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Medical Kidney

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Nephrotic syndrome

***Clinically*: >3.5 g/24h proteinuria, hypoalbuminenia, edema, hyperlipidemia, lipiduria**

***Think*: Effaces foot processes → Leaks lots of protein into urine → hypoalbuinemia**

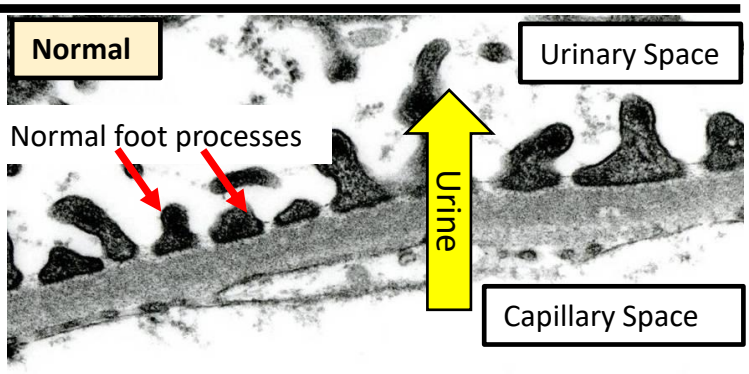
Minimal Change Disease

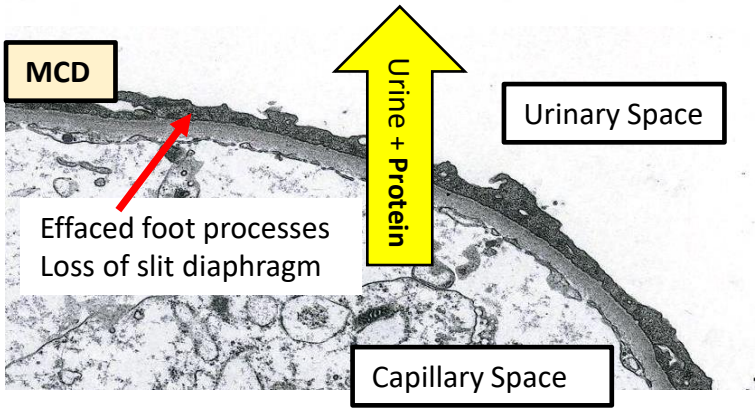
Most common in **Kids**.

Often after **medication or recent illness** → autoantibody, cytokine or some factor **alters podocytes foot processes** (lose size barrier) and **negative charge of GBM** (lose charge barrier) → **leakage of albumin**.

Can only see on EM (normal H&E and IF), hence the name, "minimal change"

Treat with steroids and underlying cause. Often doesn't require a bx in kids.





Focal Segmental Glomerulosclerosis *aka "FSGS"*

Focal (<50% of glomeruli; vs diffuse)
Segmental (<50% of *each* glomerulus; vs global)

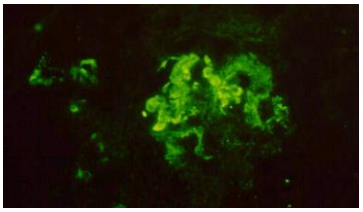
Usually, adults with Nephrotic +/- hematuria, HTN, decrease in GFR
More common in African Americans

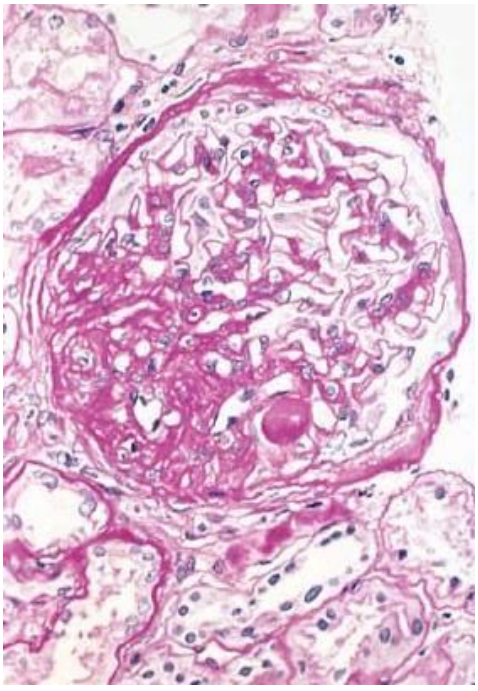
Pathogenesis unclear (*NOT* immune complex)
Can be **secondary to: HIV, heroin, sickle cell disease, obesity**

H&E: Focal & segmental sclerosis, Uninvolved gloms look ok
IF: Trapped IgM &C3 in sclerotic areas (passive not real complexes)
EM: Widespread effacement of foot processes

Usually progresses to ESRD, poor response to steroids

Several variants, including:
Collapsing (poorer prognosis)
Tip lesion (better prognosis)
Cellular
Perihilar





Membranous Nephropathy

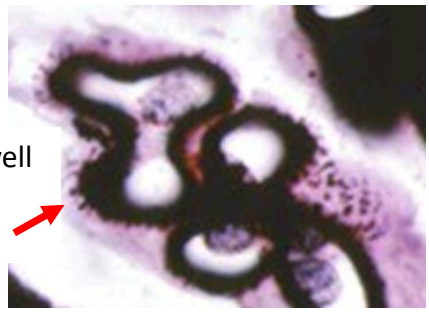
Can be **primary** (idiopathic) with **antibodies to M type phospholipase A2 receptor** (PLA_2R) on podocytes (autoantibody highly specific) *or*

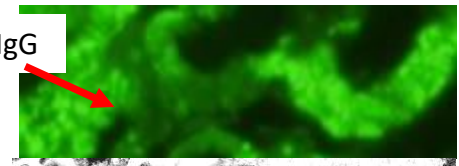
secondary to: **Drugs, infection (Hep B, syphilis), tumors, SLE**
Rat model: Heyman nephritis

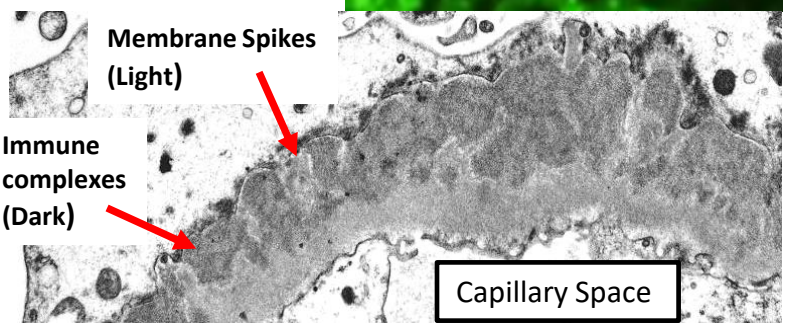
Immune complex mediated:
Antibodies react with antigen on underside of podocytes→ activate complement→ **effaced podocytes lose slit diaphragm** (lose size barrier) and **produces more basement membrane *between* complexes** (alters charge barrier) → **form spikes of GBM**, which also appears thicker (hence name)

H&E: Diffuse thick membranes
Jones Silver: Spikes
IF: Granular IgG and C3 complexes
Can do specific PLA_2R staining for primary
EM: Subepithelial electron dense deposits
With spikes of membrane in between

Variable outcomes.







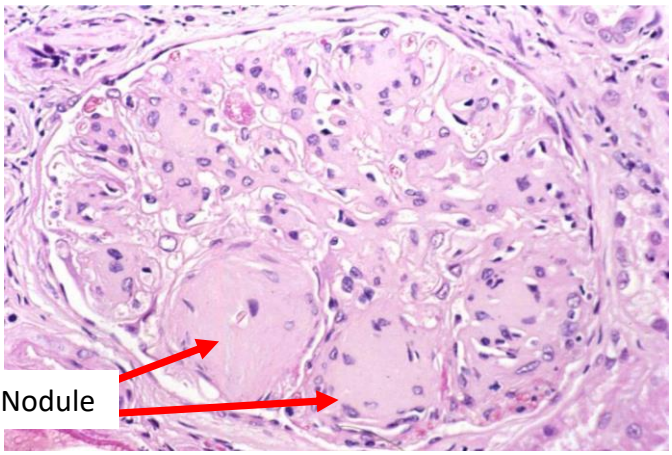
Diabetes Nephropathy

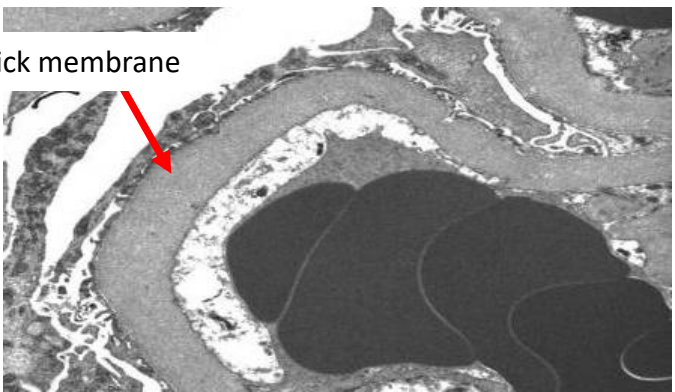
History of DM, often with HTN and poor glycemic control.

Often causes **proteinuria**, but *not* outright nephrotic *syndrome*

Marked thickening of GBM (lose charge barrier) → altered GBM causes loss of foot processes (lose size barrier) as well as **increased mesangial matrix.**
Vascular hyalinosis also.

H&E: **Mesangial matrix expansion/sclerosis** (**Kimmelstiel-Wilson nodules**), **thick GBM**, glomerulosclerosis, hyalinosis of arterioles→ highlight with PAS
IF: non-specific
EM: thick GBM and expanded mesangium





Nephritic Syndrome

Inflammation in the Glomeruli → Endocapillary hypercellularity with neutrophils

Hematuria (urine with dysmorphic RBCs and RBC casts), **HTN, decreased GFR** (renal insufficiency), edema, oliguria, +/- proteinuria.

Acute Post-Infectious/Streptococcal Glomerulonephritis

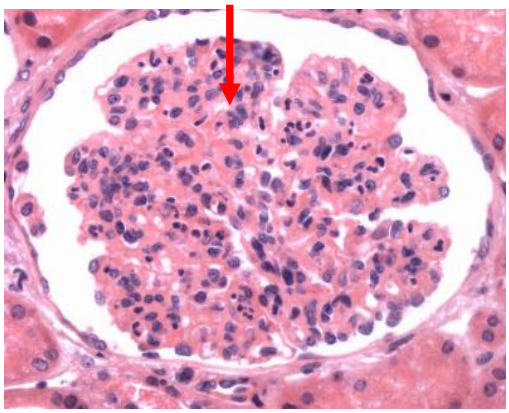
More common in **children**, 1-4 wks after infection
Classically, after **Group A Strep** (*S. pyogenes*)
Currently, *Staph* infection actually more common
Present with fever, malaise, smoky urine, oliguria
Low serum complement; ASO titers;

Immune mediated:
Circulating complexes or planted antigen → bound by **antibodies** → complement activation → **recruit PMNs** → **break down GBM & podocytes with big holes** → **leak RBCs** with some protein → **glomerular cells proliferate and hypertrophy**

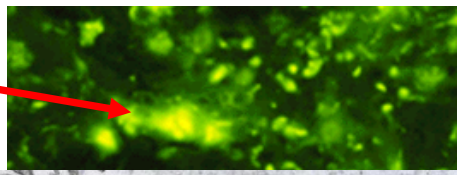
H&E: Hypercellular gloms, PMNs, occluded lumens, +/- crescents
IF: IgG, C3, "Lumpy bumpy" granular
EM: Subepithelial humps, focal subendothelial and mesangial deposits without GBM reaction to deposits (as seen in membranous)

Good prognosis with usual spontaneous resolution

Hypercellular gloms, closed capillary loops, **PMNs**, swollen endothelial cells,



IF: Lumpy bumpy IgG



EM: Subepithelial humps

System Lupus Erythematosus

Causes **diverse renal disease** (can essentially present in *almost any way*: Nephrotic, nephritis, asymptomatic, or mixed) → **major cause of morbidity and mortality** in lupus!

Most common in **women of child-bearing age.**
Acute or insidious in onset; chronic remitting and relapsing course
Primary target organs: skin, joints, kidney, serosal membranes

ANA is highly sensitive , but not very specific
Anti-dsDNA and anti-Sm antibodies are less sensitive but more specific

H&E: Diverse (5 recognized patterns)
IF: "Full House" all antibodies (IgG, IgM, IgA) and complements (C3, C1q)
EM: Tubuloreticular inclusions (TRI) are common

Membranoproliferative Glomerulonephritis (MPGN Type I)

Younger, Usually nephrotic and nephritic

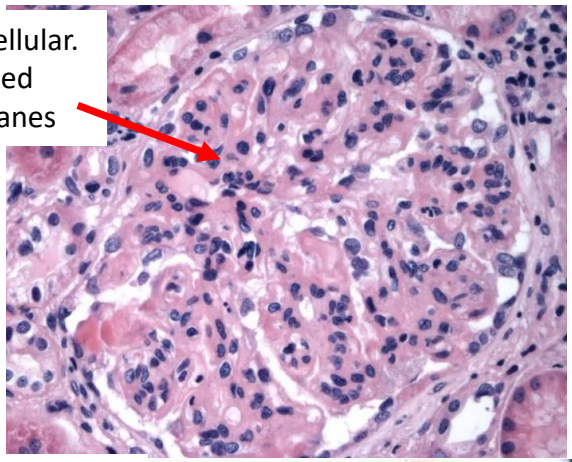
Idiopathic or 2° to: Hep C, Malignancy, SLE

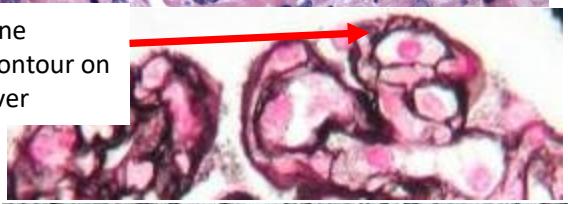
Circulating immune complexes → trapped in glom under endothelium → activate complement → attract inflammatory cells → **new membrane made on inside**

Low serum complement.

H&E: **Thickened, double GBMs (tram tracks);** Mesangial and endocapillary hypercellularity common.
IF: Intense C3>IgG granular
EM: **Subendothelial deposits, reduplicated GBM**

No good therapy. Slowly progresses usually.



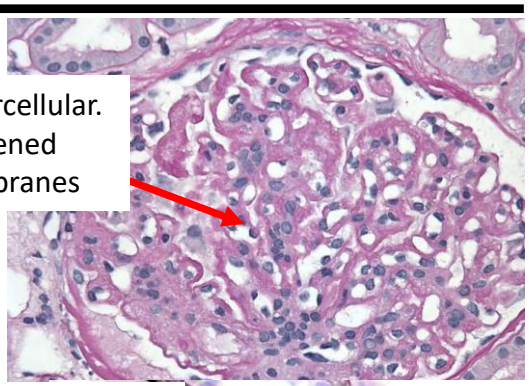


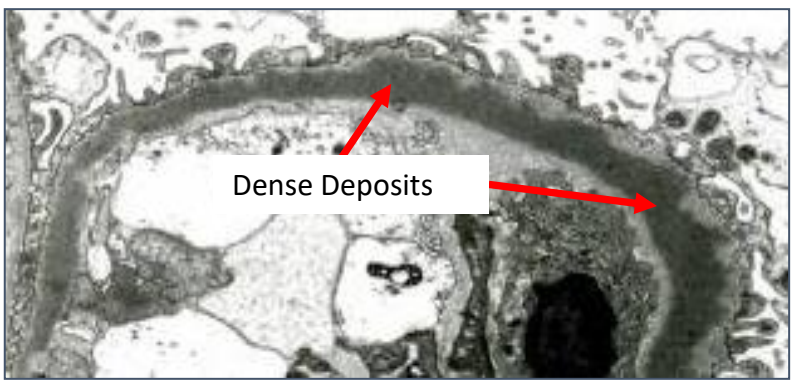
Dense Deposit Disease (MPGN type II)

Rare. Younger.

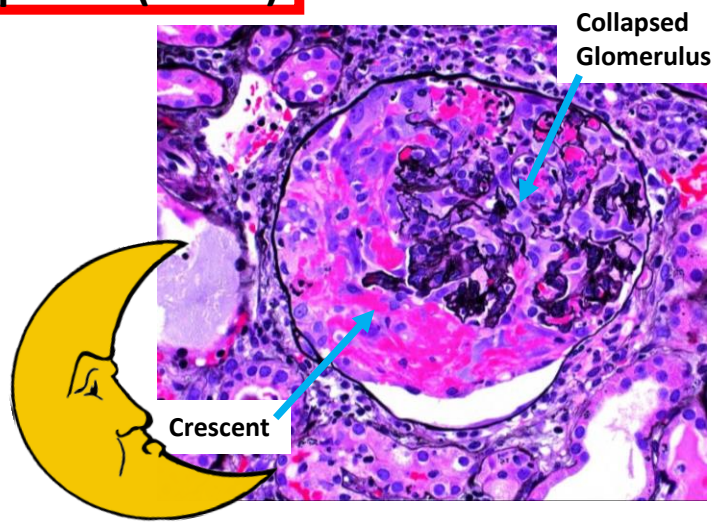
Autoantibody binds and activates C3 convertase → Chronic activation of alternate complement pathway

H&E: Thickened ribbon like capillaries, few double contours of GBM. Diffuse, Hypercellular.
IF: Linear and granular C3.
EM: **Ribbon of *intra-membranous* dense deposit**





Rapidly Progressive Glomerulonephritis (RPGN)

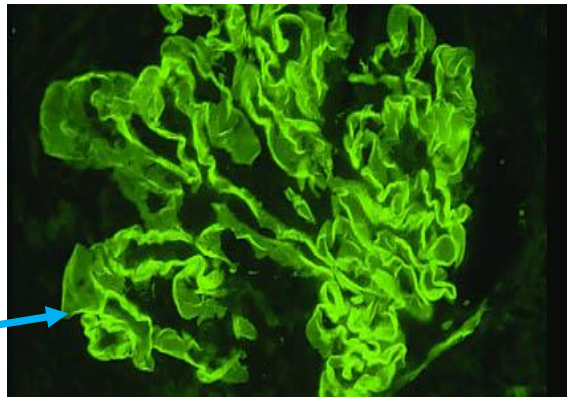


Clinically: Rapid onset (weeks) of acute nephritis (hematuria, HTN) but more **severe oliguria/anuria, elevated creatinine**.

Pathology: Severe damage to glom with necrosis → Leakage of material with parietal epithelial response → "**crescents**" on light microscopy

Must treat immediately—Poor prognosis
Often irreversible.

Anti-GBM Disease



Autoantibody attacks part of collagen IV in GBM → activates complement→ severely damage GBM → leak RBC & protein → Crescent formation → compresses glomerulus

Most severe form of RPGN→ diffuse crescents

Also often **impacts lung: "Good Pasture Syndrome"**
→Alveolar hemorrhage→ hemoptysis

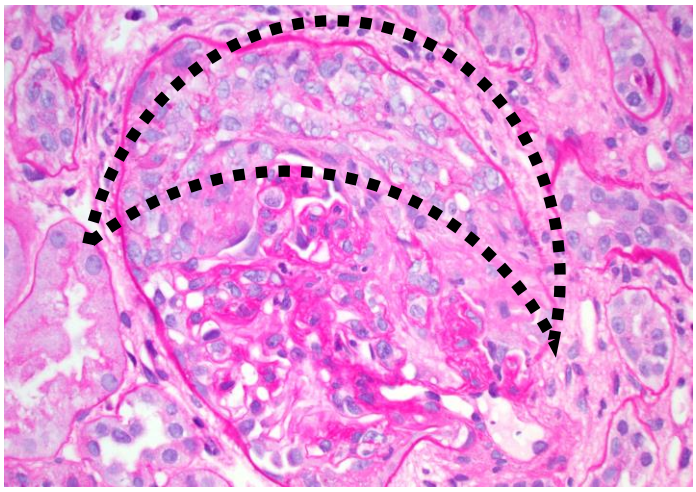
H&E: Crescent formation
IF: Linear staining with IgG & C3

Immune Complex RPGN

Many immune complex diseases (e.g.., Lupus, MPGN, HSP, etc..) can present with breaks in the GBM → crescents

Looks like underlying immune complex disease, but with crescents in gloms.

Pauci-Immune Glomerulonephritis (ANCA)



Vasculitis with involvement of glomeruli
NO or minimal immune complexes

Anti-neutrophil Cytoplasmic Antibodies (ANCA)
2 types of ANCA: MPO-ANCA (formerly p-ANCA) seen with microscopic polyangiitis and Churg-Strauss, and PR3-ANCA (formerly c-ANCA) seen in Wegner's.

ANCAs bind PMNs→ activate PMNs → Severe damage → parietal epithelium reacts and **makes crescents**.

Asymptomatic Hematuria/Proteinuria

Usually picked up on urinalysis

IgA Nephropathy

"Berger's disease"

Most common glomerulonephritis worldwide.
Very common in **Asia**.
Often follows a respiratory or GI illness.

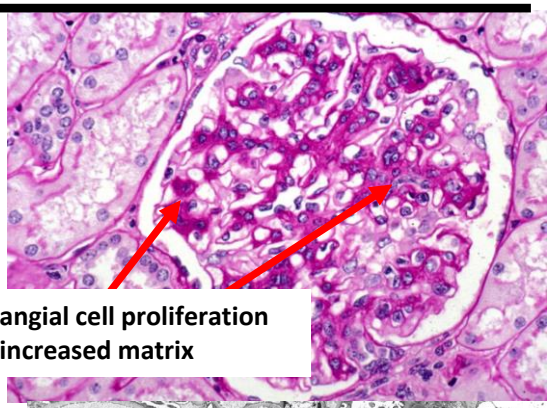
Recurrent **Hematuria** with mild proteinuria.

Genetic or acquired abnormality of immune regulation: elevated serum IgA levels, and abnormal IgA immune complexes accumulate in mesangium.

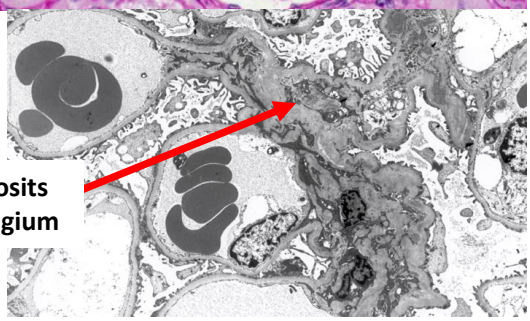
IgA-antigen immune complexes in circulation → planted in the mesangium → **mesangial cell proliferate** and make more mesangium.

H&E: Normal or Mesangial widening
IF: Mesangial IgA deposition
EM: Mesangial deposits

Can see crescents, sclerosis, or endocapillary proliferation too. Essentially, Kidney part of HSP.



Mesangial cell proliferation and increased matrix



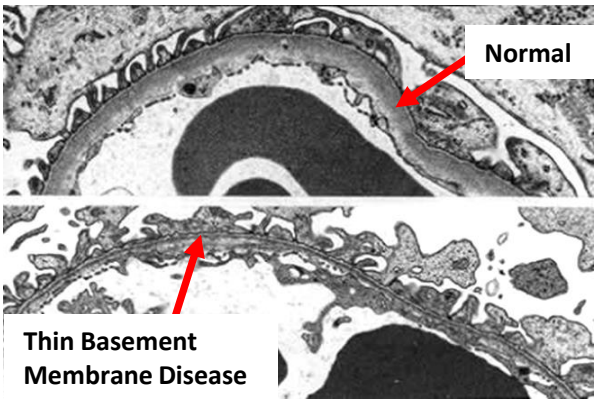
EM: Deposits in mesangium

Thin Basement Membrane Disease

"Benign Familial Hematuria"

Isolated persistent microhematuria that does not progress. Normal renal function.
Usually autosomal dominant.
Mutations in *COL4A3* or *COL4A4* genes

H&E and IF: Normal
EM: **Diffusely thin GBM** (<200nm)



Normal

Thin Basement Membrane Disease

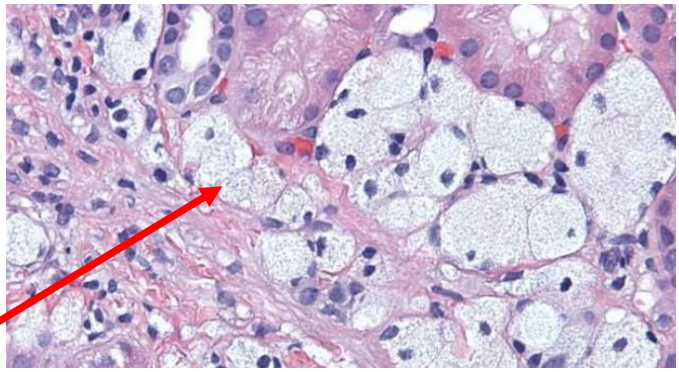
Alport Syndrome

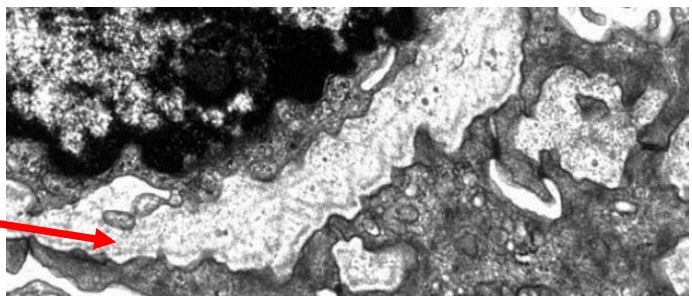
Inherited collagen type IV mutation.
Mostly X-linked dominant (males).

Present with asymptomatic hematuria/proteinuria.

Progressive loss of renal function.
Sensorial deafness.
Ocular abnormalities.

H&E: global & segmental sclerosis;
interstitial foam cells and FSGS pattern.
IF: Absence of staining with specific collagen type IV subunits
EM: Splitting and lamellation of GBMs (basket weave)

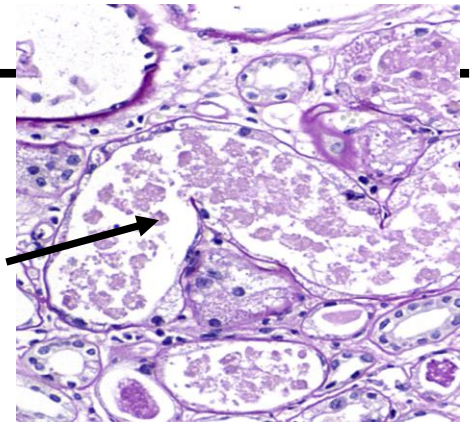




Tubular and Interstitial Diseases

Acute Tubular Injury

"ATI" or "ATN"



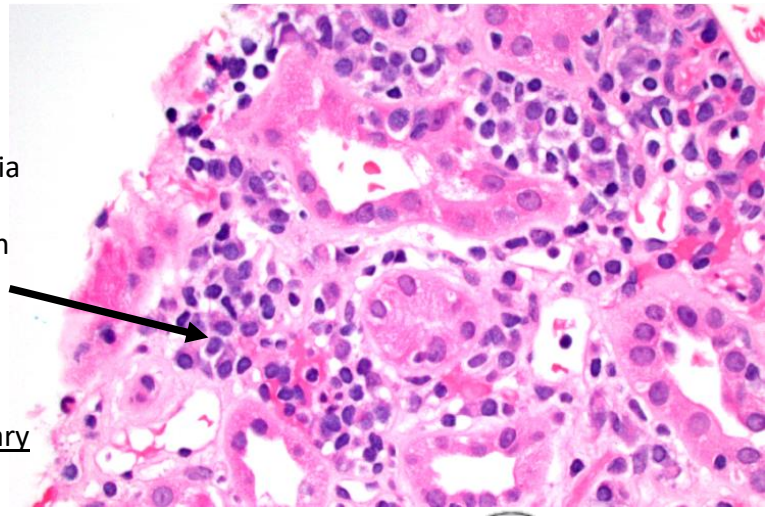
Clinically, "**Acute Kidney Injury**" (AKI) = rapid reduction in renal function (increased creatinine >1.5 x)

Proximal Tubular epithelial necrosis/attenuation → can slough off into urine → granular casts.

Causes: **Ischemia, direct toxic injury**

If remove inciting insult→ **usually recover**

Tubulointerstitial Nephritis



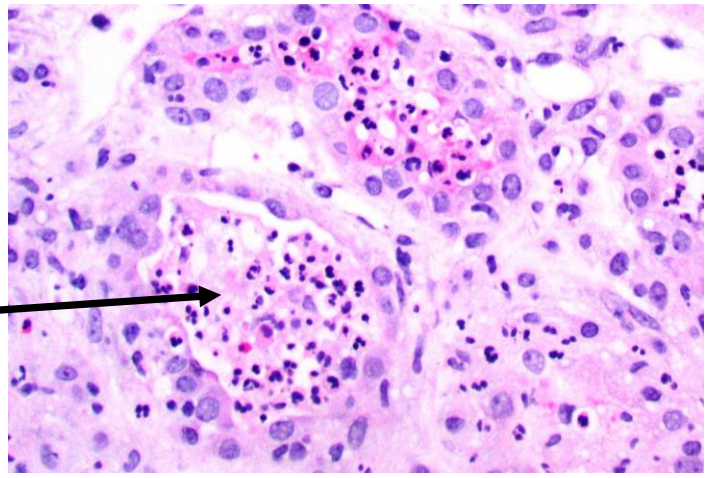
Acute Drug-induced Interstitial Nephritis
Most frequently seen with antibiotics
Start drug→ fever, eosinophilia, hematuria, pyuria
Idiosyncratic reaction (any dose)
Interstitial inflammation with mostly lymphs with classically Eos and macrophages. Tubulitis.

Analgesic Nephropathy
Caused by excessive intake of *analgesic mixtures* → Chronic tubulointerstitial nephritis and papillary necrosis

Reflux Nephropathy/Obstructive Pyelonephritis

Common cause: **Vesicoureteral reflux, calculi**
Grossly: **Blunting of calyx**. Irregular corticomedullary scars. Dilated ureter.
Dilated and atrophied tubules. Thyroidization.
Often superimposed pyelonephritis

Acute Pyelonephritis



Acute suppurative inflammation of kidney.

Usually caused by bacterial infection, either from ascending from bladder (UTI) due to vesicoureteral reflux (most common) or hematogenous spread.
Usually Gram-Neg Bacilli from gut, esp. *E. coli*.

Acute inflammation with intratubular PMNs and tubular necrosis.

Can form an abscess.

Non-Inflammatory Vascular Disorders

Nephrosclerosis

"Benign Nephrosclerosis"

Hyaline arteriolosclerosis

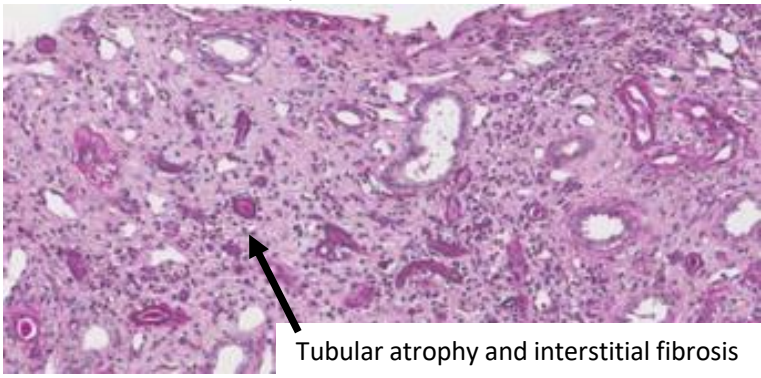
Sclerosis of renal arterioles/arteries
→ Narrows lumen→ ischemia

Two mechanisms:
1) Medial and intimal thickening
2) Hyaline deposition

Causes: Hypertension and Diabetes mellitus

Ultimately causes **Globally sclerotic glomeruli, Tubular atrophy,** and **interstitial fibrosis**

Malignant hypertension→ fibrinoid necrosis of arterioles, onion-skinning



Tubular atrophy and interstitial fibrosis

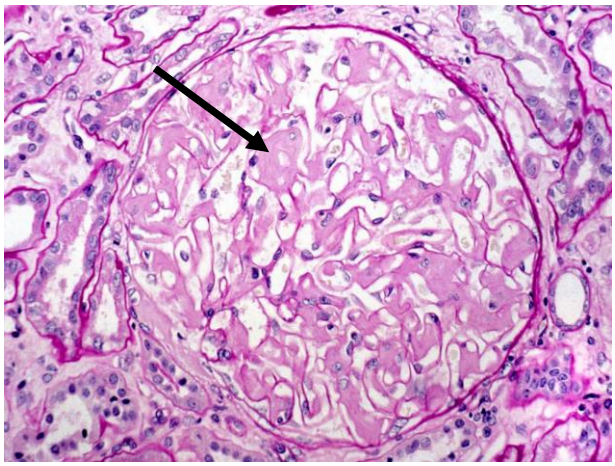
Amyloidosis

Deposits of **abnormally folded protein** (rich in **β-sheets) in vessels and tissues**→ obstructs flow and makes rigid (impaired vasoreactivity)

Extracellular eosinophilic amorphous material (H&E)
Congo Red Stain → "Apple green" birefringence
Trichrome → greyish (vs Fibrosis→ bright blue)

Can subtype to determine etiology using IF, IHC, and/or mass spec

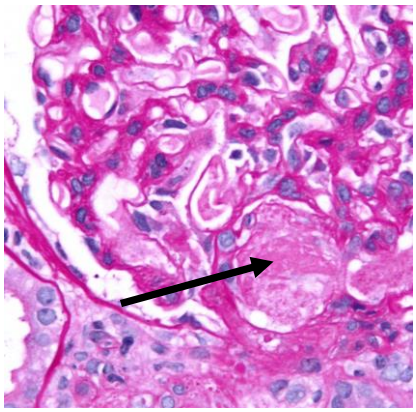
EM: randomly oriented fibrils (8-12 nm)



Thrombotic Microangiopathy (TMA)

Look for "bland" (non-inflamed) <u>thrombi</u> in vessels

Disseminated Intravascular Coagulation (DIC)—Consumptive coagulopathy where systemic activation of the coagulation cascade leads to thrombosis of small vessels throughout the body (and also bleeding). Can occur in many settings (e.g., sepsis, trauma, etc…). See fibrin thrombi in small vessels.



Thrombotic Thrombocytopenic Purpura (TTP)—thrombotic microangiopathy with widespread platelet thrombi in small vessels→ hemolytic anemia, purpura, thrombocytopenia, renal dysfunction. Results from ADAMTS13 deficiency. See platelet-rich occlusive thrombi.

Hemolytic Uremic Syndrome (HUS)—Similar to TTP (thrombotic microangiopathy), but thrombi mostly limited to kidneys. Usually in Kids after eating *E. Coli* O157:H7 (makes Shiga-like toxin toxic to endothelial cells), which also causes bloody diarrhea.

Vasculitis

Inflammation of the blood vessel walls.

Can be ***infectious*** or ***non-infectious***.

Clinical findings are diverse and depend on the organ(s) involved.
Generally have **constitutional symptoms** (fever, myalgias, malaise), +/- localized tissue damage due to **ischemia or bleeding** (leading to single or multiorgan dysfunction). **Elevated CRP and ESR**.

Classified mostly based on this size of the vessel usually involved and the organs involved.

Many systemic rheumatologic diseases (e.g., Rheumatoid arthritis, sarcoidosis, and Systemic Lupus Erythematosus) can have associated vasculitis.

Main immunological mechanisms of Non-infectious vasculitis:

1) Immune Complex-associated Vasculitis—Antigen-antibody/complement complexes deposit in the vessel wall→ recruit inflammatory cells. Seen with many systemic immunological conditions (e.g., SLE), drug hypersensitivity, and viral infections.

2) Antineutrophil Cytoplasmic Antibodies (ANCA) —Antibodies react with neutrophil cytoplasmic antigens (ANCAs)→ activate neutrophils → degranulate → damages vessels.
2 types of ANCA: *MPO-ANCA* (formerly p-ANCA) seen with microscopic polyangiitis and Churg-Strauss, and *PR3-ANCA* (formerly c-ANCA) seen in Wegner's.

3) Anti-endothelial Cell Antibodies — Antibodies to endothelial cells

Variable Vessels
Behçet's disease
Cogan's syndrome

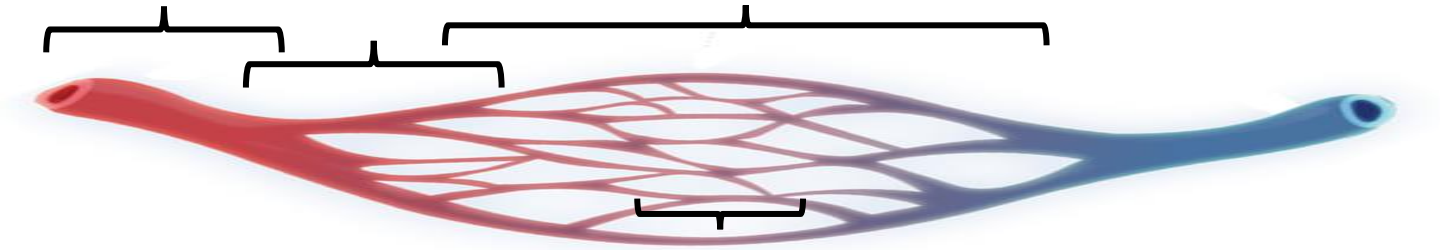
Small Vessels
Immune complex
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulin vasculitis, SLE, Goodpasture disease

ANCA
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegner's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Medium Vessels
Immune complex
Polyarteritis nodosa

Anti-endothelial cell
Kawasaki disease

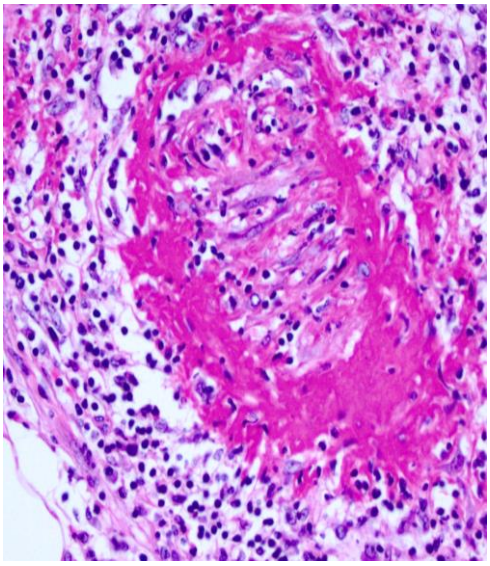
Large Vessels
Granulomatous
Giant-cell arteritis
Takayasu arteritis



Capillaries only
Anti-endothelial cell
Anti-GBM disease

Based on the Chapel Hill Consensus Conference of 2012

Medium Vessel Vasculitis



Involves main visceral arteries and their branches.
Inflammatory aneurysms and stenoses are common.

Polyarteritis Nodosa (PAN)
Transmural necrotizing arteritis of medium or small arteries (without glomerulonephritis or vasculitis of arterioles, capillaries, or venules) with mixed inflammation, fibrinoid necrosis, and thrombosis. Frequently involves renal artery and GI tract.
Often patchy/segmental.
Immune complex mediated.
~30% have chronic Hepatitis B

Small Vessel Vasculitis

Often neutrophil-predominant and **leukocytoclastic**→ fibrinoid necrosis, thrombosis, RBC extravasation.

ANCA-mediated

Microscopic Polyangiitis (MPA)
Necrotizing vasculitis of small/medium vessels. Mixed inflammation with fibrinoid necrosis. Very commonly involves kidney and lung. MPO-ANCA usually positive.

Granulomatosis with Polyangiitis (Wegner's)
Necrotizing granulomatous inflammation. Commonly impacts lung, nasal cavity, and kidney.
In lung/head see granulomas with geographic central necrosis and associated vasculitis→ form ulcers and nodules. In kidney can see crescentic glomerulonephritis. PR3-ANCA positive.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
Eosinophil-rich and necrotizing granulomatous inflammation. Often impacts the lung. Associated with asthma and eosinophilia. MPO-ANCA usually positive.

Immune complex-mediated

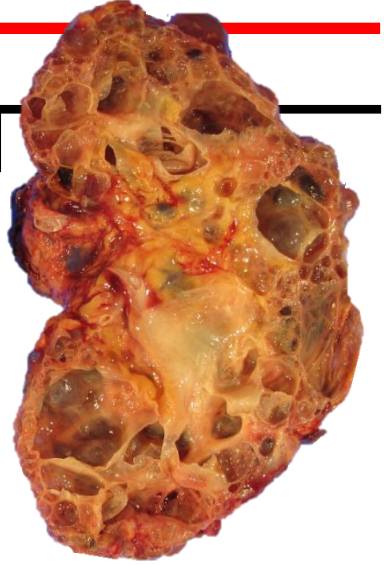
IgA Vasculitis (Henoch-Schönlein purpura)
Vasculitis with IgA1-dominiant immune deposits.
Often involves skin (palpable purpura), GI tract (abdominal pain), kidney, and joints (arthritis).
Most common systemic vasculitis in kids. Usually self-limited and post-infectious (often after URI).

Cryoglobulinemic Vasculitis
Serum cryoglobulins (Ig that precipitate out of solution at < 37°C)→ vessel deposits→ vasculitis. Often involves skin, kidney, and peripheral nerves. Highly associated with Hep C and monoclonal gammopathy.

Anti-Endothelial Cell Antibody-mediated

Anti-Glomerular Basement Membrane (GBM) Disease (Goodpasture Syndrome)
Impacts capillaries in kidney, lung, or both. In lung→ hemorrhage. In kidney→ crescentic glomerulonephritis.

Cystic Kidney Diseases



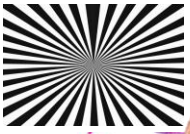
Autosomal Dominant Polycystic Kidney Disease

Most common cystic kidney disease and genetic kidney disease.
Mutations in PKD1 or PKD2. (~1/500-1000 people)
Near total penetrance eventually.

Progressive formation of cysts → massive renal enlargement.
Cysts lined by flattened to cuboidal epithelium.
Frequent asymptomatic liver cysts and berry aneurysms.

Chronic flank pain. Renal failure. HTN. UTI's.

Autosomal Recessive Polycystic Kidney Disease



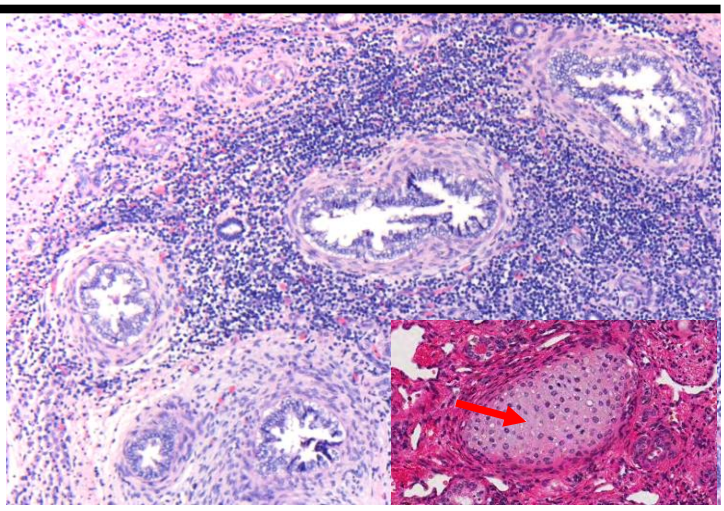
Rare. Autosomal Recessive.
Mutations in PKHD1.

Distinctive radiating pattern of cysts in cortex and medulla lined by cuboidal cells.

Accompanied by bile duct plate malformation → congenital hepatic fibrosis.

Often results in stillbirth or early neonatal death

(Multicystic) Renal Dysplasia



Due to abnormal metanephric differentiation.
(**Maldeveloped**; Despite name, ***not*** a neoplasm!)
Usually sporadic.

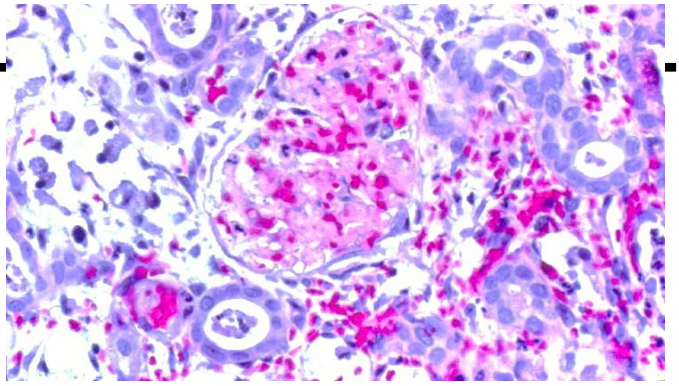
Variable cyst formation.
Abnormal, immature nephrons.
Disorganized parenchyma,
Immature glomeruli and tubules. Smooth muscle collarettes.
Metaplastic cartilage.
Usually associated ureteral abnormality

Acquired (Dialysis-associated) Cystic Disease
Occurs in the setting of long-term dialysis. Cysts lined by tubular epithelium. Frequent calcium oxalate crystals. Usually asymptomatic. Special RCC variant can occur in this setting: Acquired cystic disease-associated renal cell carcinoma

Simple Cysts
Very common. Single or multiple. Lined by a single layer of cuboidal to atrophic epithelium.

Transplant Pathology

Hyperacute Rejection



Immediate (mins to hours). Extremely rare today.
Pre-sensitizied patient with circulating antibodies.

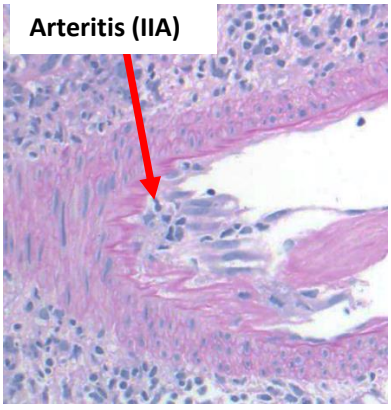
Neutrophil and platelet margination
Endothelial damage
Intravascular coagulation and **<u>necrosis</u>**.

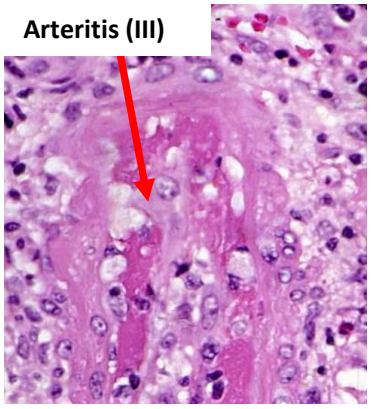
Acute T Cell–Mediated Rejection

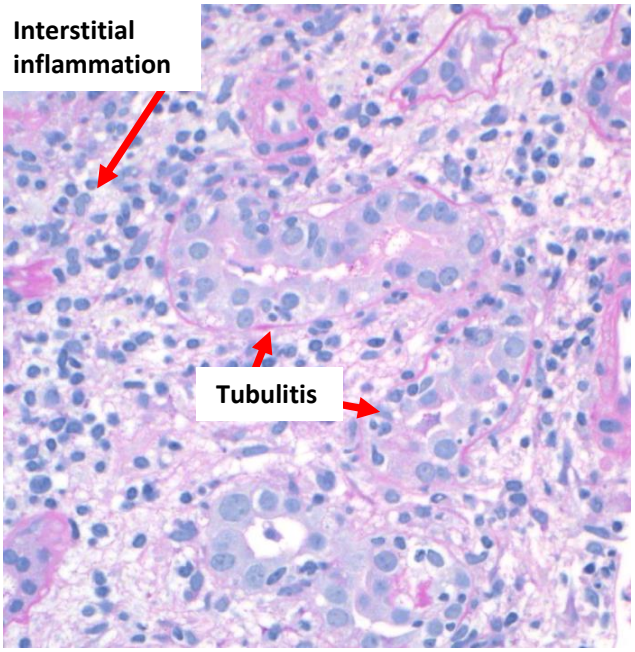
Mediated by T cells
Clinically: Increase in Creatinine & Renal failure

Mild (I): **Interstitial T-cell inflammation, edema,** and **Tubulitis**
Moderate/severe (II-III): **Arteritis and endotheliitis**

Only score non-fibrotic/atrophic areas







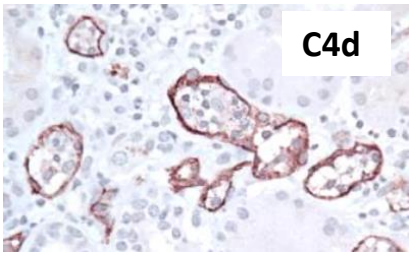
***<u>DDX</u>*: BK Polyoma virus, Obstruction, (Allergic) Interstitial nephritis, PTLD**

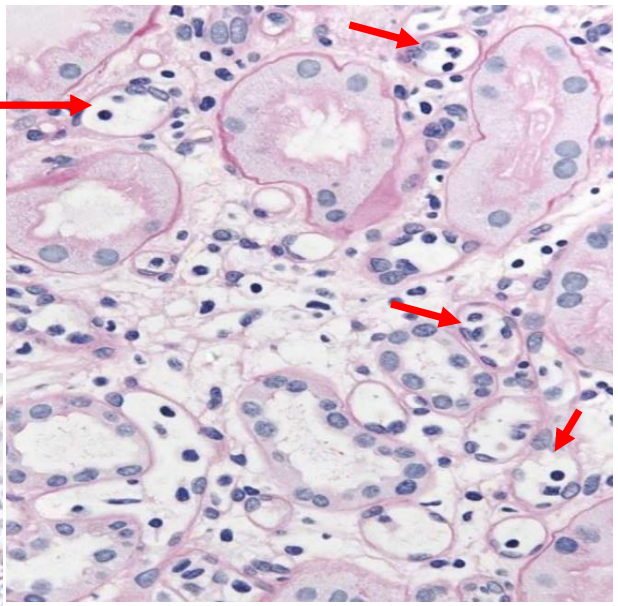
Acute Antibody Mediated Rejection

"Humoral" Antibody-mediated
Antibodies made by recipient attack HLA antigens on endothelium→ microvascular inflammation (glomerulitis and peritubular capillaritis)

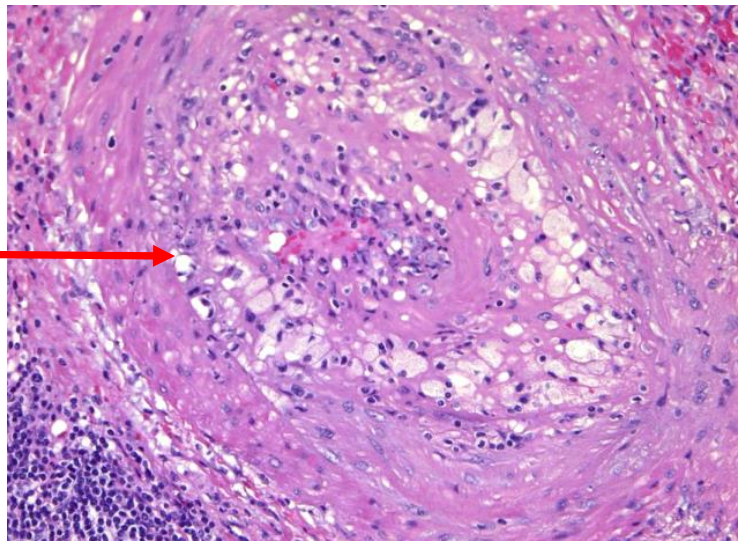
<u>Histopathology (not entirely specific, but suggestive):</u>
Neutrophils and/or mononuclear cells in peritubular capillaries and/or glomeruli (→).
ATN-like and arteritis.

<u>More ***specific*** findings:</u>
IHC or IF: **(+) C4d**
Serum: **(+) DSA**





Chronic Rejection



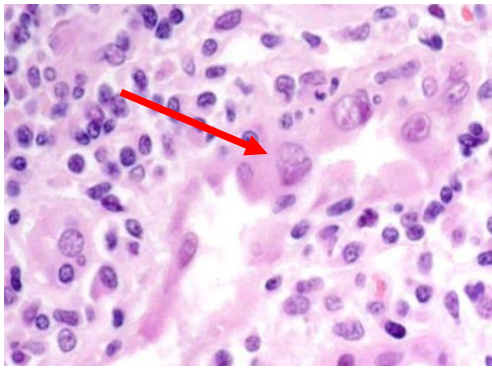
Months to years post-Transplant
Gradual increase in serum Creatinine
Progressive proteinuria

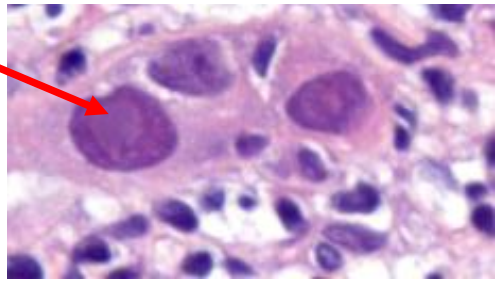
"Transplant Arteriopathy": Concentric proliferation of smooth muscle and foam cells

"Transplant Glomerulopathy": Double contouring of GBMs

<u>Chronic Allograft Nephropathy</u>
→ Damage from many etiologies (Multifactorial: ischemia, HTN, reflux, rejection) → **Tubule atrophy and fibrosis**

Polyomavirus Nephropathy





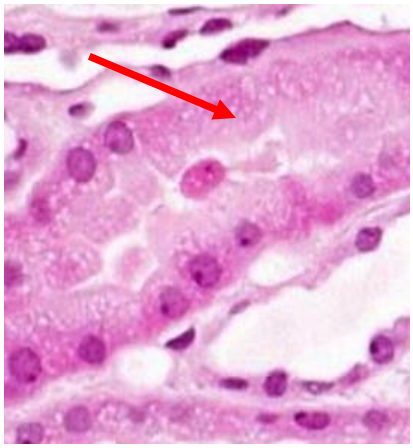
Usually **BK virus**
Virus common in bladder mucosa→ immunosuppression→ infection of renal parenchyma

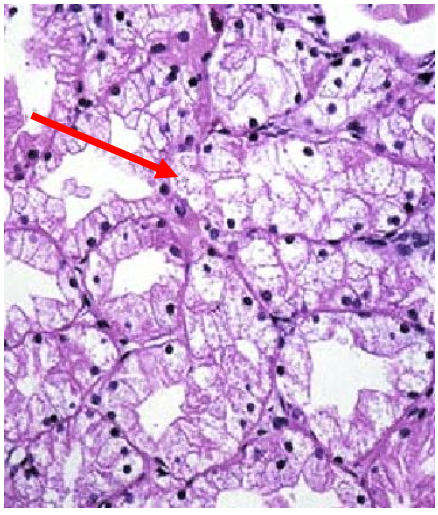
Inclusions in tubular epithelium
Interstitial inflammation → tubular injury/atrophy
Can <u>mimic rejection</u> histologically (but + inclusions and no vasculitis/endotheliitis)

IHC: **(+) SV40**

Treatment→ **antivirals and reduce immunosuppression** (opposite of rejection!)

Calcineurin Inhibitor Toxicity





E.g., Cyclosporine and Tacrolimus (used for immunosuppression)

Present with AKI clinically

Histologically <u>not</u> specific:
<u>Isometric vacuolization of renal tubules</u>
Arteriolar hyaline
Thrombotic microangiopathy