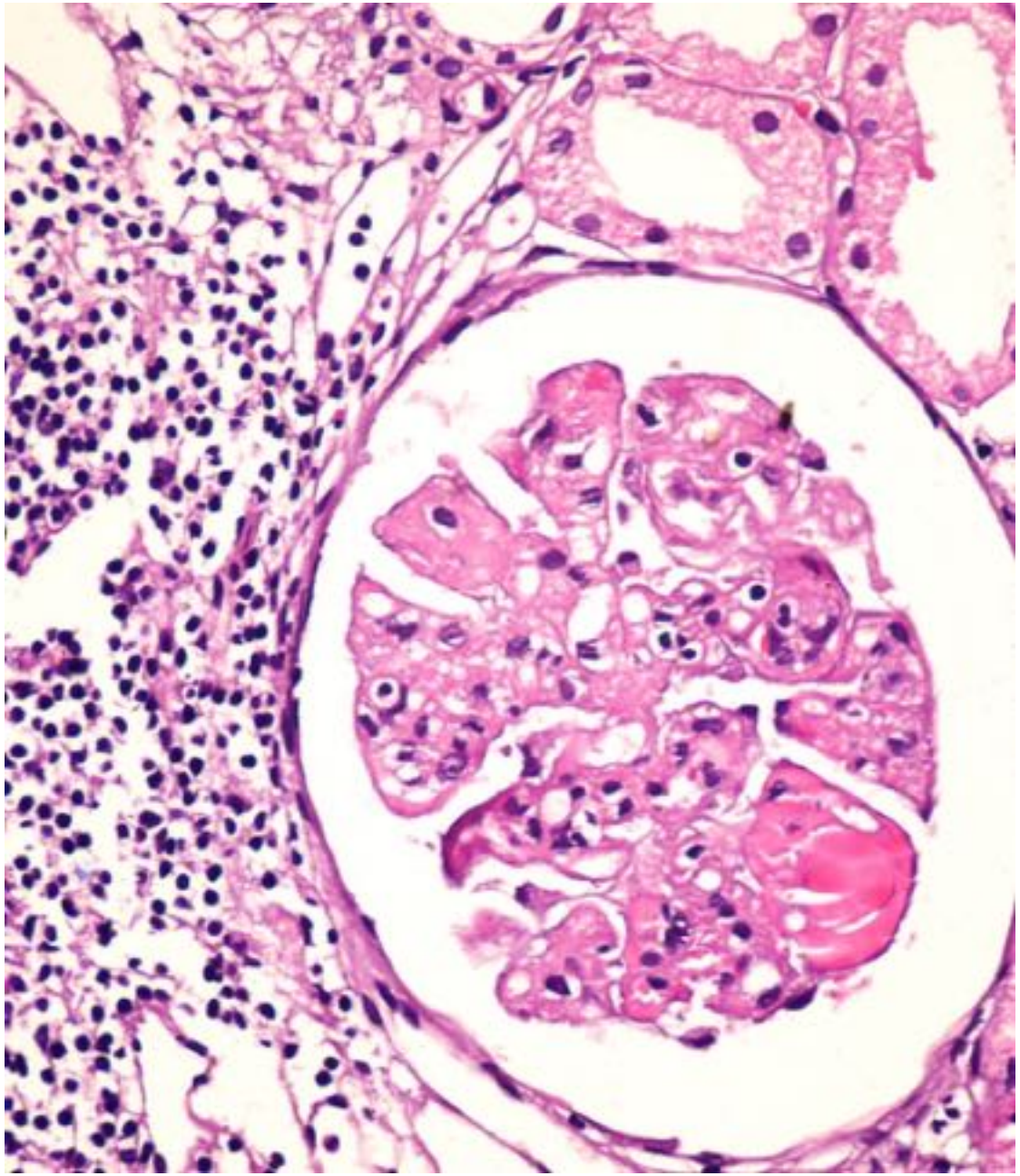


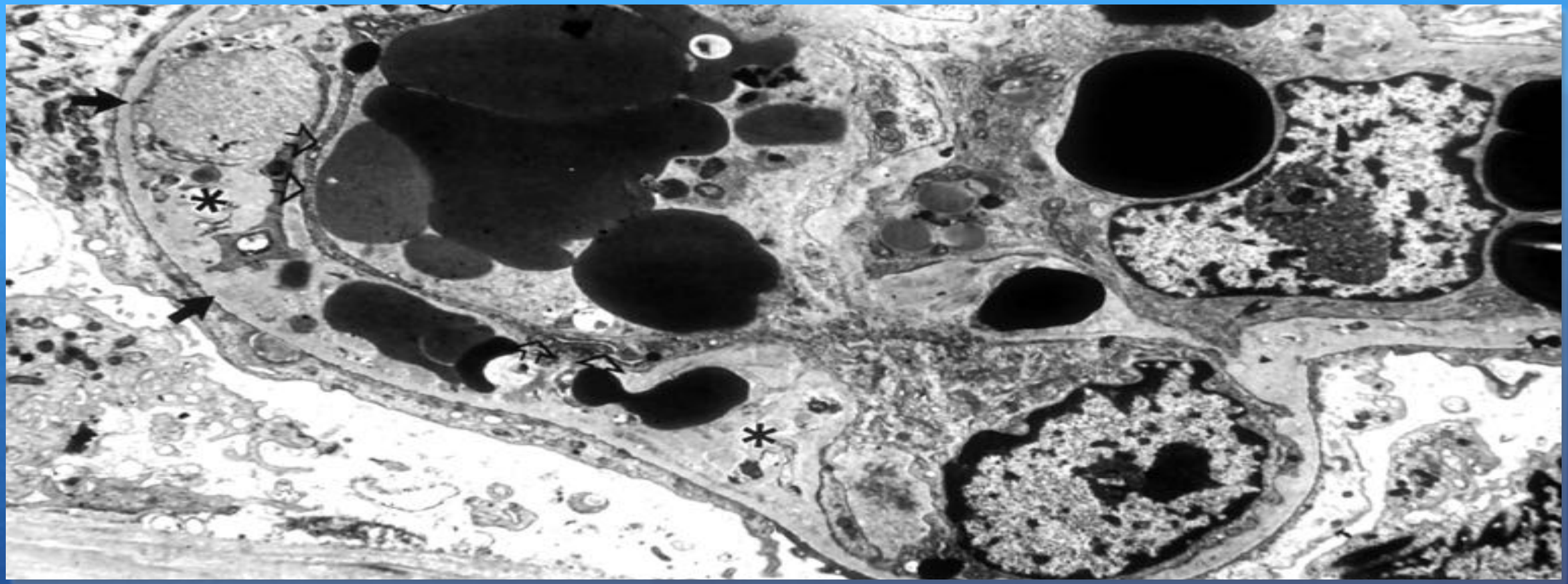
Glomerular (acute)

occasional thrombus formation (not a must)

Differential Diagnosis

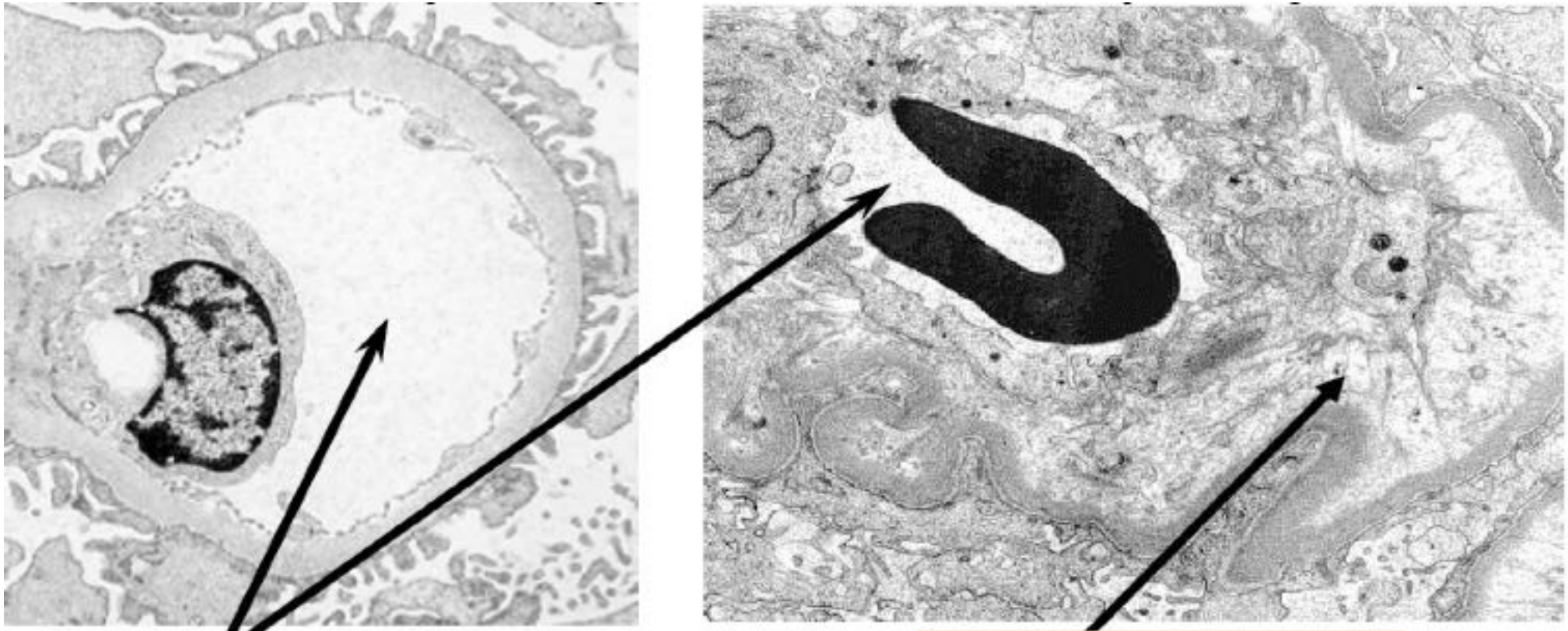
MPGN (cryo)

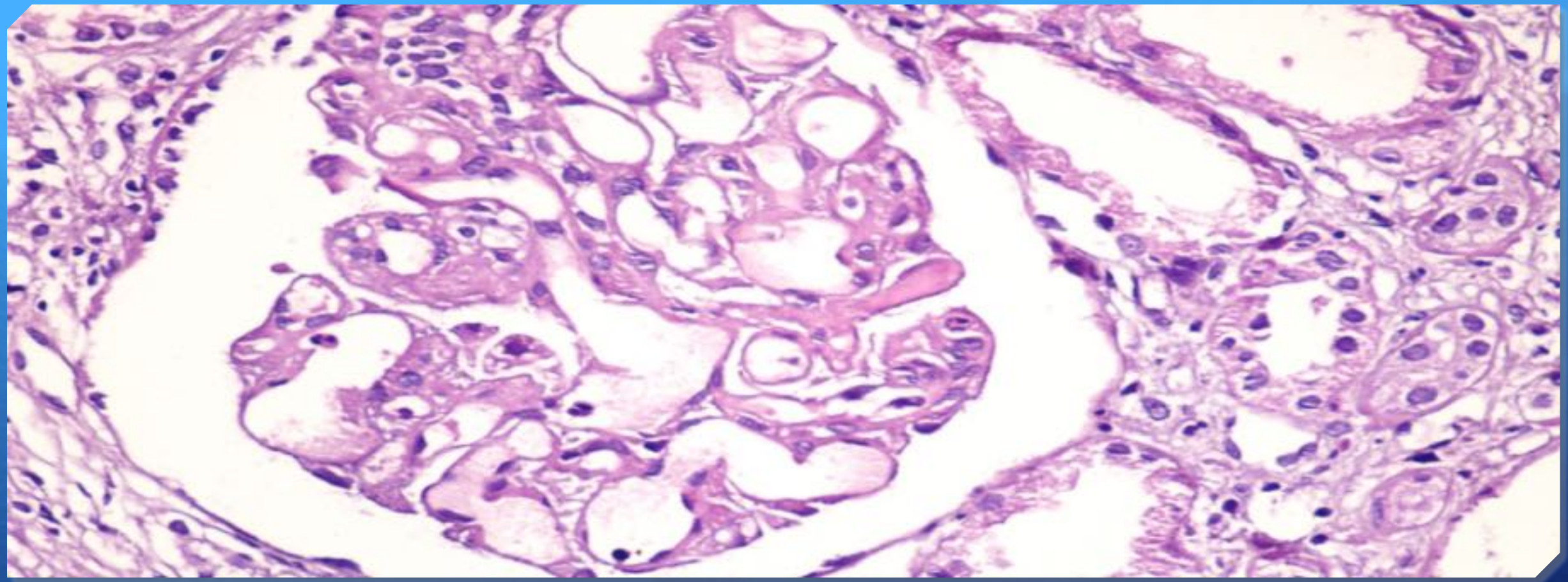




Glomerular (acute)

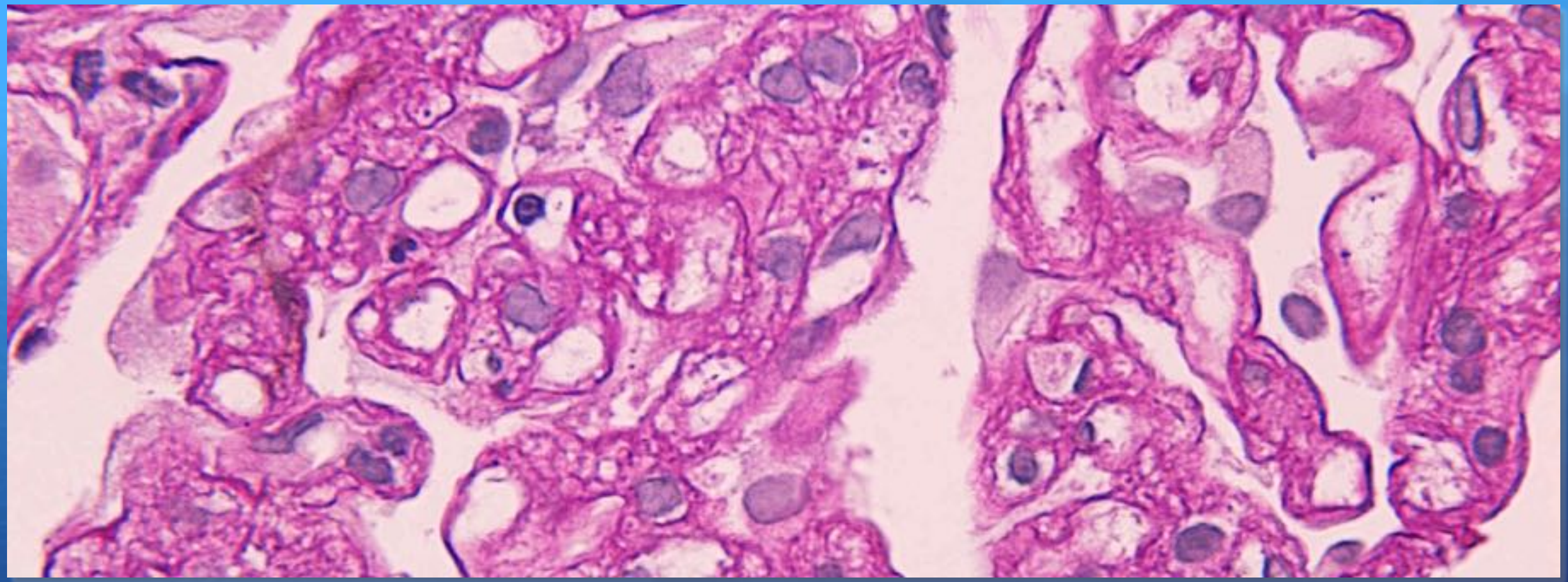
endothelial swelling and detachment from the underlying GBM


Lumen
Subendothelial expansion



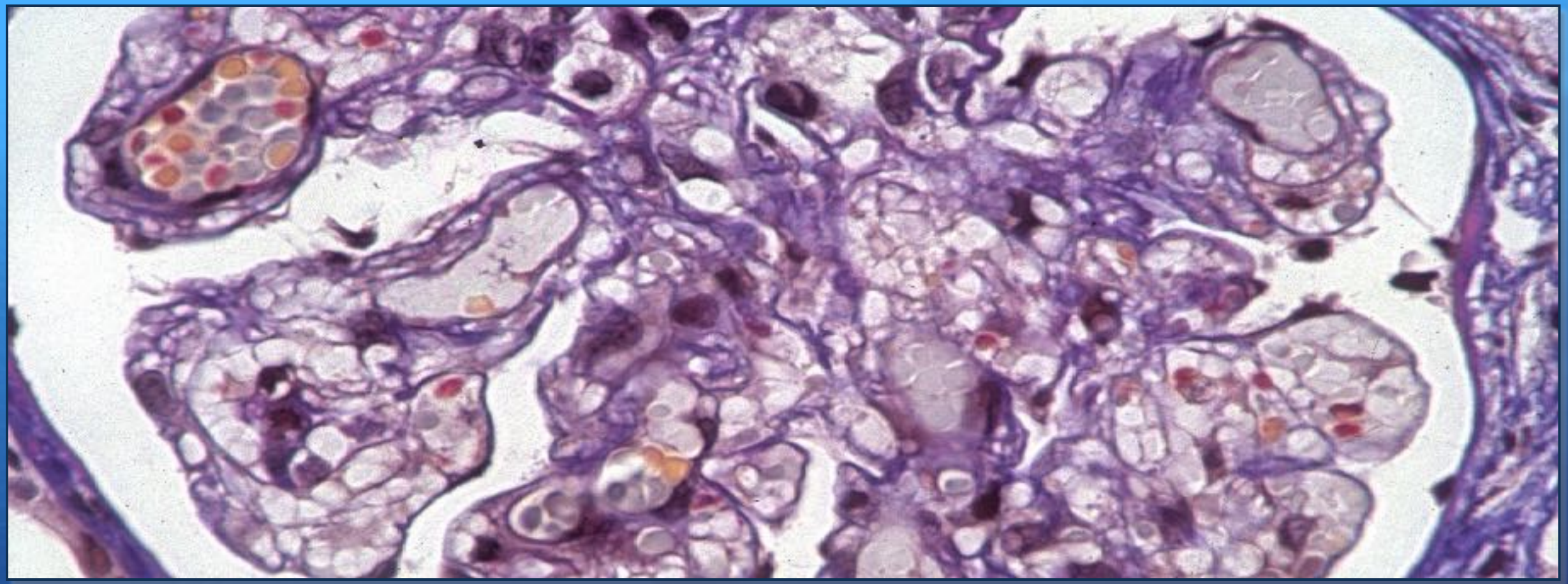
Glomerular (Chronic)

Mesangiolysis and capillary microanuerysm



Glomerular (Chronic)

- Subendothelial new basement membrane formation resulting in global or segmental duplication of glomerular basement membranes



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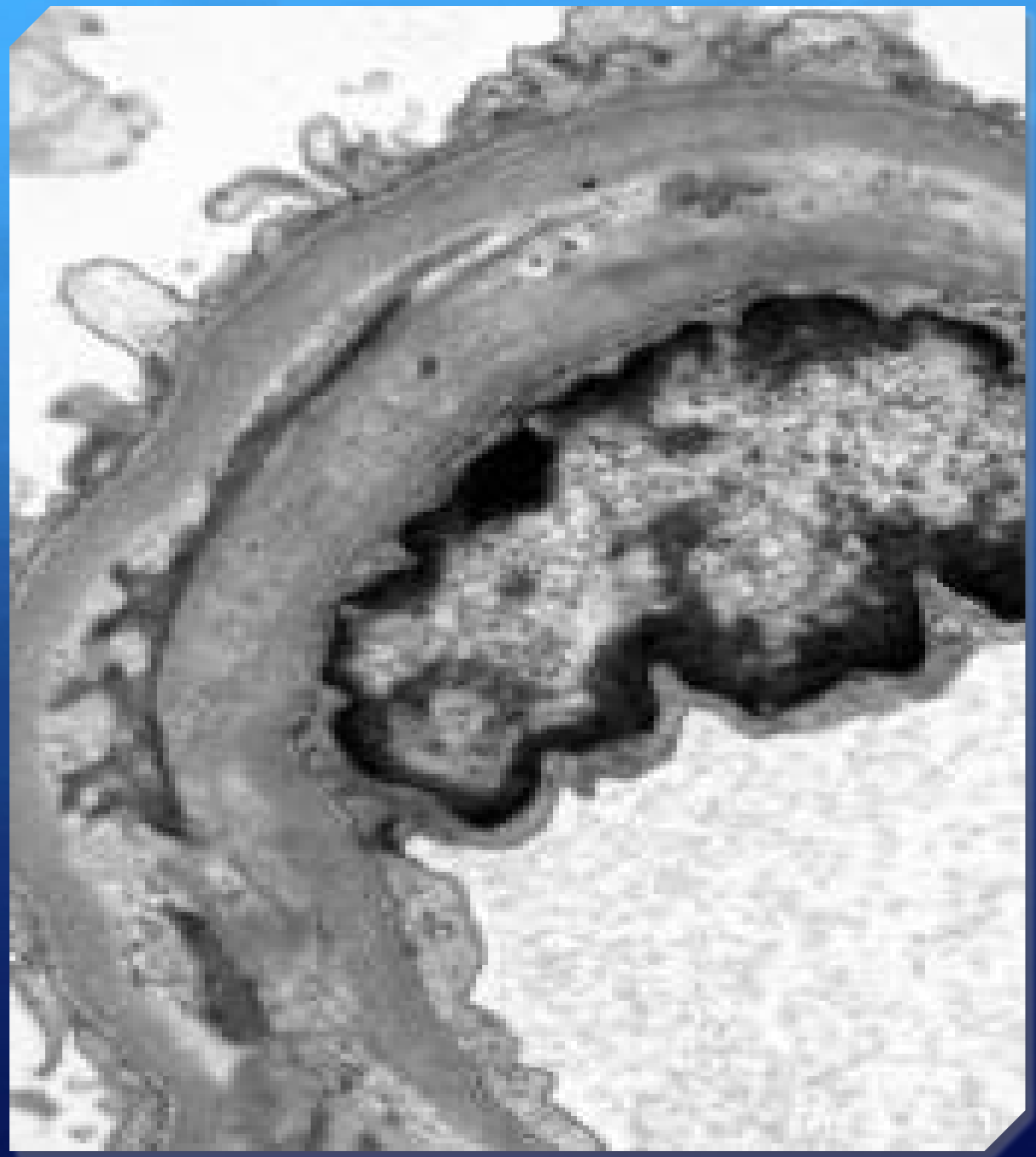
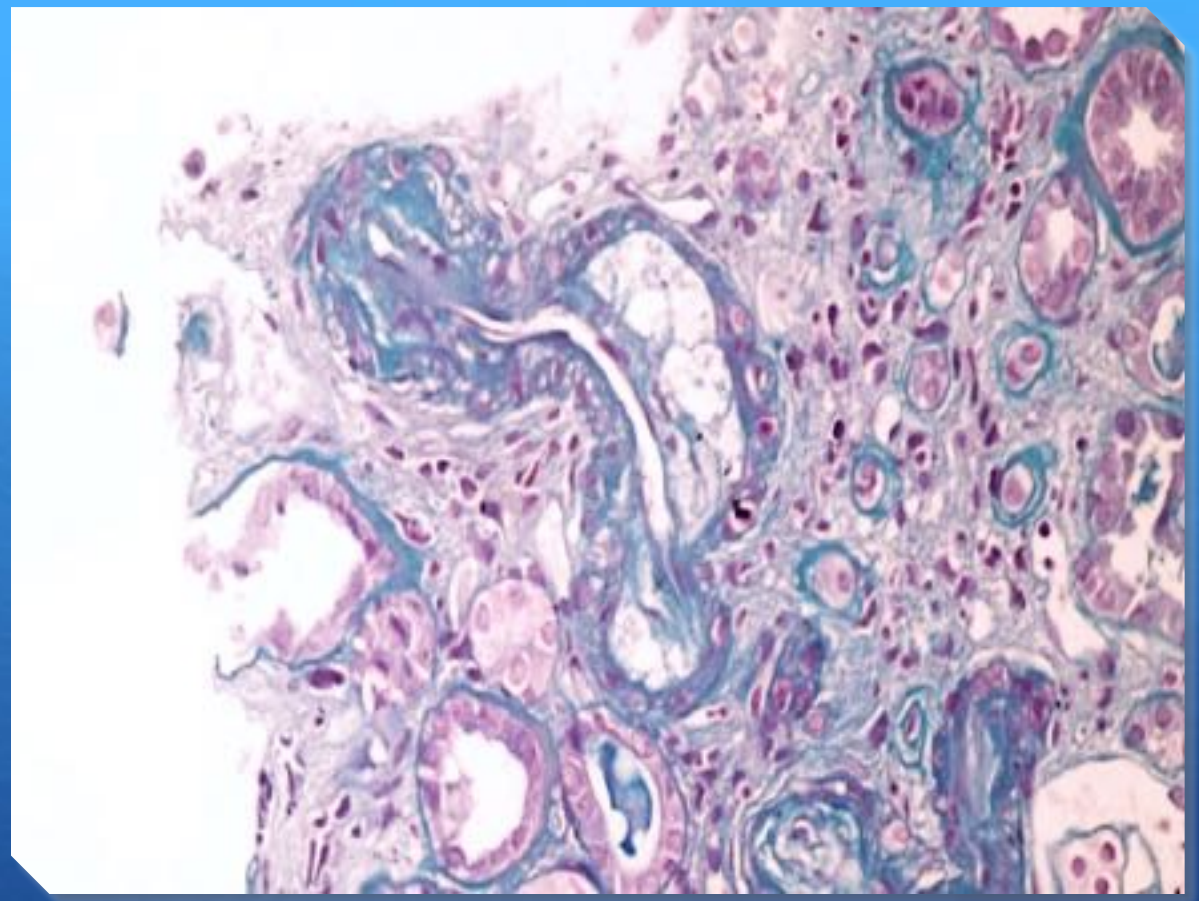
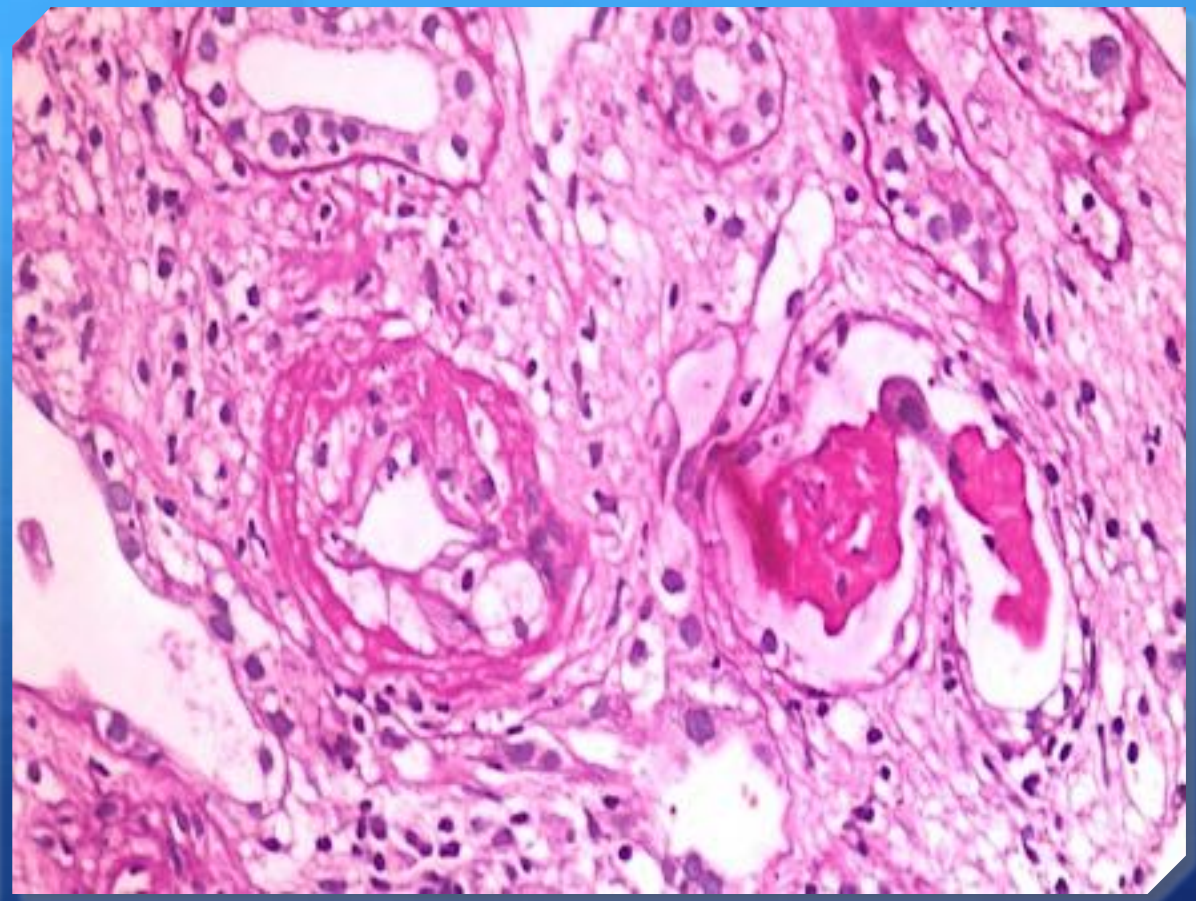
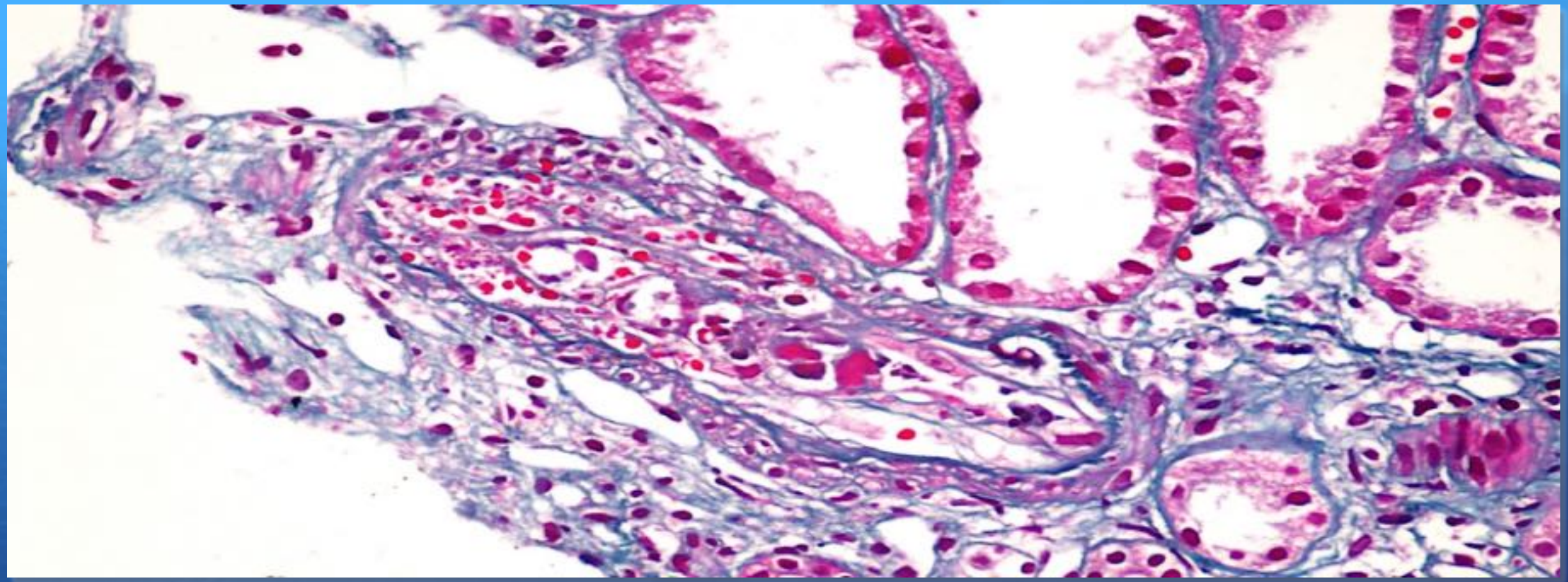






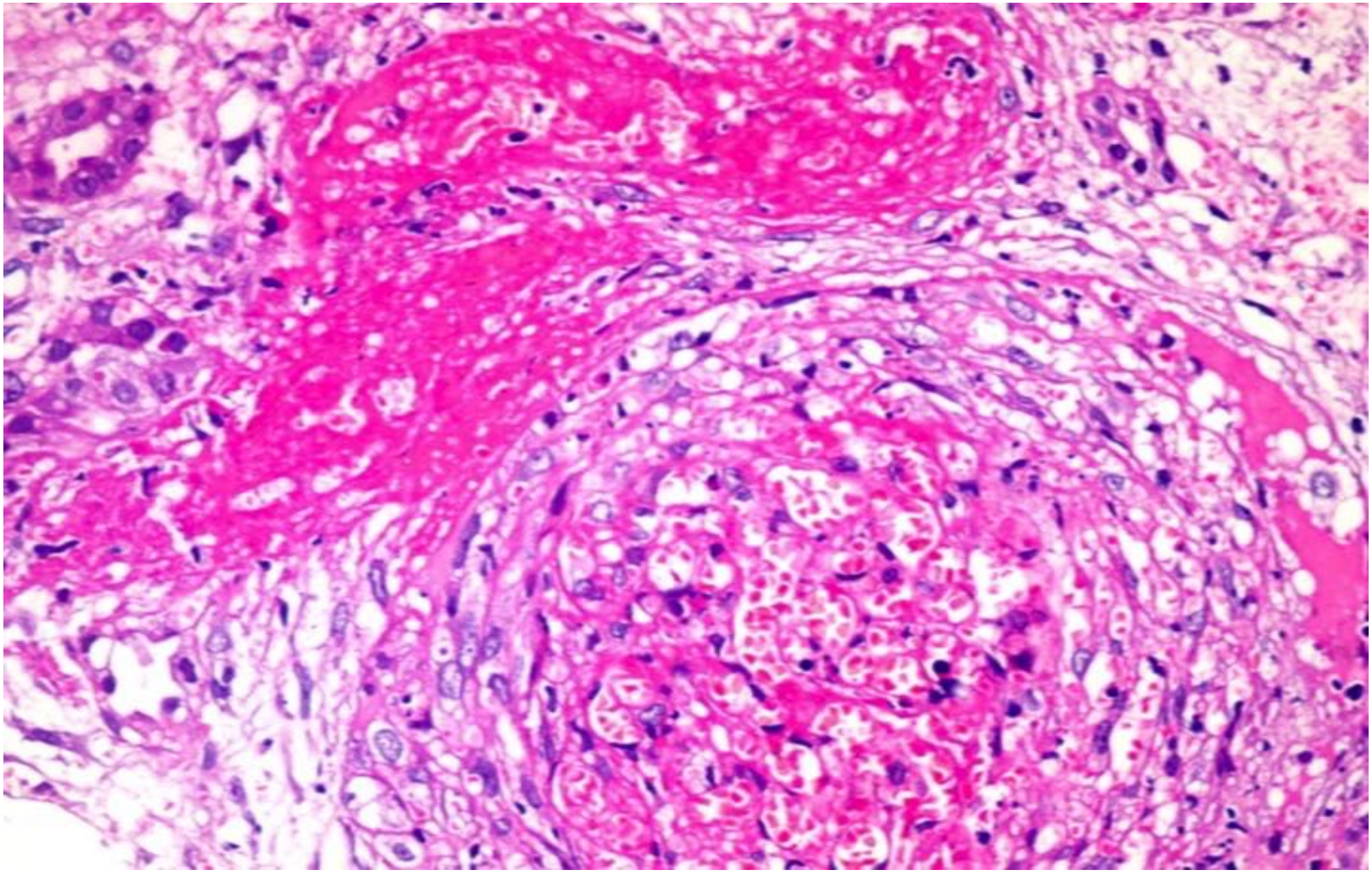
Vascular (Acute)

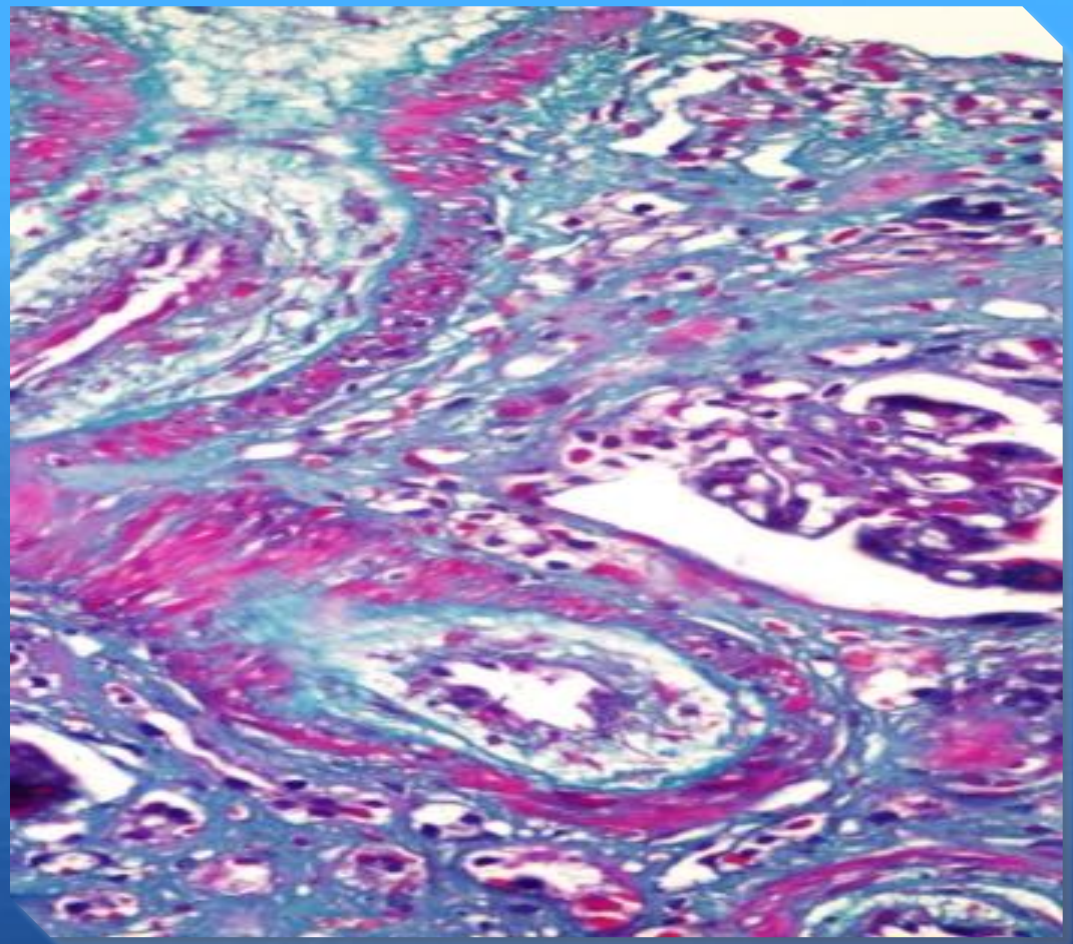
Endothelial Swelling

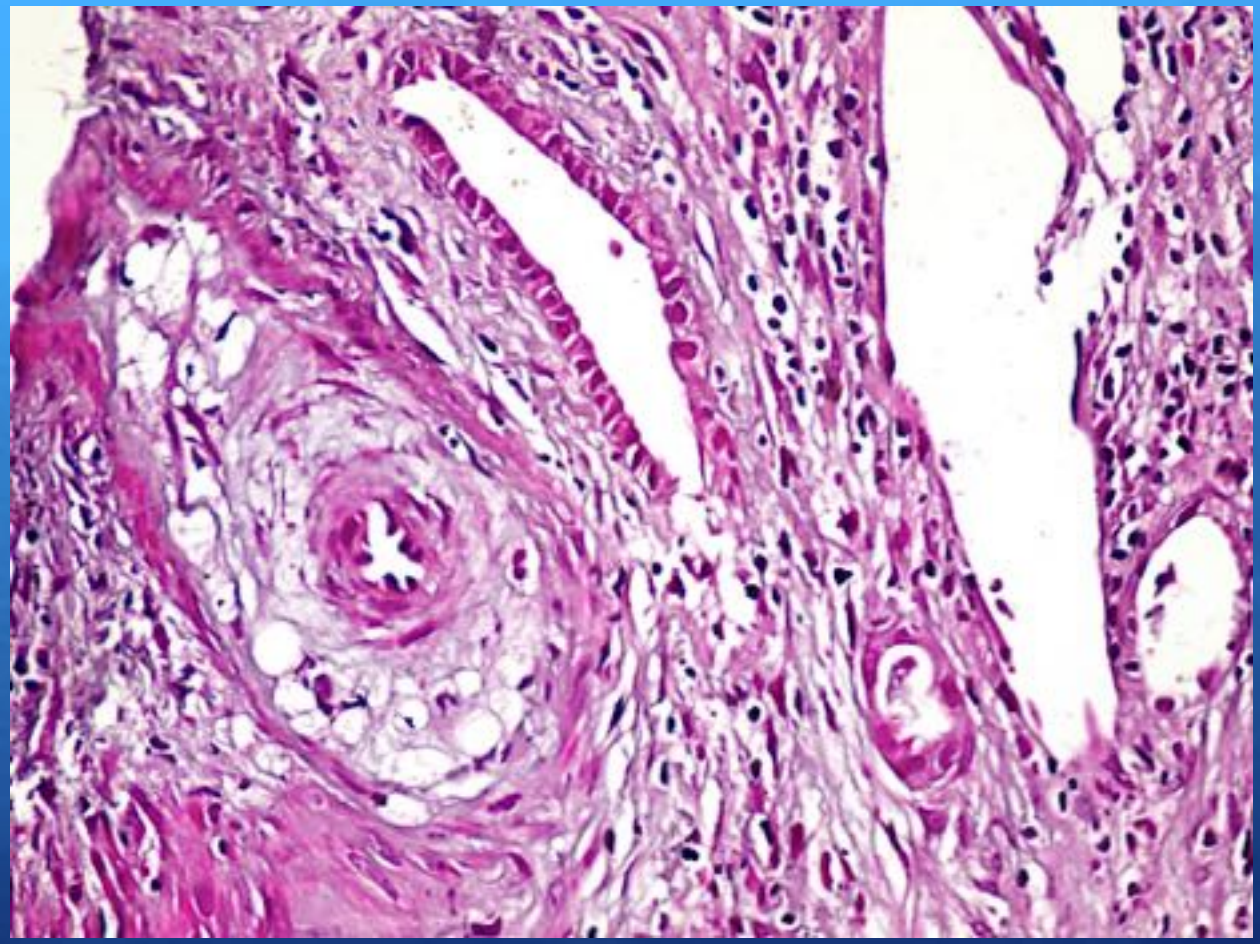


Vascular

Endothelial swelling and red cell fragmentation



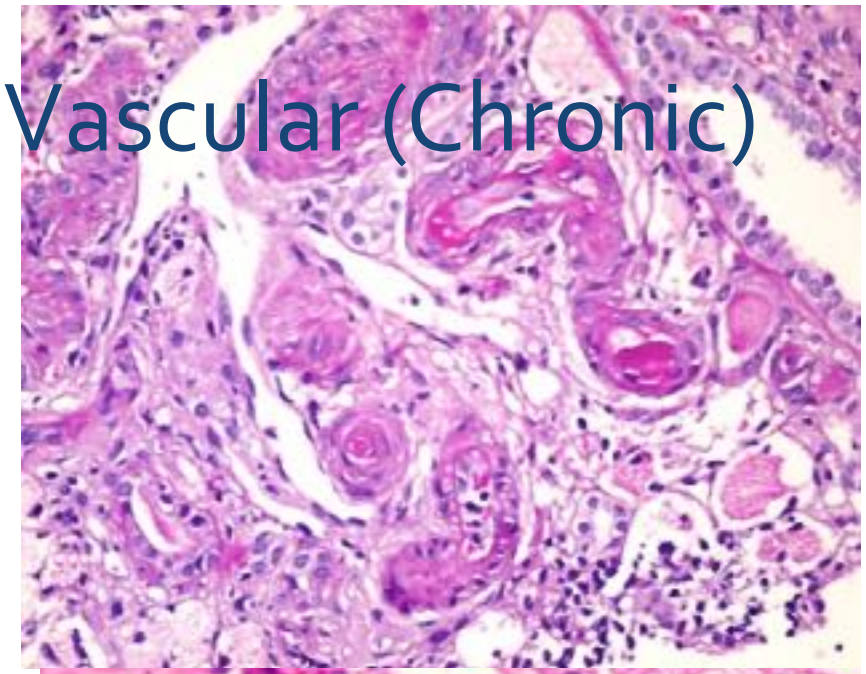


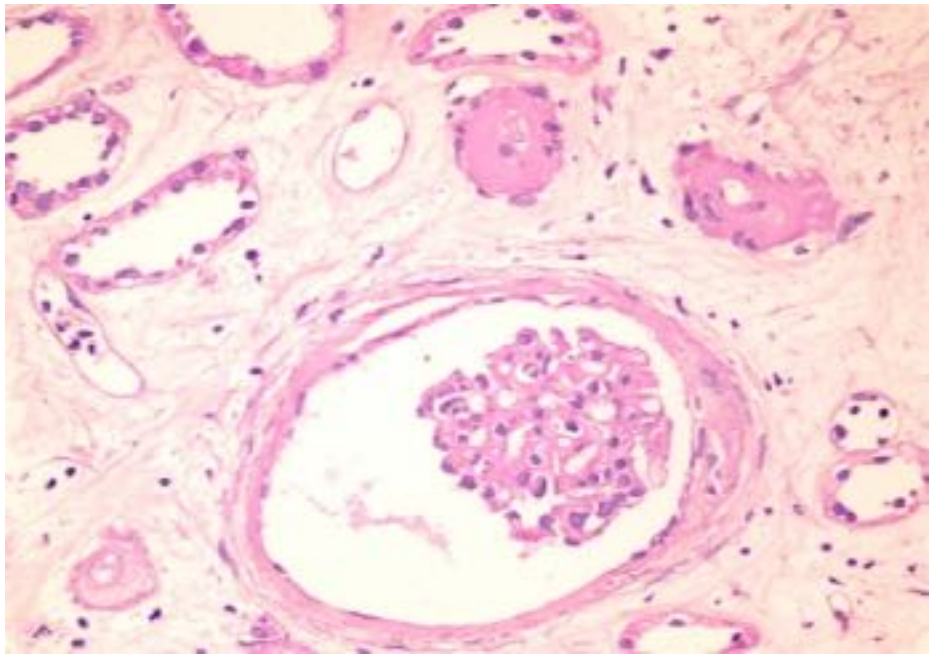


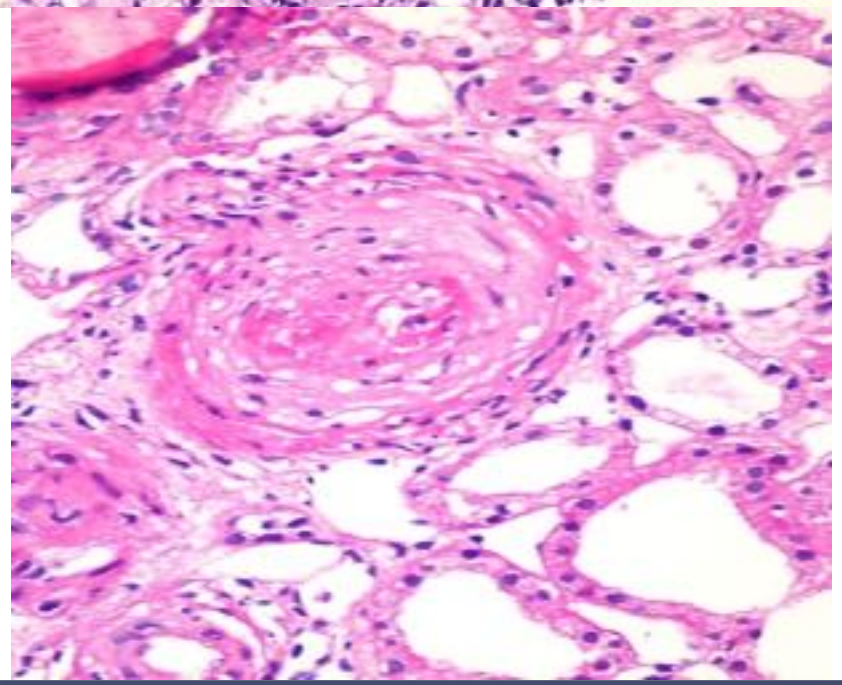
Vascular

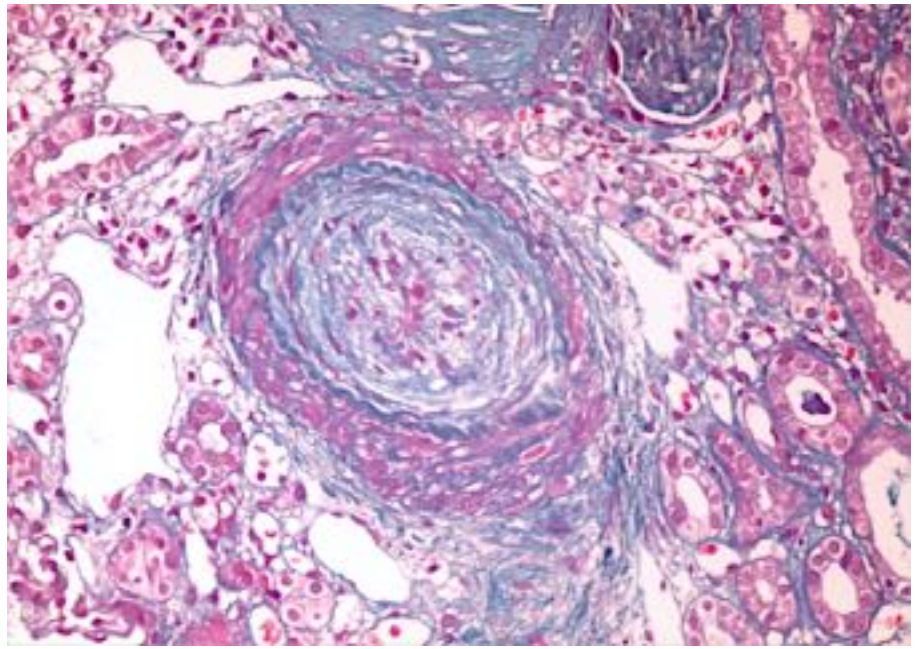
Mucoid Intimal swelling

Vascular (Chronic)



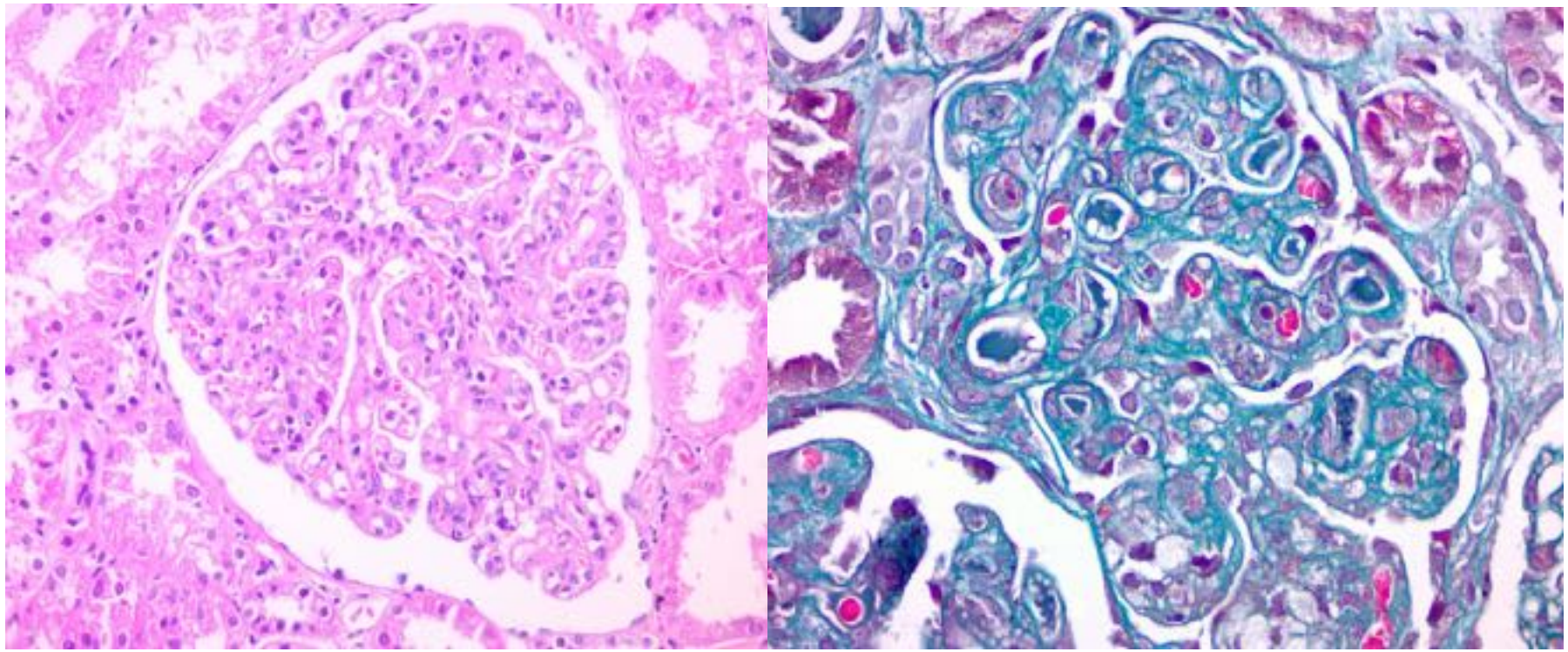






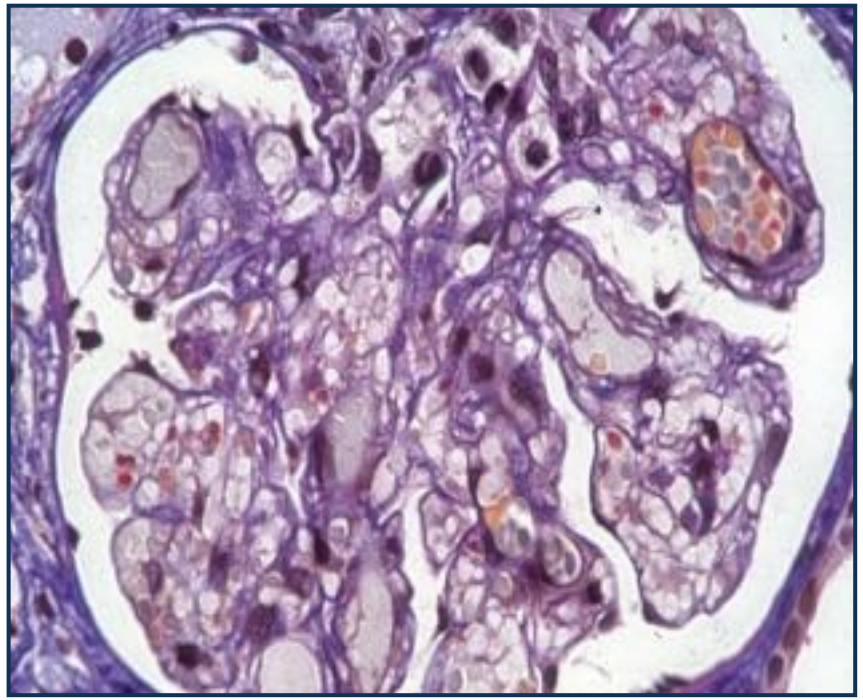
Differential Diagnosis

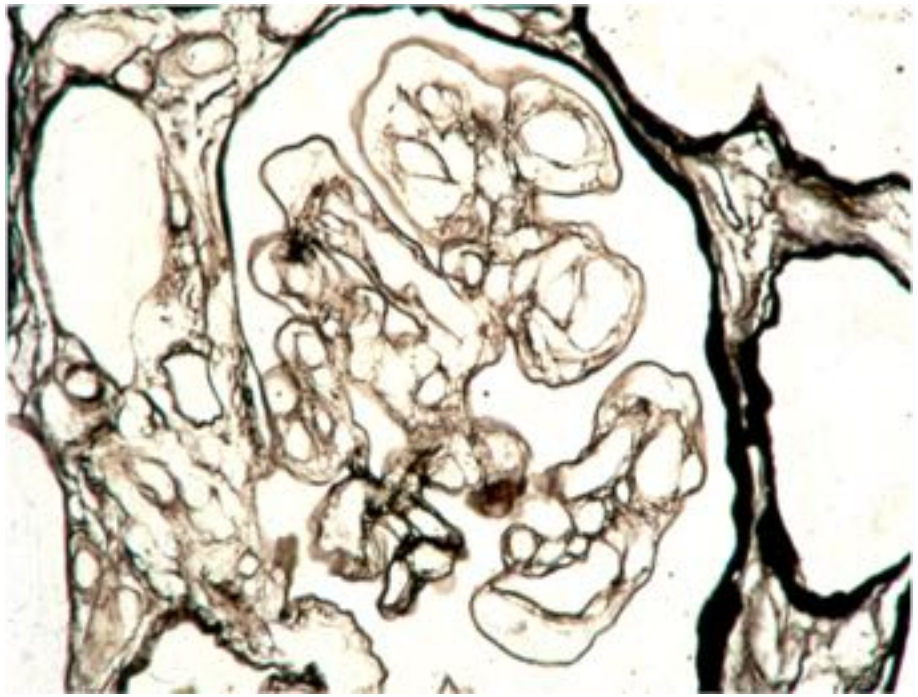
- MPGN



Differential Diagnosis

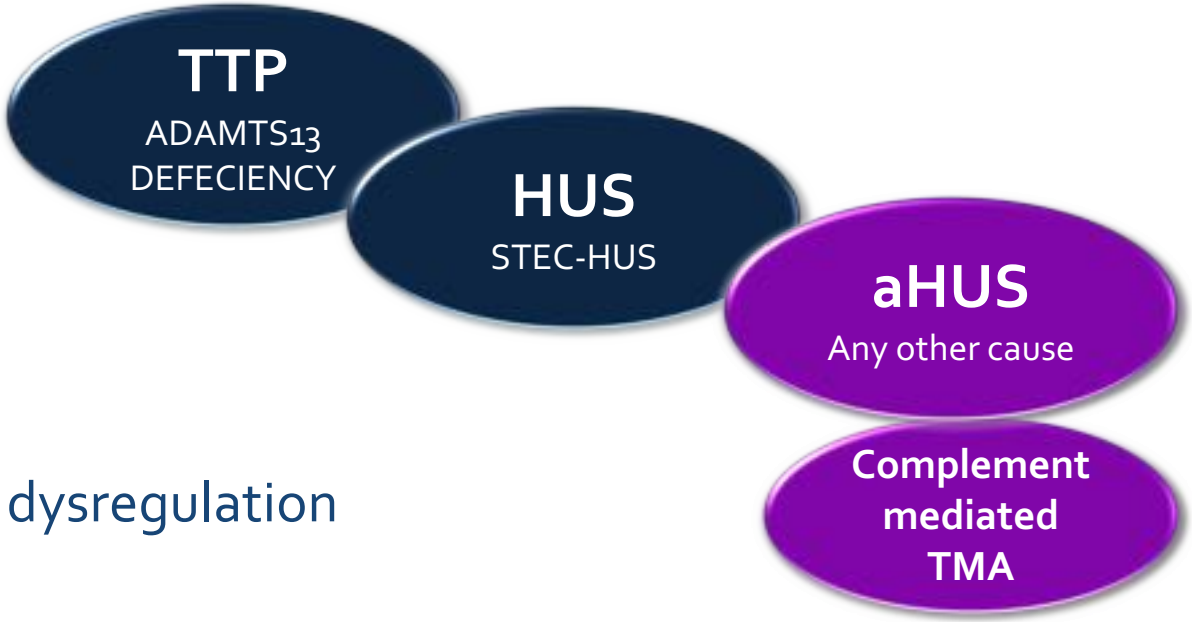
- Transplant Glomerulopathy versus Chronic TMA





Classification

- Challenging and constantly evolving
- Historically:

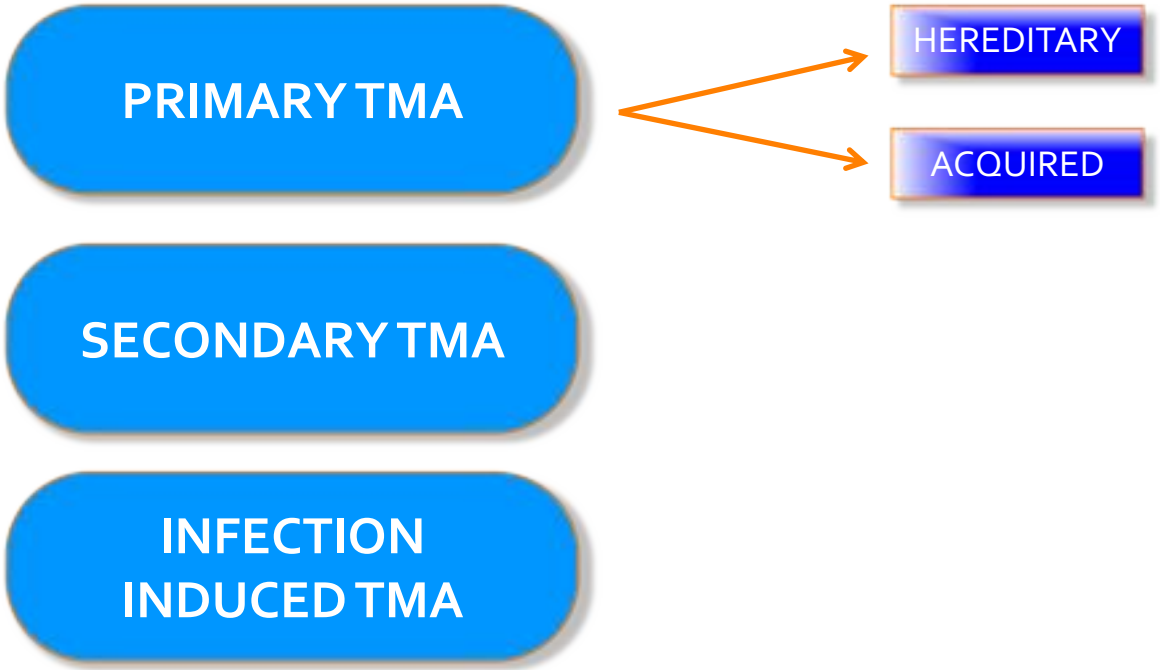


- Complement dysregulation

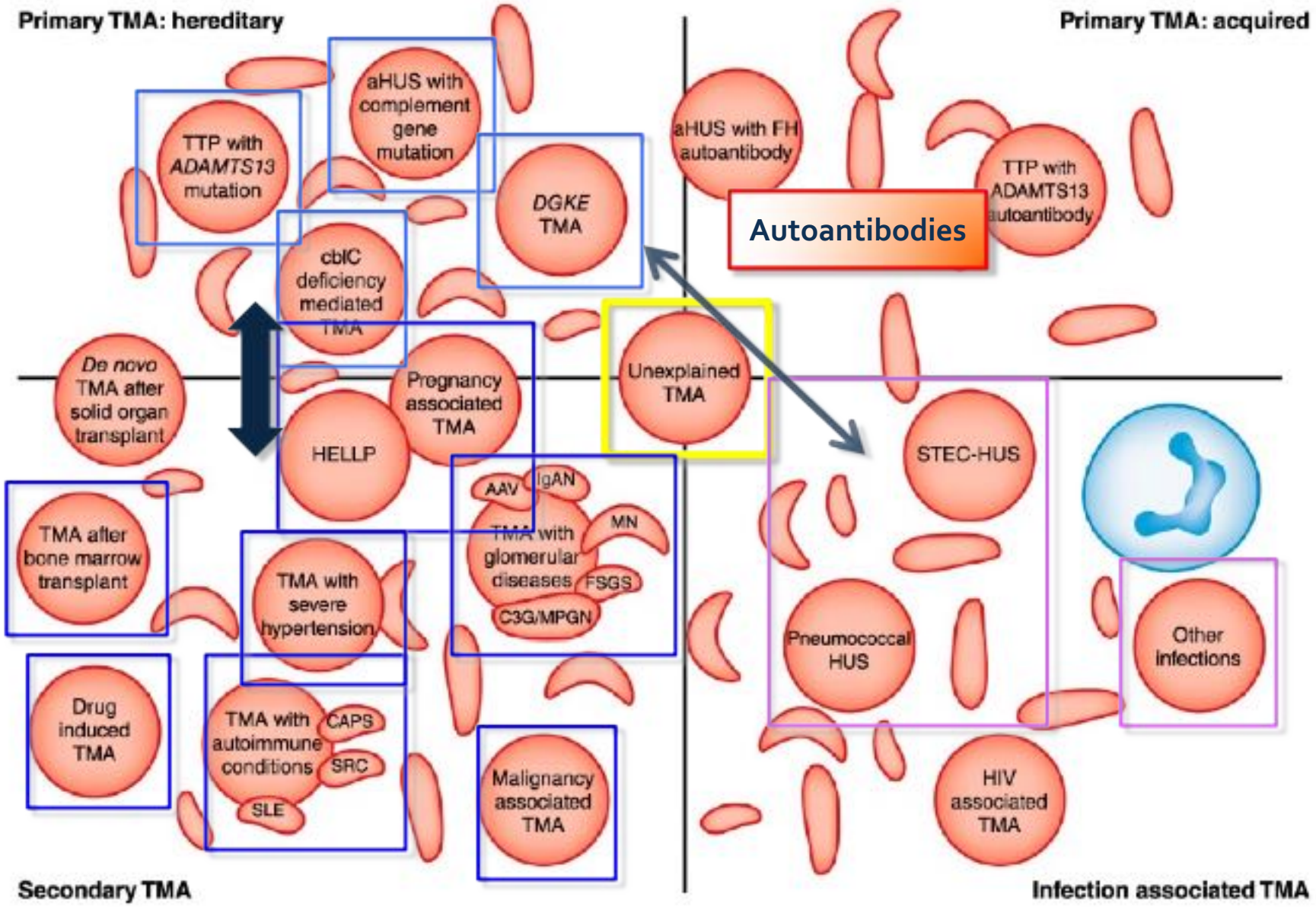
Different Nomenclature leads to difficult interpretation

Classification

- Current approach



Brocklebank et al. Clin J Am Soc Nephrol 13, March, 2018


Primary TMA: hereditary
Primary TMA: acquired
aHUS with complement gene mutation
TTP with ADAMTS13 mutation
DGKE TMA
cblC deficiency mediated TMA
aHUS with FH autoantibody
TTP with ADAMTS13 autoantibody
Autoantibodies
De novo TMA after solid organ transplant
Pregnancy associated TMA
HELLP
Unexplained TMA
STEC-HUS
AAV
IgAN
MN
TMA with glomerular diseases
FSGS
C3G/MPGN
TMA after bone marrow transplant
TMA with severe hypertension
Drug induced TMA
TMA with autoimmune conditions
CAPS
SRC
SLE
Malignancy associated TMA
Pneumococcal HUS
Other infections
HIV associated TMA
Secondary TMA
Infection associated TMA

TMA & Monoclonal Gammopathy

- New data from the Mayo Clinic indicate that the association of TMA with monoclonal gammopathies is far more frequent than previously appreciated
- Of 146 patients with TMA, monoclonal immunoglobulin in 20 patients (13.7%)
- Among patients 50 and older, the prevalence of monoclonal gammopathy was 21%, which is approximately five-fold higher than the 4.2% expected rate in this population.
- Fifteen patients had monoclonal gammopathy of undetermined significance, one had multiple myeloma, one with smoldering myeloma, two had POEMS syndrome, and one had T-cell lymphocytic leukemia
- Hypothesis:
  - ✓ Direct endothelial injury by the M-protein (more susceptible to the development of TMA after another insult)
  - ✓ indirectly via functional inhibition of proteins that regulate thrombosis

Kidney International (2017) 91, 691–698

Prognosis

- Degree of histologic damage rather than initial clinical severity is the best predictor of long-term prognosis
- Three main patterns that correlate with long term prognosis
  - ✓ Renal glomerular compartment (young children, good prognosis)
  - ✓ Dominating arterial compartment (older children and adults, poor prognosis)
  - ✓ Adults with both glomerular and vascular involvement (poor prognosis)
- Severity (cortical necrosis, TMA involving >50% of glomeruli at time of presentation)
- Stage: Early (potentially reversible) have to be distinguished from late (irreversible) "sclerosing" changes, Segmental sclerosis was associated with decreased GFR long term

Complete diagnostic algorithm for thrombotic microangiopathy

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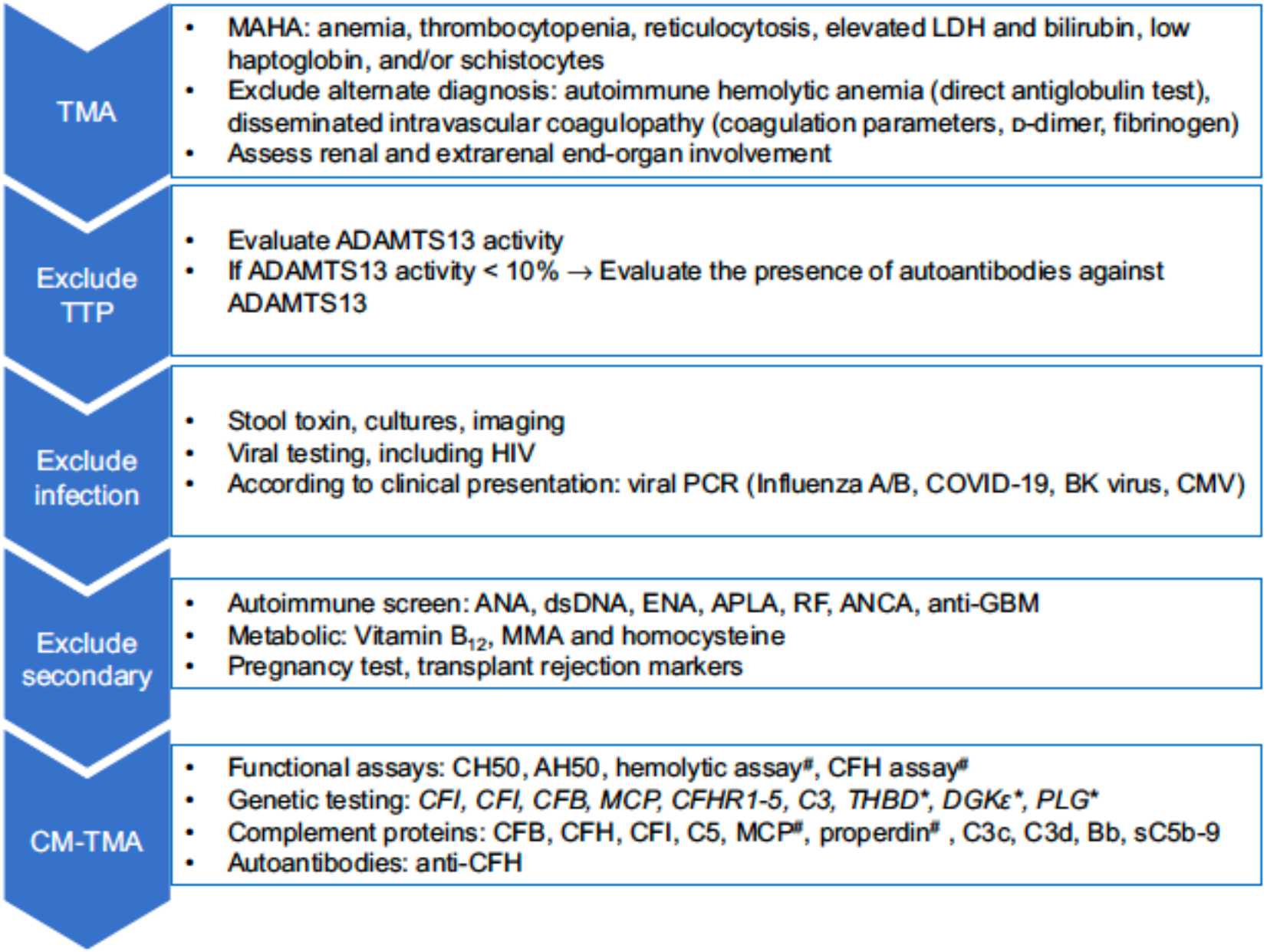
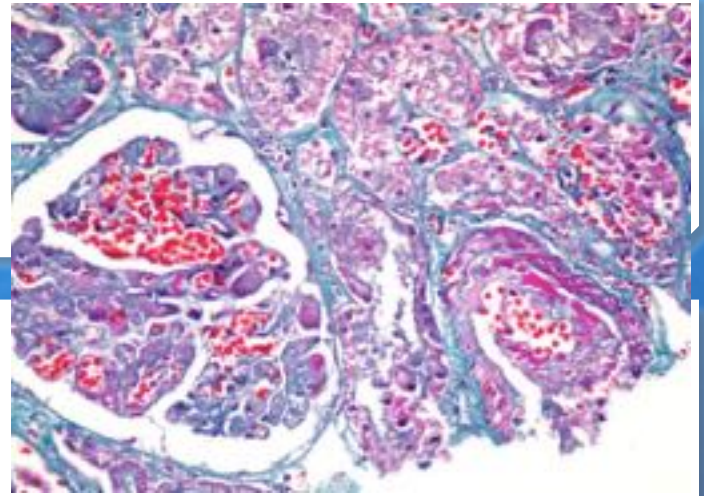


Take Home Message



- TMA is a descriptive and a non specific morphological term…

  ……..it is NOT a disease

- The pathologist can report suggestive features

- It is important to identify the underlying cause of the histologically observed "TMA", as some of them could be managed

TMA is NOT HUS/TTP

THANK YOU