Introduction to Renal Pathology

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Aim of Biopsy

- To Establish a Diagnosis
- As an Aid to Therapy
- To Ascertain the Degree of Activity or Chronicity in a Disease Process

Division of Biopsy

- Light Microscopy

  Fixed Tissue

- Immunodiagnosis

  Immunofluorescence (IF) – PBS/Transport Medium – Michael's Fixative

  Immunoperoxidase (IP) – Fixed Tissue

- Electron Microscopy

  Buffered Glutaraldehyde or Paraformaldehyde Fixative

Stains Used in Renal Biopsies

- Haematoxylin and Eosin (H&E)
- Periodic Acid Schiff (PAS)
- Periodic Acid Silver Methenamine (PAMS)
- Masson Trichrome (MT)
- Congo Red (CR)
- Elastic Stains (EVG)
- Toluidine Blue – Semi-Thin (Resin) Sections

Immunofluorescence (IF)/ Immunoperoxidase (IP)

- IgA, IgG, IgM, C3 and C1q
- Kappa and Lambda
- Interpretation require location of the staining and strength (0-3+) of staining for diagnosis

Renal Biopsy

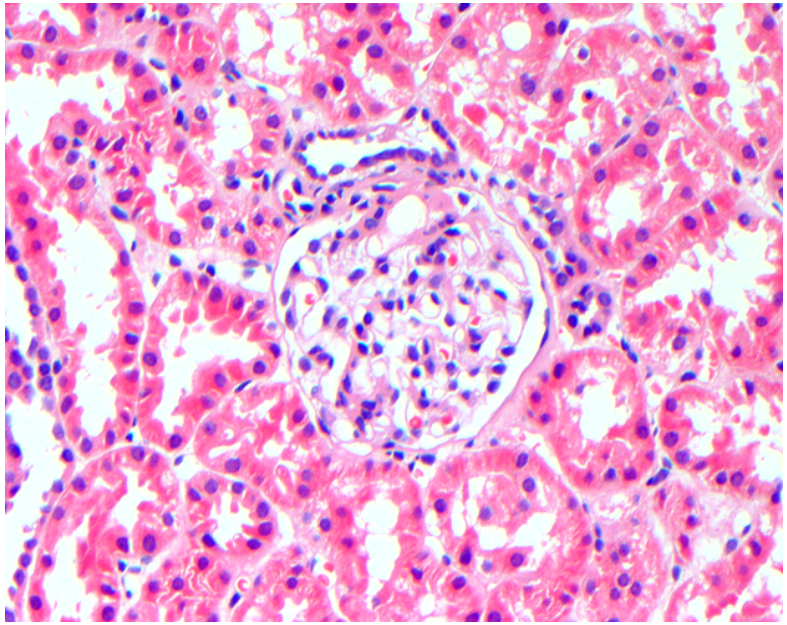
- Cortex

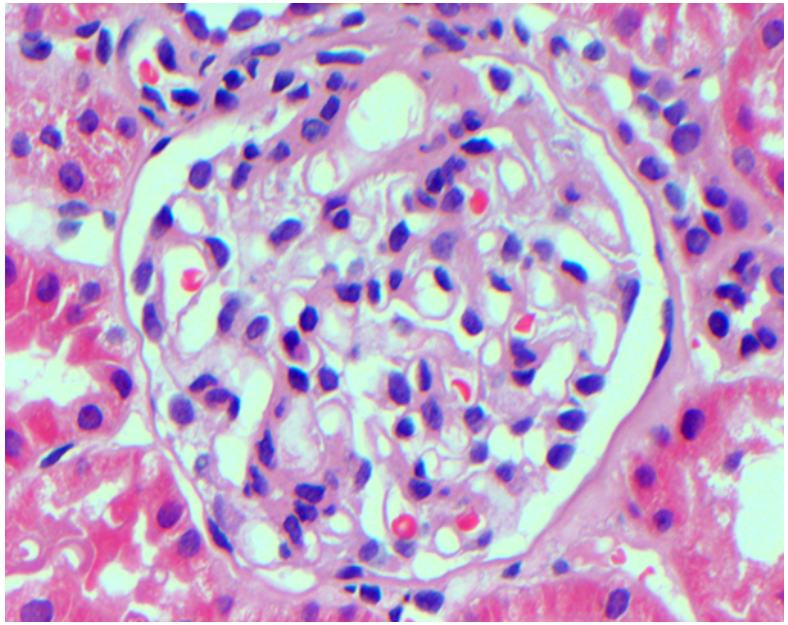
Glomeruli
Tubules; Proximal (mostly) and Distal
Blood Vessels

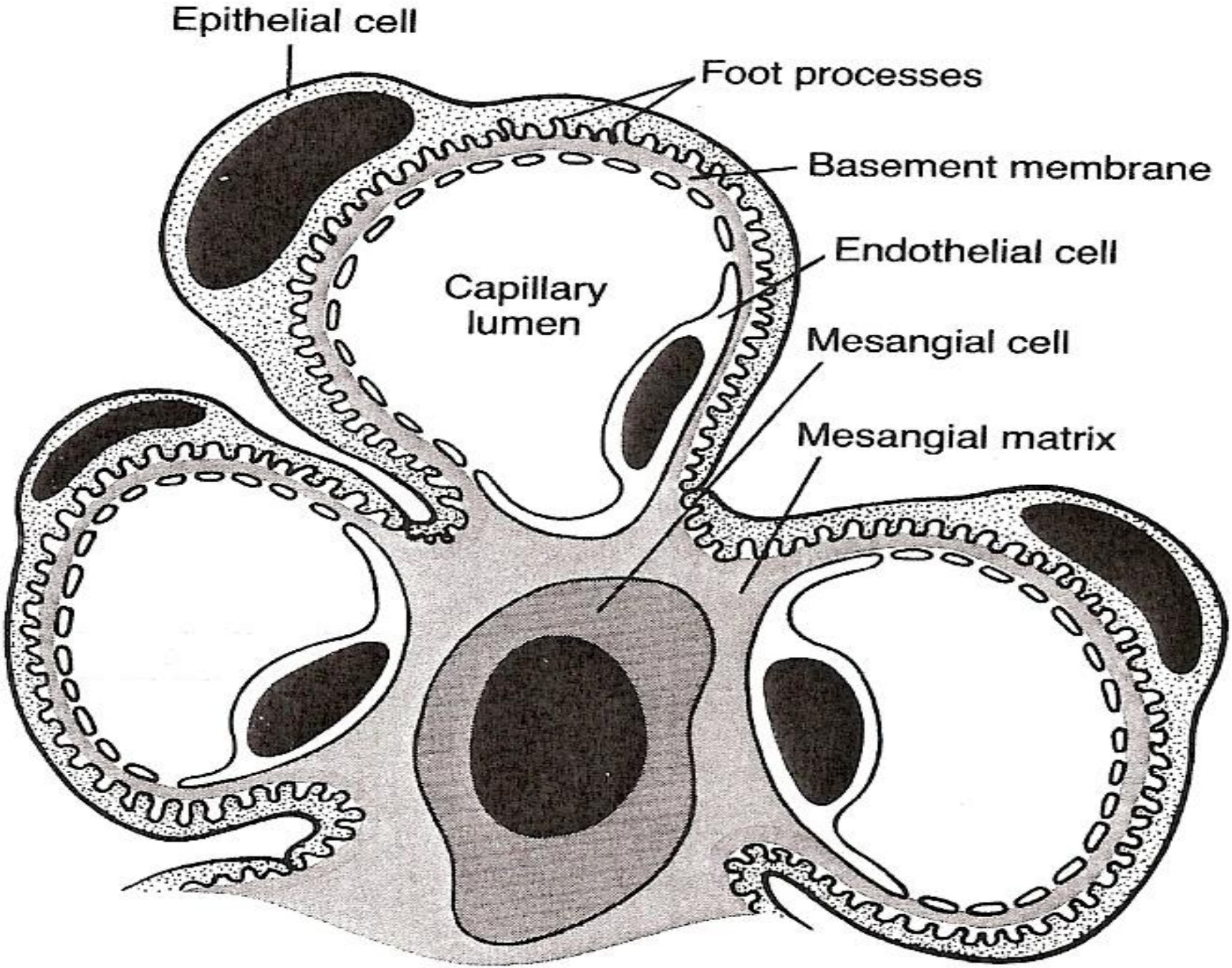
- Medulla

Tubules
Blood Vessels

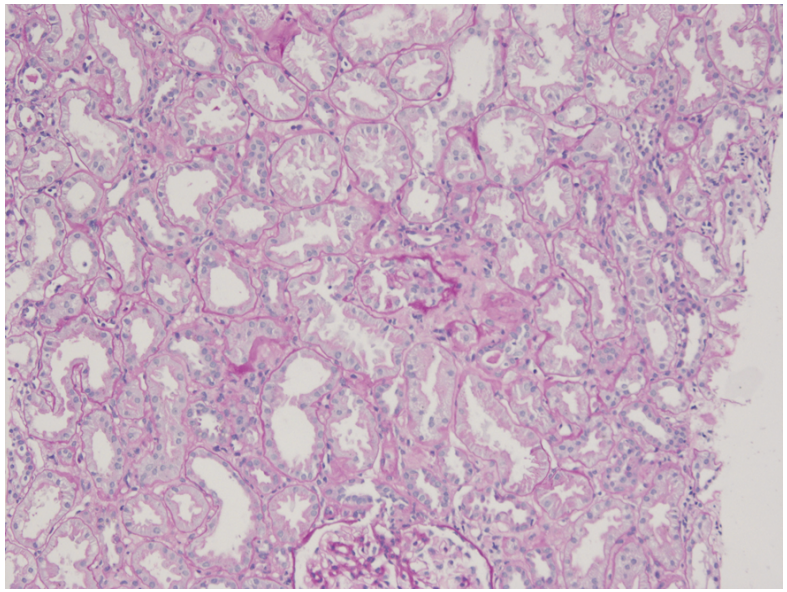
Normal Glomerulus

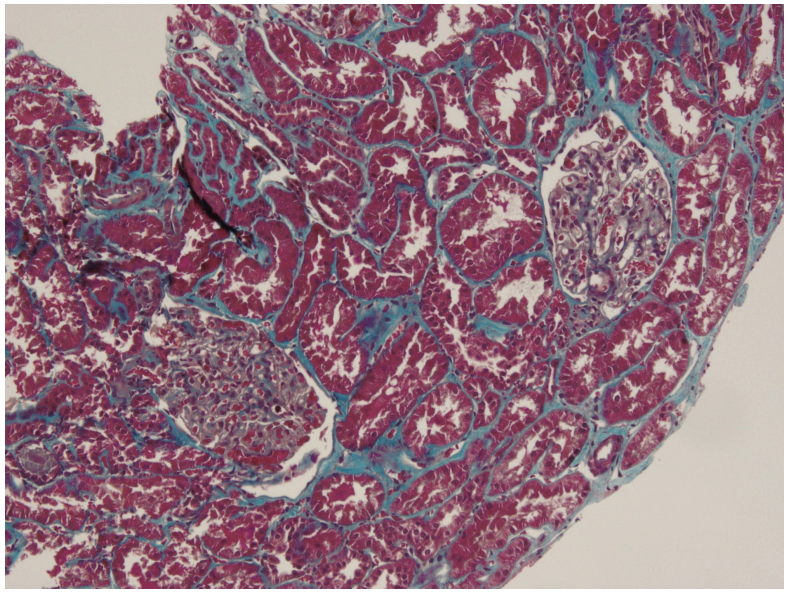




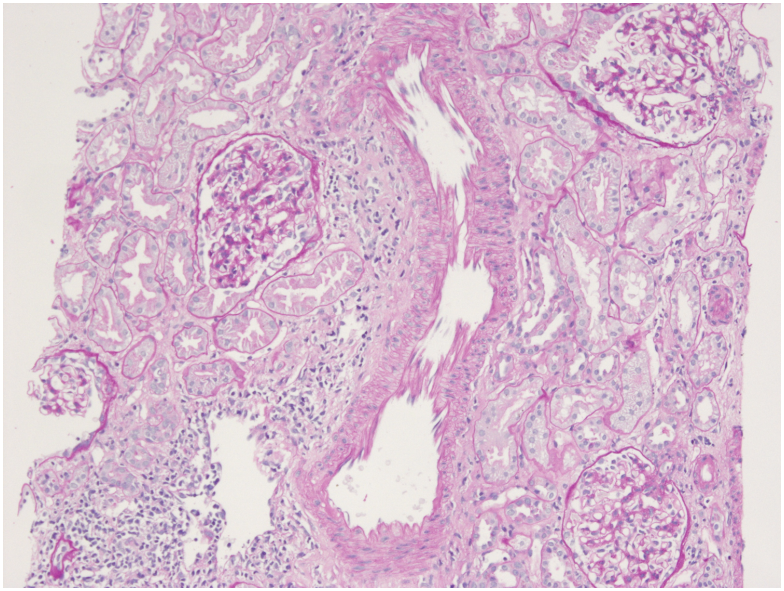

Epithelial cell
Foot processes
Basement membrane
Endothelial cell
Capillary lumen
Mesangial cell
Mesangial matrix

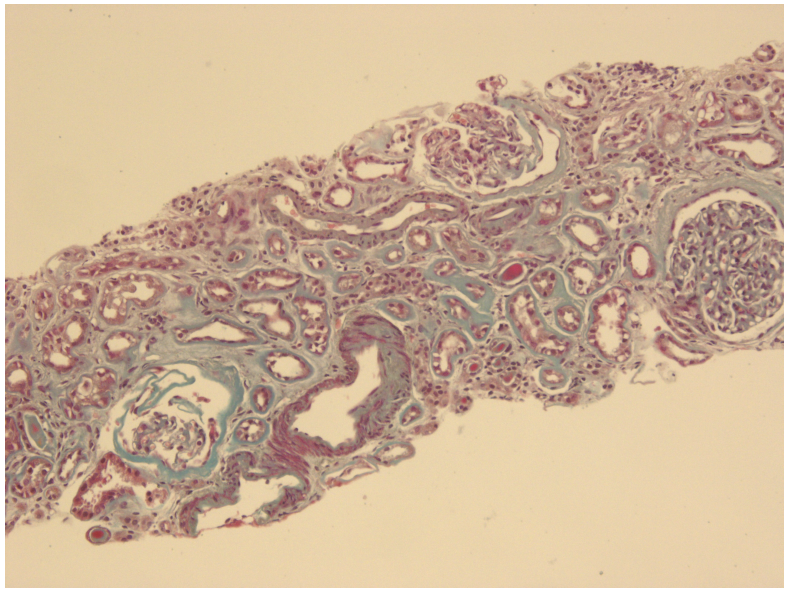
Normal Tubules





Normal Blood Vessels





Pathogenesis of Glomerular Injury

- Usually immune mediated
- Immune mechanisms:
  - Antibody-mediated injury
    - In situ immune complex deposition
    - Circulating immune complex deposition
    - Cytotoxic antibodies
  - Cell-mediated immune injury
  - Activation of alternate complement pathway

Glomerular Response to Injury

- Cellular proliferation
  - Mesangial cells, endothelial cells ("endocapillary hypercellularity"), parietal epithelial cells
- GBM thickening
- Glomerular scarring (sclerosis)
  - Focal and diffuse

Glossary of Descriptive Terms

- Diffuse
  - 50% or more of the glomeruli are involved
- Focal
  - <50% of the glomeruli are involved
- Global
  - Affecting the whole glomerulus
- Segmental
  - Affecting <50% of the surface area of an individual glomerulus

Basic Morphological Patterns of Glomerulonephritis

- **Non-proliferative**
  - Minimal change disease
  - FSGS
  - Membranous nephropathy
- **Proliferative**
  - Acute endocapillary proliferative GN
  - Membranoproliferative GN
  - Mesangial proliferative GN

Diagnosis of Glomerular Disease

- Morphological pattern
- Immunohistochemistry (immunoglobulins and complement components)
- Electron microscopy
- Clinical context
- Other clinical investigation eg.serology

- A morphological pattern is not a diagnosis!

Classification of Glomerulonephritis

- Primary Glomerulonephritis

The kidneys alone are involved

- Secondary Glomerulonephritis

The kidneys are involved in a systemic disease process eg. SLE, systemic vasculitis

Histology associated with proteinuria

- Isolated proteinuria or nephrotic syndrome
  - Minimal change disease
  - FSGS
  - Membranous glomerulopathy
  - Diabetes
  - Amyloidosis

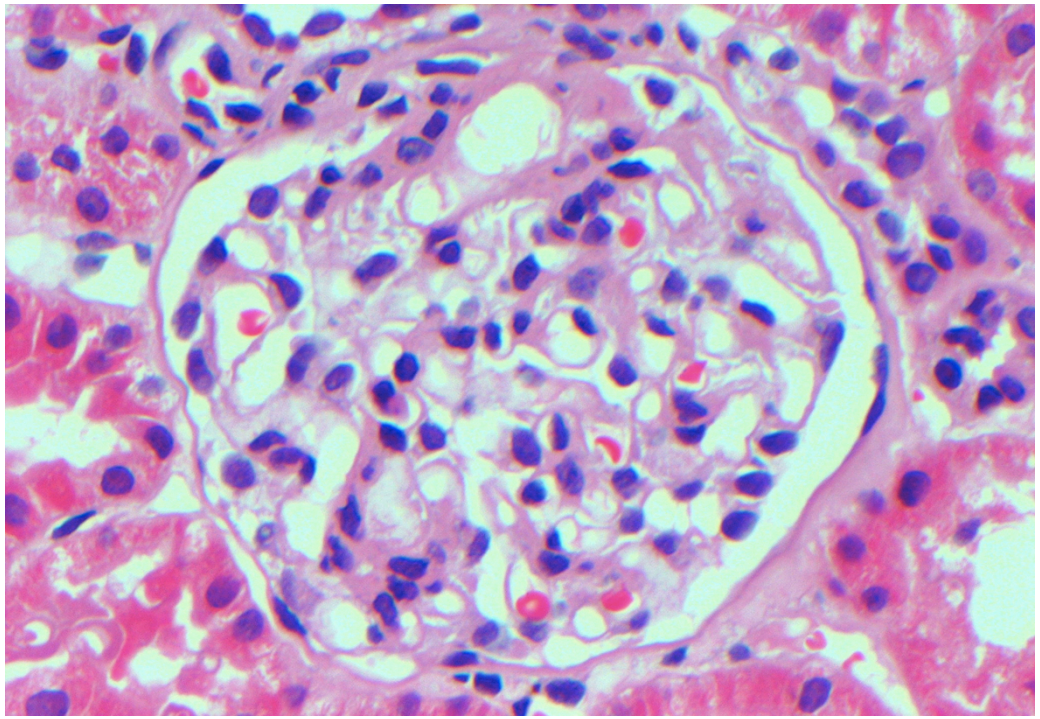
Minimal Change Disease (MCD)

- Present with nephrotic syndrome
- 80% <6 years
- M:F - 2:1 in children
- Most common cause of nephrotic syndrome in children
- May also occur in adults (usually elderly)
- Good response to steroids
- Secondary causes: NSAID's, lymphoma

Histology of MCD

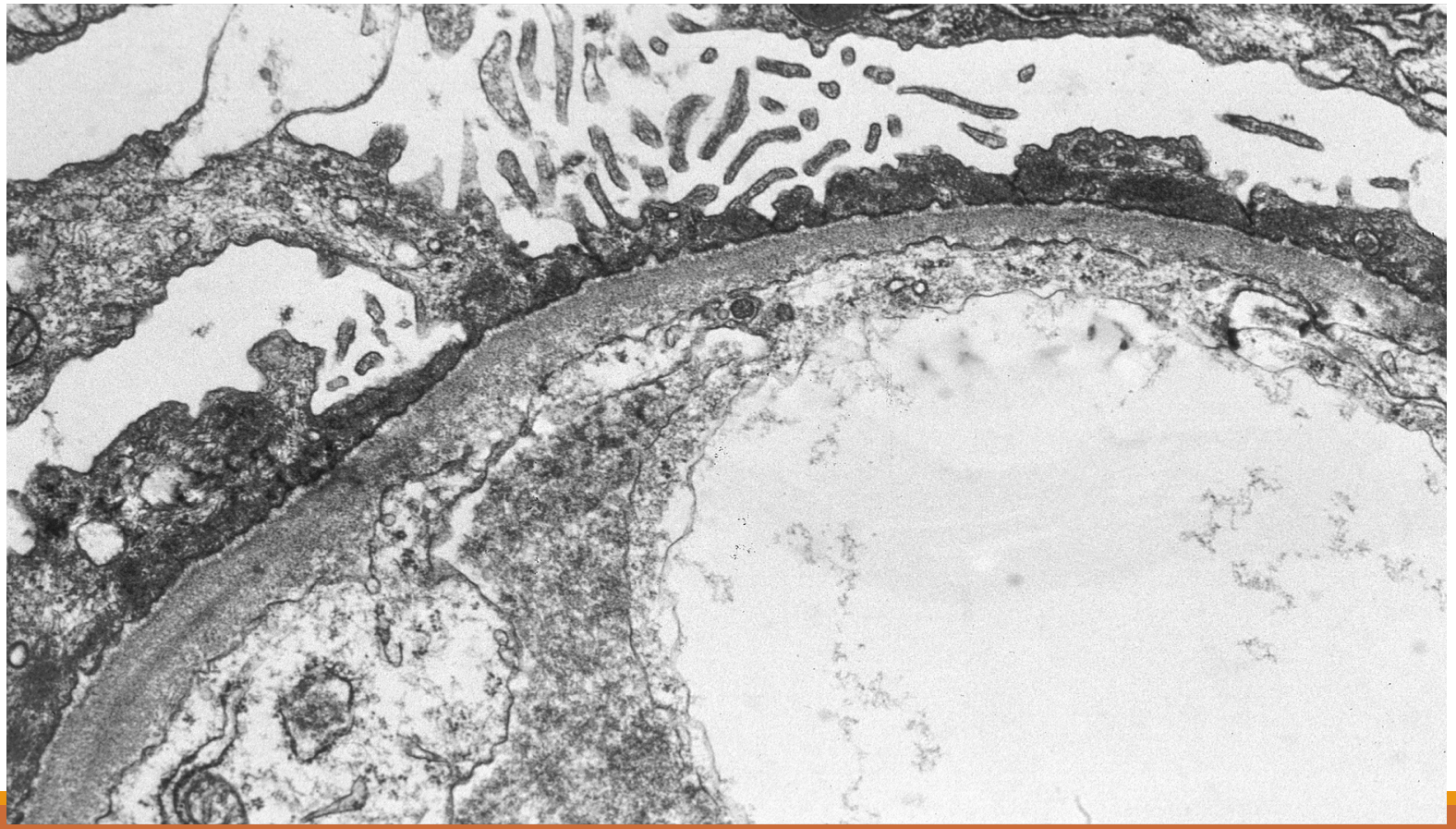
Light microscopy – normal glomeruli

Immunohistochemistry - negative



Histology of MCD

EM – diffuse effacement of foot processes



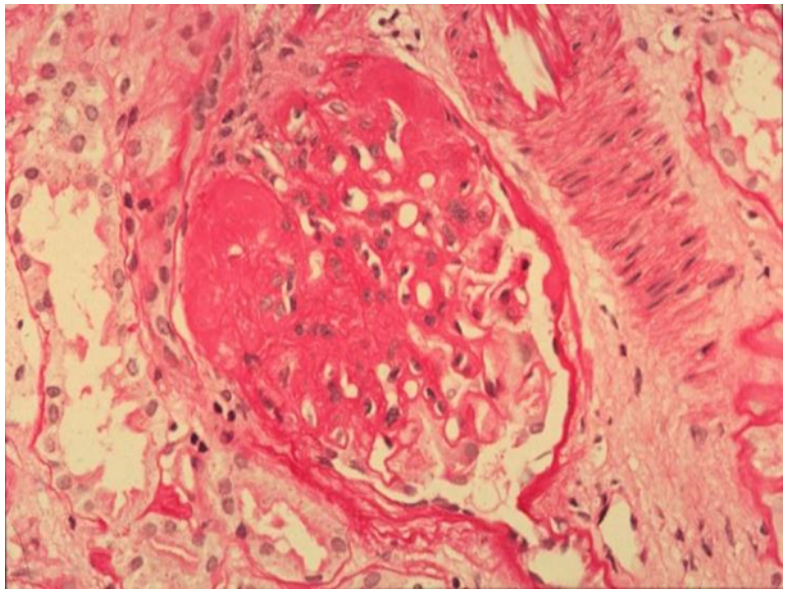
Focal Segmental Glomerulosclerosis (FSGS)

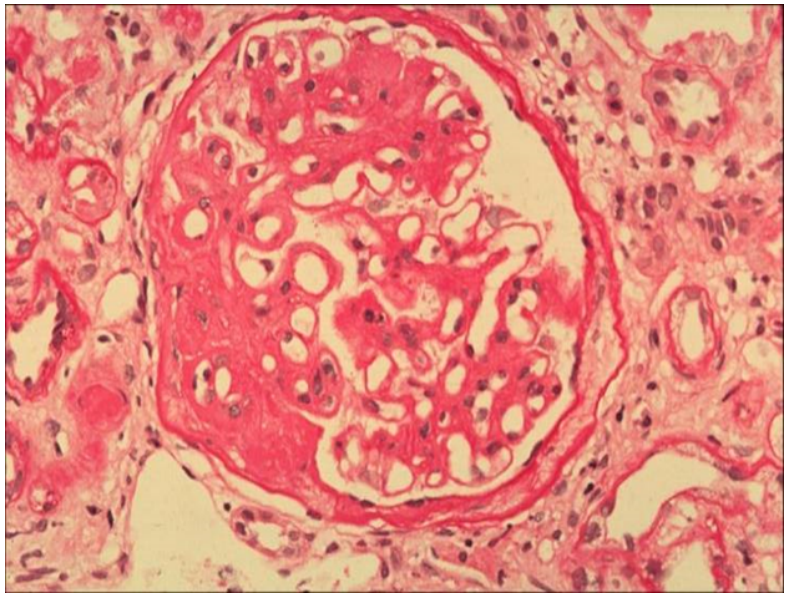
- Primary FSGS - idiopathic
- Secondary FSGS (mediated by adaptive structural-functional responses) eg. associated with hypertension or obesity
- FSGS associated with specific aetiological factors eg. HIVAN, heroin nephropathy, familial FSGS
- Several histological patterns (Columbia Classification)

Histology of FSGS

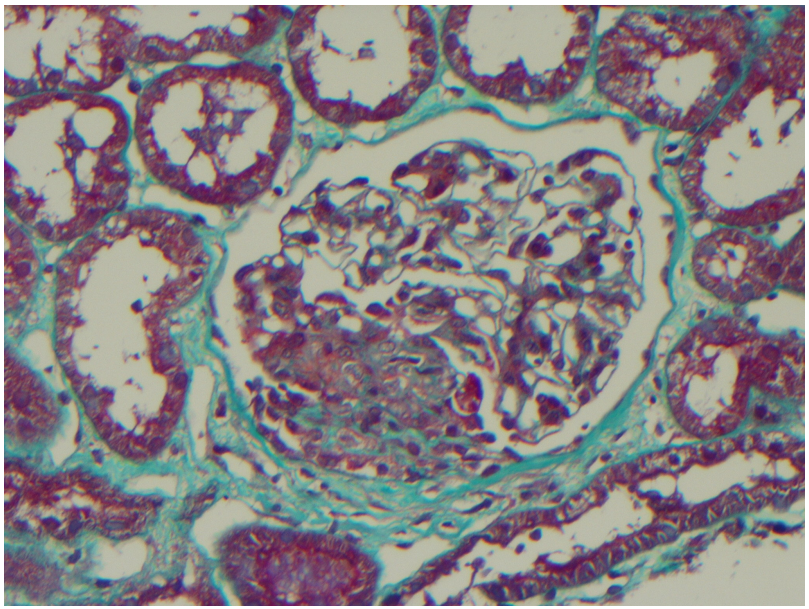
- Light microscopy
  - Segmental sclerosing lesions (juxtaglomerular glomeruli affected first)
  - Podocyte caps
- Immunohistochemistry
  - Coarse, granular deposition of IgM, C3 +/- C1q in sclerosed segments
  - Weak mesangial deposition of IgM

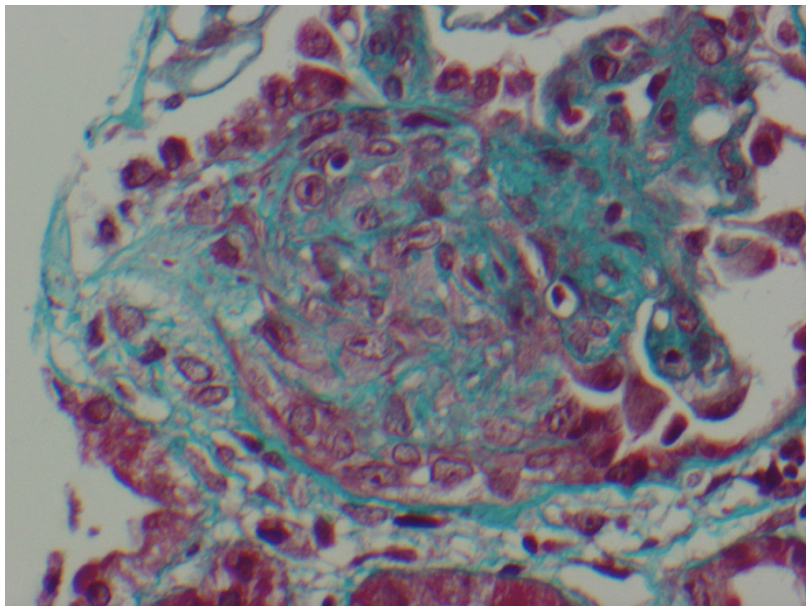
Histology of FSGS



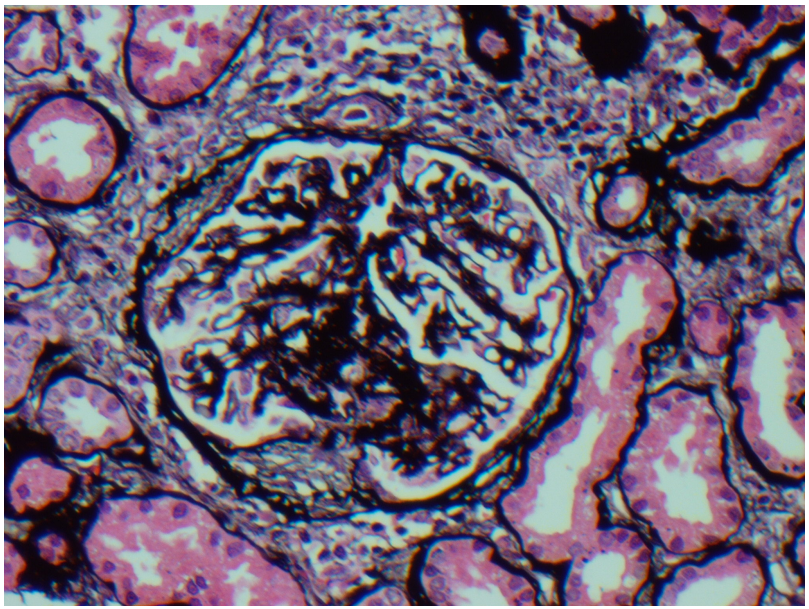


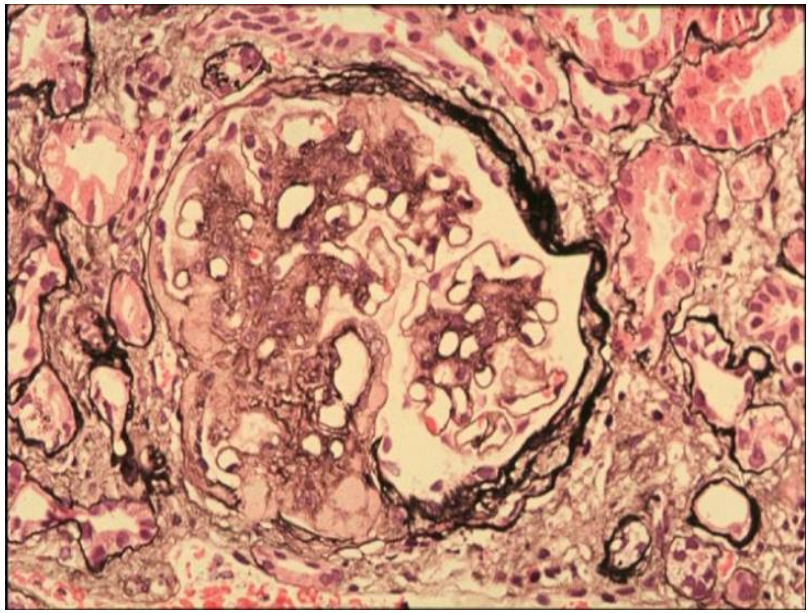
Histology of FSGS





Histology of FSGS





Membranous Nephropathy (MN)

- Most common cause of nephrotic syndrome in adults
- Secondary causes include: drugs eg. Gold, penicillamine; underlying malignancy eg. lung and colon, melanoma; SLE; infections eg hepatitis B
- Variable clinical course. Proteinuria persists in 60%, only 10% progress to renal failure within 10 years, 40% eventually develop renal insufficiency

Histology of MN

Light microscopy

- Irregular thickening of glomerular basement membrane with spike formation visible on silver stain

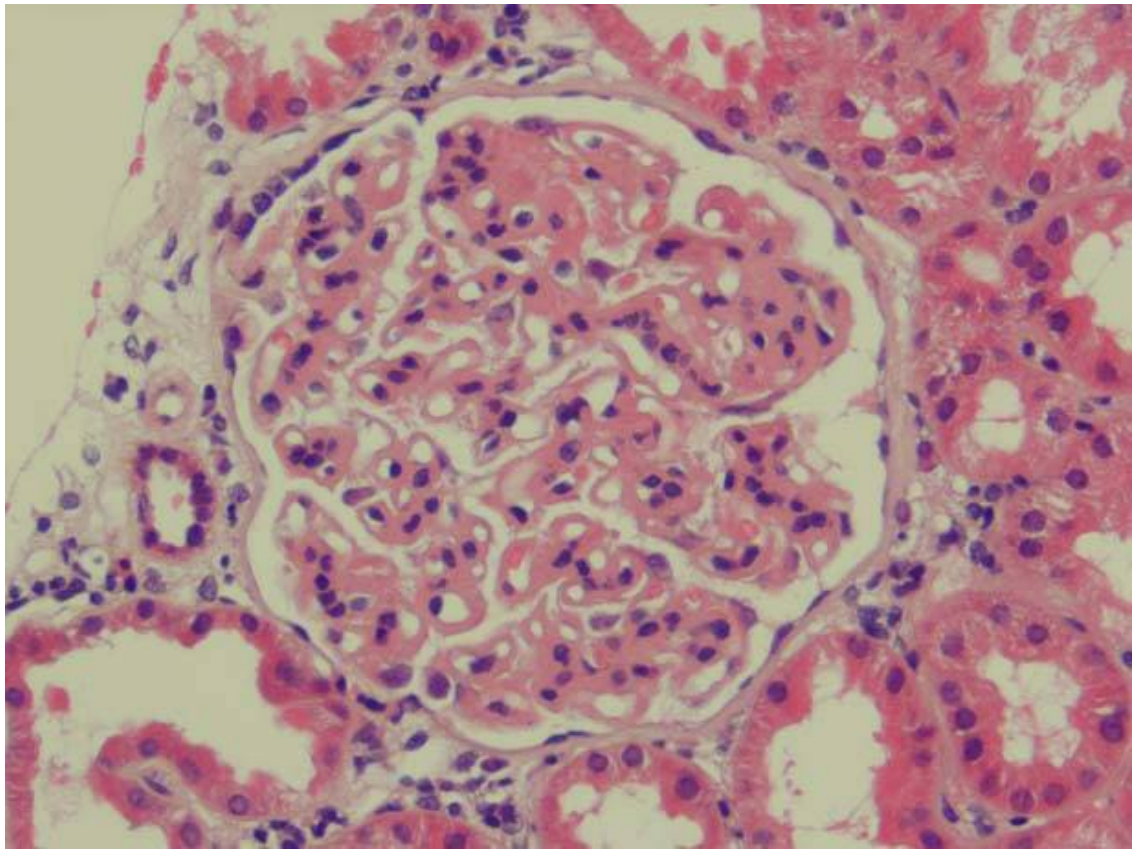
Immunohistochemistry

- Granular deposition of IgG and C3 along peripheral capillary loops

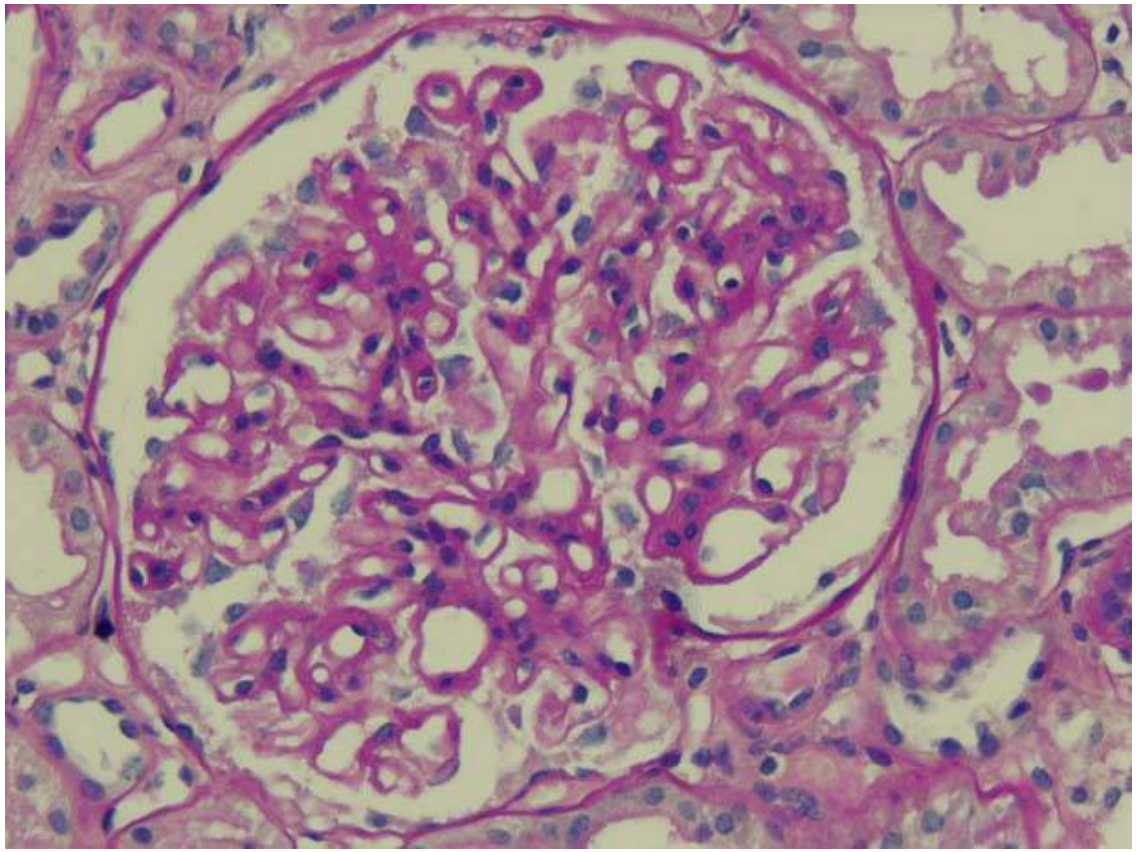
EM

- Subepithelial immune complexes
- Basement membrane material between deposits (“spikes”)
- Effacement of foot processes

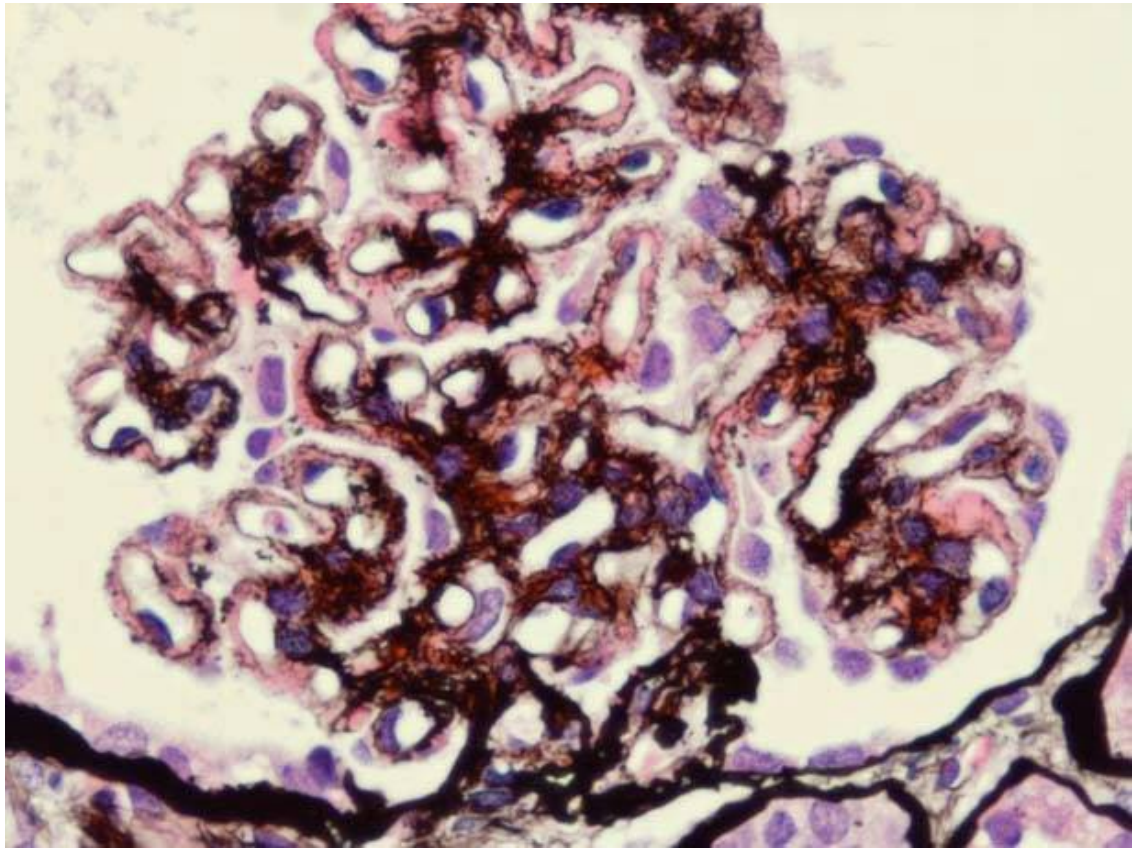
Histology of MN



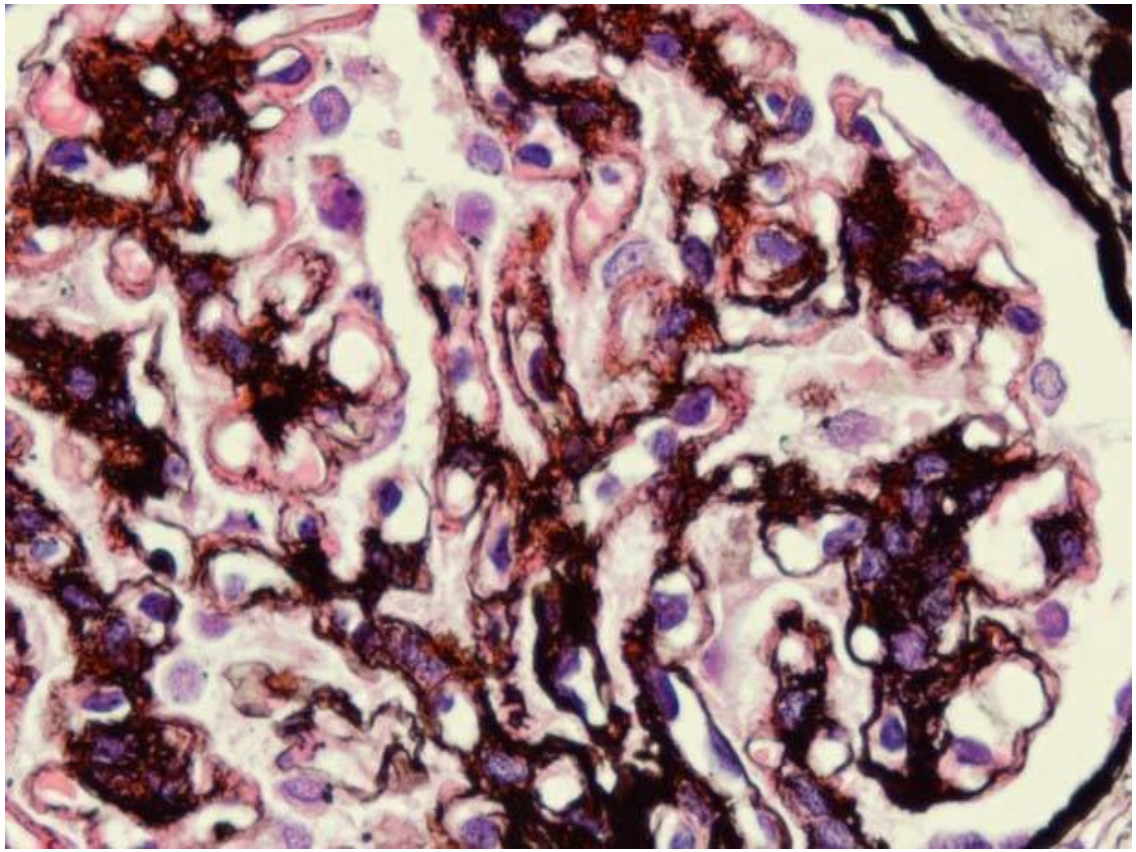
Histology of MN



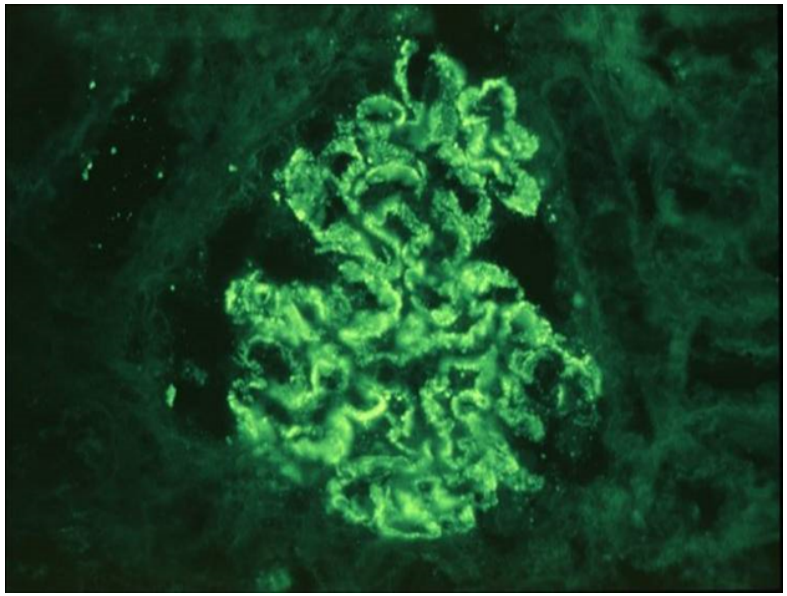
Histology of MN

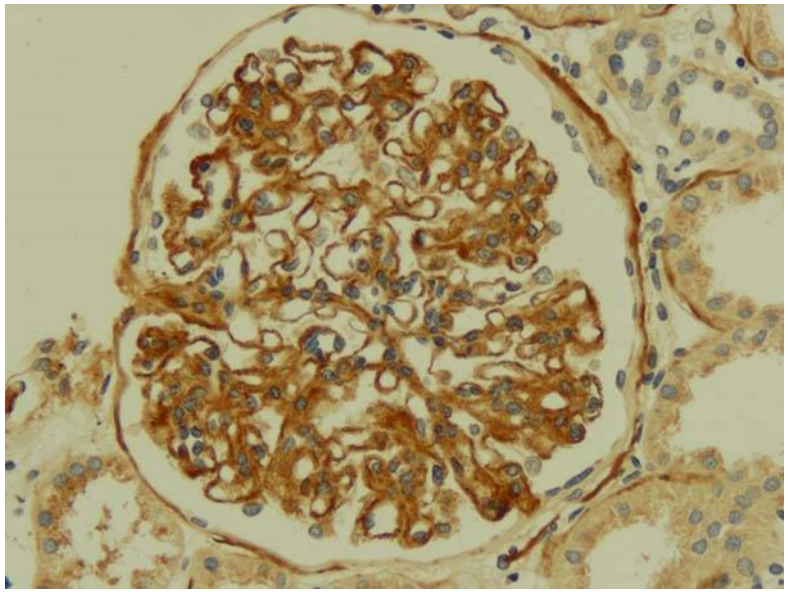


Histology of MN

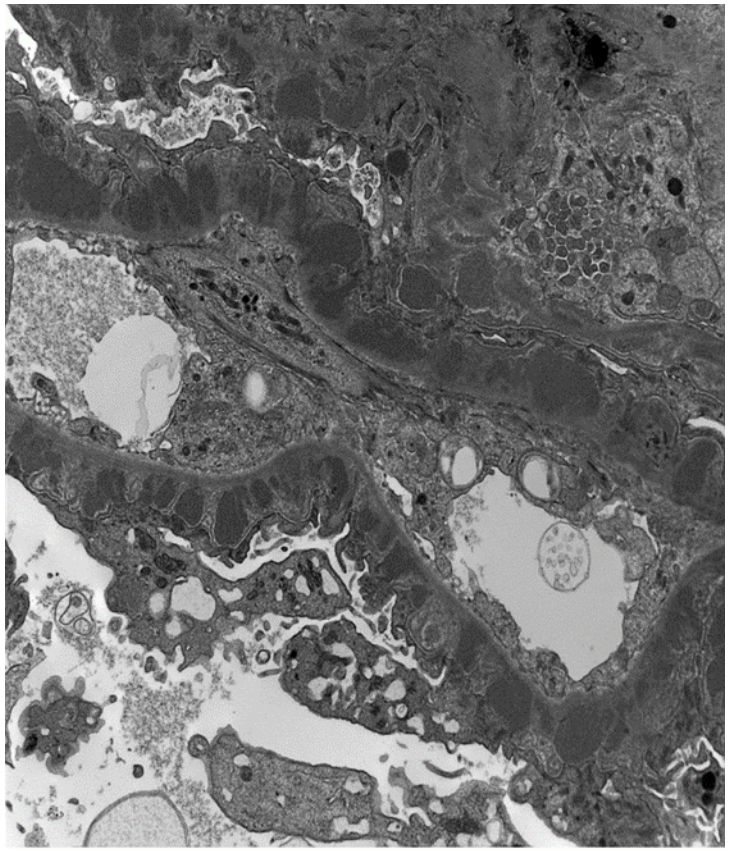


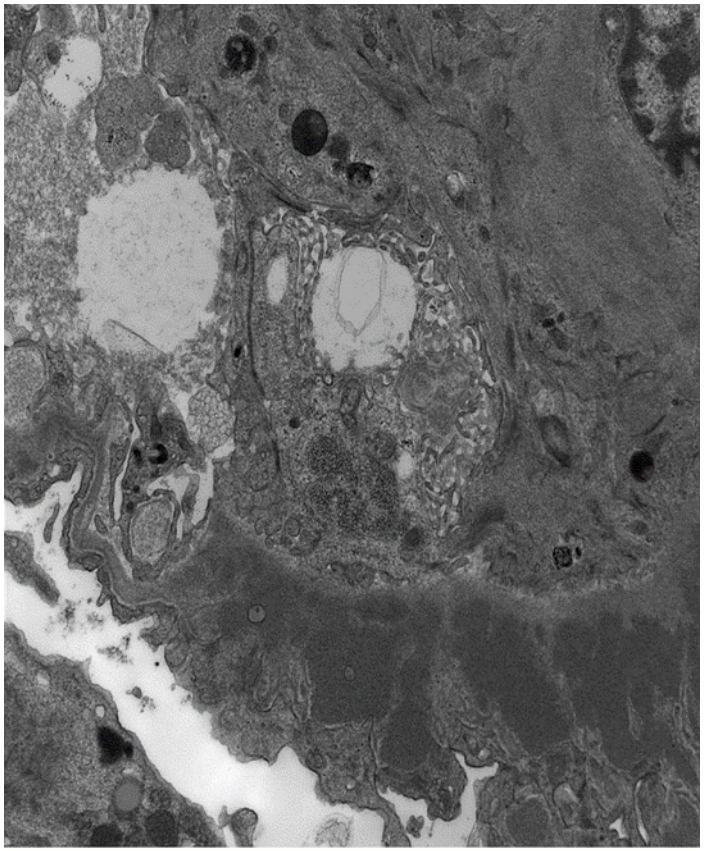
IF/IHC of MN -IgG



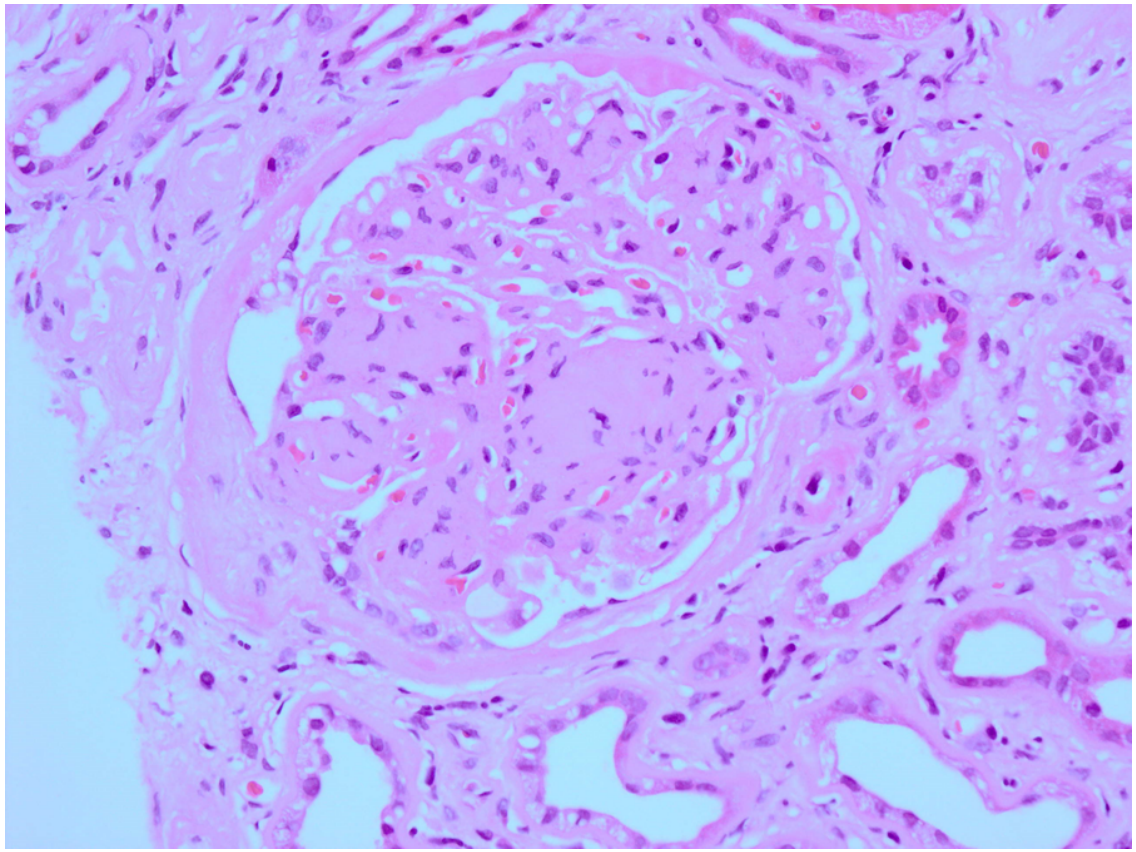


EM of MN

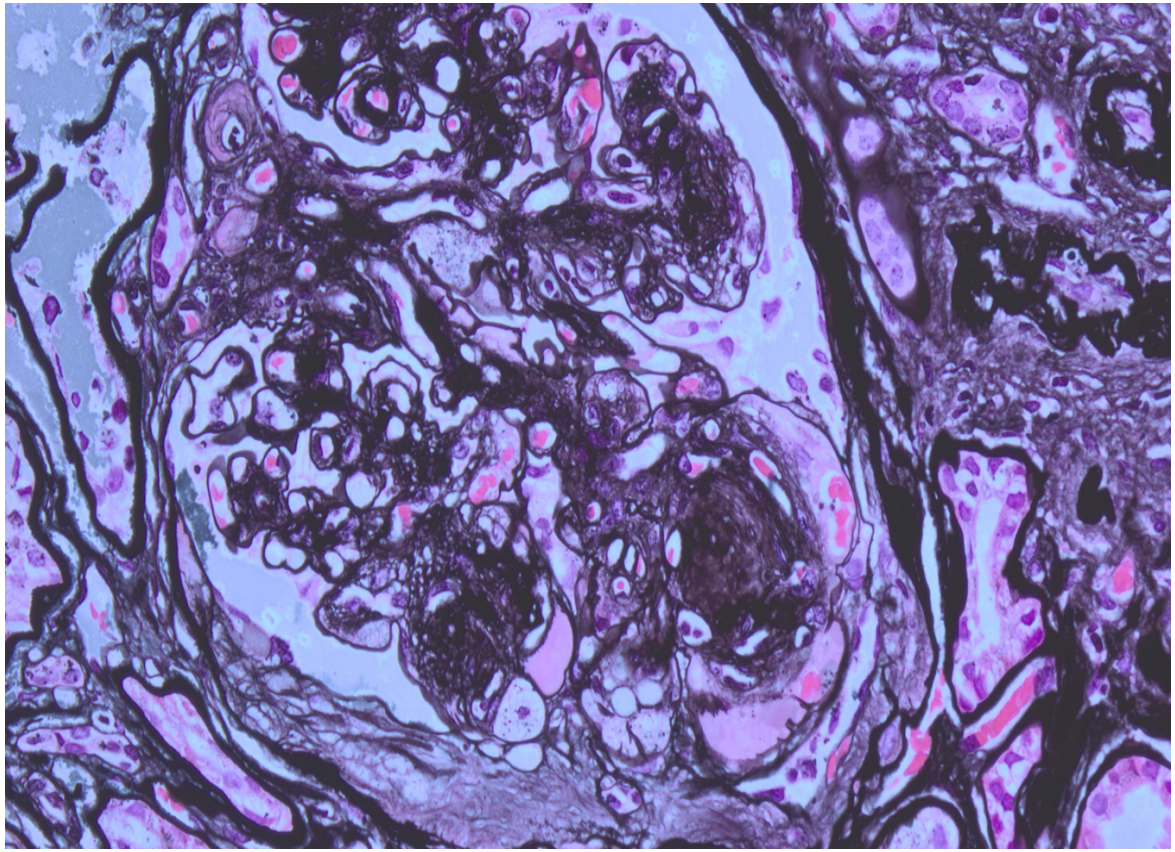




Histology of Diabetic Nephropathy



Histology of Diabetic Nephropathy



Histology associated with haematuria

- Isolated haematuria or acute nephritic syndrome
  - Mesangial Proliferative GN (eg, IgAN)
  - Focal and Segmental Proliferative GN (eg, LN, Infective Endocarditis)
  - Diffuse Proliferative GN (eg, PIGN, LN)
  - Crescentic GN (eg, Anti-GBM, Vasculitic GN)

IgA Nephropathy (IgAN)

Most common primary glomerulonephritis in the world

Usually present with haematuria

Present 1-2 days after respiratory, GI or urinary tract infection

Children and young adults

M:F = 2:1

Persistent and slowly progressive disease

50% recur in renal transplant

Henoch Schonlein purpura (HSP) – systemic IgA, renal manifestations similar

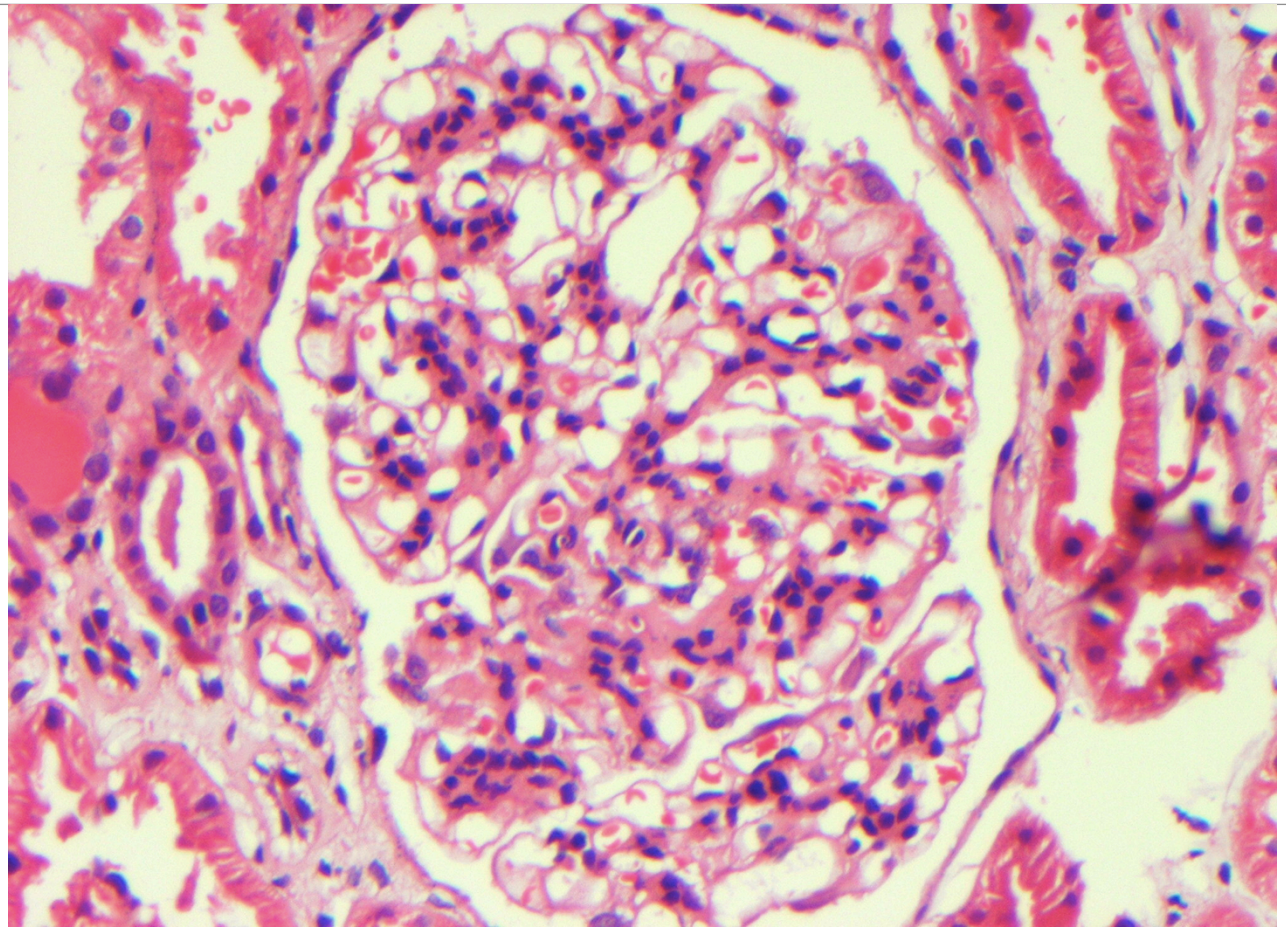
Histology of IgAN

- Light microscopy
  - Variable! Often mesangial proliferative but may be focal/ diffuse proliferative or sclerosing
  - Oxford Classification is predictor of prognosis
  - (M, E, S, T)
- Immunohistochemistry
  - Dominant deposition of IgA in mesangium, accompanied by C3. May have deposits elsewhere in glomerulus.

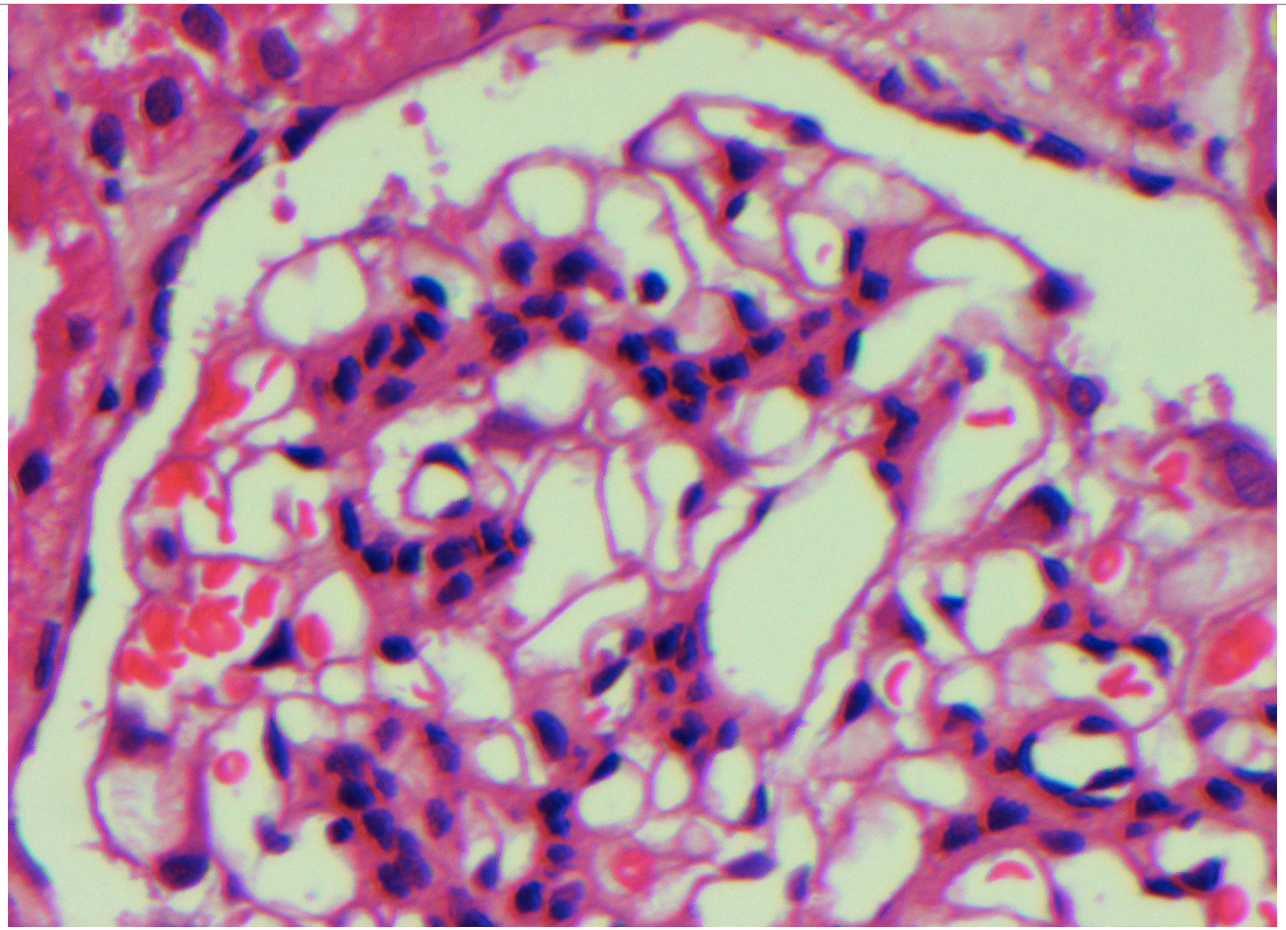
Histology of IgAN

- EM
  - Mesangial and paramesangial electron dense deposits. 25% capillary wall deposits

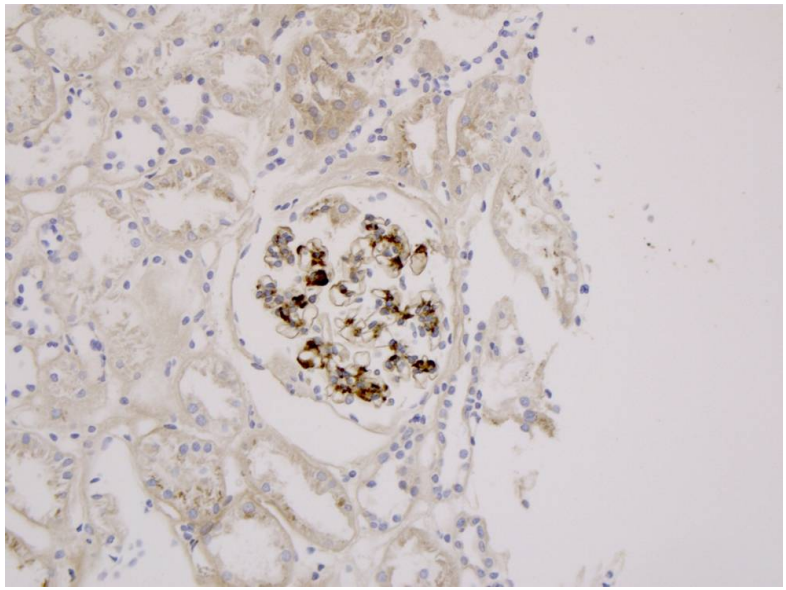
Histology of IgAN

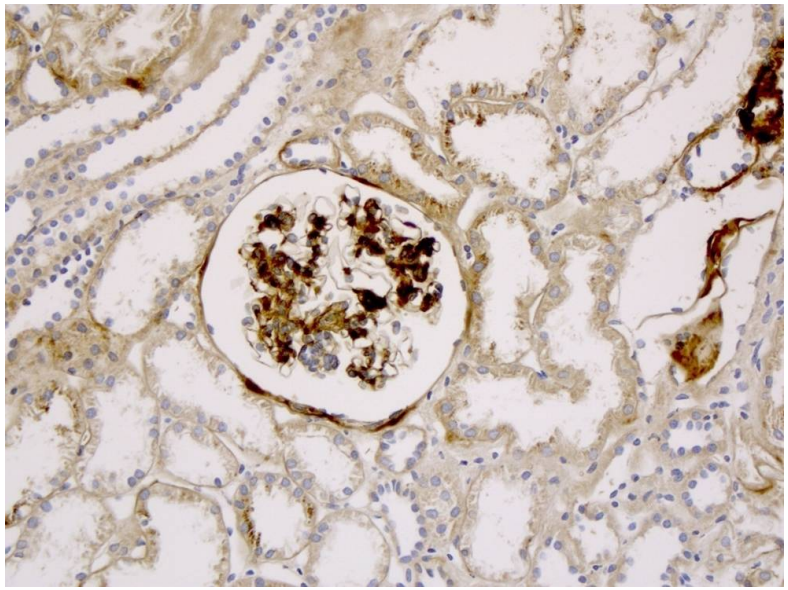


Histology of IgAN

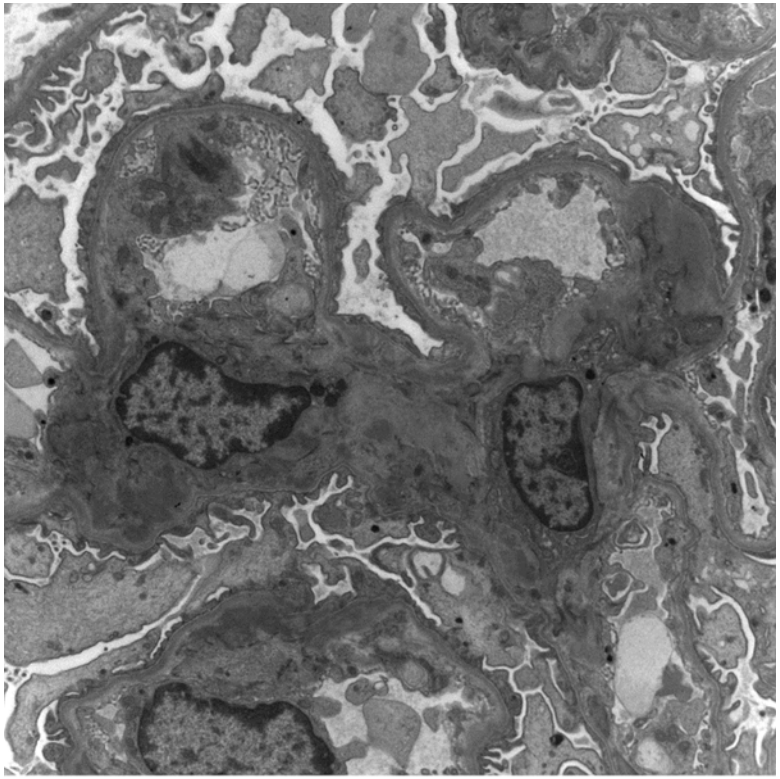


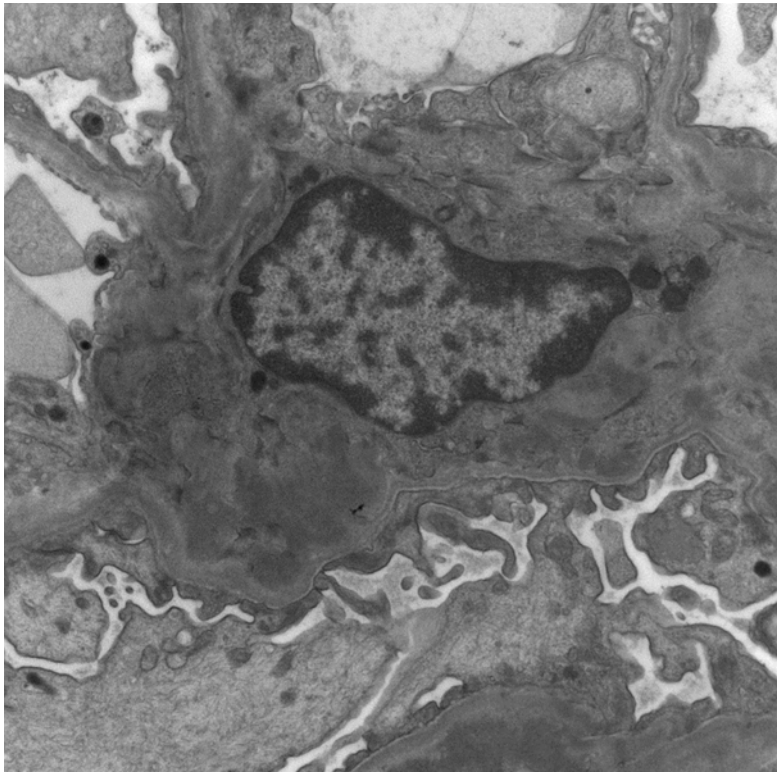
IP of IgAN





EM of IgAN





Post-infectious glomerulonephritis

- Commonly seen in children
- Present with nephritic syndrome 2-3 weeks after streptococcal throat or skin infection
- Group A beta-haemolytic streptococci (strains 12, 4 & 1) most commonly
- 95% resolution in children
- Adults may have persistent renal abnormalities

Histology of Post-infectious GN

Light microscopy

- Enlarged, hypercellular, “bloodless” glomeruli
- Endocapillary hypercellularity – swelling of endothelial cells and infiltration of neutrophils
- Mesangial proliferation
- May have crescents

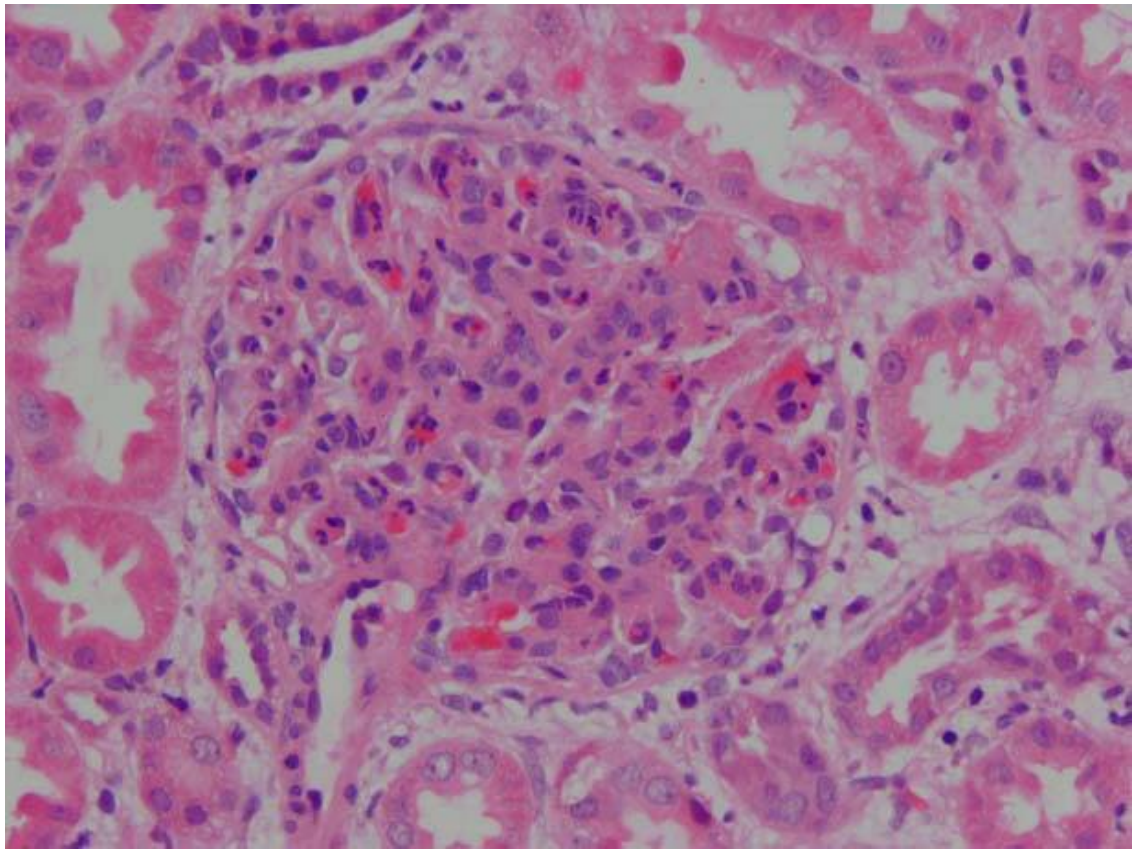
Immunohistochemistry

- Coarse, granular IgG, IgM and C3 along peripheral capillary loops

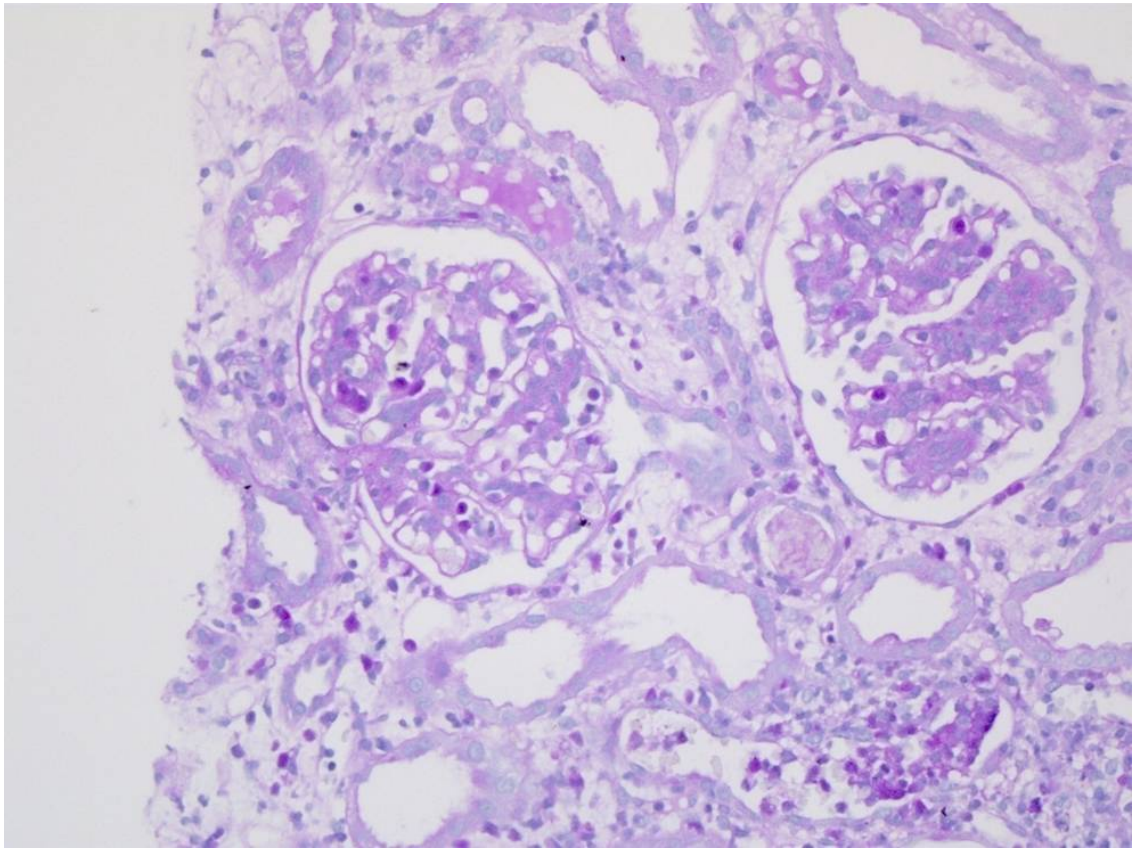
EM

- Subepithelial “hump-like deposits”

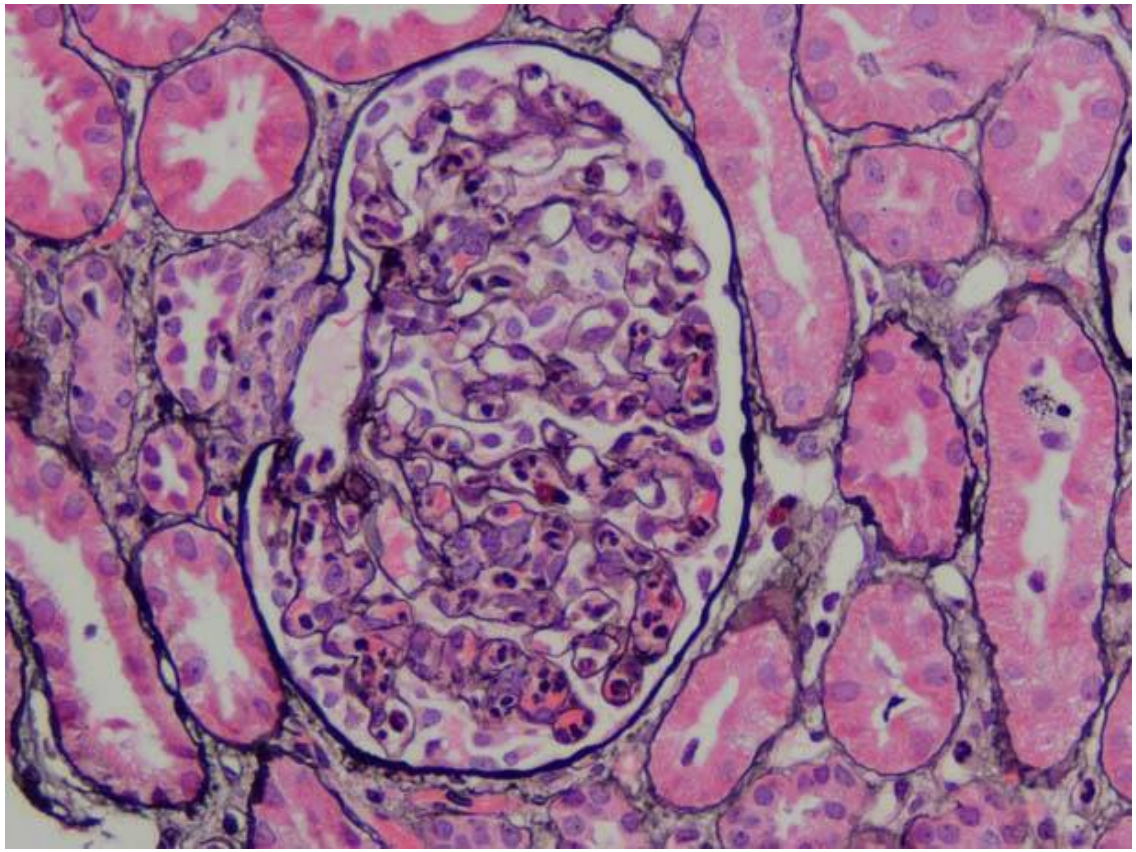
Histology of Post-infectious GN



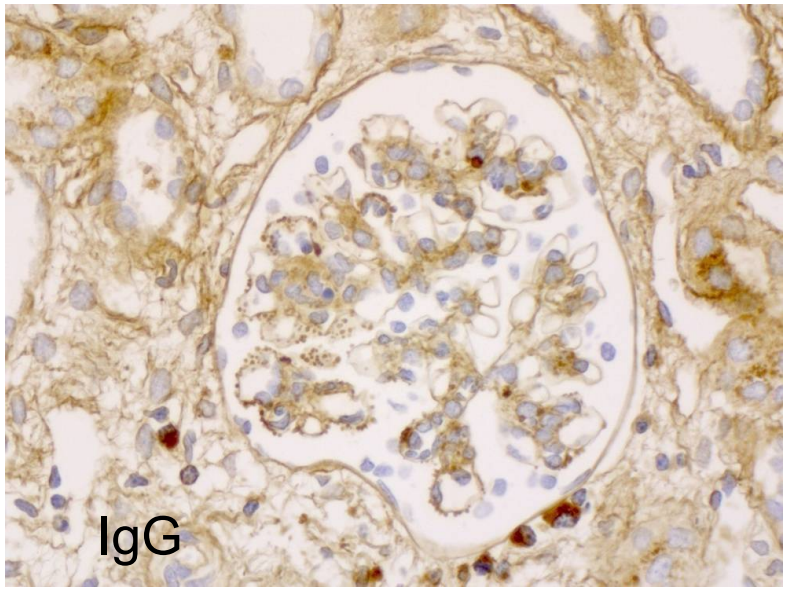
Histology of Post-infectious GN

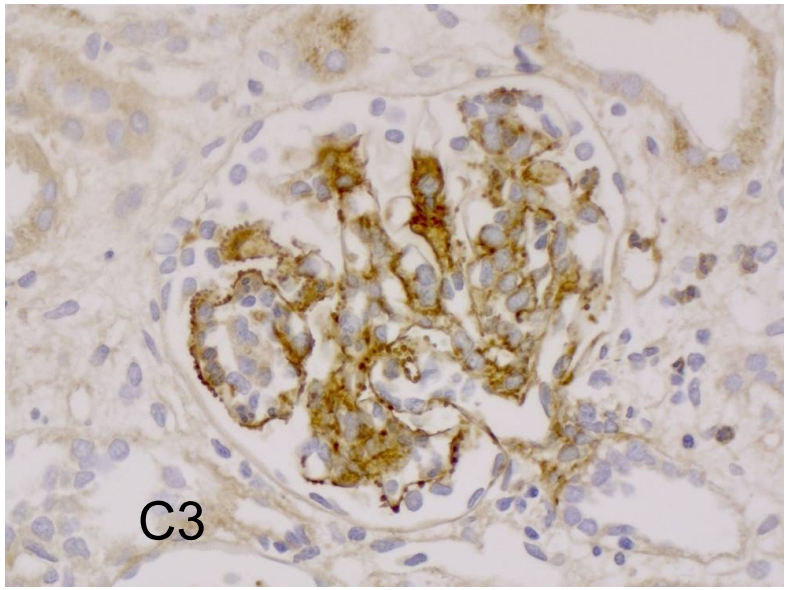


Histology of Post-infectious GN



IP of Post-infectious GN





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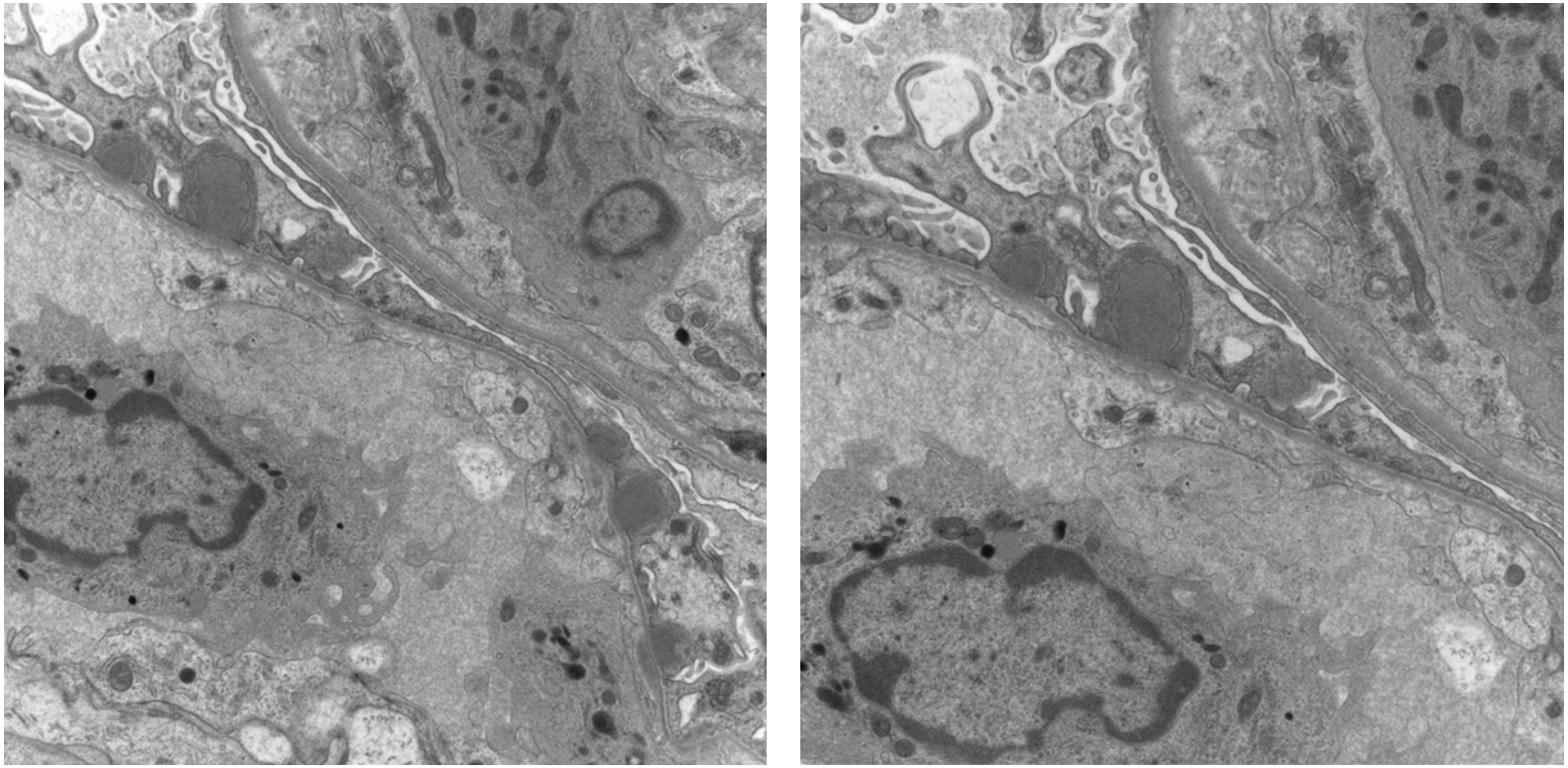


Membranoproliferative GN

- Primary or secondary
- Primary may be Type I, II or III
- 2/3 cases are Type I
- Type II is dense deposit disease
- Type III is very rare
- Secondary, eg cryoglobulinaemia, hepatitis C

Histology of Membranoproliferative GN

Light microscopy

- Glomeruli have a “lobular” appearance and are hypercellular
- Mesangial proliferation (may also be endocapillary)
- Thickening of glomerular basement membranes with “double-contouring” or “tram-track” appearance
- Visible linear deposits in capillary walls in DDD

Histology of Membranoproliferative GN

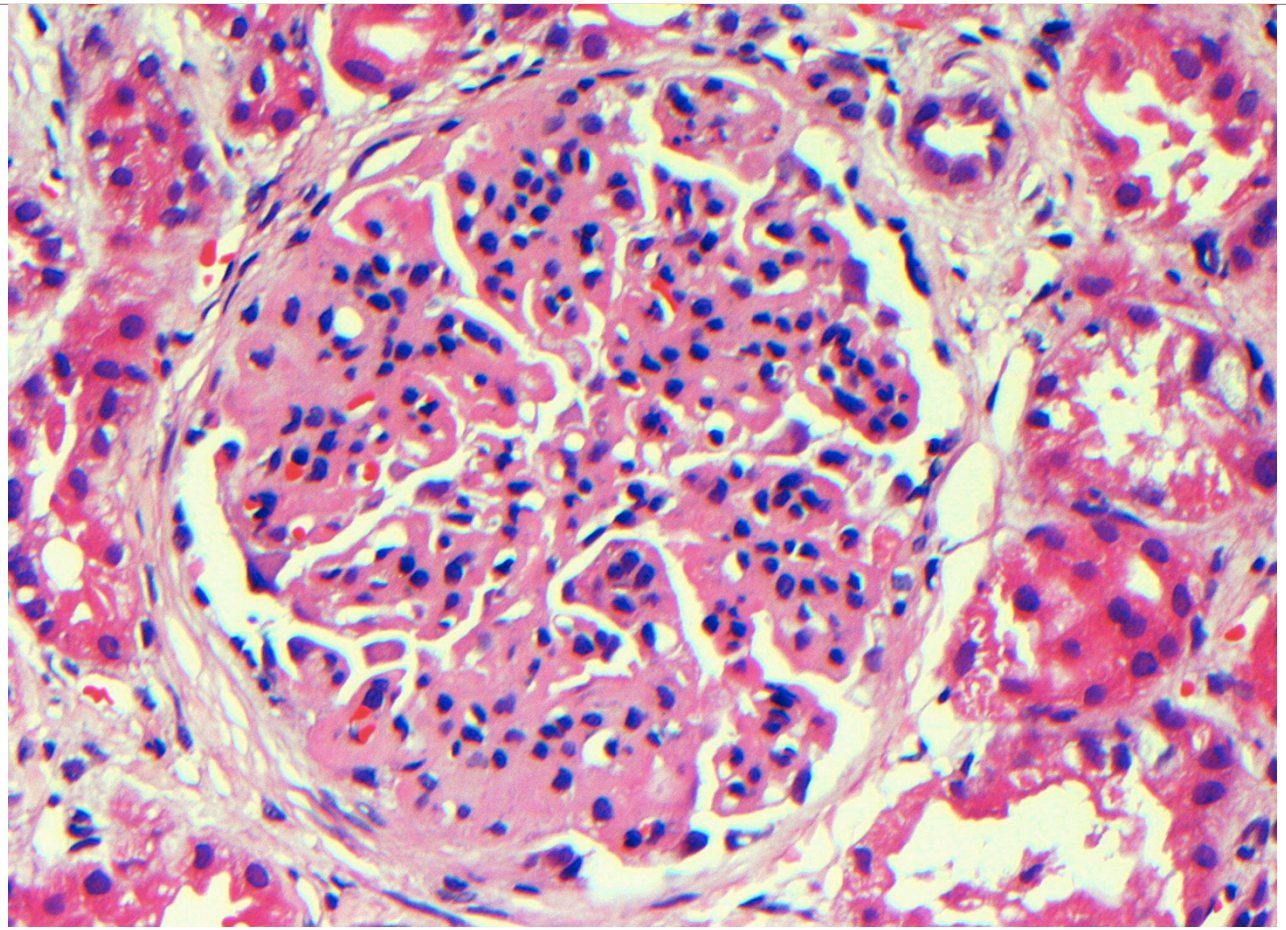
Immunohistochemistry

- Coarse granular C3 and IgG Type I mesangial and subendothelial
- Linear C3 Type II (DDD)

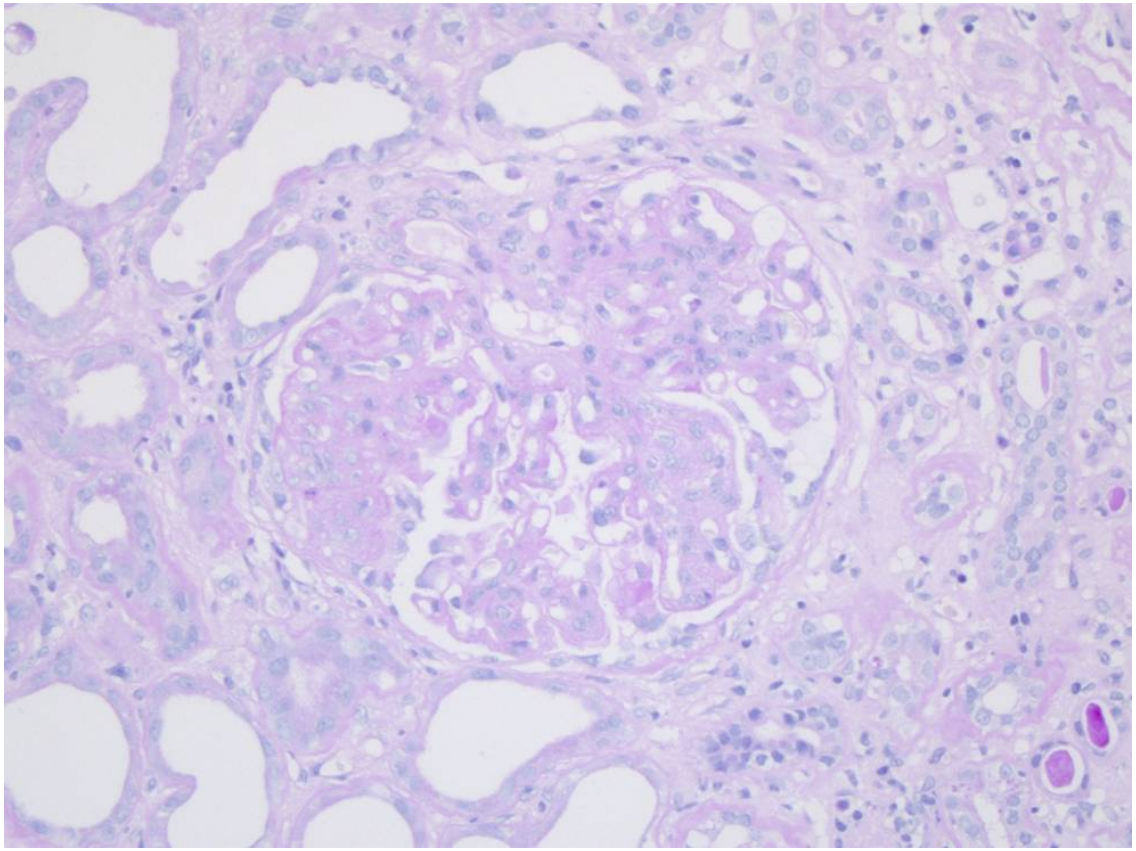
EM

- Type I subendothelial deposits
- Type II dense ribbon-like intramembranous deposits

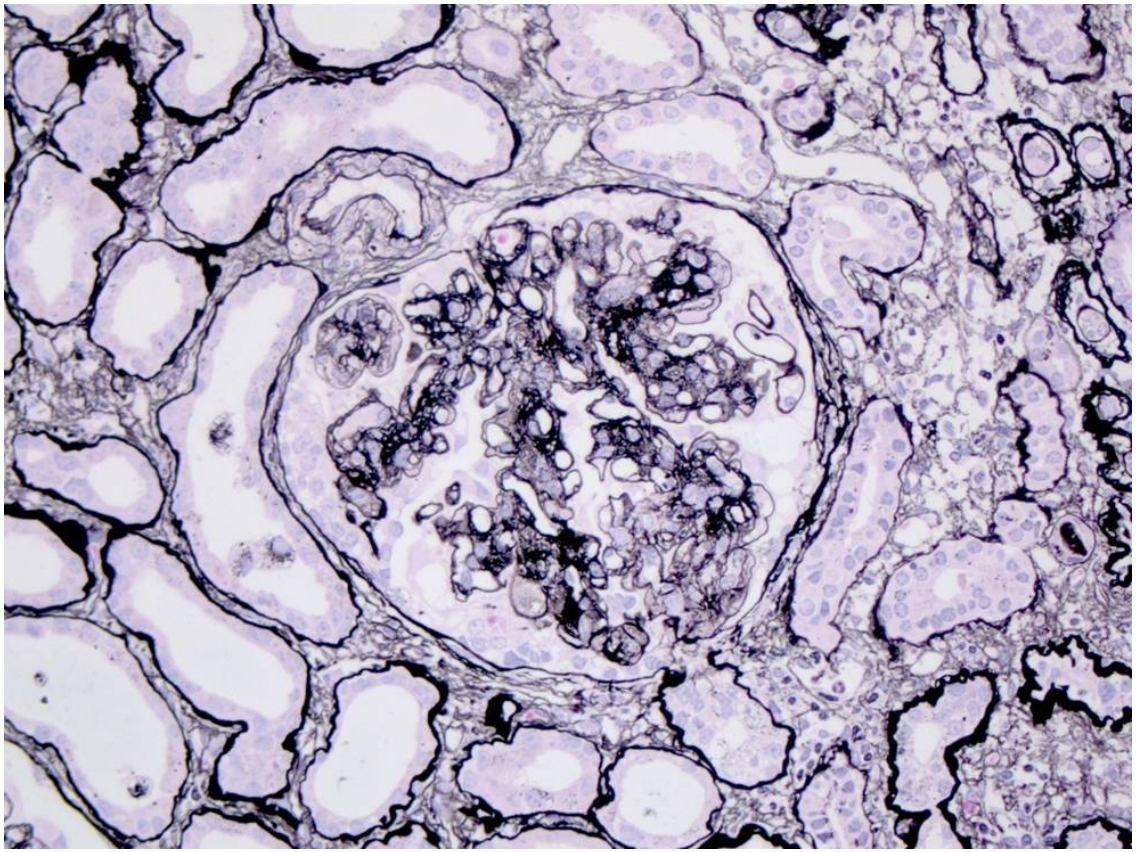
Membranoproliferative GN



Membranoproliferative GN



Membranoproliferative GN



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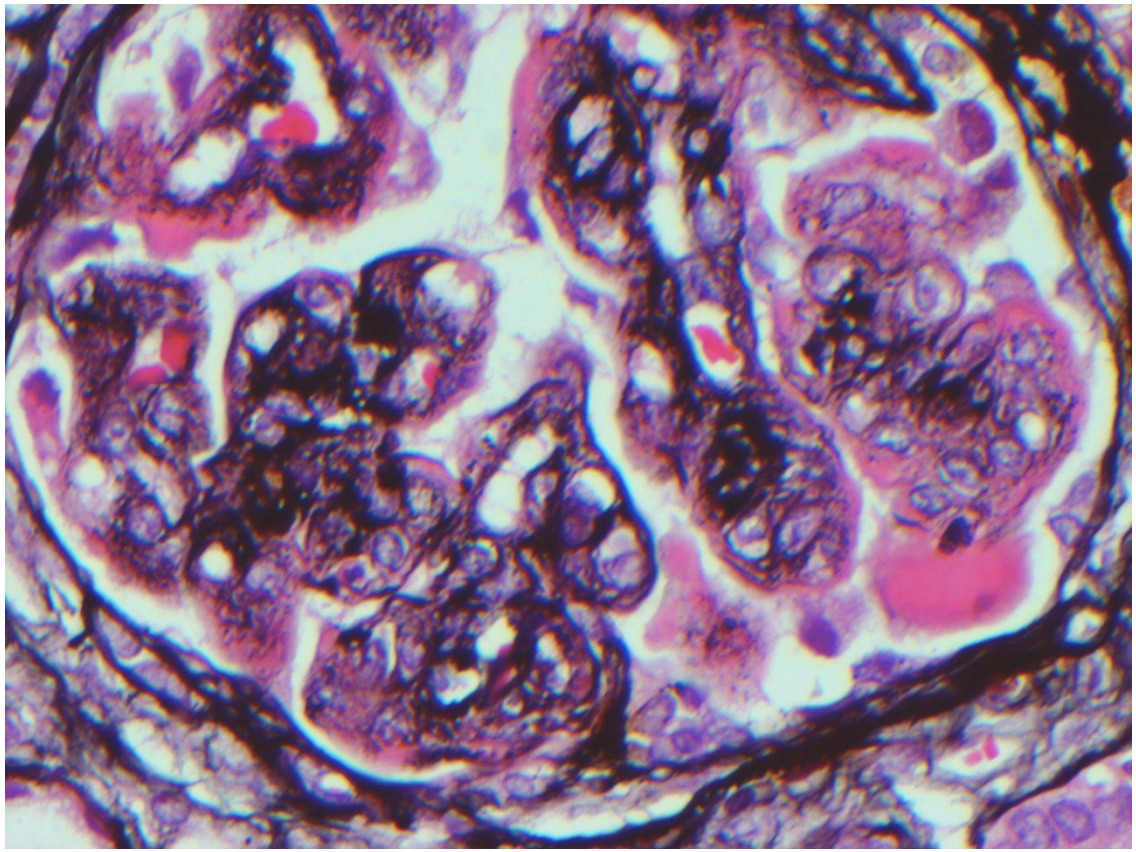
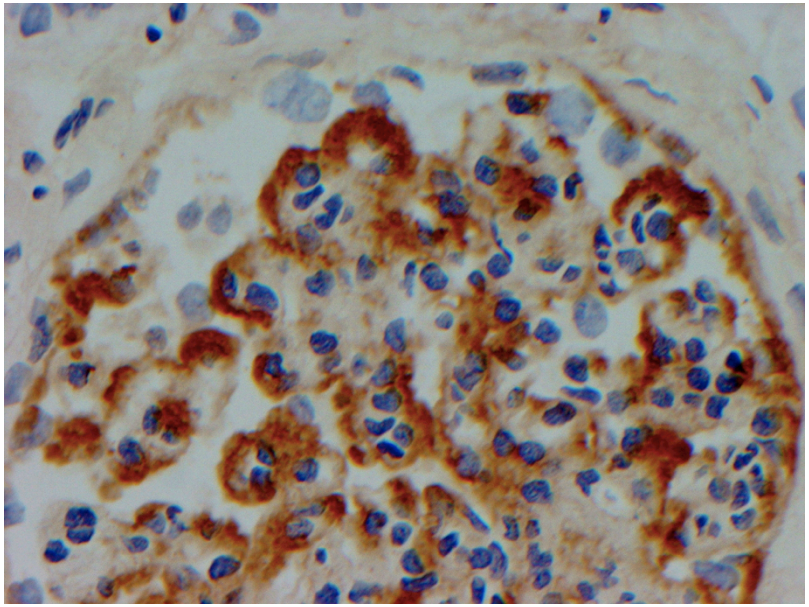
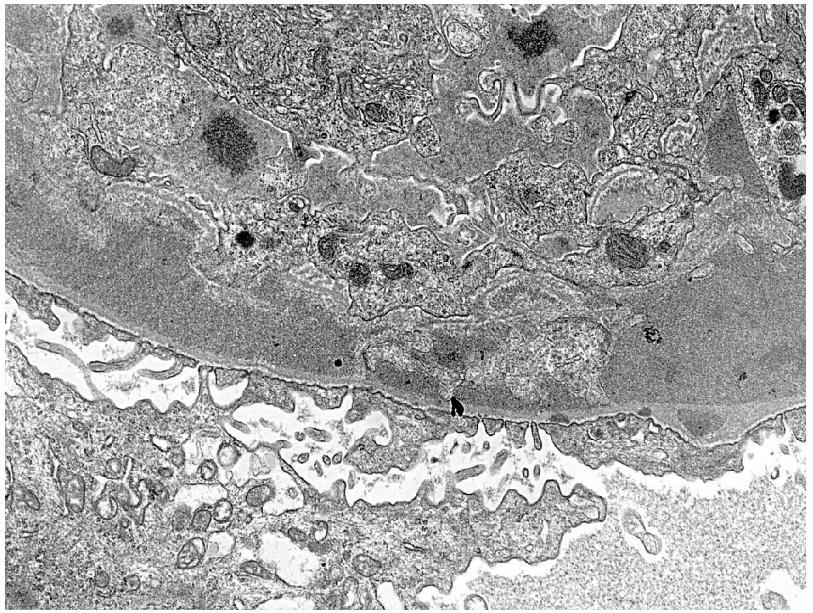


Membranoproliferative GN





Crescentic GN

Often referred to clinically as “rapidly progressive glomerulonephritis”

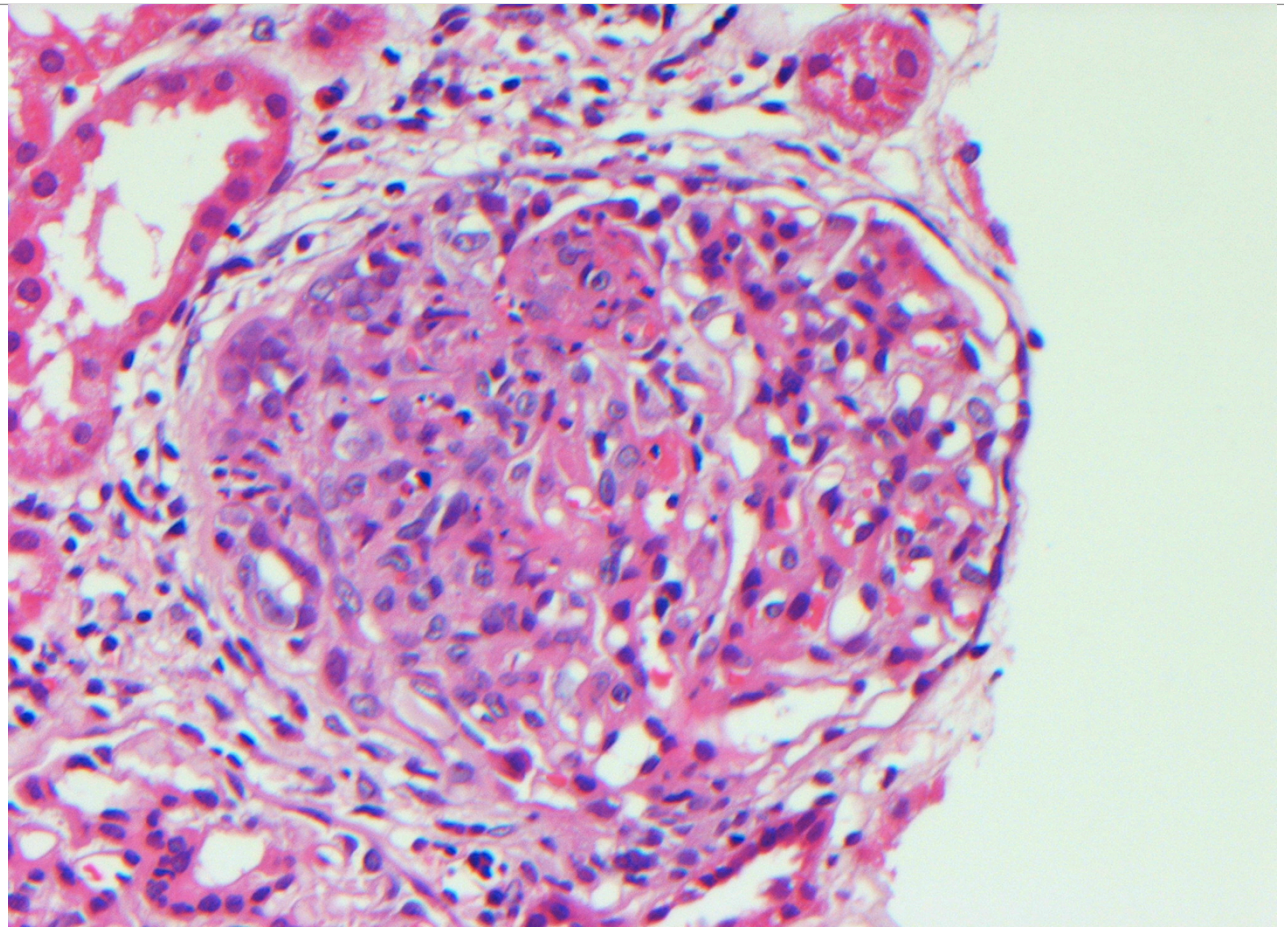
Morphological pattern rather than a diagnosis

Histologically means that >50% glomeruli show crescents

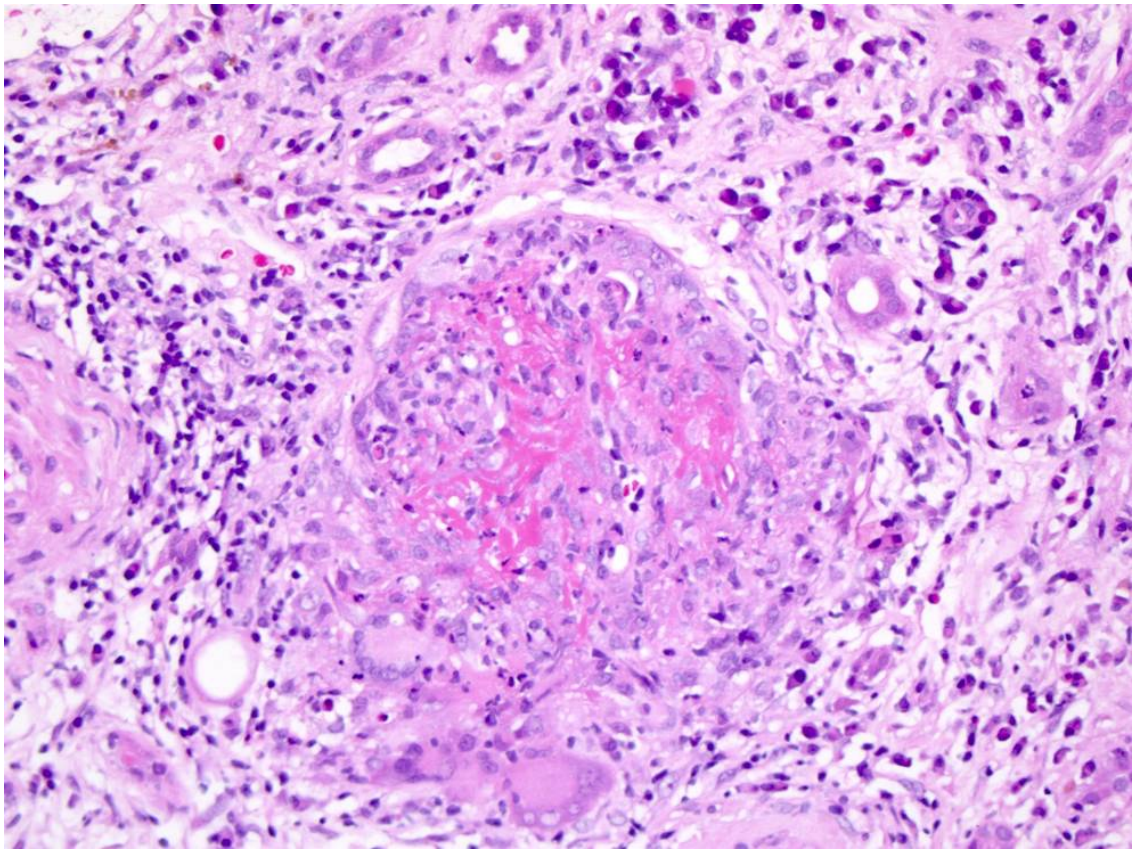
May be immune eg. SLE, pauci-immune eg. Wegener’s granulomatosis or non-immune eg. Anti-GBM disease

Underlying pattern of glomerular injury varies with cause

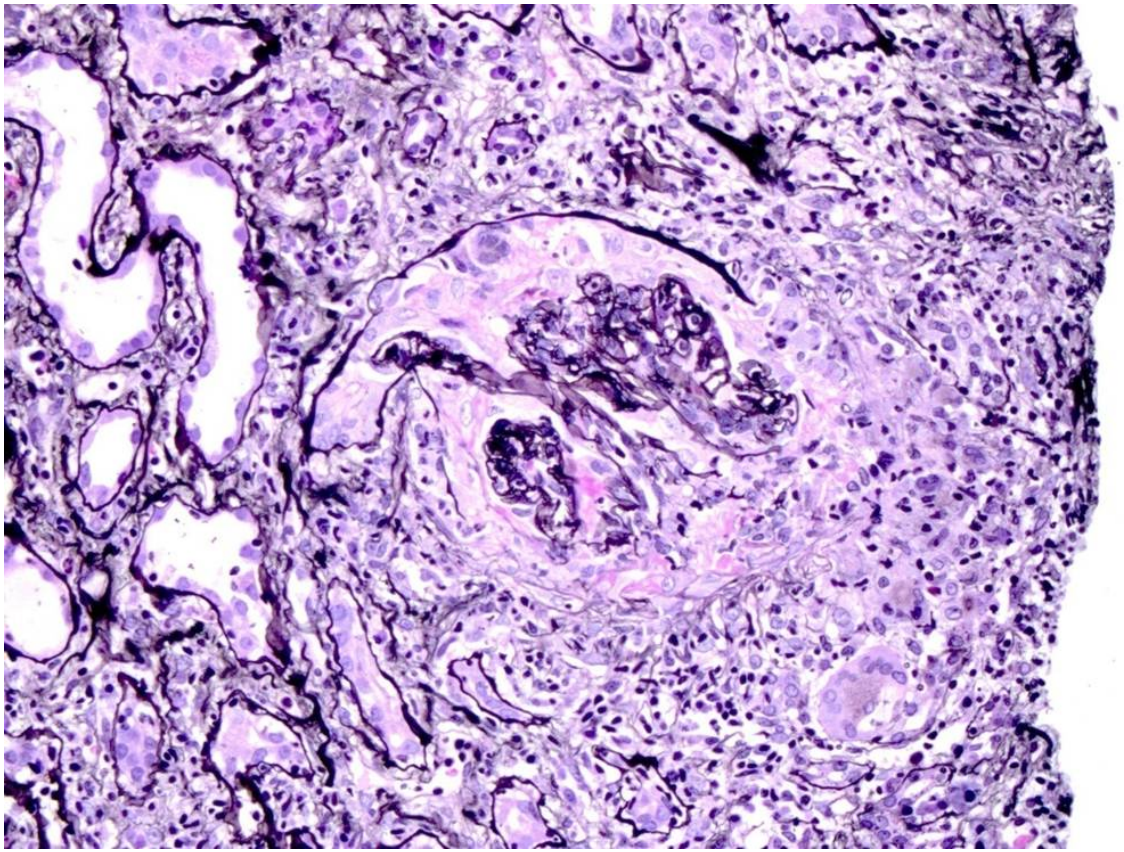
Histology of Crescentic GN



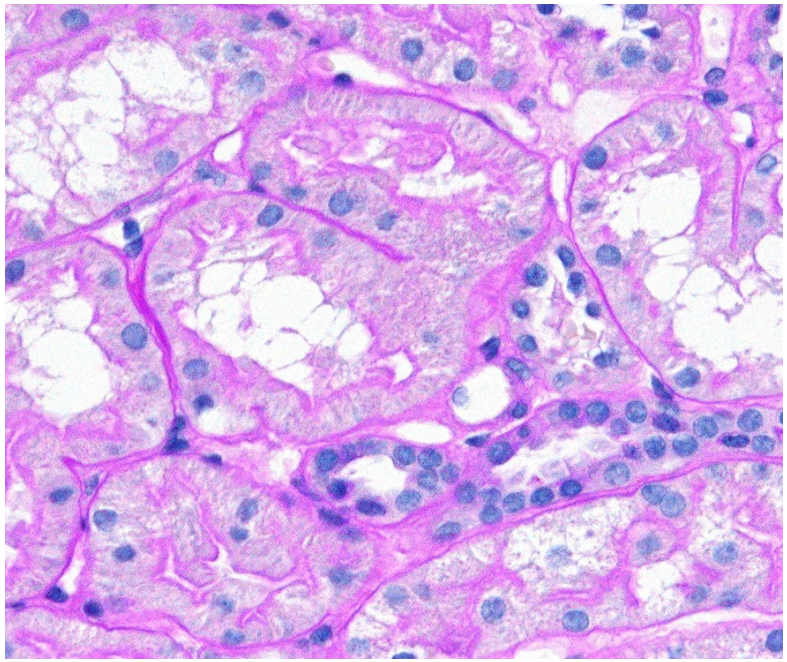
Histology of Crescentic GN

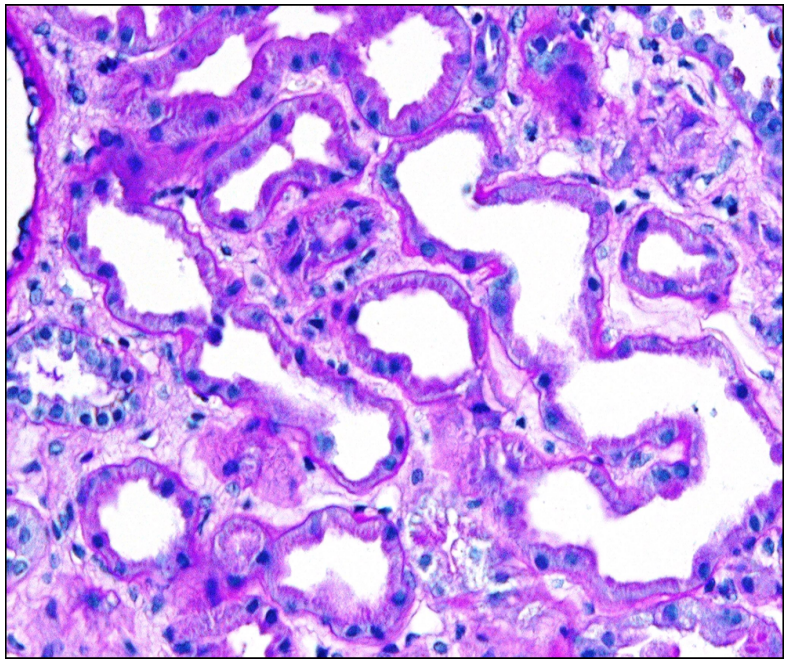


Histology of Crescentic GN

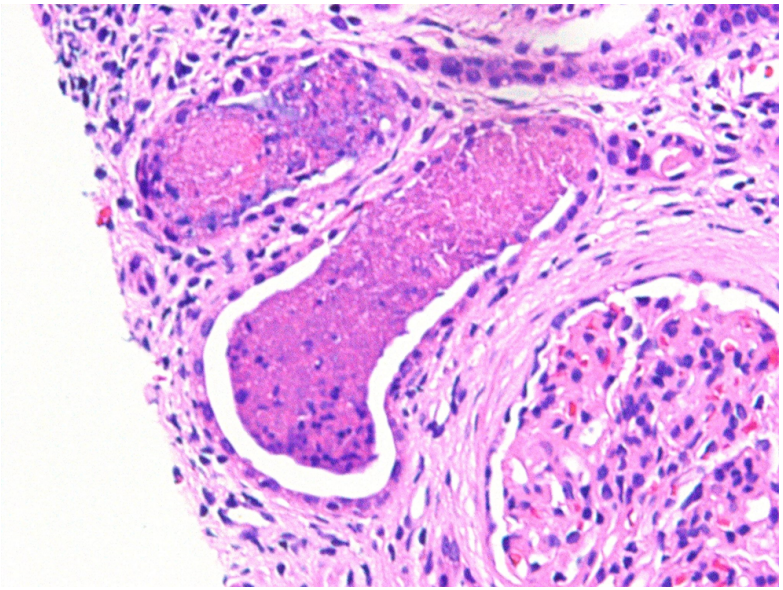


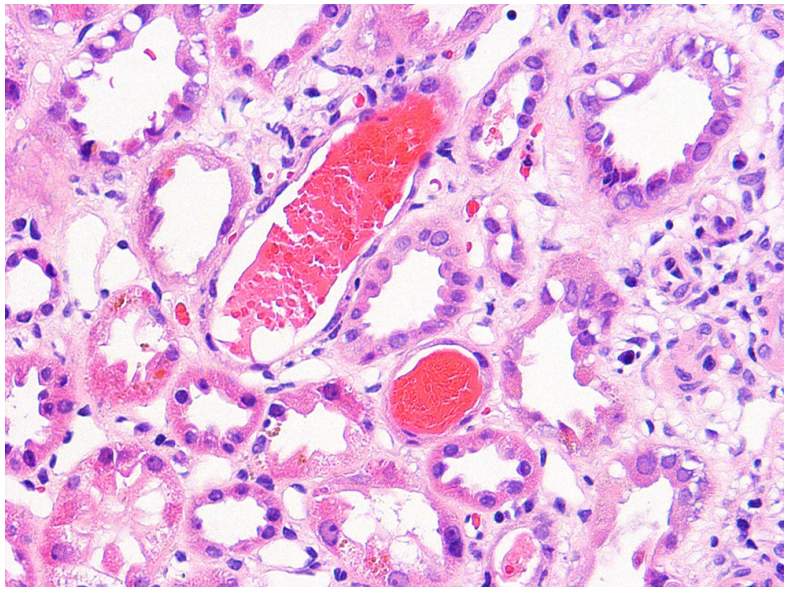
Acute Tubular Injury (ATI)



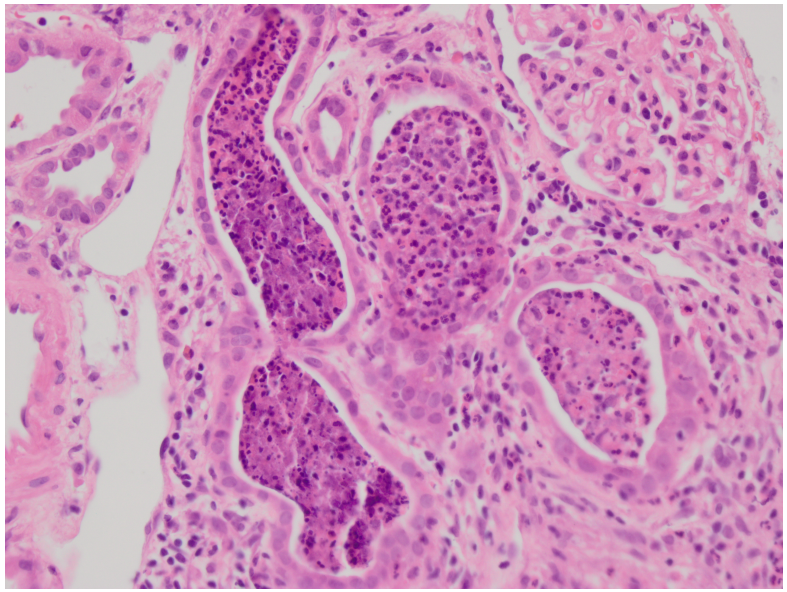


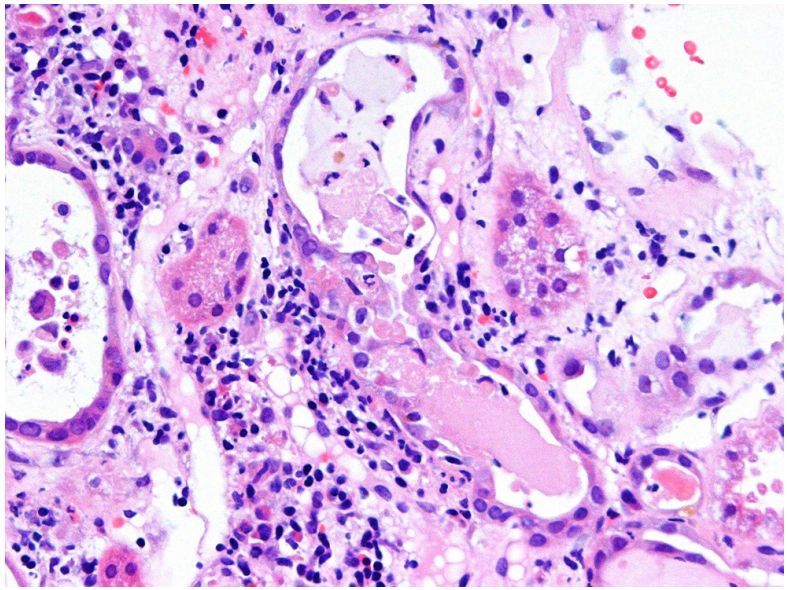
Tubular Casts



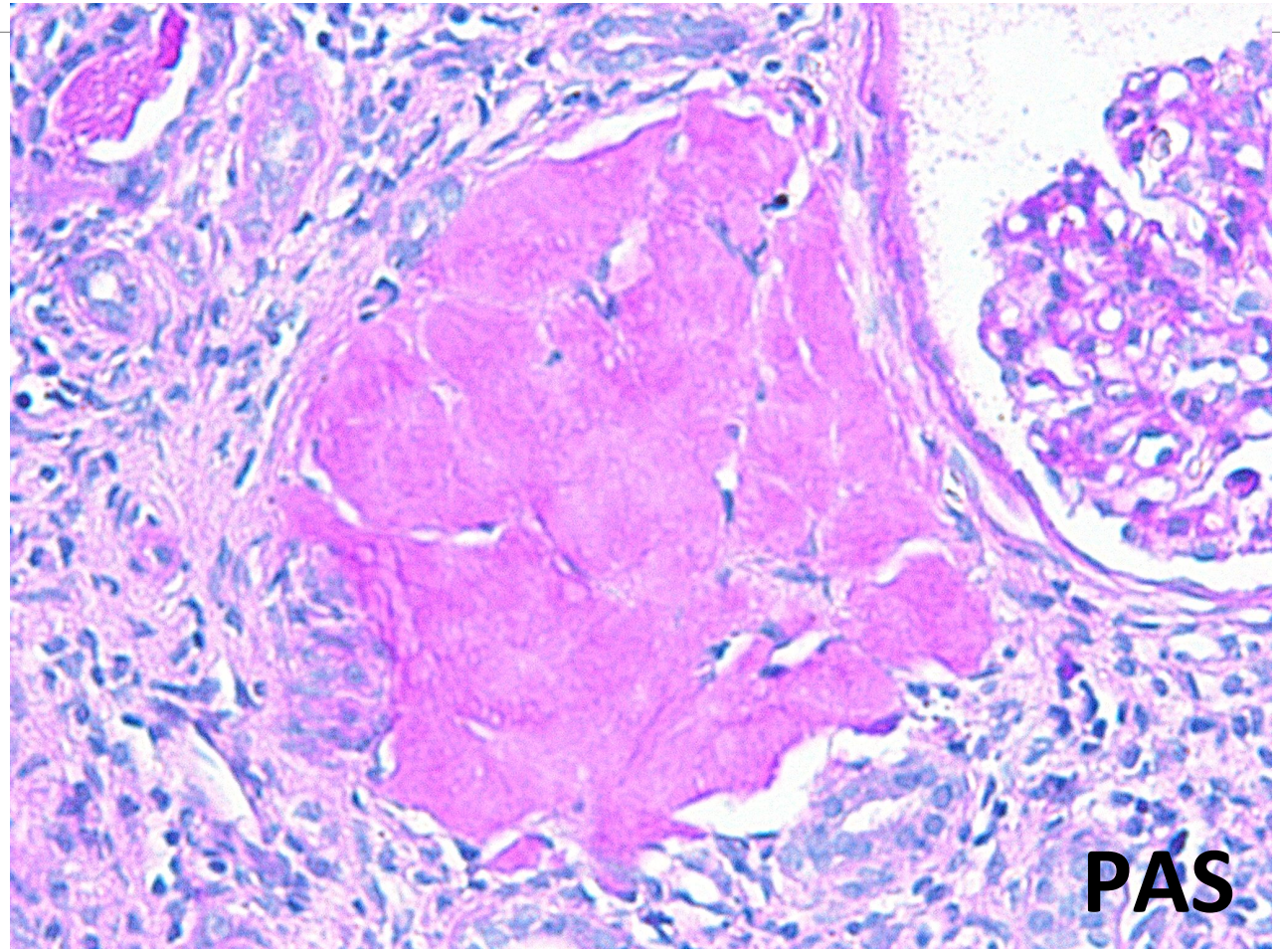


Tubular Casts

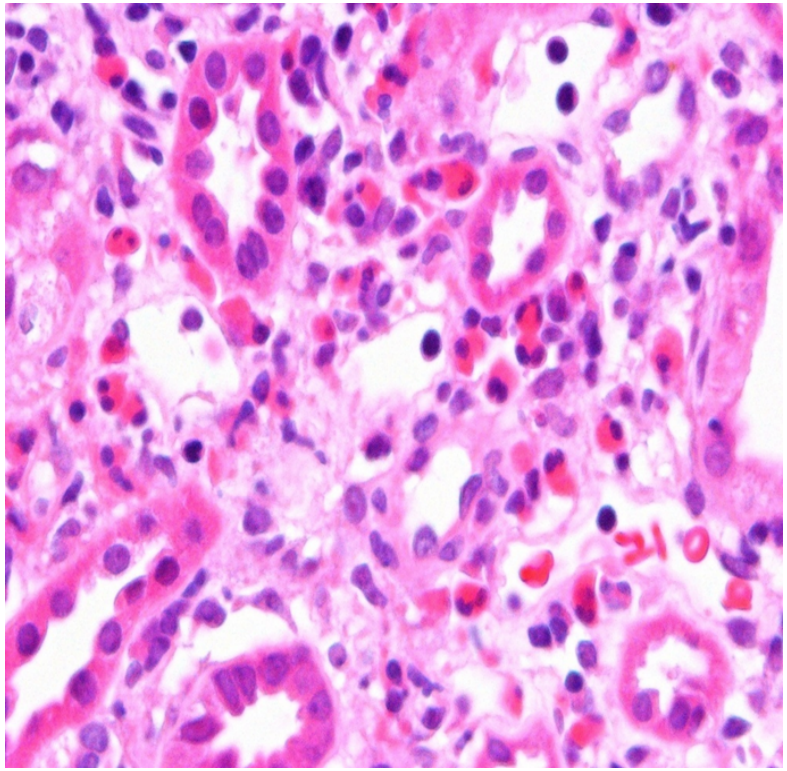


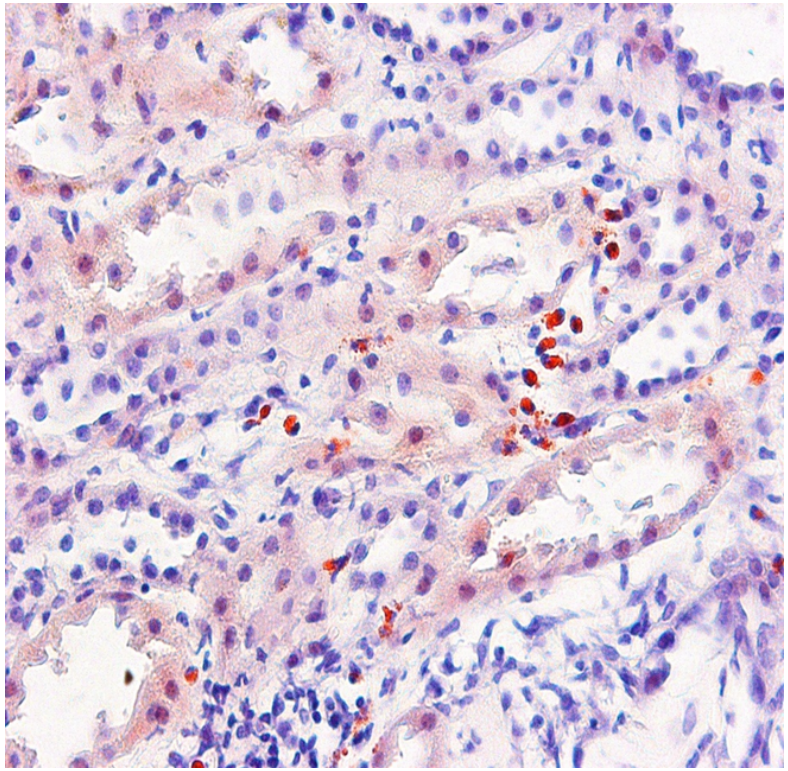


Uromodulin (Tamm-Horsfall Protein) Cast

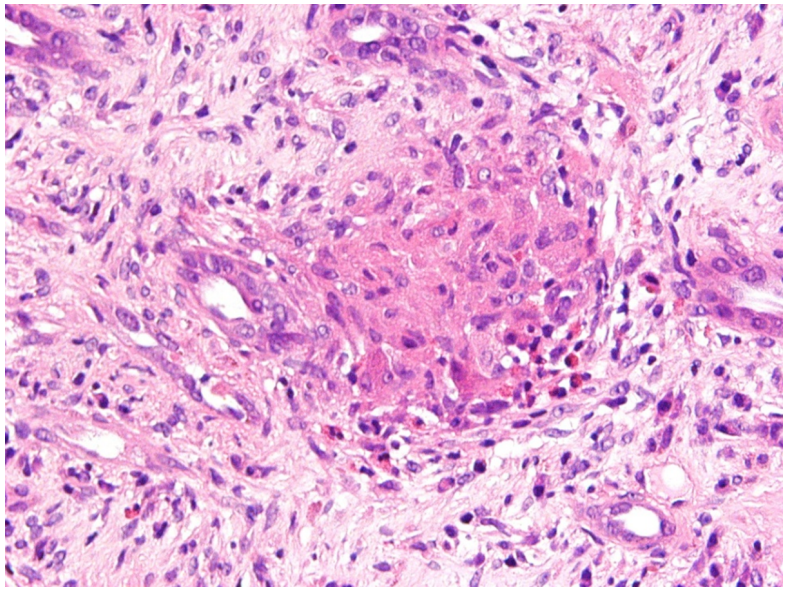


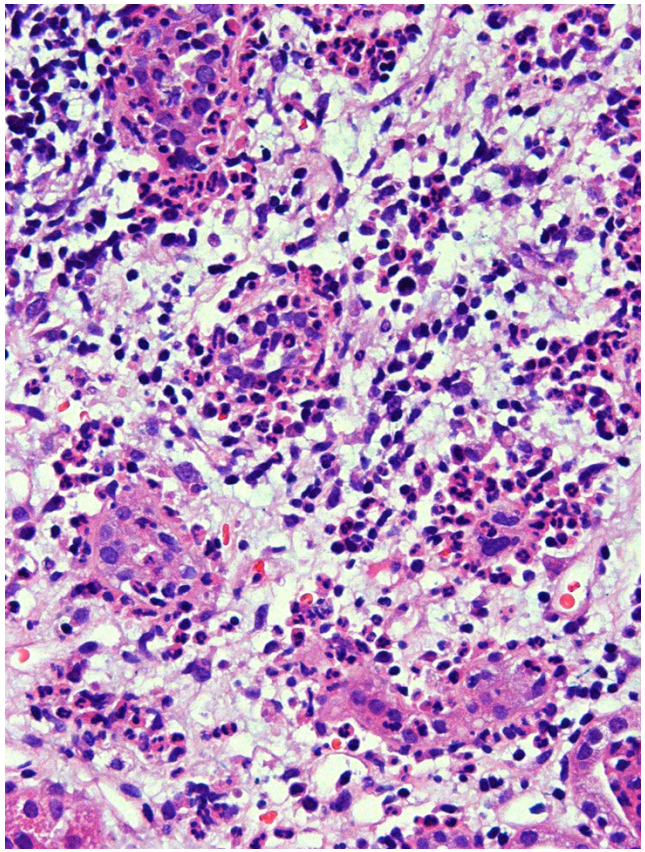
Tubulointerstitial Nephritis (TIN)





Tubulointerstitial Nephritis (TIN)





Causes of TIN

TIN with eosinophils

- Drugs
- Parasites
- Cholesterol emboli

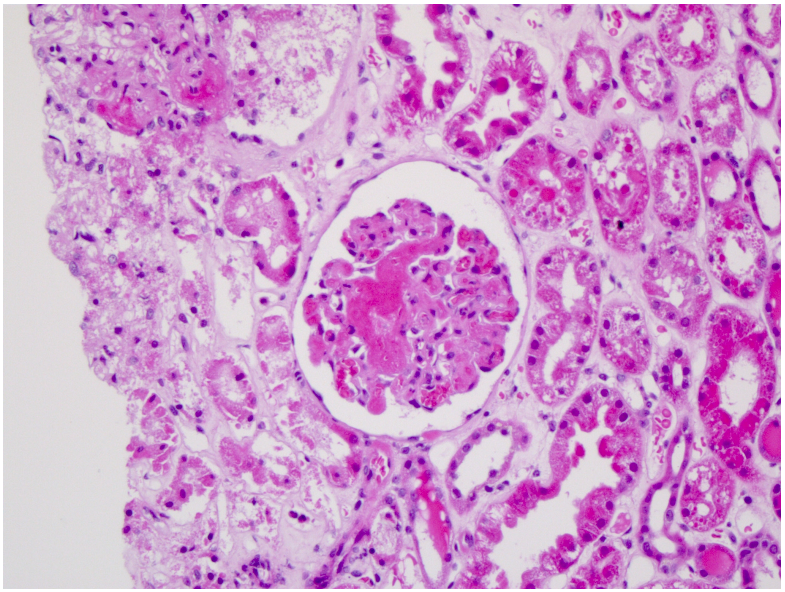
TIN with neutrophils

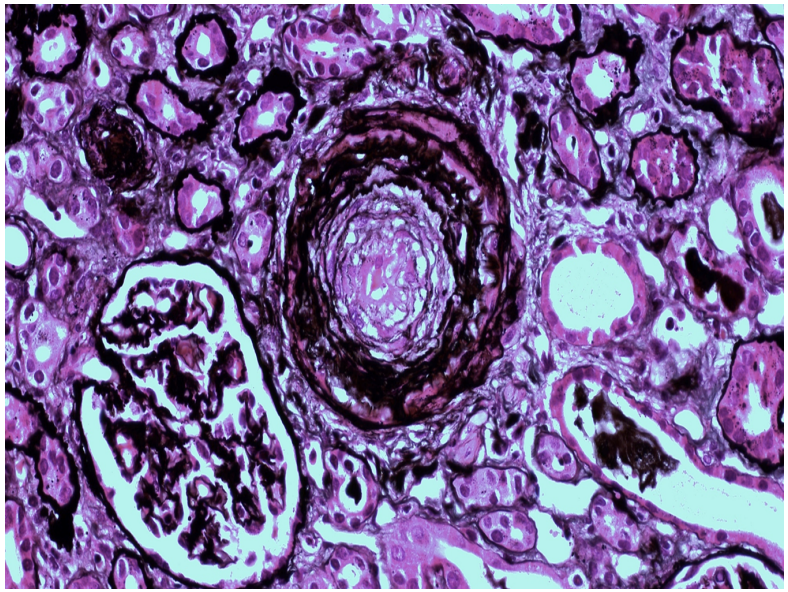
- Bacterial infection

TIN with lymphocytes/plasma cells

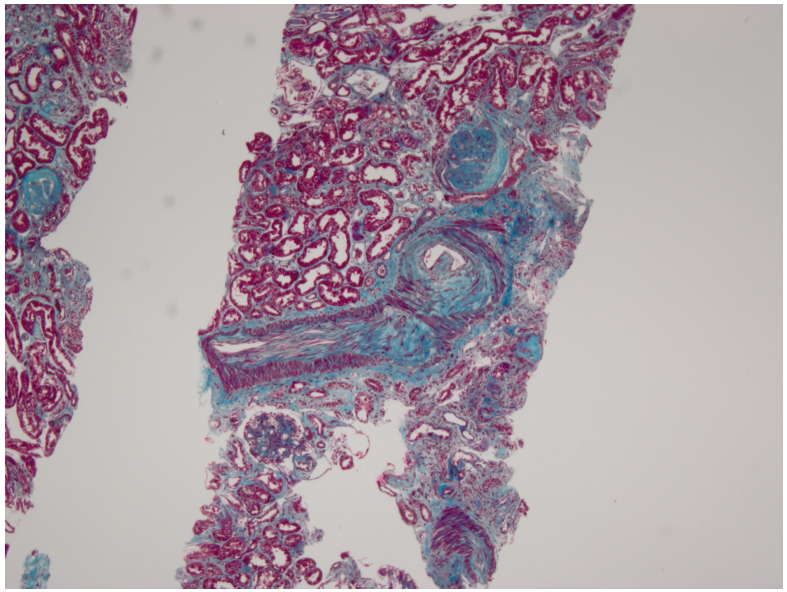
- Viral infection
- Toxins
- Drugs
- Autoimmune disease
- Neoplasm
- IgG4-RD
- Anti-TBM nephritis

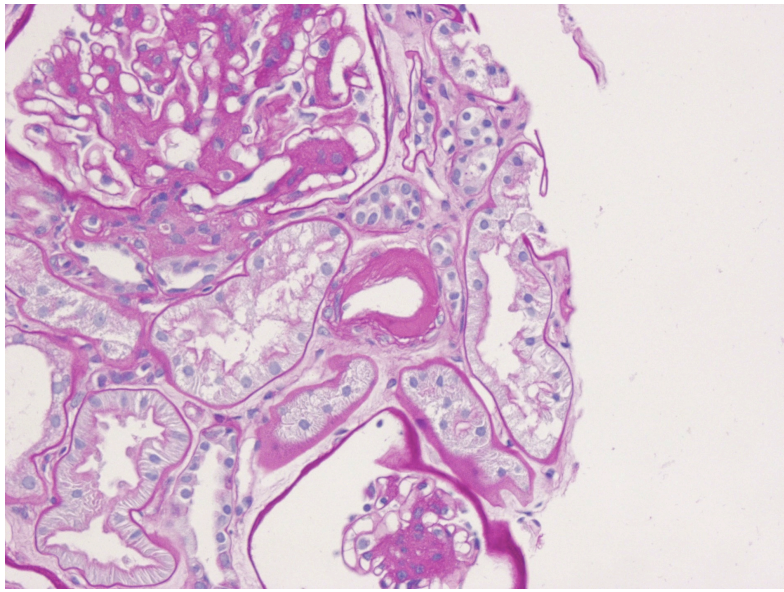
Thrombotic Microangiopathy



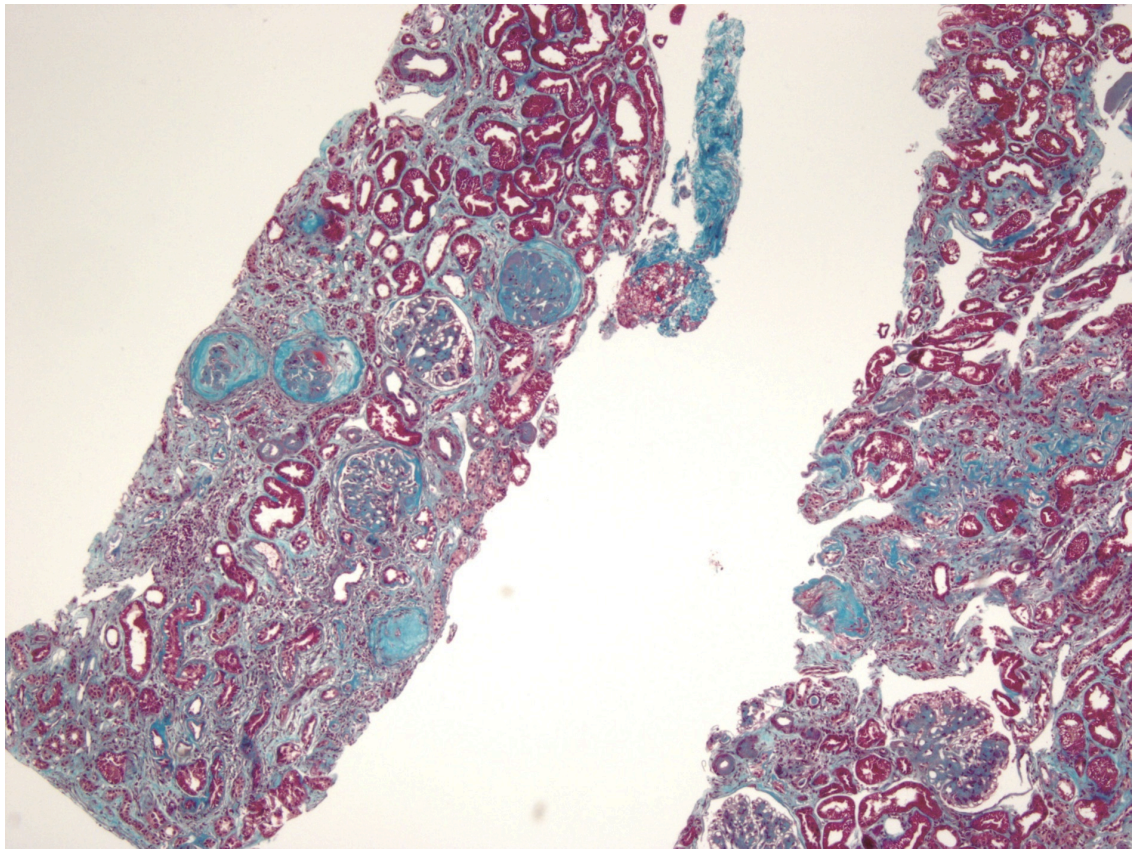


Chronic Vasculopathy





Tubulointerstitial Fibrosis



The Structure of the Renal Biopsy Report

Glomeruli

Tubules

Interstitium

Blood Vessels

Immunofluorescence/Immunoperoxidase

Electron Microscopy

Comment

Diagnosis

The Structure of the Renal Biopsy Report

The biopsy consists of X cores of renal cortex and medulla containing X glomeruli of which X are globally sclerosed.

Glomeruli

There is focal mild increase in mesangial cellularity and matrix. No thickening of the capillary basement membrane. There is focal splitting of the capillary basement membrane on PAMS stain. No vacuolation or spikes on PAMS stain. No segmental sclerosing lesions. There is diffuse endocapillary hypercellularity. There is focal necrosis. No crescents.

Tubules/Interstitium

No red or white cell casts. There is severe acute tubular injury. There is moderate inflammation. No significant tubulointerstitial fibrosis.

Blood vessels

There is moderate arteriosclerosis. No arteriolar hyalinosis. No vasculitis. Congo red stain for amyloid is negative.

The Structure of the Renal Biopsy Report

IHC
No staining for IgA, IgG, IgM, C3 and C1q.

EM
XX

Comment
The biopsy shows acute tubular injury suggestive of perfusion related injury. There is chronic vasculopathy. There is no evidence of an active glomerulonephritis or tubulointerstitial nephritis. There is minimal chronic damage.

Kidney biopsy–
Acute tubular injury.

Further Reading

Robbins & Cotran Pathologic Basis of Disease
Vinay Kumar, Abul K. Abbas, and Jon C. Aster

Diagnostic Atlas of Renal Pathology
Agnes B. Fogo and Michael Kashgarian