

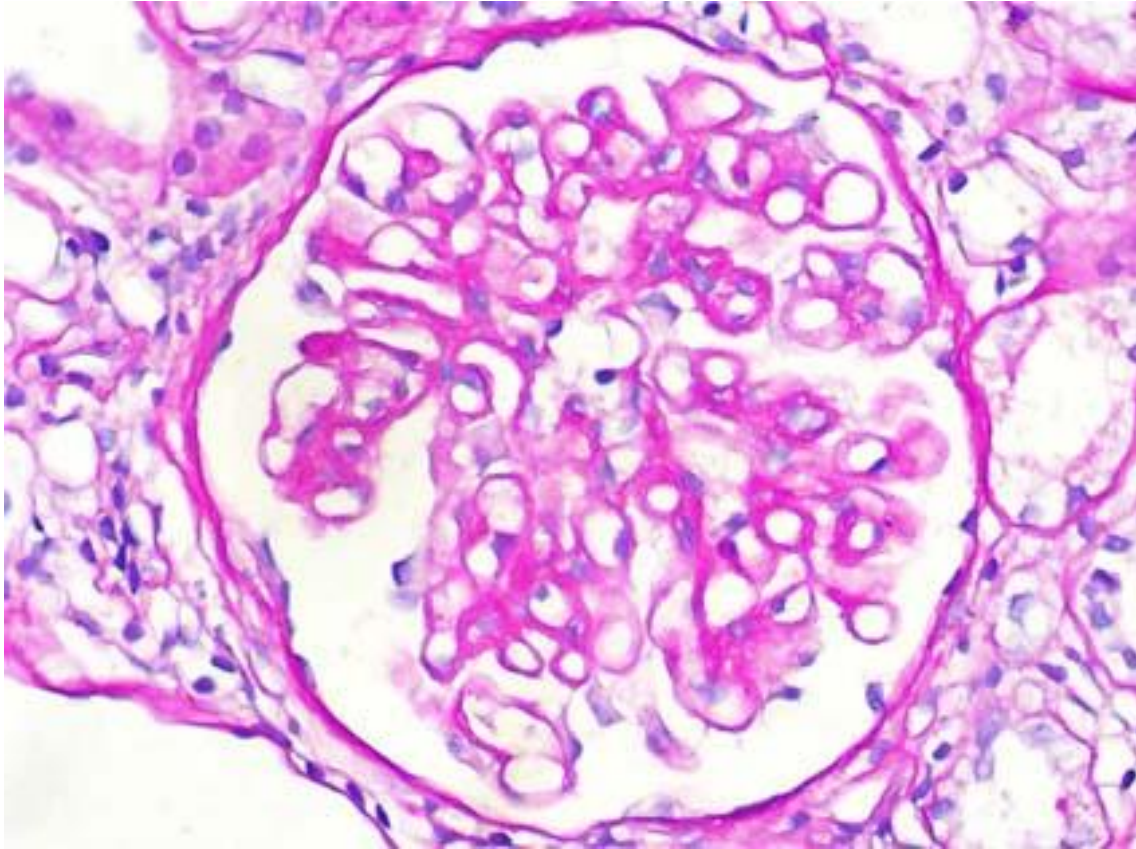
Glomerulonephritis- inflammation in the kidneys

A PATIENT EDUCATION TOOL:

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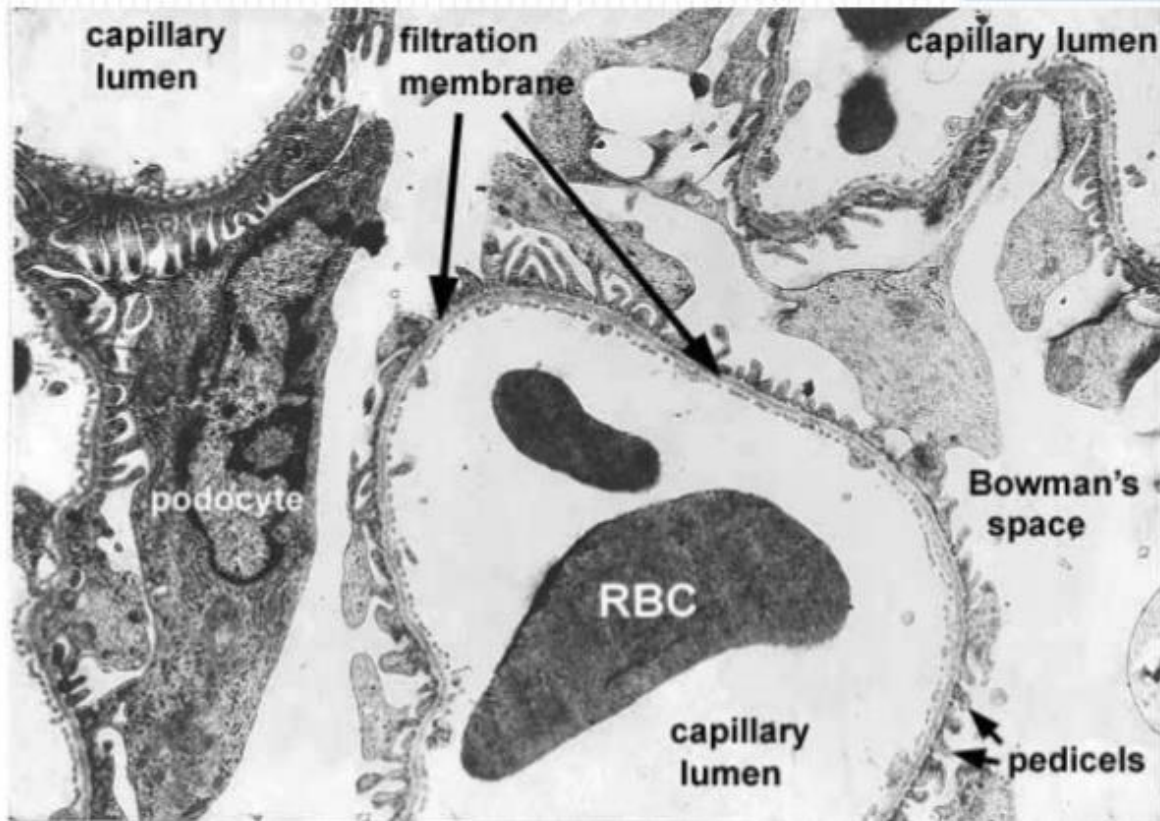
Normal kidney filtering unit- “glomerulus”



This is a healthy glomerulus seen under a light microscope with basic stain for cells. These slides are produced after processing a kidney biopsy and can help diagnose the cause of kidney injury and protein leakage (proteinuria).

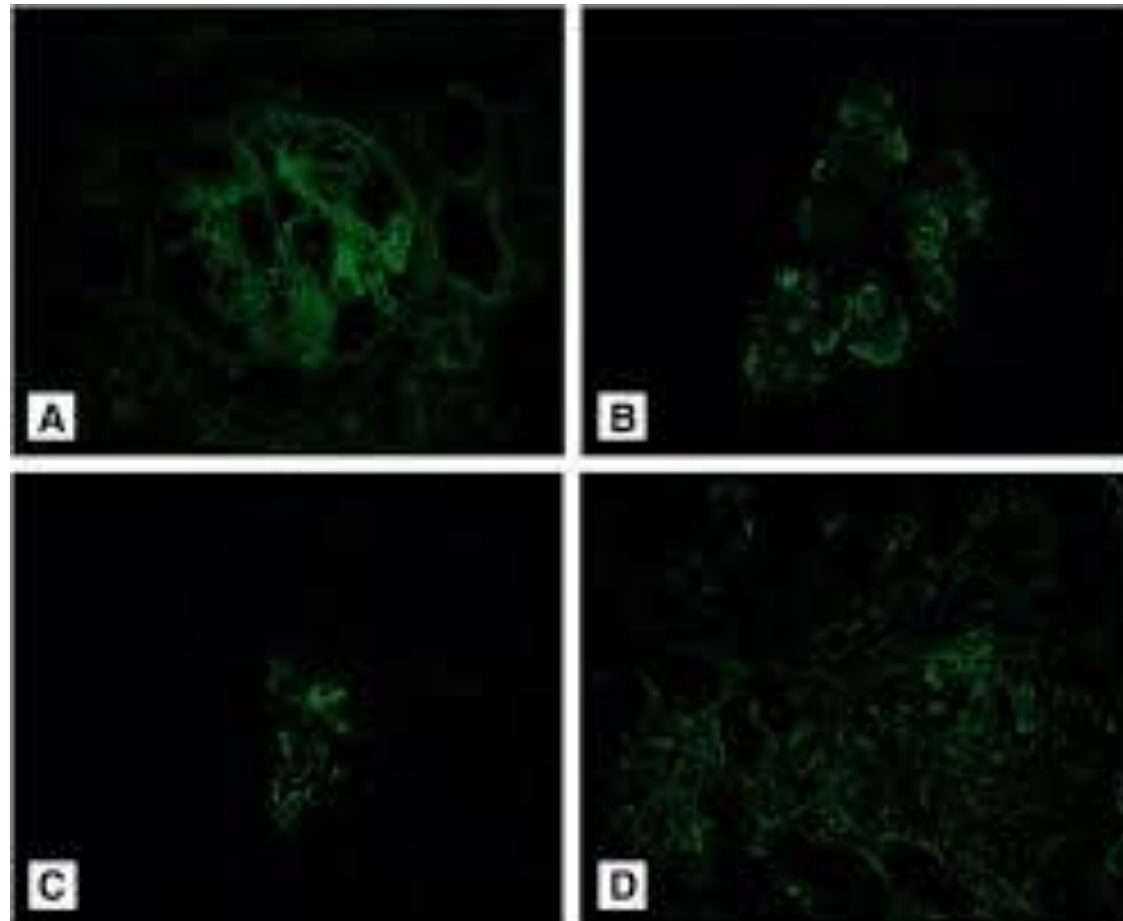
Normal electron microscope picture of kidney filtering unit “glomerulus”

Glomerular Filtration Membrane



This is a picture of a healthy kidney under an electron microscope. Capillary lumen represents the inner space of small blood vessels (capillaries). Filtration membrane is the tissue barrier that separates blood and urine. Bowman's space is the area where urine floats. RBC represents red blood cell in the capillary lumen. Podocyte and pedicels are foot processes that extend from the filtration membrane. Tissues that line inner space of the capillary lumen are called “endothelial” and the tissues that line outer space of the capillary lumen including podocytes and pedicles are called “epithelial”.

Normal immunofluorescence stain of kidney filtering unit “glomerulus”



Types of Glomerular Disease 1/2

- ▶ Proteinuria and blood in urine (hematuria) are the most common manifestations of glomerular diseases.
- ▶ Proteinuria can be classified by the amount of protein that leaks into the urine:
 - ▶ Nephrotic: > 3.5 grams of protein in 24 hour collection of urine-**severe**
 - ▶ Sub nephrotic: 0.5-3.5 grams of protein in 24 hour collection of urine-**moderate**
 - ▶ Mild proteinuria <0.5 g-**low grade**
- ▶ Glomerular diseases are called “nephrotic” if proteinuria is severe and called “nephritic” if proteinuria is moderate to low grade but hematuria is also present.
- ▶ Glomerular diseases can progress slowly or rapidly. When they progress rapidly they are called “ RPGN (rapidly progressive glomerulonephritis)” which can quickly result in need for dialysis.

Types of Glomerular Disease 2/2

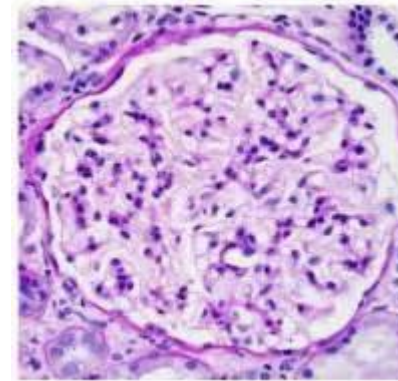
- ▶ Glomerular diseases can also be classified by the parts of the kidney effect.
- ▶ Glomerular diseases can be primary or secondary. Primary diseases originate in the kidney. Secondary diseases are caused because of a problem somewhere else in the kidney. However both primary and secondary glomerular diseases share same histological and clinical characteristics.

1. Nephrotic Disorders

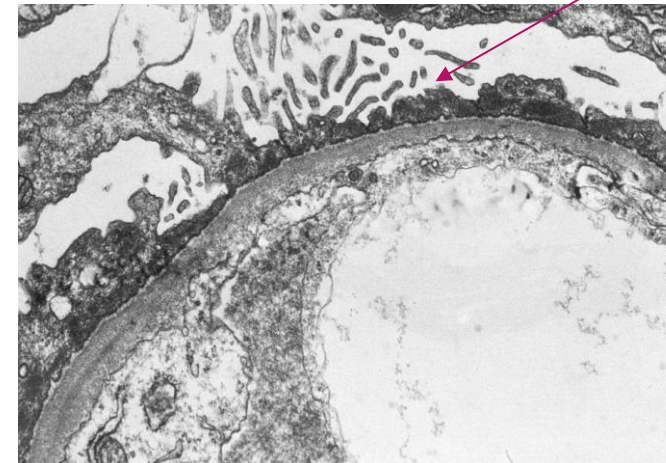
- ▶ Minimal Change disease
- ▶ Focal Segmental Glomerulosclerosis
- ▶ Membranous glomerulonephritis
- ▶ Membranoproliferative glomerulonephritis
 - ▶ Diabetic nephropathy

Minimal Change Disease (MCD)

- ▶ High level of protein in urine
- ▶ Normal light microscopy “**Nil disease**”
- ▶ Usually no blood in urine (no hematuria)
- ▶ Common in children (genetic component)
- ▶ In some cases easily treated with steroids like prednisone
- ▶ Kidney clearance (creatinine) usually normal or almost normal
- ▶ No positive antibody tests (serology) for this found yet

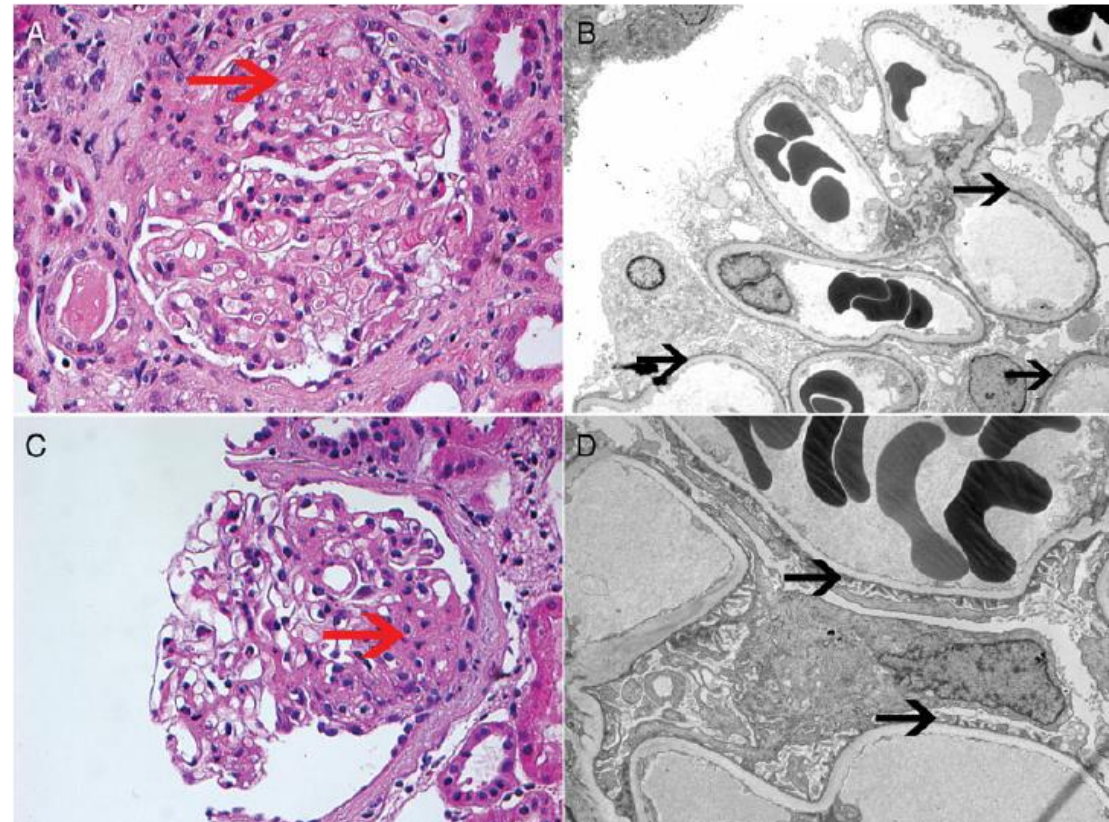


Absent foot processes or podocytes cause massive leakage of protein into urine.



Focal Segmental Glomerulosclerosis (FSGS)

- ▶ High level of protein in urine
- ▶ Can be missed on biopsy if sample obtained from non scarred area
- ▶ Many diagnoses fit this pattern
- ▶ Usually no blood in urine
- ▶ Some foot process degeneration but scarring is the most prominent aspect
- ▶ Many associations: including obesity, HIV, high blood pressure, diabetes and many others
- ▶ Can look like minimal change disease
- ▶ Can be hard to treat



FSGS associated with HIV is called “HIVAN”

HIVAN: Pathology

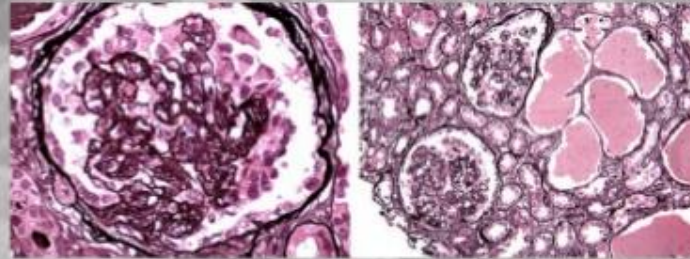


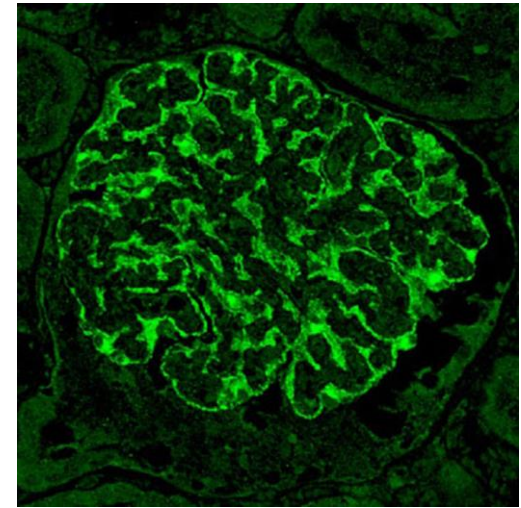
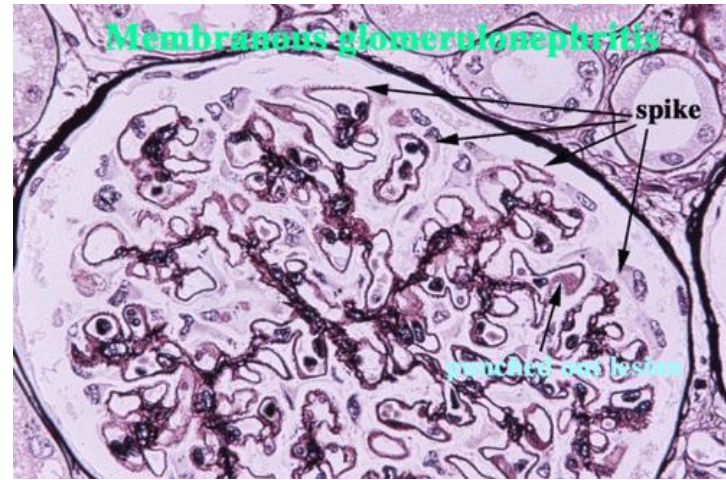
Figure 1. The pathology of HIVAN from human kidney biopsy samples. Typical pathologic changes of HIVAN include global glomerular collapse with overlying epithelial cell crowding and hypertrophy (left panel) as well as tubular microcystic disease (right panel) (images courtesy of Dr Vivette D'Agati).

Membranous Glomerulonephritis (MGN)

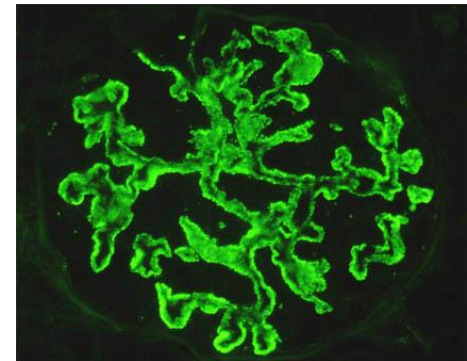
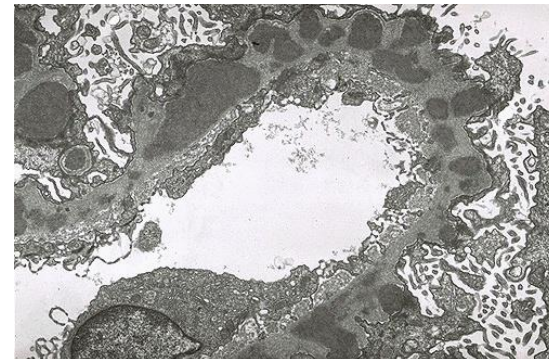
- ▶ High level of protein in urine
- ▶ Filtration membrane (basement membrane) becomes thickened-

That's why its called “membranous”

- ▶ Usually no blood in urine
- ▶ A blood test called anti phospholipase A2 can help diagnose primary types, can stain for it on biopsy too
- ▶ Secondary form can be associated with cancer, autoimmune disease, certain drugs, and chronic infections
 - ▶ Most common glomerulonephritis in elderly

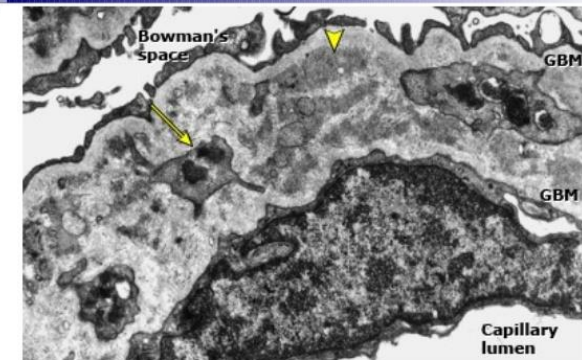
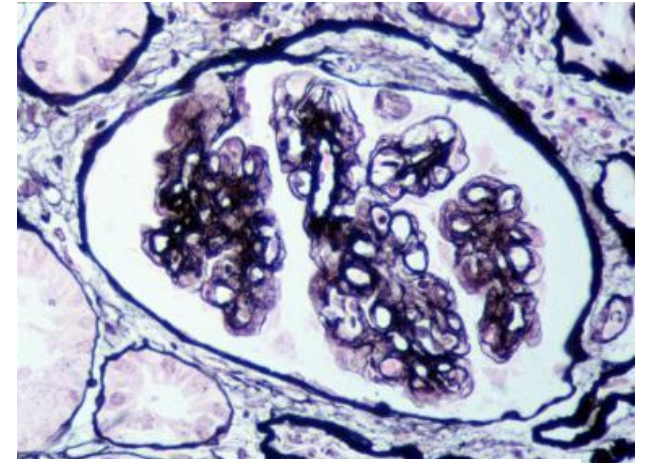


AntiPLA2R



Membrano-proliferative Glomerulonephritis (MPGN)

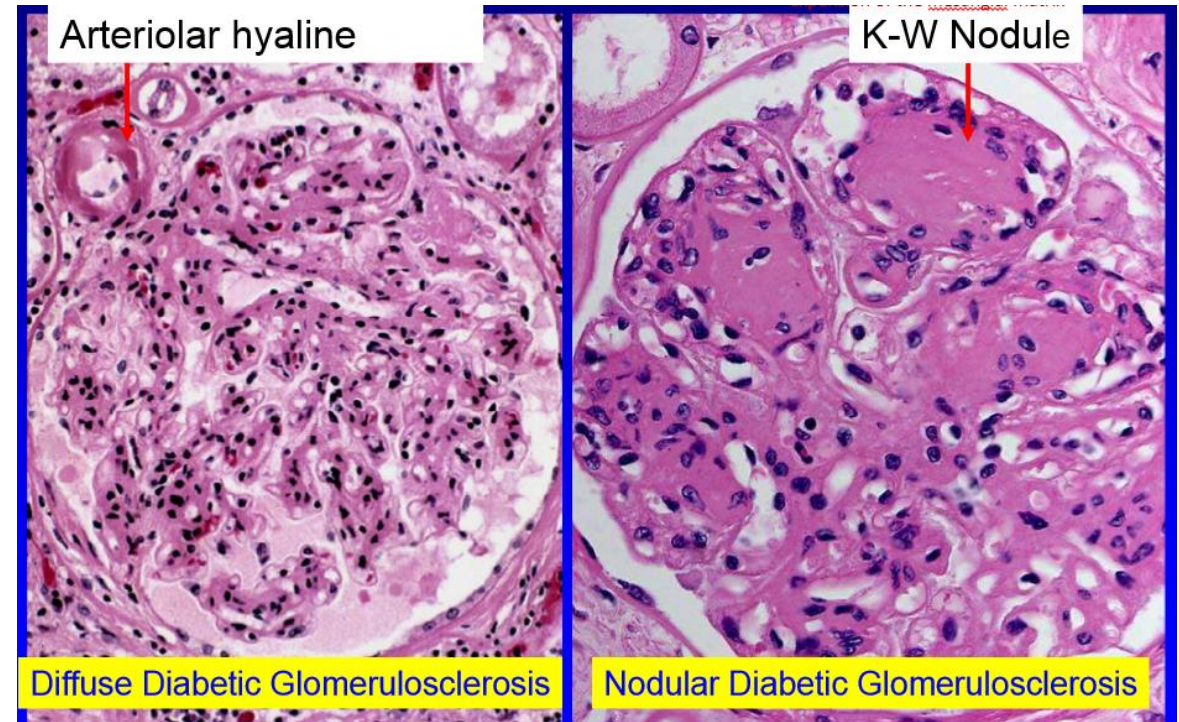
- ▶ Severely elevated levels of protein in urine
- ▶ Many diagnoses fit this pattern
- ▶ Duplication of basement membrane-called “double contouring” or “tram track” basement membrane (*under electron microscope see duplication of basement membrane*)
- ▶ Associations:
 - ▶ Associated with Hepatitis C
 - ▶ Chronic infections, autoimmune disease
 - ▶ Antibodies that clump in cold: Cryoglobulins
 - ▶ Multiple myeloma



Electron micrograph in type I membranoproliferative glomerulonephritis shows marked thickening of the glomerular capillary wall by immune deposits (arrowhead) and by interposition of mesangial cell processes (arrow). There are two layers of the glomerular basement membrane (GBM) surrounding the mesangial interposition that account for the double-contour appearance on light microscopy.

Diabetic Nephropathy

- ▶ Severe proteinuria
- ▶ 80% of protein leakage in diabetics is caused by this especially in patients who have been diabetic for 10-15 years
- ▶ Large sized kidneys
- ▶ People who have this tend to also have diabetic disease in eyes and nerves (retinopathy, neuropathy)



2. Rapidly Progressing Glomerulonephritis (RPGN)

- ▶ Anti-neutrophil cytoplasmic antibody (ANCA) associated
- ▶ Good Pasture's Disease
- ▶ Crescentic IgA nephropathy (Henoch Schonlein Purpura)
- ▶ Lupus nephritis

ANCA Associated Vasculitis Types

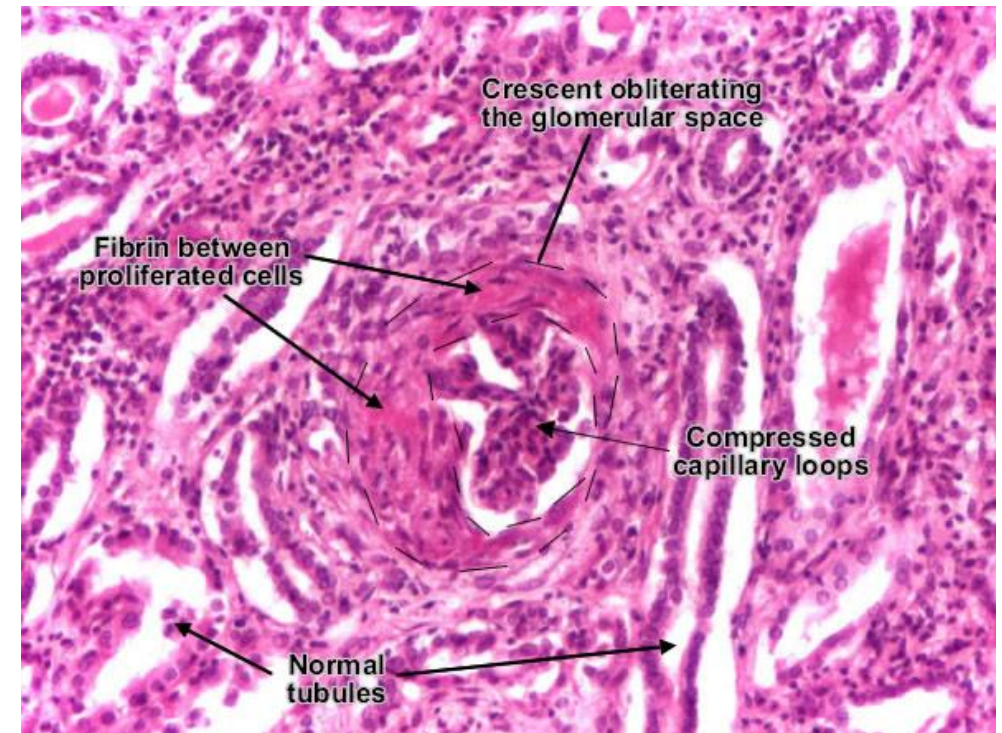
- ▶ Moderate protein in urine but lots of blood (nephritic)

Crescents are seen: they are a pattern of inflammation and reflect severe damage to kidney filtering units

- ▶ Group of diseases that cause antibody mediated damage and inflammation at small vessels of the kidney: granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EPGA, Churg Strauss)
- ▶ Antibodies that cause the damage are called C-ANCA (anti-PR3) or P-ANCA (anti-mpo) Old names for ANCA associated vasculitis:

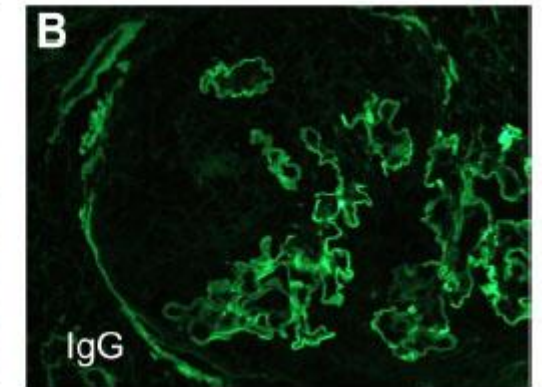
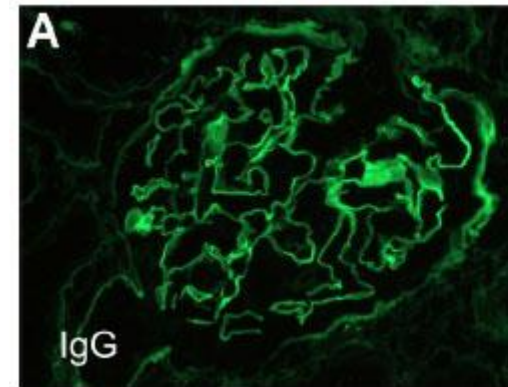
Pauci-immune pattern : nothing shows up when looked for antibodies under immunofluorescence.

- ▶ Associations:
 - ▶ Cancer
 - ▶ Hepatitis B most often and rarely hepatitis C
 - ▶ Aggressive course can be seen especially in C-ANCA can result in rapid need for dialysis



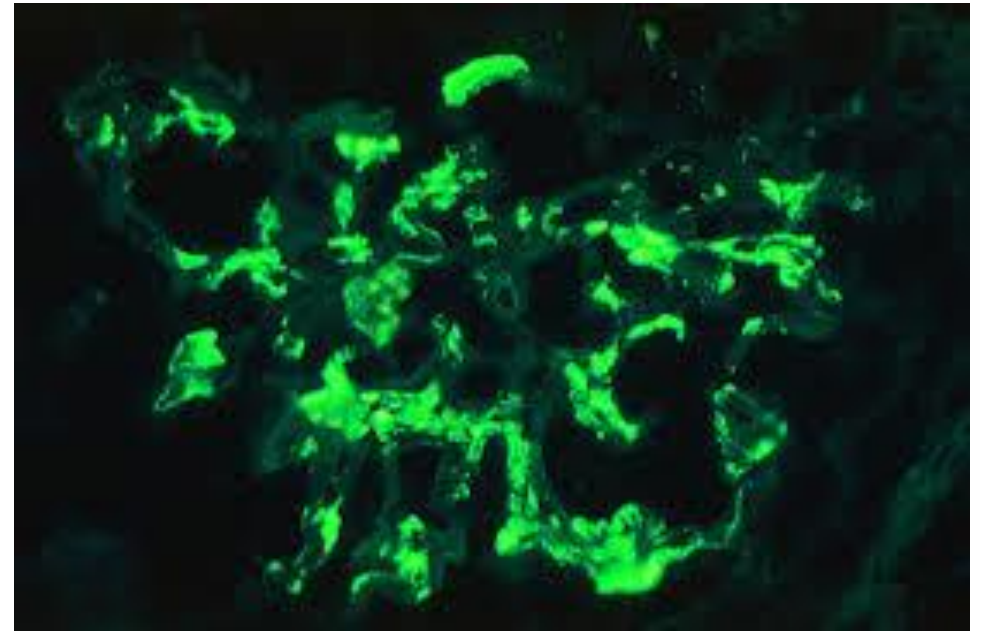
Good pasture's disease

- ▶ Usually causes moderate to severe levels of protein and usually causes large amounts of blood in urine
- ▶ Crescents can be seen due to severe kidney damage
- ▶ Immunofluorescence shows linear staining of IgG antibodies that target the glomerular basement membrane
- ▶ Associations:
 - ▶ After transplanting patients with-Alports syndrome who lack type IV collagen-this disease can occur
 - ▶ Can have aggressive course and result in need for dialysis rapidly



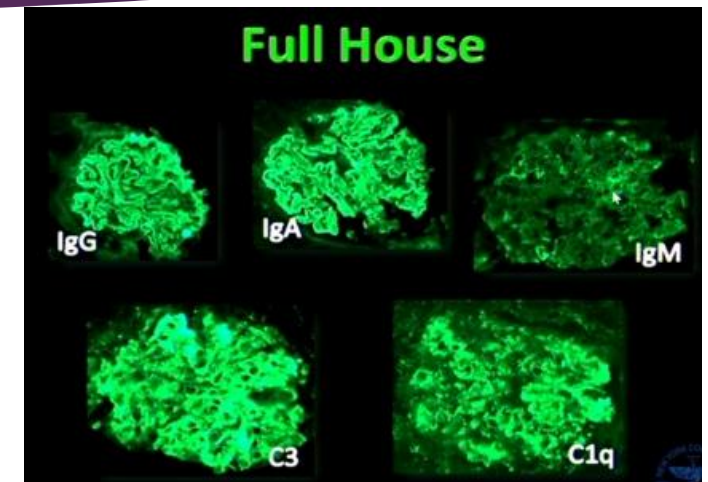
Crescentic IgA Nephropathy

- ▶ Most aggressive subtype of IgA (rare compared to more common IgA nephropathy-see other slide)
- ▶ Light microscope shows crescents
- ▶ Can see IgA antibodies under immune fluorescence to look for antibodies
- ▶ Associations:
 - ▶ HIV Can be associated with certain aggressive IgA nephropathies
 - ▶ Henoch shonlein purpura a skin and blood autoimmune disease is associated with crescentic IgA nephropathy
 - ▶ Rapid course can result in dialysis need rapidly

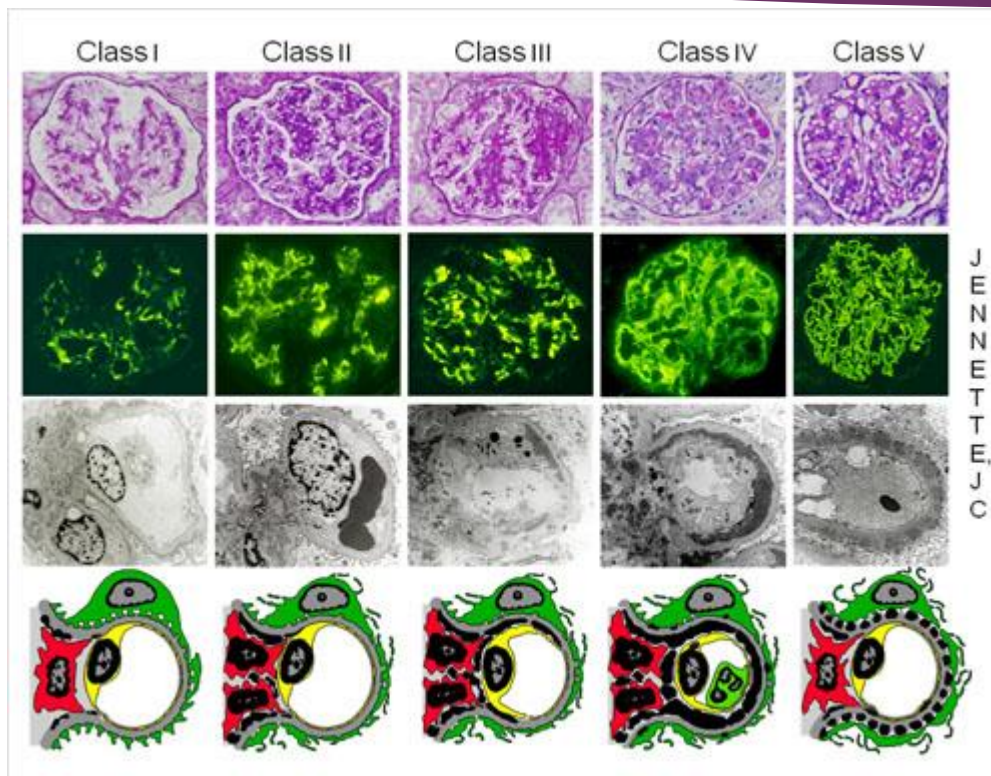


Lupus Nephritis

- ▶ Common in young women
- ▶ Biopsy findings and presentation differs based on lupus type
- ▶ Some protein leaking dominant (nephrotic) – Type V
- ▶ some with lots of blood and inflammation (nephritic) Types III and IV
- ▶ See full range of antibodies under immunofluorescence, called full house, denotes severe antibody directed damage against kidney (called a full house immunofluorescence)
- ▶ See next slide for the types of lupus induced nephritis or kidney inflammation



LUPUS NEPHRITIS CLASSIFICATION



I. Minimal change- mild, good prognosis*
II. Mesangial- interstitium- variable prognosis
III. Focal Proliferative- spotty glomeruli
IV. Diffuse Proliferative – aggressive
V. Membranous – (basement membrane) heavy proteinuria (nephrotic)
VI. Advanced Sclerosis- end stage

WHO= World Health Organization

ISN= International Society of Nephrology

RPS= Renal Pathology Society

*Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; 65: 521

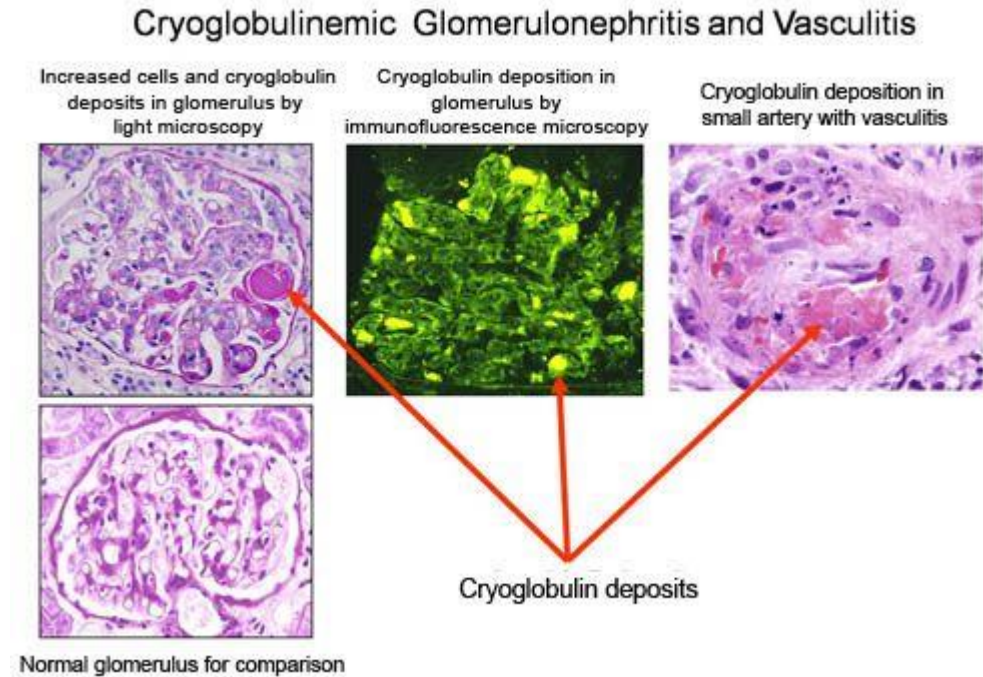
*Note type 1 means minimal disease not same meaning as previously presented minimal change disease

3. Other systemic disease that presents with “tram tracking” pattern

- ▶ Cryoglobulinemic vasculitis
- ▶ Myeloma kidney (see MM disease later)
- ▶ Thrombotic-micro-angiopathy
- ▶ C3 glomerulonephritis

Cryoglobulins causing vasculitis

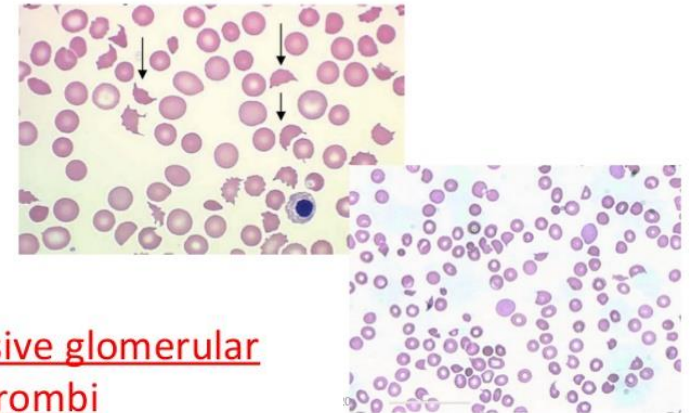
- ▶ Mid range levels to severe levels of protein in urine, often with blood in urine
- ▶ Tram tracking pattern seen
 - ▶ Under immunofluorescence can see cryoglobulin antibody of IgM type
- ▶ Associations:
 - ▶ Hepatitis C
 - ▶ Cryoglobulin (IgM)



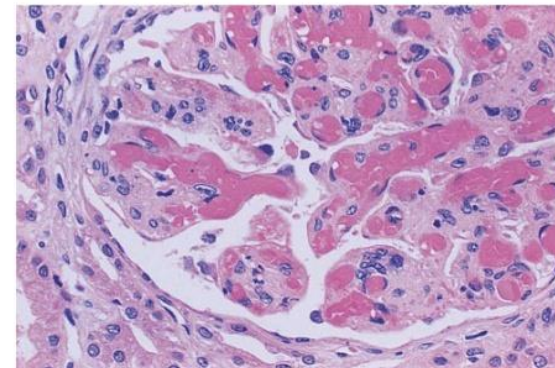
Thrombotic microangiopathy

- ▶ A disorder of complement leading to clots in small vessels of kidney
- ▶ Tram tracking seen
- ▶ Low grade to mid range protein in urine, bleeding in urine can be seen as well
- ▶ Systemic anemia resulting from blood cells being destroyed- hemolysis-can be seen
- ▶ New specific drugs available to treat some forms of this. (Eculizumab)
 - ▶ Associations:
 - ▶ HIV
 - ▶ Transplant medications
 - ▶ Organ Rejection
 - ▶ Chemotherapy drugs
 - ▶ Vascular endothelial growth factor blocking drugs
 - ▶ In rare cases aspirin or plavix
 - ▶ Shigella infection
 - ▶ Genetic mutations

Peripheral smear in TMA

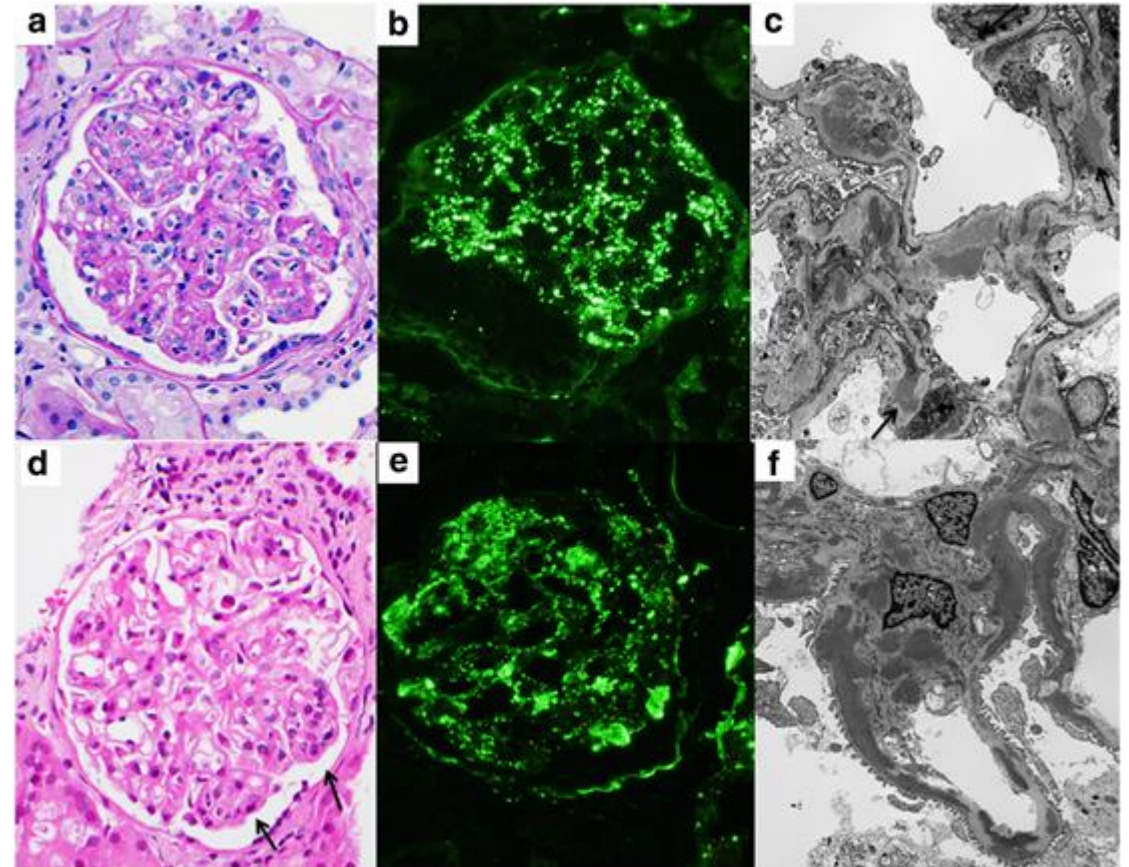


Renal Biopsy- Extensive glomerular capillary thrombi



C3 Glomerulonephritis, Dense deposit disease

- ▶ Tram tracking on light microscopy
- ▶ Deposition of complement protein C3
- ▶ Can be genetic or acquired see next
- ▶ Variable protein leakage and bleeding can be seen (nephritic)
 - ▶ No definitive treatment yet but experimental trials ongoing.
 - ▶ Associations:
 - ▶ Genetic
 - ▶ C3 nephritic factor can be an autoimmune cause of this syndrome.

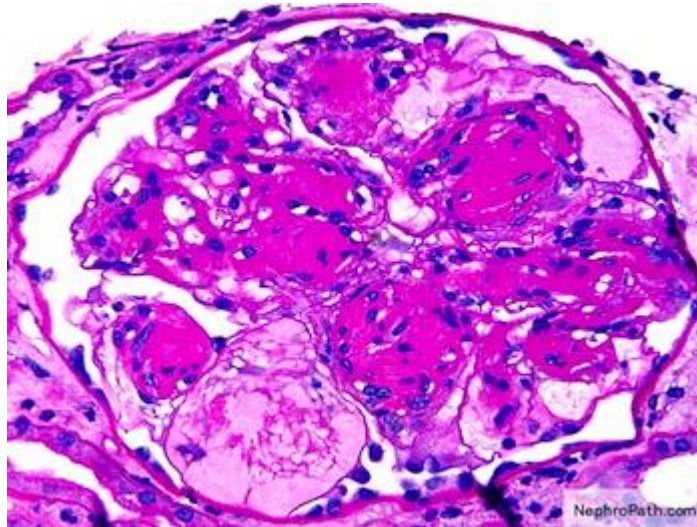


4. Multiple myeloma like diseases causing inflammation in kidney

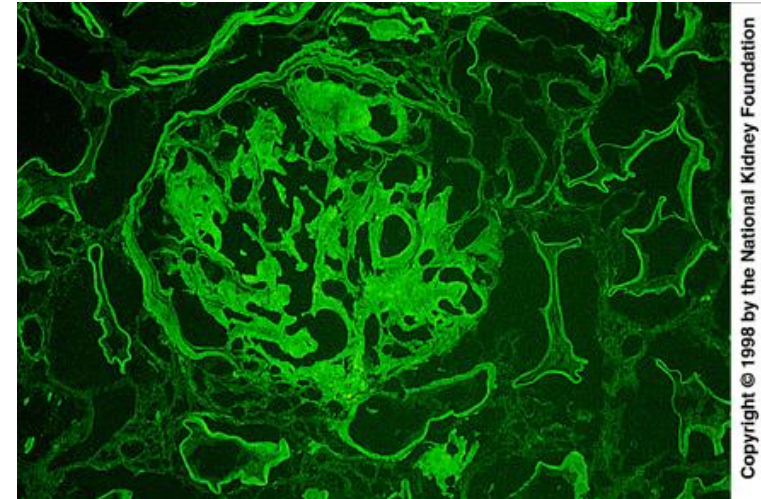
- ▶ Multiple myeloma is a type of bone marrow cancer that can result in abnormal antibody protein production that can produce some deposition in organs-especially kidney with different patterns of disease
- ▶ Light chain disease LCDD
- ▶ Myeloma cast nephropathy
- ▶ Heavy chain deposition disease HCDD
- ▶ Amyloidosis

Light Chain deposition disease

- ▶ Tram tracking pattern
- ▶ Evidence of multiple myeloma
- ▶ Protein leakage usually more than inflammation or blood in urine-but variable amounts of protein in urine and variable presentation
- ▶ Albumin in urine more than antibody protein in urine
- ▶ Not amyloid like pattern (negative congo red stain)

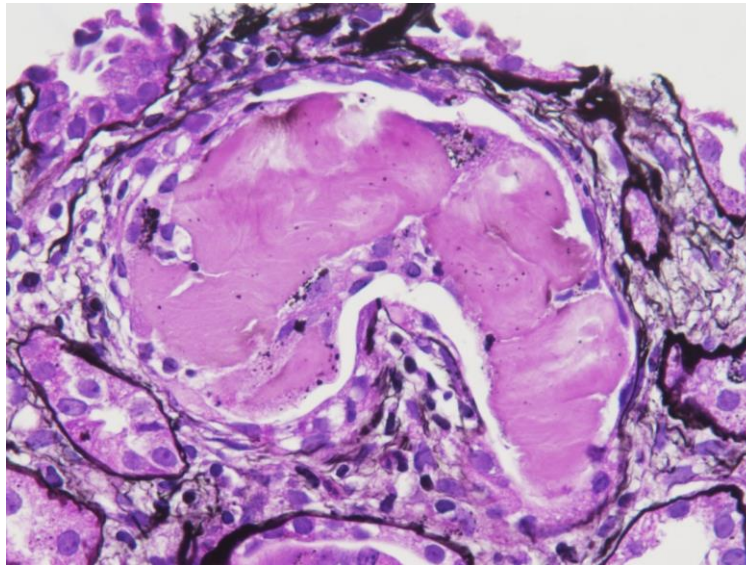


K or L
Light chain

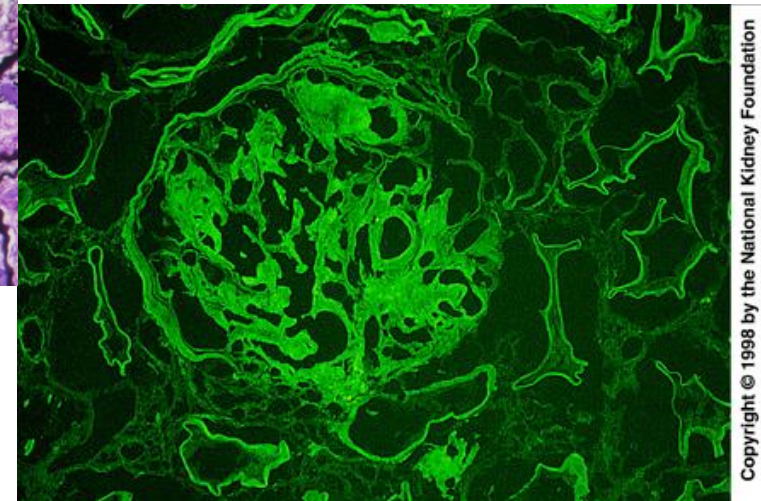


Cast Nephropathy

- ▶ Tram tracking pattern
- ▶ Multiple myeloma diagnosis
- ▶ Negative congo red stain
- ▶ Antibody protein in urine > albumin protein in urine
- ▶ Caused by abnormal myeloma antibody protein in tubules functionally blocking urine flow rather than myeloma protein infiltrating and destroying kidney tissue



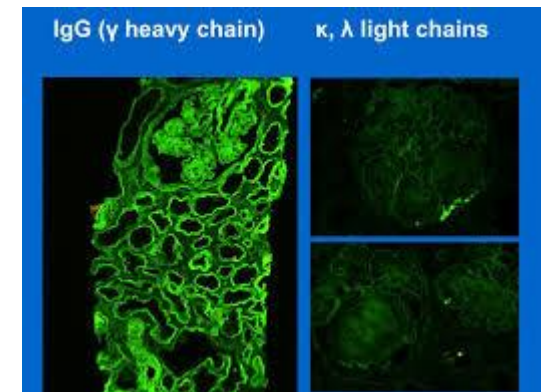
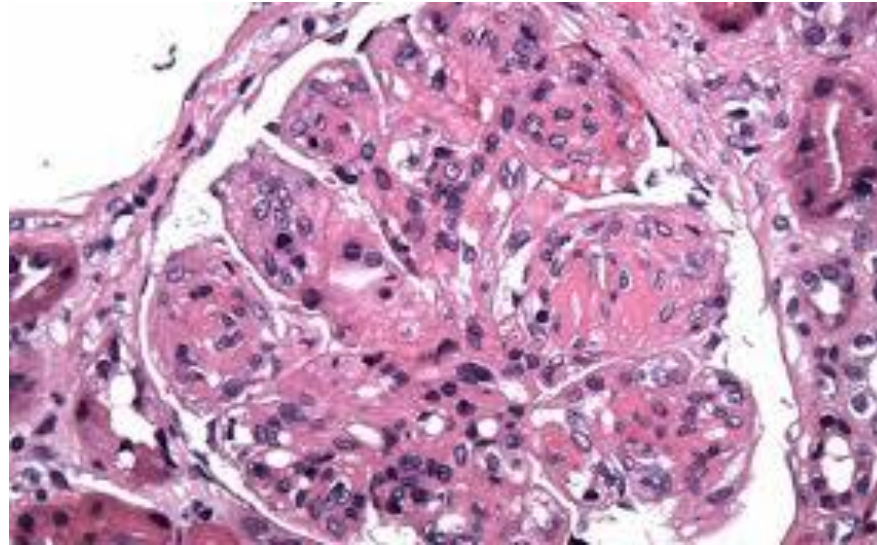
Note cast in tubule not glomerulus



K or L
Light chain type

Heavy chain deposition disease

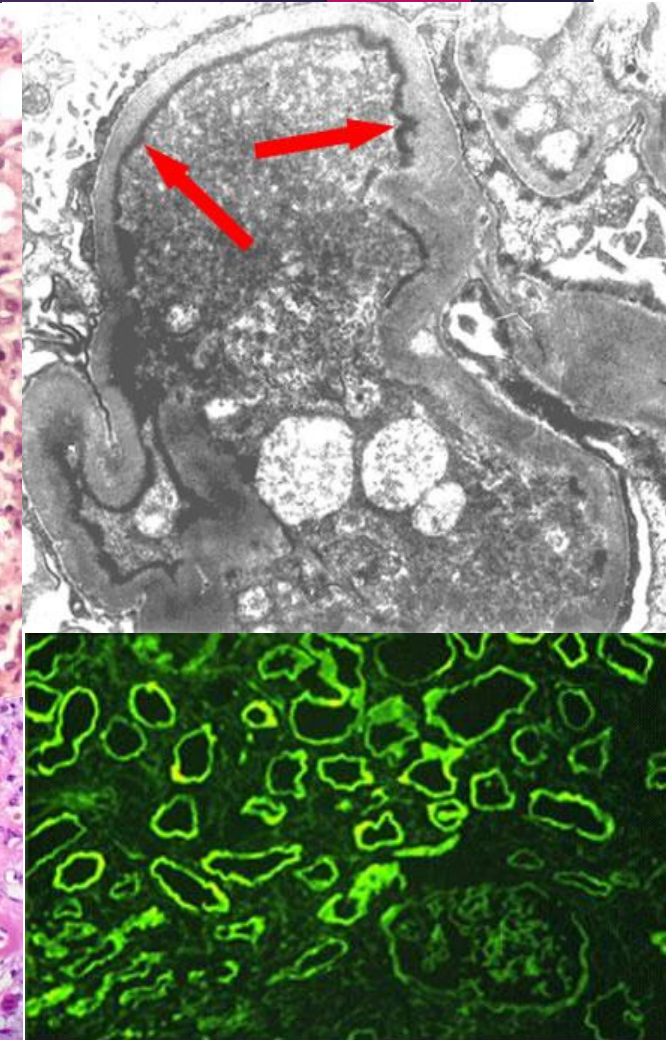
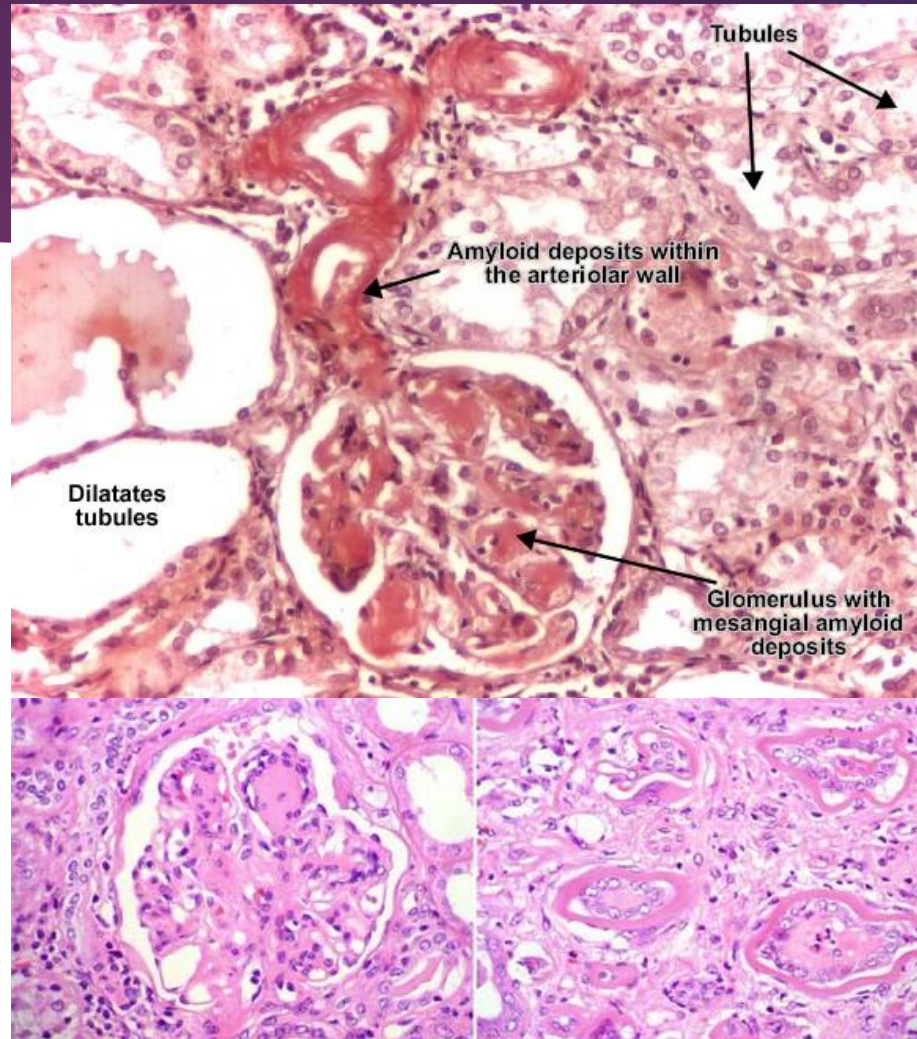
- ▶ Tram tracking pattern
- ▶ Myeloma diagnosis
- ▶ Albumin levels in urine more than antibody protein levels in urine
- ▶ Same idea as light chain deposition disease but caused by the heavy chains of antibodies



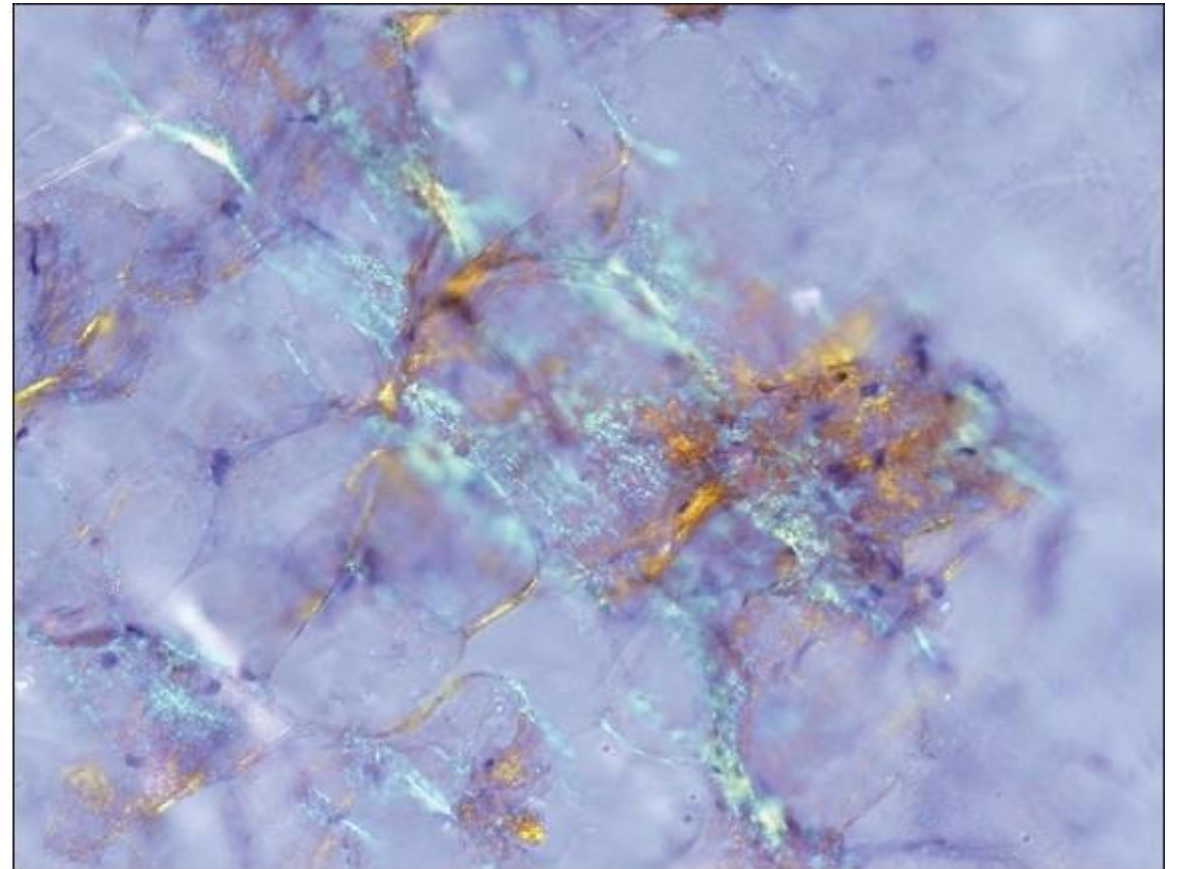
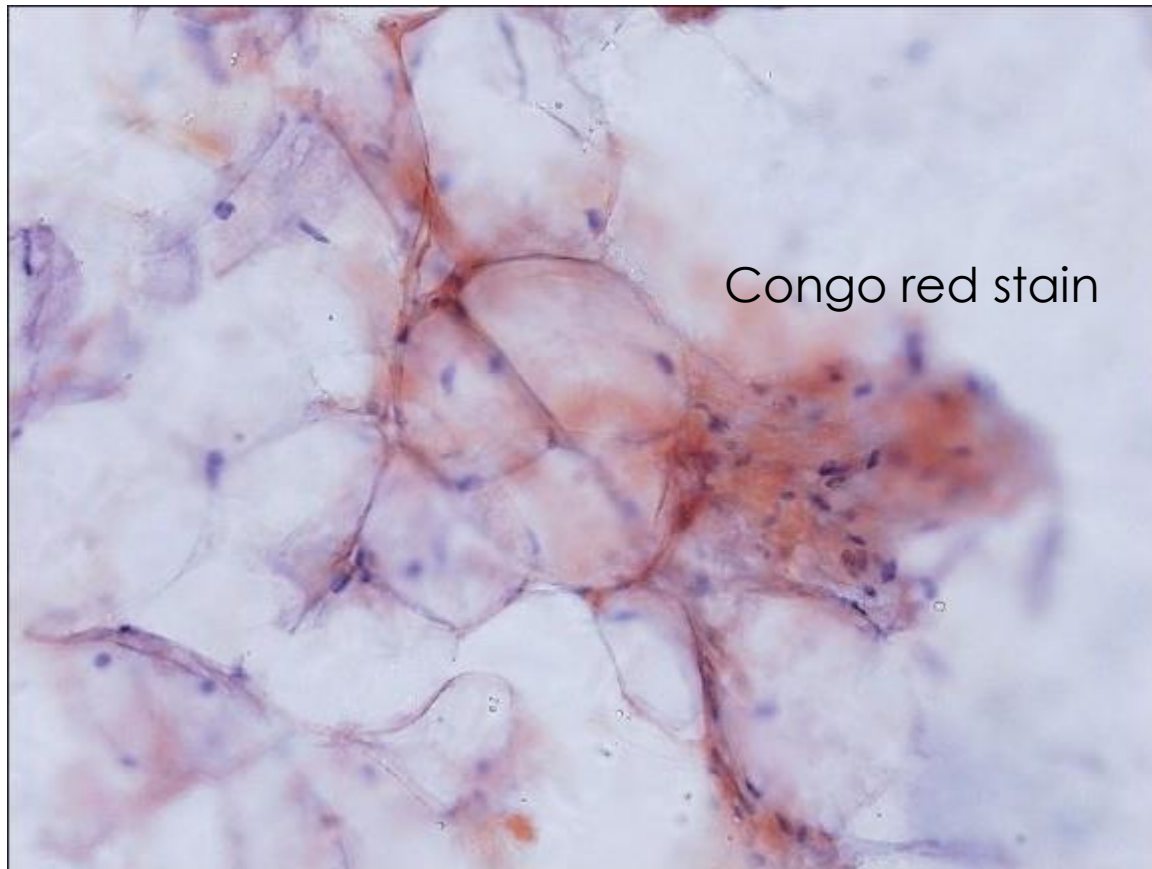
Heavy chain

Amyloidosis

- ▶ Tram tracking pattern
- ▶ Heavy protein in urine (more than blood and inflammation)
- ▶ Albumin protein level in urine more than antibody protein level in urine
- ▶ Congo red staining positive for amyloid protein
 - ▶ Genetically mutated transthyretin protein can cause damage in heart and liver damage from a form of amyloidosis (T) amyloidosis doesn't usually affect kidneys directly
 - ▶ Multiple myeloma can be cause for amyloid protein (light chain forms into amyloid like sheet instead of causing light chain deposition disease) (AL) amyloidosis
 - ▶ Rheumatoid arthritis can be cause for amyloidosis (AA) amyloidosis
 - ▶ Usually causes big sized kidneys



Can see amyloidosis in fat cells –so
called fat pad biopsy

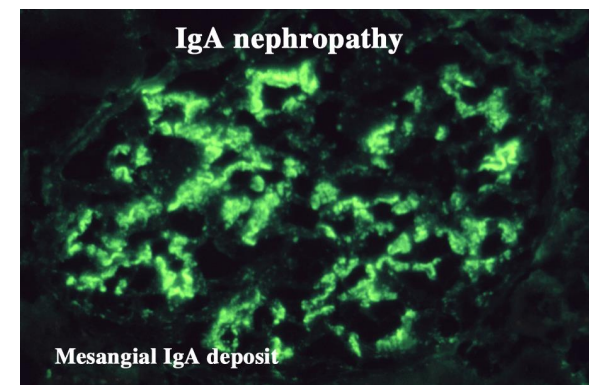
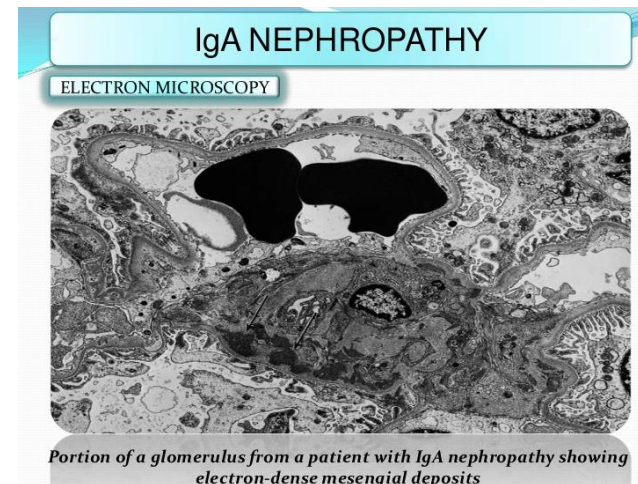
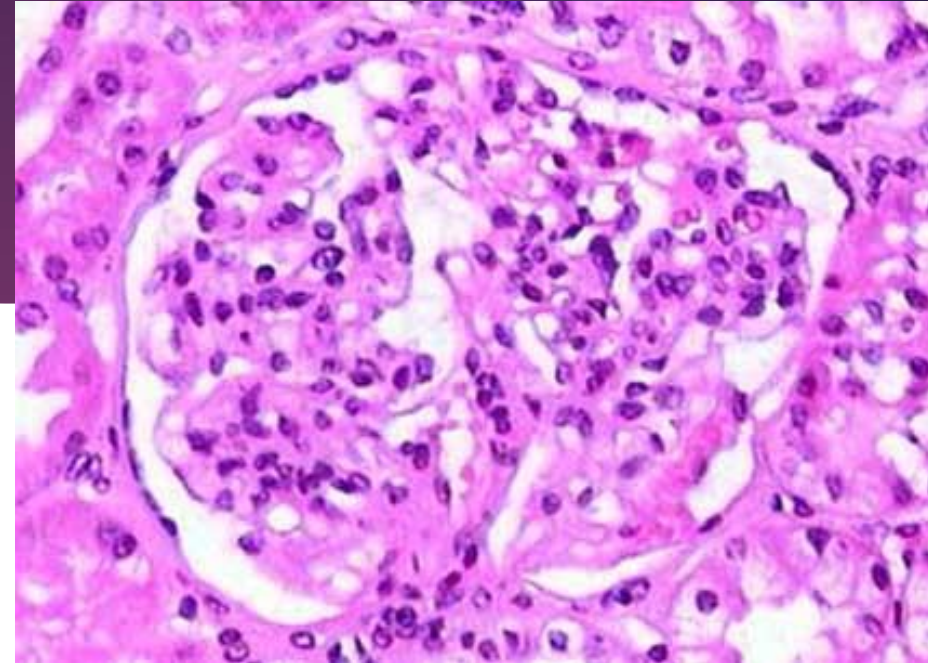


5. Other immune glomerulonephritis types

- ▶ Non crescentic IgA nephropathy
- ▶ Post strep GN
 - ▶ Post infectious Immune complex GN
 - ▶ HIVIC
- ▶ AIN and mimics
 - ▶ Cholesterol emboli
 - ▶ IgG4 GN

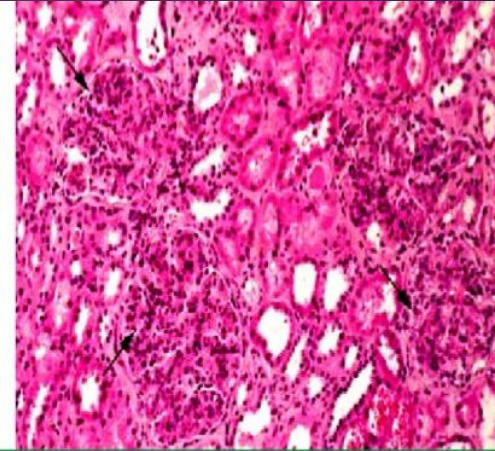
IgA nephropathy

- ▶ **MOST COMMON Glomerulonephritis WORLDWIDE**
- ▶ Low grade protein in urine and some blood in urine
Though amount varies
- ▶ Preserved renal function or only slight worsening
- ▶ This describes most common cases not “crescentic” IgA
See that slide for more information
- ▶ Hematuria common and offers a good prognosis
- ▶ Can flare immediately after infections
- ▶ Associations
 - ▶ HIV
 - ▶ Asian patients
 - ▶ Patients with cirrhosis
 - ▶ Due to abnormal antibody tagging with sugar molecules (glycosylation) and abnormal deposition

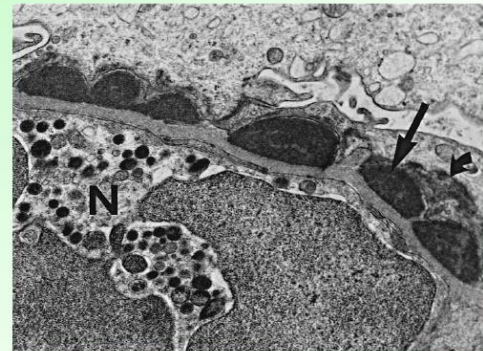


Post streptococcal glomerulonephritis

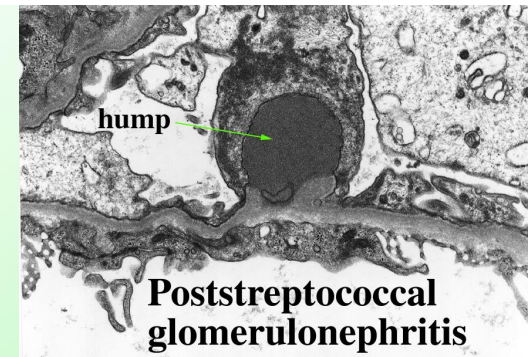
- ▶ Variable proteinuria
 - ▶ Neutrophil type Inflammatory cells present in kidney on biopsy
 - ▶ Happens after infection with streptococcus (after 2 weeks time)
 - ▶ Nephritic meaning blood/inflammation in urine
- >protein leakage
- ▶ Treat underlying infection
 - ▶ Clinical diagnosis is made and then is supported by biopsy findings



Low power light micrograph showing diffuse, proliferative glomerulonephritis as may be seen in postinfectious glomerulonephritis. The glomeruli are so hypercellular (arrows) that open capillary lumens cannot be seen and the glomeruli may be hard to distinguish from the surrounding interstitium.

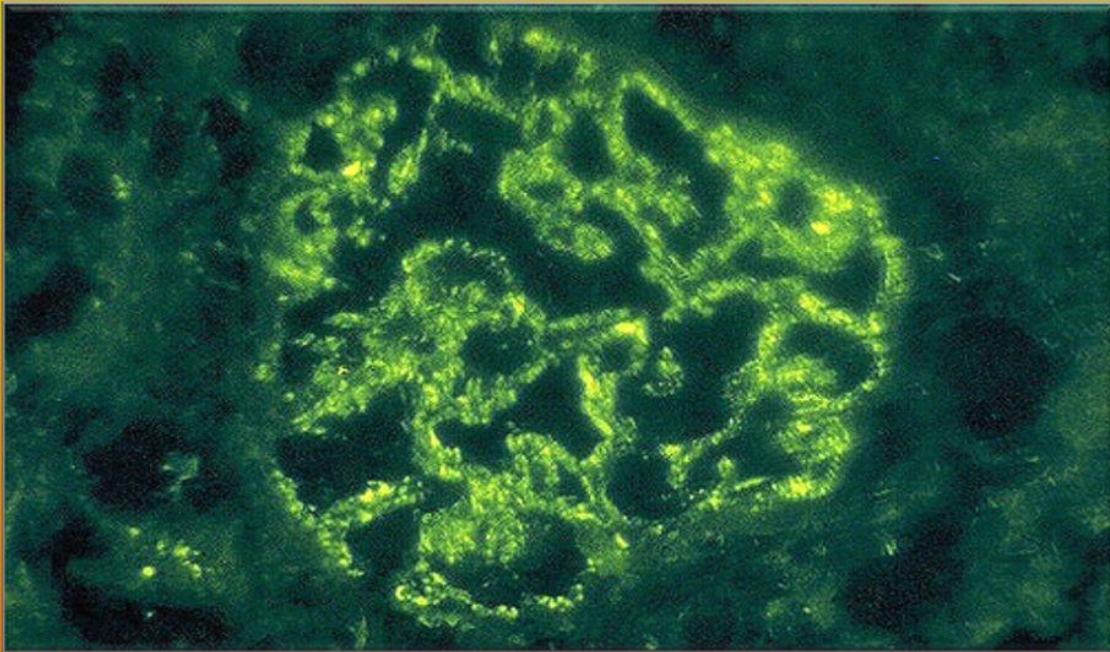


EM of a portion of a glomerular capillary from a patient with APSGN showing subepithelial dense deposits and a neutrophil (N) margined against the basement membrane with no intervening endothelial cytoplasm.



Post strep glomerulonephritis immunofluorescence

Post-streptococcal GN



- Post-streptococcal glomerulonephritis is immunologically mediated, and the immune deposits are distributed in the capillary loops in a granular, bumpy pattern because of the focal nature of the deposition process

Typical pattern in post streptococcus GN on immunofluorescence-which is how antibodies are found when evaluating a biopsy: shows IgG antibody and C3

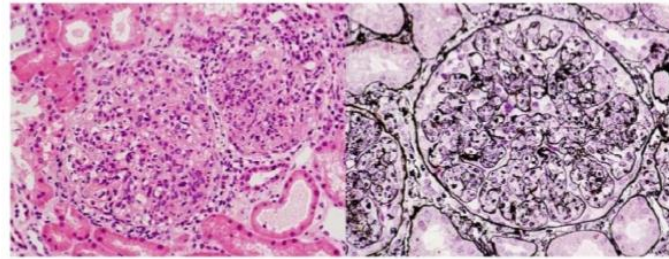
Post infectious glomerulonephritis and immune complex glomerulonephritis

- ▶ Protein leakage and inflammation is present
- ▶ Neutrophil type Inflammatory cells present in kidney
- ▶ Can have complexes of antibodies and bacterial/viral proteins that can be detected as deposits and on immuno-fluorescence
- ▶ Lag period after infection before it develops- about 2 weeks
- ▶ Treatment usually involves treating underlying infection

Associations

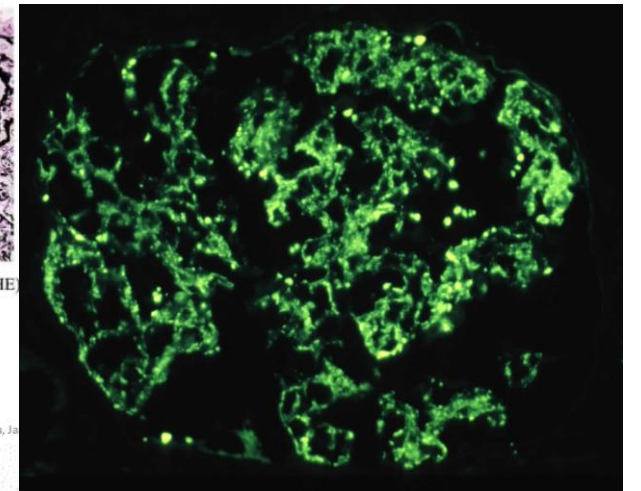
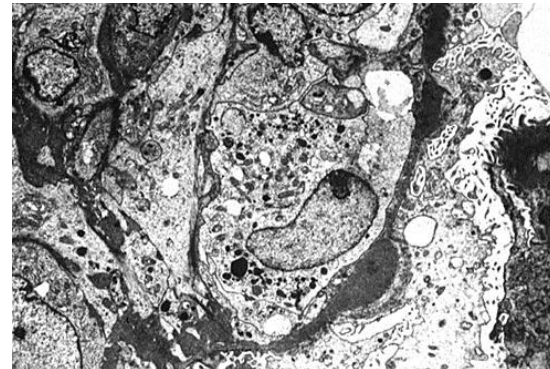
- ▶ Positive signs for systemic Infection
 - ▶ Acute infection
 - ▶ Chronic infection Like endocarditis (heart valve infection)
or osteomyelitis (bone infection)
(with organism other than streptococcus)

a) Light microscopy

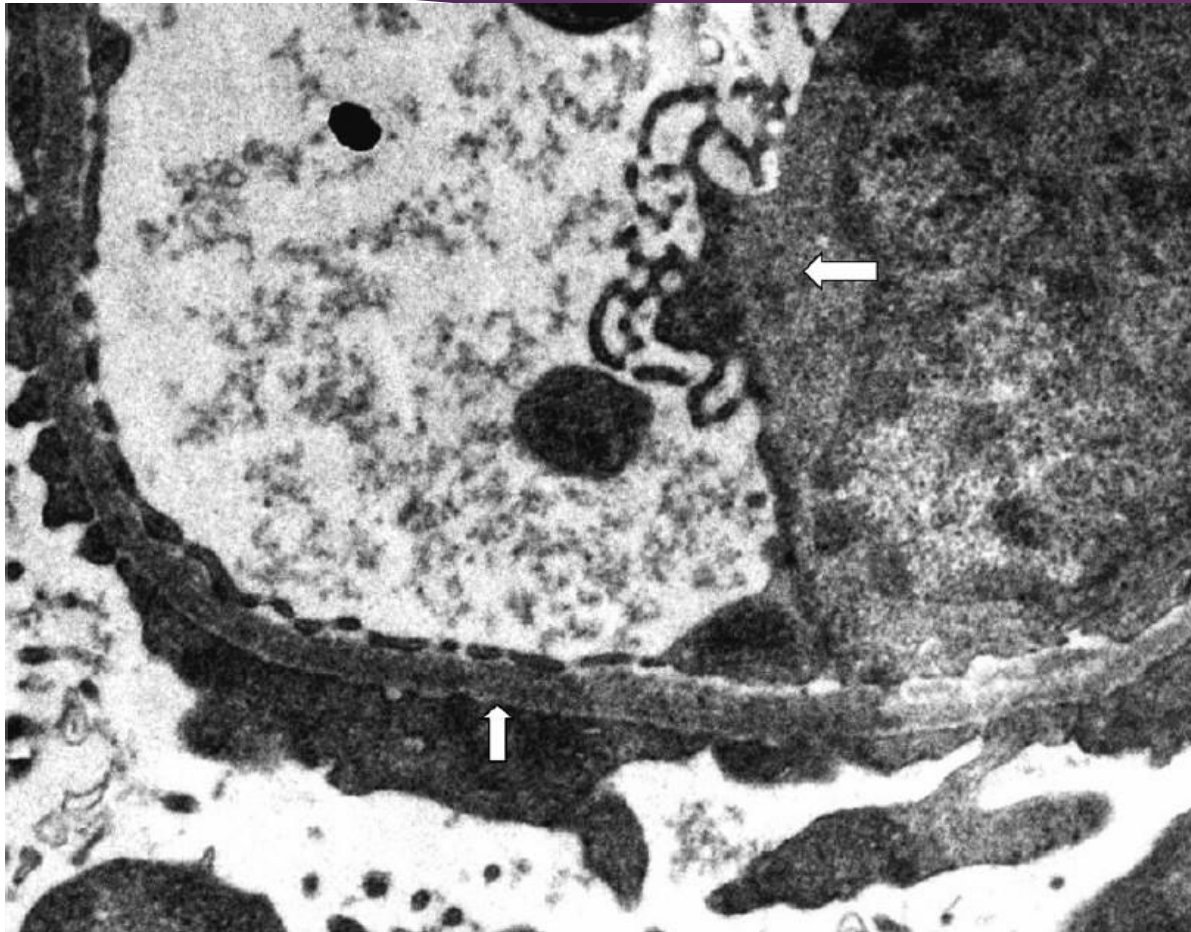


Left: Diffuse global endocapillary hypercellularity with neutrophils predominant infiltration (HE)
Right: Global endocapillary hypercellularity with mesangiolysis/microaneurysm (PAM)

M Nagata. PIGN and variants. Division of kidney and vascular pathology, graduate school of human sciences, University of Tsukuba, Japan



HIVIC-HIV associated immune complex disease



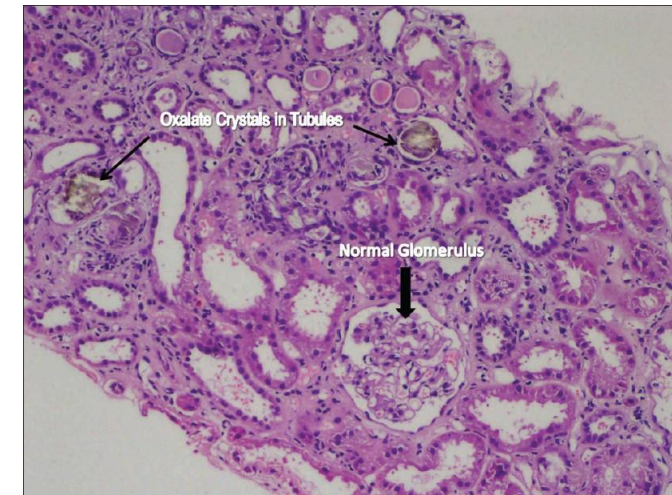
HIV can also cause kidney damage and inflammation
With blood and protein in urine that are caused by HIV virus and antibody complexes depositing in kidney

These can be seen under electron microscope and immunofluorescence

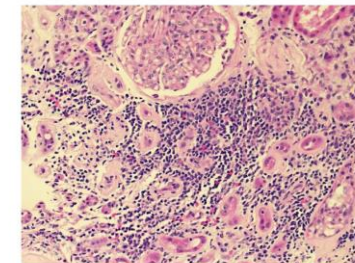
This disorder is called HIVIC

Acute Interstitial Nephritis (AIN)

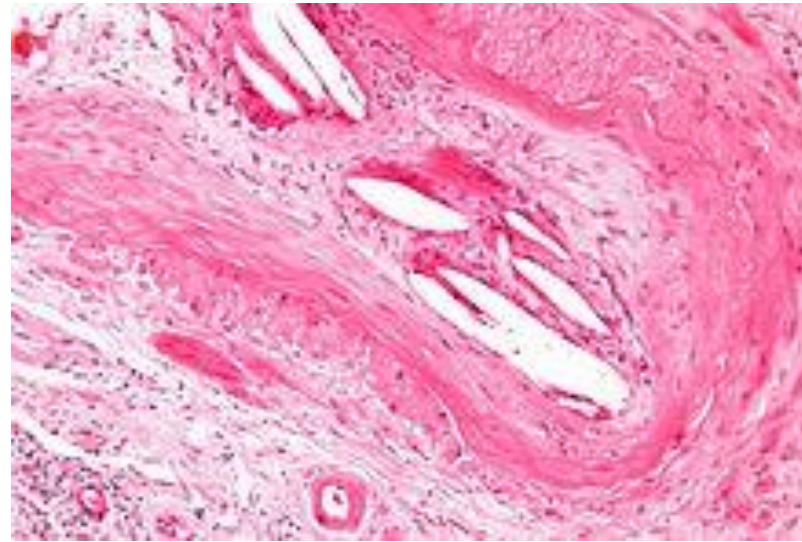
- ▶ Lymphocytes type inflammatory cells infiltrate into kidney
 - ▶ Low grade proteinuria to mid range proteinuria
- variable levels of blood in urine usually small amounts
- ▶ Almost always see white blood cells seen in urine analysis
 - ▶ Eosinophil type allergy cells increase in blood and at times in urine (but not always in urine)
 - ▶ Usually has rash accompanying a rise in serum creatinine (with decline of kidney function) and allergy cells increase in number in blood
 - ▶ Associations
 - ▶ Can be seen with MANY drugs
 - ▶ Proton pump inhibitors
 - ▶ Histamine blockers
 - ▶ Penicillin
 - ▶ Quinolone antibiotics
 - ▶ Many other antibiotics
 - ▶ Granulomatous (a type of immune cell formation) AIN can be much more aggressive



Chronic Interstitial Nephritis



Cholesterol Emboli



Can see kidney damage from cholesterol plaque that breaks off and goes to kidney resulting in Inflammation and damage

6. Genetic diseases of kidney

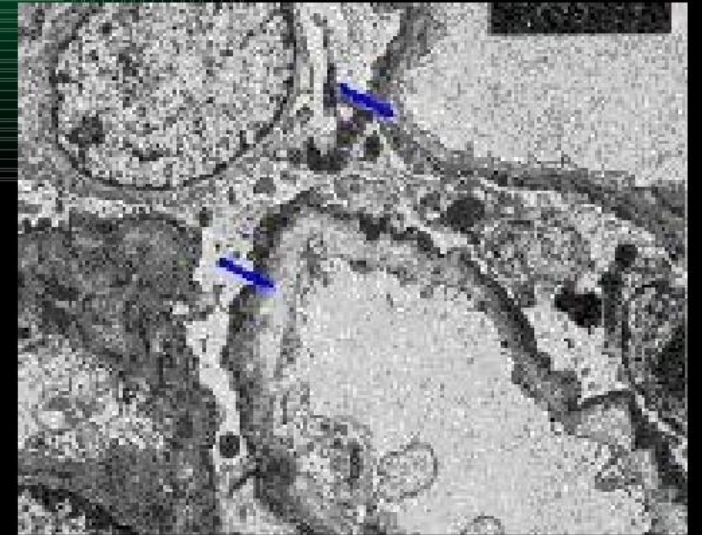
- ▶ Alport's
 - ▶ Thin Basement Membrane subtype
- ▶ Dense deposit disease and C3 glomerulo-pathy see earlier slide
- ▶ Muco-polysaccharide deposition disease / mitochondrial disease (beyond scope but Gaucher's disease can be dx on renal biopsy)

Alport's syndrome and thin BM disease

- ▶ Hearing loss
- ▶ Genetic defect of collagen type 4 subunits A3,4 (autosomal)
or A5 (sex chromosome linked this results in defective basement membrane-the barrier that keeps blood and urine separate
 - ▶ Blood in urine is seen as a result along with low grade protein leakage into urine
- ▶ Slowly progressive renal dysfunction
- ▶ Mutations in collagen type 4 subunit Alpha 3,4, and Alpha 5 subunit (α 3,4) have different transmission but have same features-with exception that alpha 5 mutations also affect skin structure and can be diagnosed with skin biopsy

Electron micrograph of kidney biopsy from a patient with Alport syndrome (AS).

Note the splitting and lamellation of the glomerular basement membrane



04/15/09

Thin basement membrane nephropathy

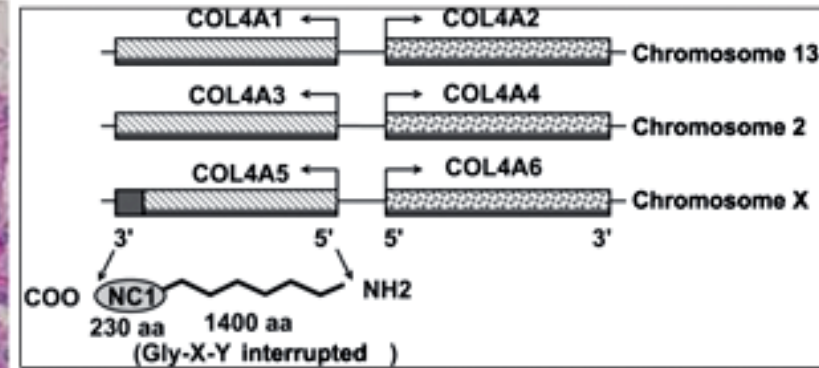
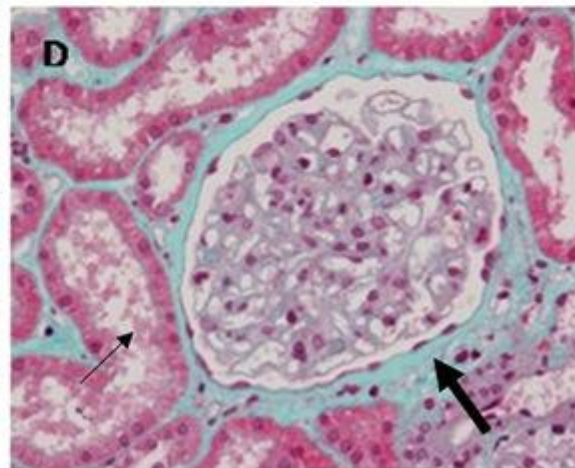
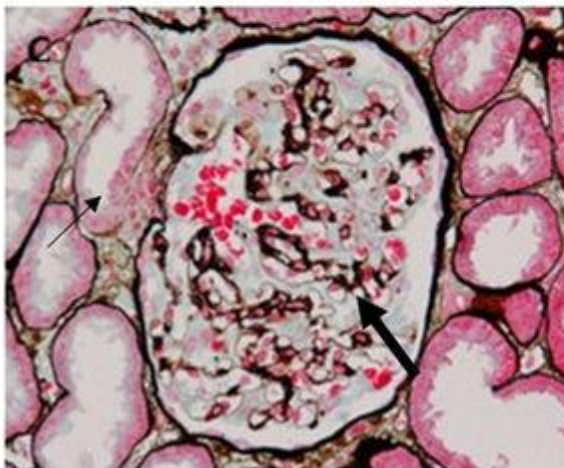
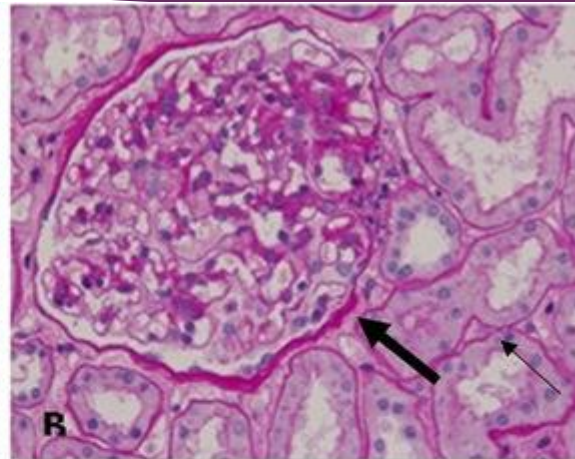
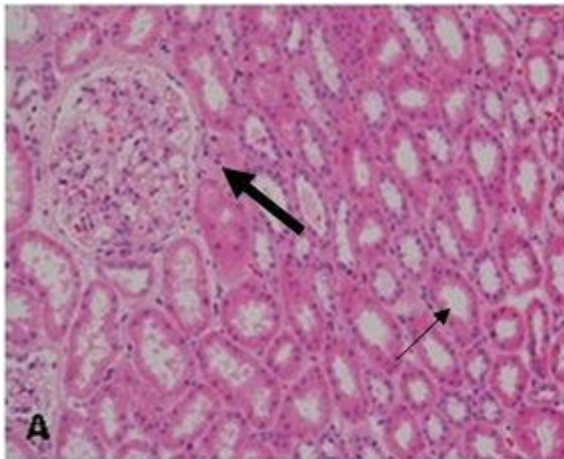


Figure 3. Genomic organization of six collagen genes type IV that are distributed in chromosomes 13, 2 and X. The 5 exons in portion 3' terminal of COL4A5, codify the domain NC1 of $\alpha 5(\text{IV})$ and are shown in red (Kashtan & Michael, 1996).

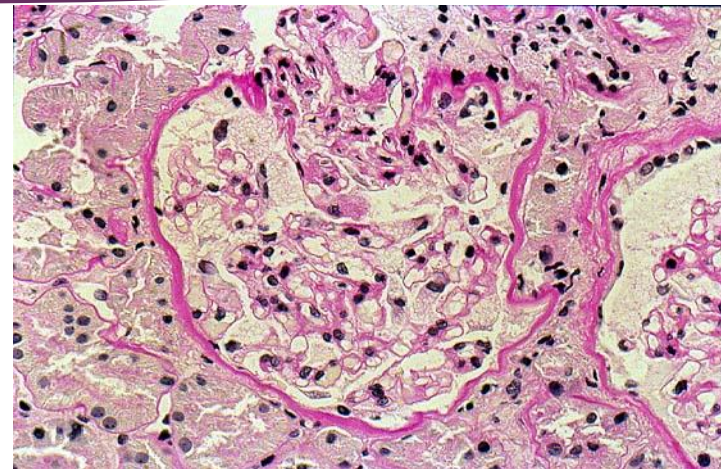
Genetic carriers of one autosomal type IV collagen mutation don't have the disease but are "carriers"

Clinically they have low grade blood in urine-
This is a more or less normal variant with only very mild risk long term

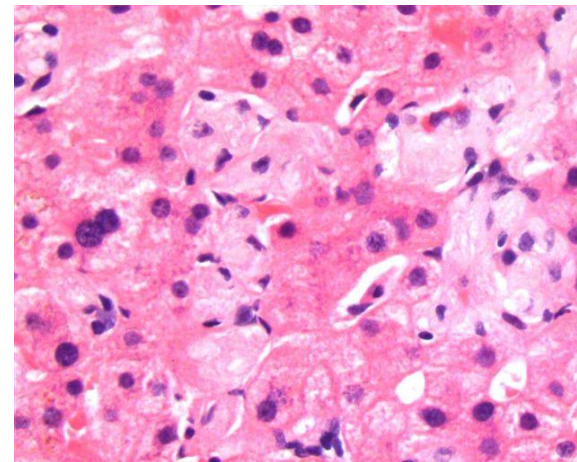
Female carriers of Alport's have similar presentation

Fabry and Gaucher's disease

Fabry and Gaucher's diseases
Are deposition diseases due to inborn
Errors of metabolism.
Please see CORE kidney page about
extensive programs at UCLA for Fabry's disease
care



Gaucher's disease
With liver deposition



7. Miscellaneous glomerulopathies

- ▶ Immunotactoid GN/Fibrillary GN
 - ▶ Malignant HTN/Scleroderma kidney

Immunotactoid GN and Fibrillary GN

- ▶ Very rare
- ▶ Usually found on electron microscope examination of kidney tissue
- ▶ Small fibrils of disordered proteins that are immune in origin
- ▶ Both with varied associations and presentation
 - ▶ Can be seen in cancer patients
 - ▶ Like multiple myeloma and lymphoma
 - ▶ Can be seen in HIV patients
 - ▶ Can be seen in patients with mixed connective tissue disease

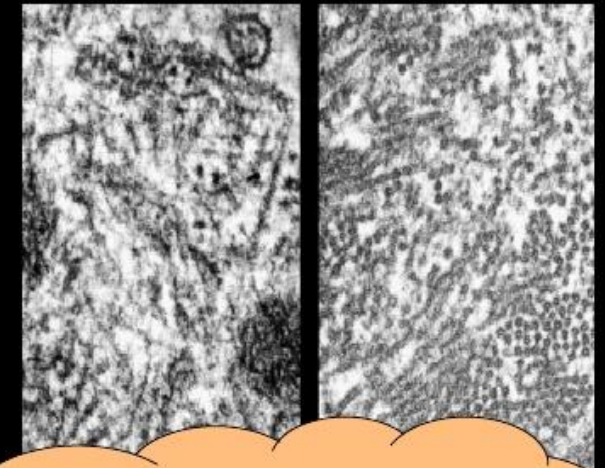
FIBRILLARY-IMMUNOTACTOID GLOMERULOPATHY: NOT DETECTED BY CLINICAL DATA

***EM** (F≤30nm, random
IT>30nm, focal organization)

***Don't stain** with congo red
(DD amyloid), and
observed in absence of
cryoglobulins or
paraproteins

***1%** of renal biopsies

***Assoc:** Monoclonal
Gammopathy, CLL,
lymphomas, GIT cancer
Mixed connective tissue



FIBRILLARY GN

Malignant Hypertension, scleroderma renal crisis

- ▶ Onion skinning from arterial damage from extreme High blood pressure
- ▶ Low to mid range proteinuria can be detected usually under 1 gram protein excretion per day
- ▶ No blood in urine usually seen
- ▶ In people with severe hypertension
- ▶ Can be seen in scleroderma renal crisis a form of hypertensive crisis found in people with a disease of connective tissue called scleroderma. People with Scleroderma and without renal crisis usually have non specific inflammation as opposed to dramatic arterial Changes.

