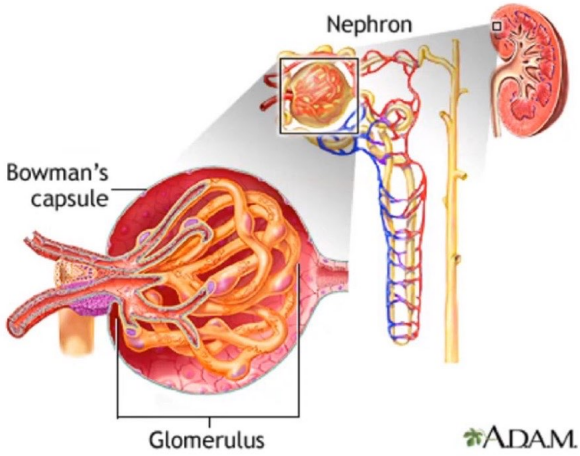
Glomerulonephritis

Nephritic syndromes & Nephrotic syndromes

Anatomy review

- Each kidney contains:
1 million nephron/glomerulus



What is Glomerulonephritis?

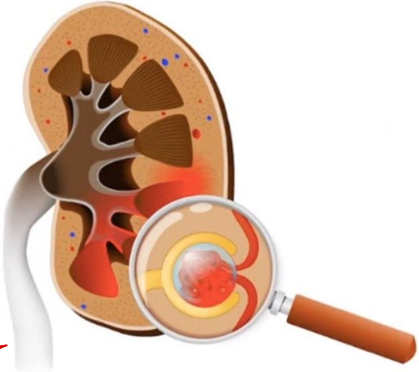
- Inflammation of the ***glomerular capillaries***
- Caused by an immunologic reaction

→ phase of reversibility → phase of irreversibility

- Active disease → Renal scarring
  (Inflammation → fibrosis)

← دائماً الهدف تبعنا نشخص المريض وهو لسا باد active عشان نمنع ال scaring

- Usually multi-focal



How Glomerulonephritis occurs?

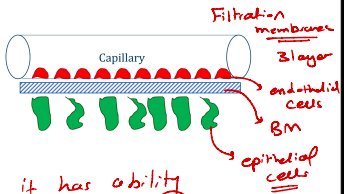
- Immune complexes deposit in the kidney (glomerulus)

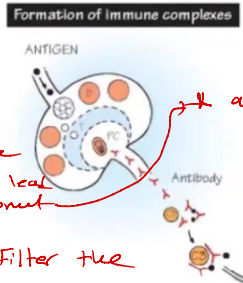
Because it's a site of Filtration there is a passage of Fluid through the capillary wall → and it's very tight can lead to trappment

- Why in glomerular capillaries?

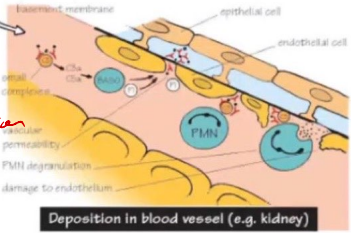
Because the Kidney have ability to Filter the Blood, it's also where things can be traped including immuno complexes.

* traped in the Filtration membrane → induce inflamation → this lead to glomerulonephritis.





also it has ability to stick to different molecules → Charge ... انواع



Glomerulonephritis

- Can manifest as **Nephritic** or **Nephrotic** syndrome

- Disease course can be:
  - Asymptomatic (hematuria, proteinuria)
  - Acute glomerulonephritis → weeks
  - Rapidly progressive glomerulonephritis → days-weeks
  - Chronic glomerulonephritis → months-years

Nephritic syndrome

1. **Proteinuria**
2. **Hematuria**
3. Impaired Kidney function (newly)
4. Edema (Recent)
5. Hypertension (new)

(mostly acute)

Proteinuria + Hematuria

Nephrotic syndrome

1. **Proteinuria - marked (+3.5 g/day)**

→ absence of hematuria

2. Impaired Kidney function (not much, not early)
3. Edema → much none
4. Hypertension (new) → Volume related

due to salt retention and volume overload.

Proteinuria

Nephritic syndrome

1. **Proteinuria**
2. **Hematuria**

3. Impaired Kidney function
4. Edema
5. Hypertension (new)

Proteinuria

+

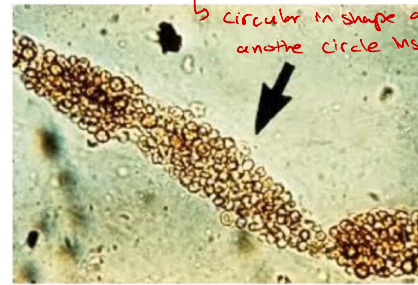
Hematuria

This is sign very specific For nephritic syndrome.

it's RBC, that are originated From the tubules.

RBC casts

- not appear Red / dark in color
- circular in shape and it has another circle inside it ⊙
  - it's a biconcave shape of RBC.



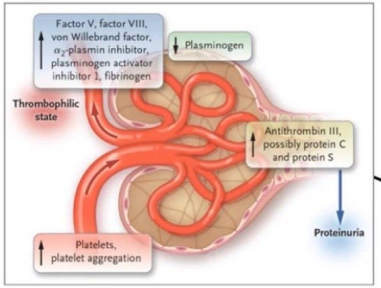
inflammation the wall of Blood vessels

Cystitis التهاب المثانة يسبب hematuria لكن ليس فيه لو كان فيه (RBC in urine) ← just جزء من

Blood leak is acutlly happend in the glumerulus it's self, then gose to the tubules and take the shape of those tubules RBC → collected in curved way → like the shape of tubules.

nephritic الـ

Nephrotic syndrome



- **Proteinuria is more marked (+3.5 g/day)**
- Prominent **edema**
- Risk of thrombosis
  - it's due to loss of proteins
  - * Antithrombotic Factors
    - Anti-thrombin III
    - in addition to protein C and protein S.
- Dyslipi**demia**

Dysfunction of protein

- **Decreases activity of lipases enzymes** (hepatic lipase, Lipoprotein Lipase)
  - these are the enzymes that cleaves lipase, present in the liver and in the Blood.

so increase level of (dyslipidemia)

Proteinuria

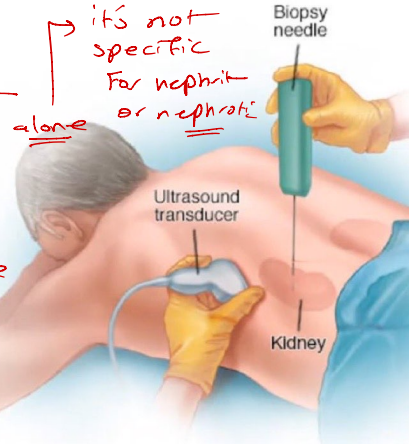
Suspected Glomerulonephritis: Indications for a Kidney biopsy

- Both Nephritic and Nephrotic are indications to preform kidney biopsy
  1) • Hematuria + proteinuria → negative / hematuria alone
  2) • proteinuria > 1g
  3) • Unexplained renal impairment

- Why perform a biopsy?

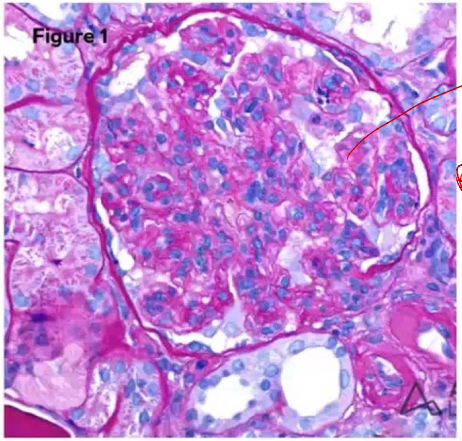
indication of biopsy 3 — it's not specific for nephritic or nephrotic

to detect the disease in active phase so you can treat it prevent progression to Fibrotic phase.



Nephritic syndrome

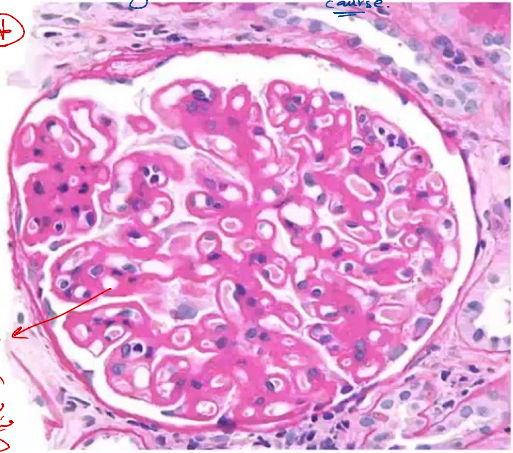
- more prominent cellularity, more prominent proliferation + it's more progressive due to much more inflamation



- Proliferative = progressive

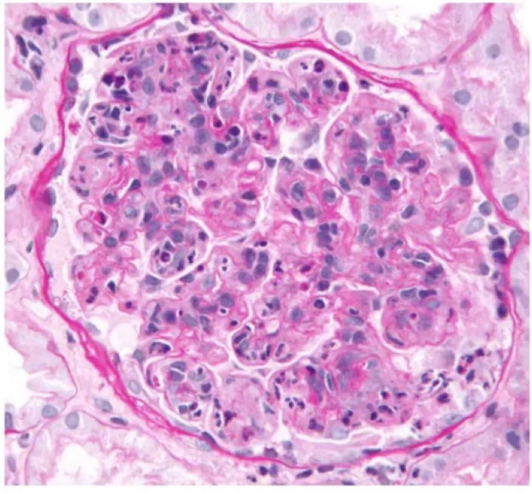
Nephrotic syndrome

- usually it's not proliferative process, it's problem in Filtration membrane.
- less inflamatory, less proliferation, slower progress- cause.



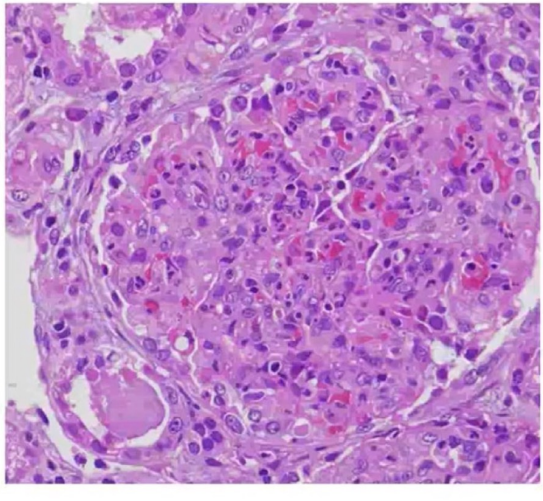
- Non-Proliferative = slow

Nephritic syndrome



- Proliferative = progressive

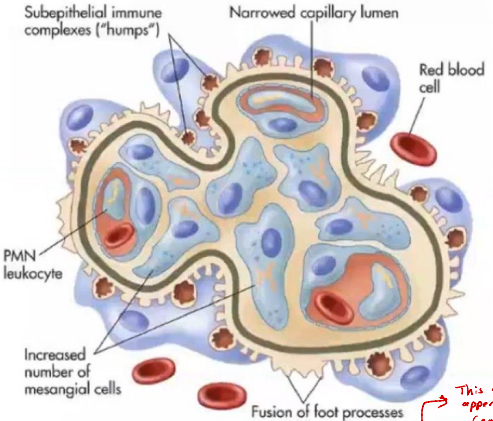
Nephritic syndrome



- Proliferative = progressive

+ Endo capillary proliferation = (progressive) more severe inflamation
+ mesangeal proliferation → less active

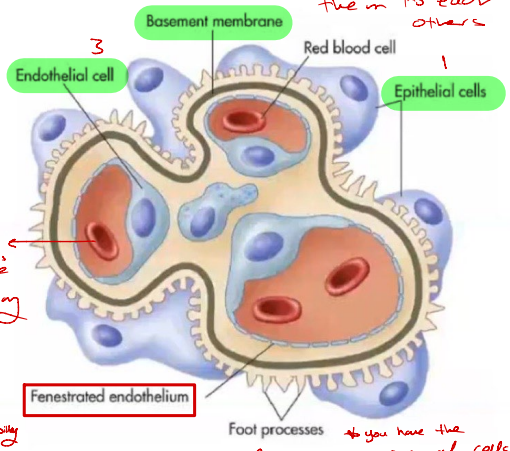
Proliferative = cellular proliferation



+ when you have proliferation →
1) proliferation in mesangeal cells.
2) proliferation inside the capillaries (endo capillary proliferation)
+ leukocytes immunologic cells.

This give closed apperance at capillary (no loop)

+ mesangeal cells = and matrix Between capillary connect them to each others



Normal capillaries

+ you have the mesangeal cells.
+ very similar to connective tissue
→ Between the capillary

Nephritic syndrome

- IgA nephropathy
- Post-infectious GN
- Lupus nephritis
- Hereditary nephritis
- **Membranoproliferative GN**
- Pauci-immune GN

- **Rare causes:**
  - Anti-Basement membrane disease
  - Others (complement deposition, immunoglobulin deposition)

Nephrotic syndrome

Primary:

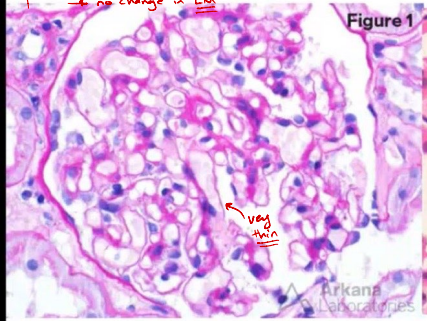
- Minimal change disease
- **Membranous GN**
- **Focal Segmental GN**

Secondary:

- Diabetic nephropathy
- Amyloid deposition
- Myeloma kidney

Minimal change disease

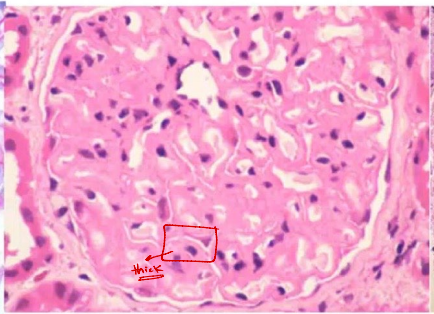
Normal light microscopy no visible lobes
- capillary lobe nice and open, not much of inflammation - BM → nice, thin
- no change in LM



- No changes on Light microscopy (present on electron microscopy)

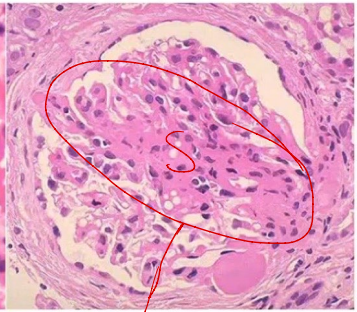
Membranous GN

we have thickness in BM



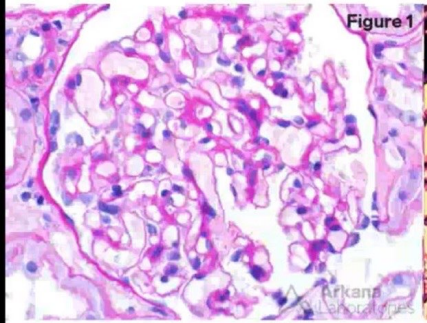
- Membrane thinning/thickening (depends on stain)

Focal Segmental Glomerulosclerosis (FSGS)



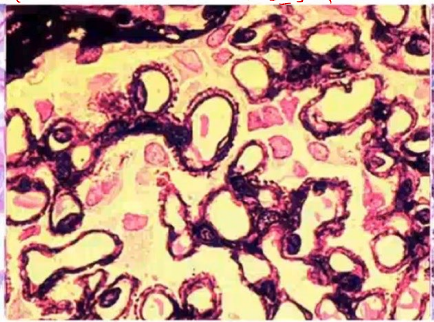
Sclerosis affect just a segment of glomerulus.

Minimal change disease



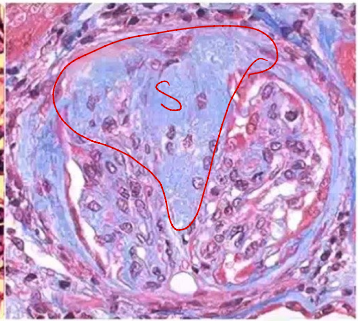
- No changes on Light microscopy
  (present on electron microscopy)
  - **Age:** Childhood (70-90%)
  - **Prognosis**: good (steroids)

Membranous GN



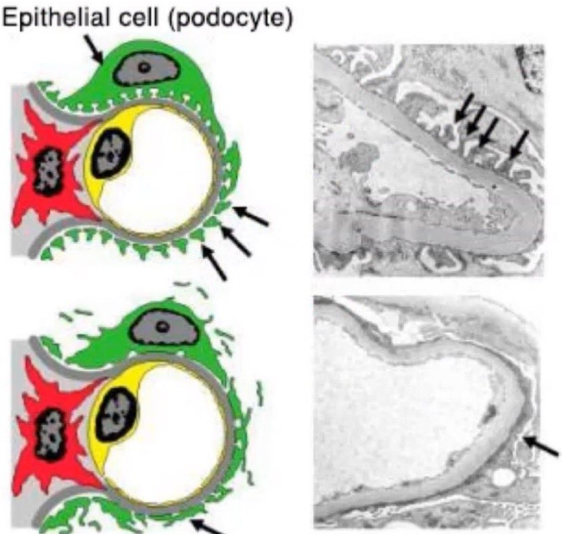
- Membrane thinning/thickening
  (depends on stain)
  - **Age:** Adulthood
  - **Prognosis**: variable (1/3 rule)

Focal Segmental Glomerulosclerosis (FSGS)



- Sclerosis in glomerulus
  - **Age: Both**
  - **Prognosis**: worst

Minimal change disease



By electron microscopy, a normal glomerular capillary has separate foot processes (arrows).

* it's not specific finding of minimal change disease → مش بس فيها
But it's the only finding in minimal change disease. FSGN →

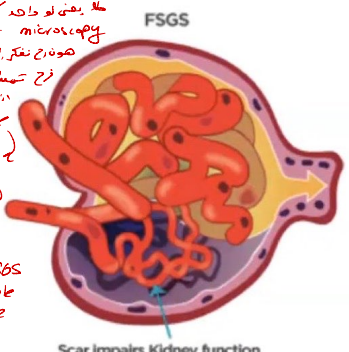
A minimal change disease glomerular capillary has fused foot processes (arrow).

effacement foot processes EM

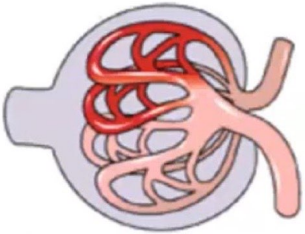
multiple spots

Focal segmental glomerulonephritis - FSGS

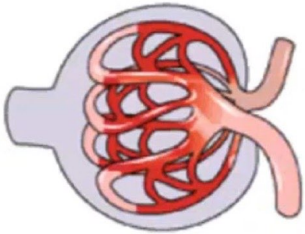
- Can be misdiagnosed/underdiagnosed even if you do biopsy
- Primary (fast) Vs secondary (slow)
- Poorly responsive to steroids
- Prognosis: depends on subtype (collapsing is worst, tip variant is the best)
- High recurrence rate after transplant



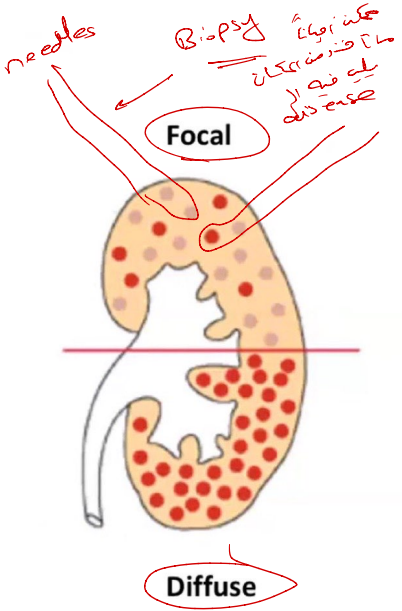
FSGS: terminology



Segmental



Global



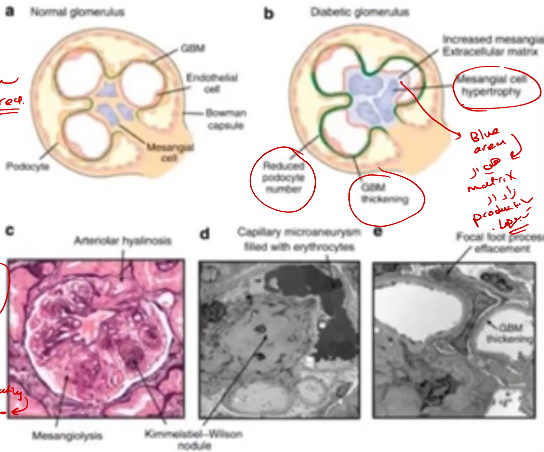
Underlying etiology– Nephrotic syndrome

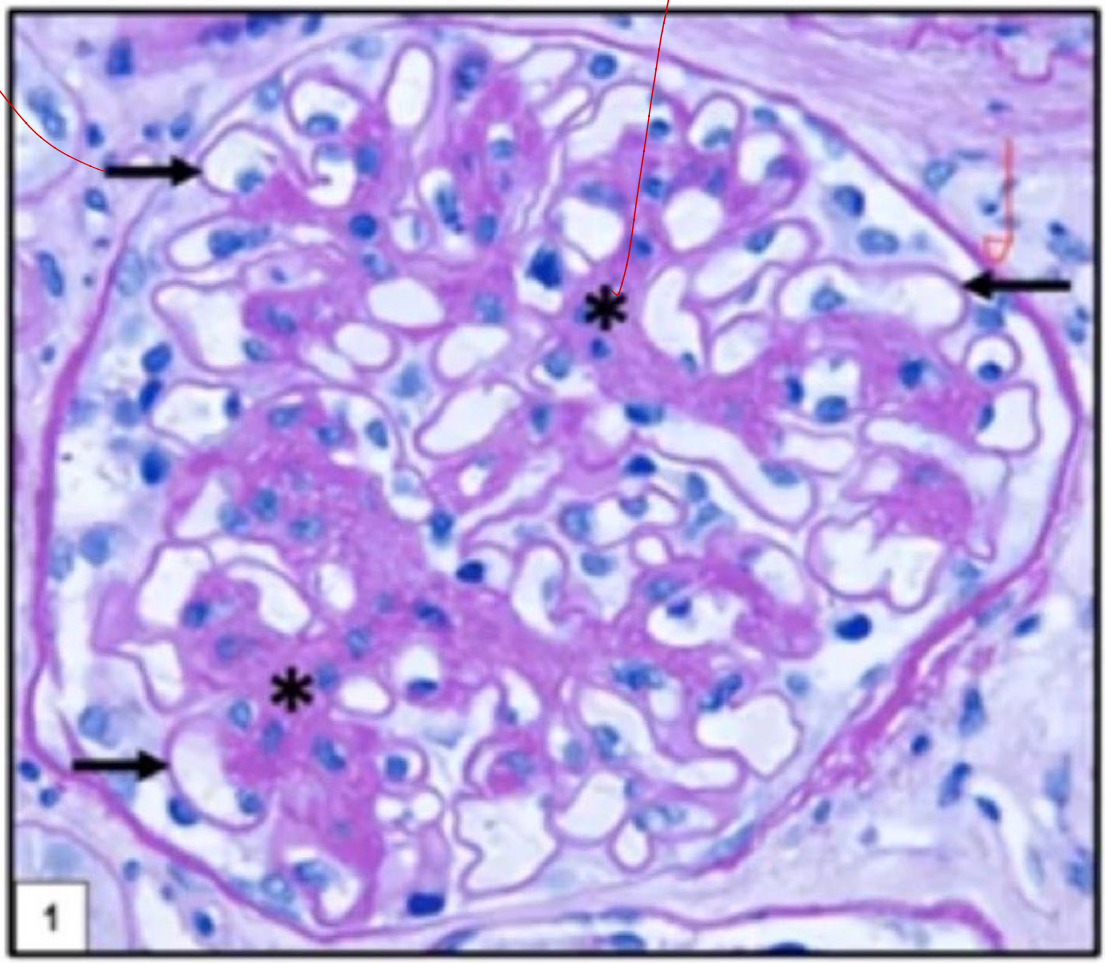
- Minimal change Secondary to ↓
  - Malignancy
  - NSAIDS
- Membranous
  - Malignancy
  - Chronic infections: hep C
  - Drugs (NSAIDs)
  - Disease: SLE
- FSGS
  - Drugs: bisphophonates
  - Genetic
  - Obesity

↓ Same thing we need to treat the underlying cause.

Diabetic nephropathy

- **Pathogenesis:**
  - Hyperglycemia induces matrix production or glycosylation of matrix prteins
- **Pathology**
  - Expansion of matrix (GBM, mesangium, vessel walls)
- **Diagnosis clues**
  - Type I DM: retinopathy precedes nephropathy
  - Type II DM: only 50% retinopathy preceds nephropathy
- **Clinical:**
  - Slowly progressive decline in KFT
  - Proteinuria, slowly worsening

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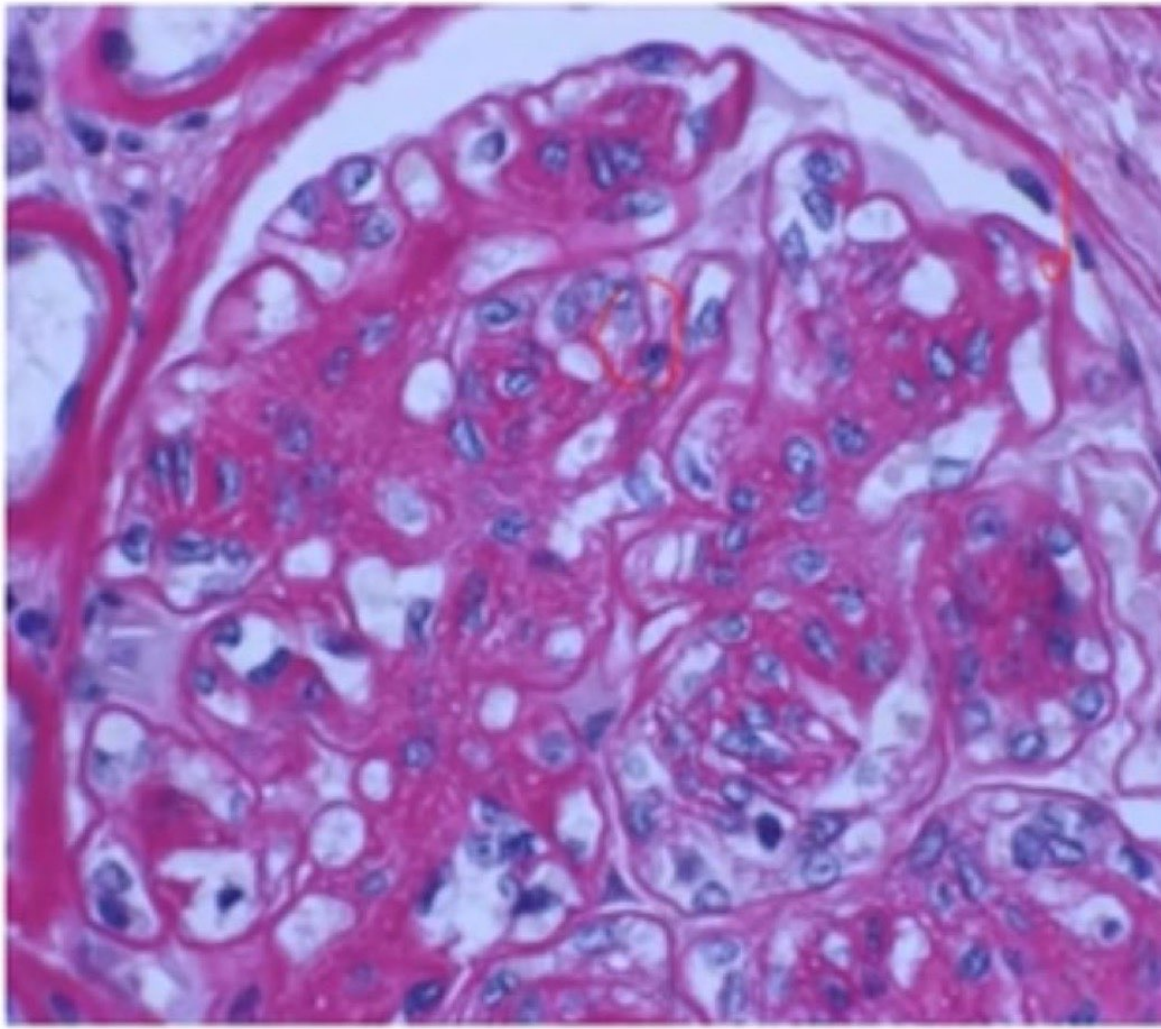
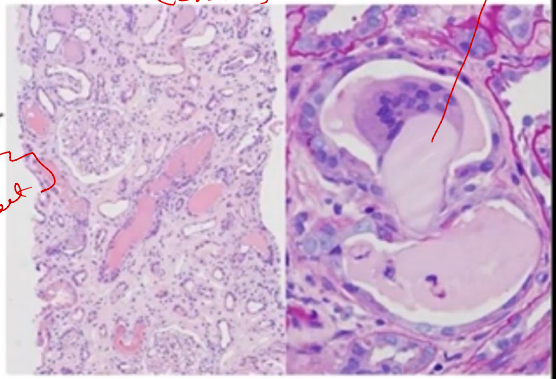


Myeloma Kidney

- Kidney disease secondary to multiple myeloma
- Pathogenesis:
  - Infiltration of toxic light chains → **tubular** injur
- Pathology
  - Light chain casts (**fractured casts**)
- Diagnosis
  - Clinical features of myeloma
  - **Proteinuria mismatch**
    - Low albumin / total protein
    - Negative dipstick but high protein in urine collection
- Useful diagnostic tests:
  - Serum Free light chains, serum & urine electrophoresis



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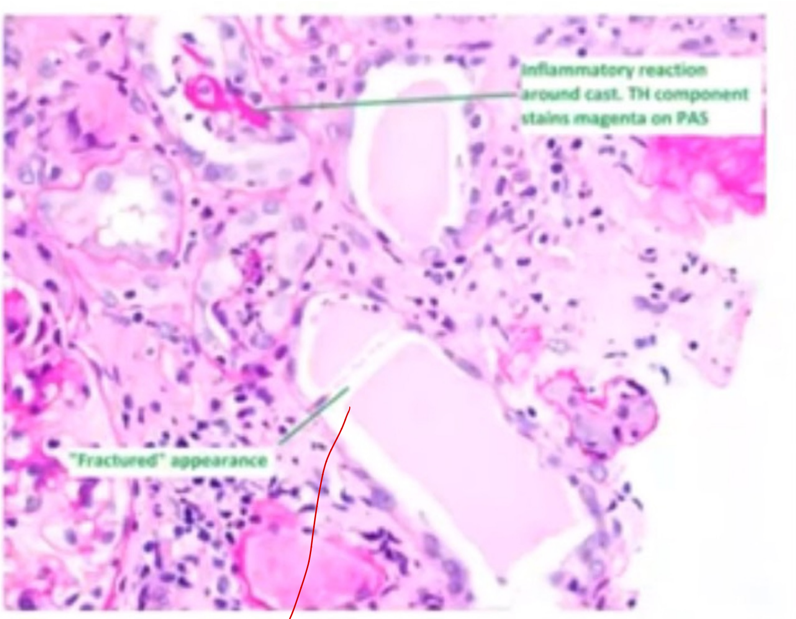


زي يلي ايده
مكسورة

Nephritic syndrome

- IgA nephropathy
- Post-infectious GN
- Lupus nephritis
- Hereditary nephritis
- **Membranoproliferative GN**
- Pauci-immune GN

- **Rare causes:**
  - Anti-Basement membrane disease
  - Others (complement deposition, immunoglobulin deposition)

→ membrane involved
- membrane changes and at the same time you have proliferation of cells.

Nephrotic syndrome

Primary:

- Minimal change disease
- **Membranous GN** → only membrane is involved no extra proliferation
- **Focal Segmental GN**

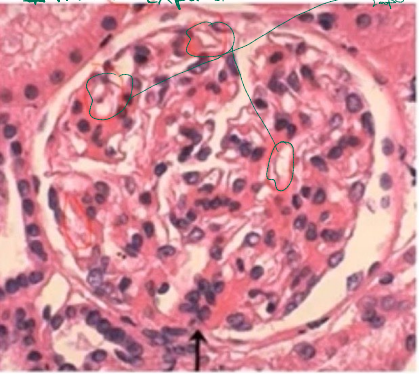
Secondary:

- Diabetic nephropathy
- Amyloid deposition
- Myeloma kidney

IgA nephropathy

most common

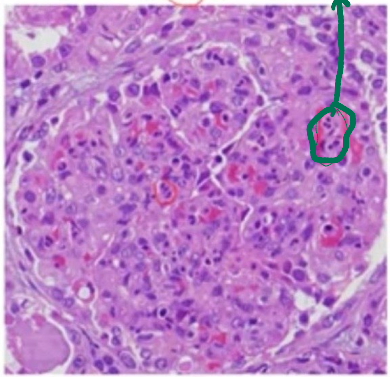
+ mesangial hypercellularity
+ matrix expansion



- Mesangial Matrix & cellularity
- IgA deposition + C3

Post-infectious GN

most severe form of proliferation
– proliferation in both (mesangial + endocapillary)

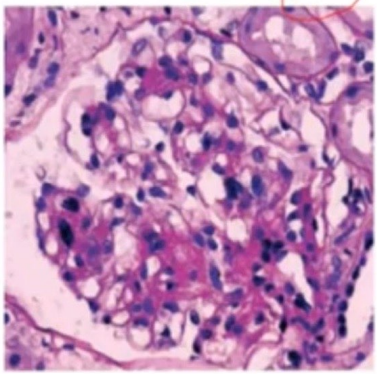


- Proliferative process
- Low C3 + C4 in blood

(Neutrophils)

Lupus nephritis (Grade I & II)

same as IgA nephropathy



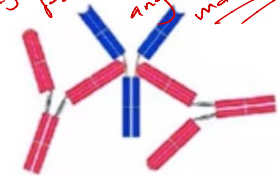
- Mesangial cellularity
- +ve IgM, IgG, IgA, C3, C4, k/L

deposition of all type of Ig and complement

(Full house staining)

IgA nephropathy (Berger disease)

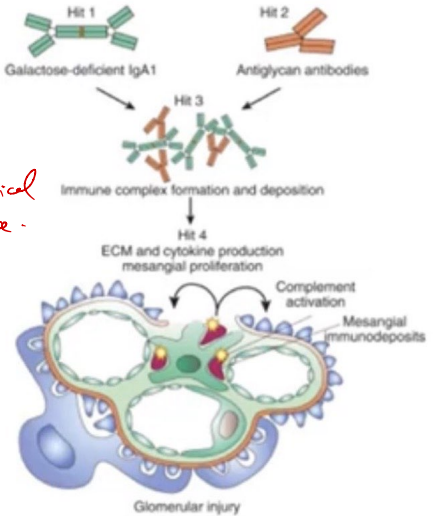
- Most common GN worldwide
- Primary or secondary
  - **2nd to:** Skin/Mucosa/Infection/Liver/neoplasia
  - **Onset of hematuria:** same time of infection
- May present with variable manifestation:
  - **Mild:** Episodic hematuria, Incidental microscopic
  - **Moderate:** Gross hematuria with AKI, Nephrotic
  - **Slow:** Slowly progressive chronic kidney disease
  - **Rapid:** Rapidly progressive glomerulonephritis



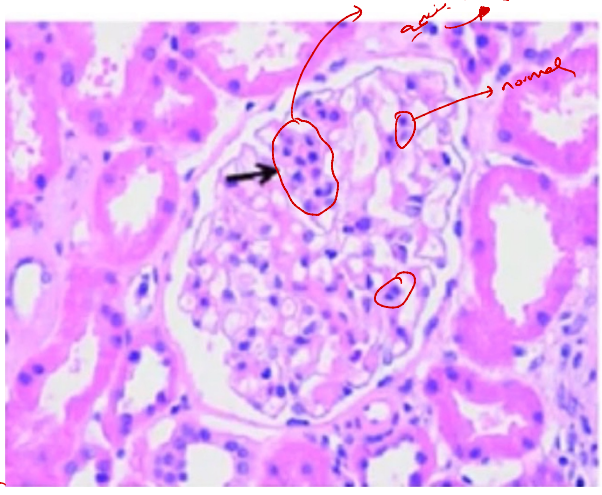
Hit 3: Anti- Gd-IgA1 - Gd-IgA1 complexes

IgA nephropathy

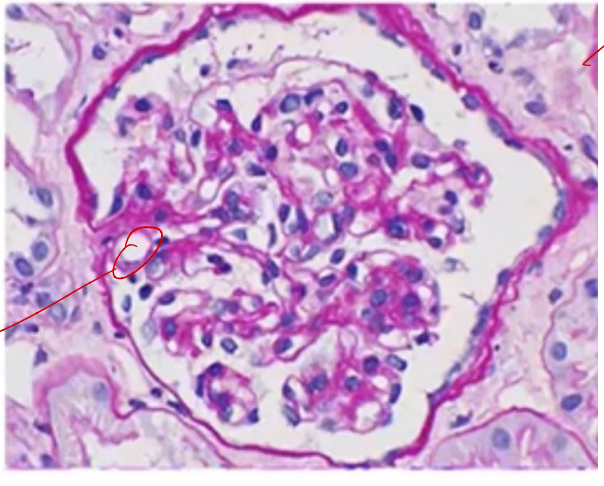
- Pathophysiology:
  - Antibodies against **IgA** antibodies → deposition in **mesangial** → deposit in kidney in mesangial area.
  - Induces mesangial matrix production and mesangial hypercellularity
- Pathology
  - Deposition of IgA in mesangial
  - Proliferation of mesangial cells



IgA nephropathy



↳ mesangial hypercellularity



open capillary

Post infectious Glomerulonephritis

infection 2W → autoimmune reaction to this infection → leads to post infectious GM

- **Manifestation:**
  - Preceded by URTs (2 weeks) or skin infection (several weeks)
  - Nephritic syndrome (hematuria, HTN, AKI)
- **Pathogenesis:**
  - Immunological, Likely C3 mediated
- **Diagnosis**
  - Tests: Antistreptolysin, anti DNAse B
  - Kidney biopsy: endocapilary proliferation with neutrophils, subepithelial hump,
  - Complement: low C3, C4 is NL
- **Prognosis & treatment**
  - Treatment/prevention: treat underlying infection
  - Prognosis is good, typically resolves within weeks

↳ if you treat the infection, it resolved

tonsle. strep throat [illegible]

* it's complement mediated [illegible]

↳ low complement in the Blood, low C3, C4

* endocapillary proliferation with neutrophils.

if you see it, it's unique for post infectious GM.

Nephritic syndromes

- IgA nephropathy
- **Lupus Nephritis (grade I & II)**
- Membranoproliferative GN

- Post-infectious GN
- **Lupus Nephritis (grade III & IV)**
- Pauci-immune GN (ANCA)
- Anti-basement membrane

Nephritic syndromes

* crescents → in Rapid form of GN
any proliferation can associated with it.

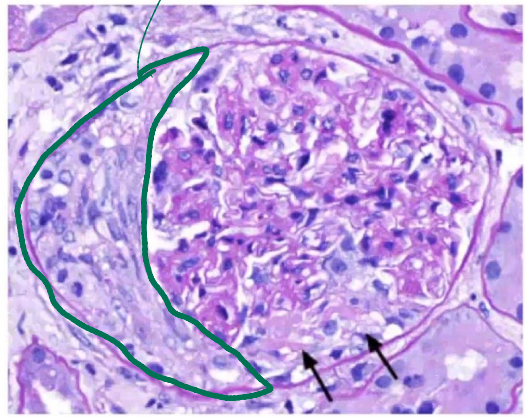
Mesangial Hypercellularity	±	Crescents	Endocapilaty Hypercellularity	±	Crescents

- IgA nephropathy
- **Lupus Nephritis (grade I & II)**
- Membranoproliferative GN

- Post-infectious GN
- **Lupus Nephritis (grade III & IV)**
- Pauci-immune GN (ANCA)
- Anti-basement membrane

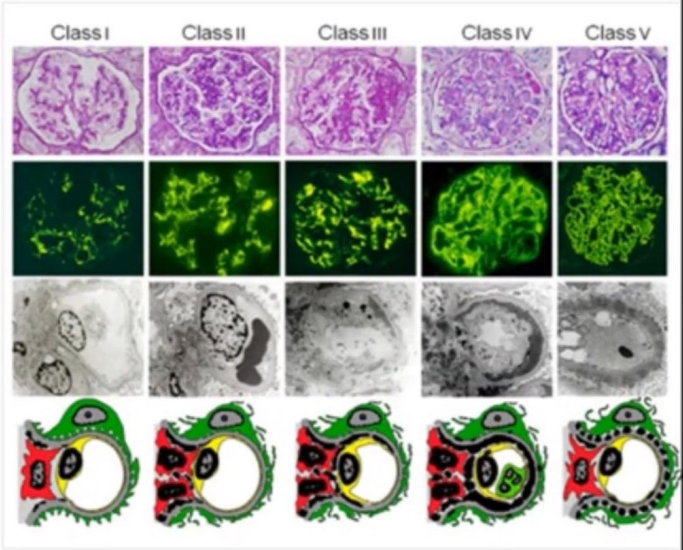
Crescentic Glomerulonephritis

- Crescentic: → indicate to severe disease
  - >50% of glomeruli
  - Proliferating epithelial cells & infiltrating macrophages
- Rapidly progressive Glomerulonephritis (RPGN)
  - Rapid decline in kidney function (days-weeks)
- Crescents are a manifestation of multiple diseases
- It is a sign of severity



Lupus nephritis

- **Class I & II**
  - Nephritic
  - Mesangial proliferation
  - Mildest form – mimics IgA
- **Class III & IV**
  - Nephritic
  - Endocapilary proliferation
  - Most severe – mimics PIGN
- **Class V**
  - Nephrotic
  - Moderate – mimics MGN



Crescentic Glomerulonephritis

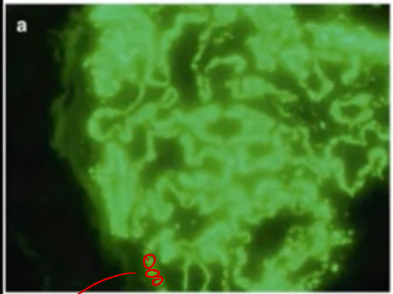
The disease process in vasculitis is not deposition in the kidney its inflammation inside the capillary itself

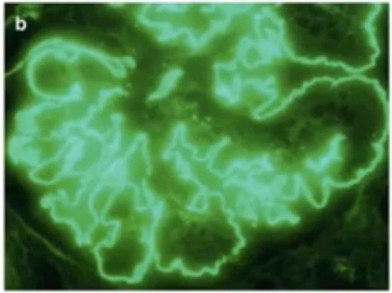
immune deposition

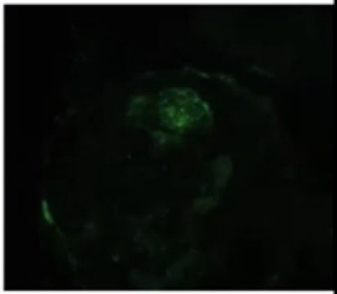
Immune complex GN
(PIGN, IgA, Lupus grade IV..)

Anti-basement membrane
(Goodpasture syndrome)

Pauci-immune GN
(ANCA vasculitis)







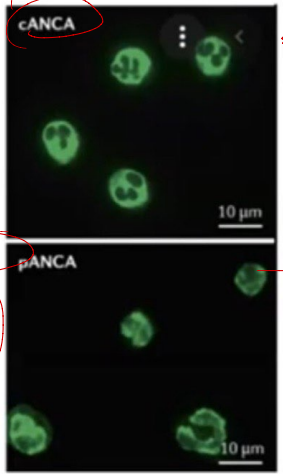
- **Immunofluorescent (IF):**
  Granular pattern
- **LM: crescents + variable**

- **Immunofluorescent (IF):**
  Linear pattern → antibody directed against proteins in the BM
- **Crescents (same stage)**
  One shot disease

- **Immunofluorescent (IF):**
  negative
  pauci-immune = no immune complexes
- **Crescents (multiple stages)**
  relapsing disease

ANCA vasculitis

- Small vessel vasculitis
  - Small vessels in kidney +/- lungs + other organs
  - RPGN: crescents at multiple stages
- Autoantibodies
  - Antibodies does NOT deposit in kidneys
  - Antibodies directed against *neutrophils* → vasculitis
- Clinical use
  - Diagnosis
  - Disease activity: relapsing disease
- Types of antibodies
  - **Cytoplasmic:** C-ANCA = **PR**3 → Granulomatosis with polyangitis
  - **Perinuclear:** P-ANCA = MPO → Microscopic polyangitis, Eosinophilc granulamatosis with polyangitis



ANCA vasculitis

	Microscopic polyangitis	Granulomatosis with polyangitis	Eosinophilic granulomatosis with polyangitis
Antibodies:	**P-ANCA: 50%,** c-ANCA: 40%	**C-ANCA: 80-90%**	**P-ANCA: 60%** Negative ANCA: 30%
Patient profile:	5^{th}-7^{th} decade, slight male predominance. White > black		
Kidney:	Rapidly progressive GN	Rapidly progressive GN	Less frequent kidney involvement
Lung:	Necrotizing vasculitis (with granulomatous inflammation)	Necrotizing vasculitis With granulomatosis + sinus involvement	Asthma: eosinophilic rich and granulomatous
Other manifestations:	Abdominal involvement (ischemia/infarction, perforation) Peripheral neuropathy: Mononeurtis multiplex +/- CNS involvement Skin nodules (more with GPA, EGPA)		

anywhere

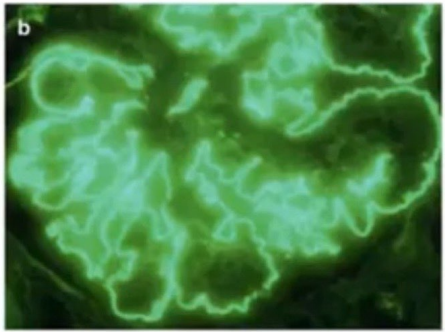
mainly in lung

Renal sinus pulmonary

vessels

Antiglomerular basement membrane (ABGM)

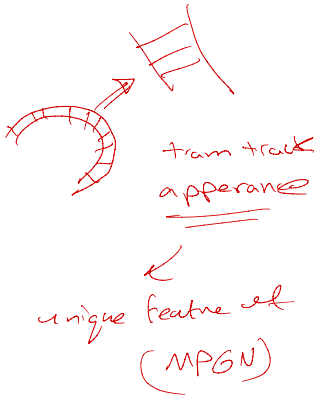
- **Antibodies**
  - Directed to basement membrane (collagen IV)
- **Rare disease**
  - 0.5-0.9/million/year
  - Peak 20-30, smaller peak 60-70
- **Affected organs:**
  - Kidney: RPGN
  - Alveolus: pulmonary hemorrhage
  - Others: Eyes/Cornea, Cochlea, Brain
- **Pathology**
  - LM: crescent at same stage (all active or all subacute or all chronic)
  - IF: **Linear pattern**



Linear immunofluorescence

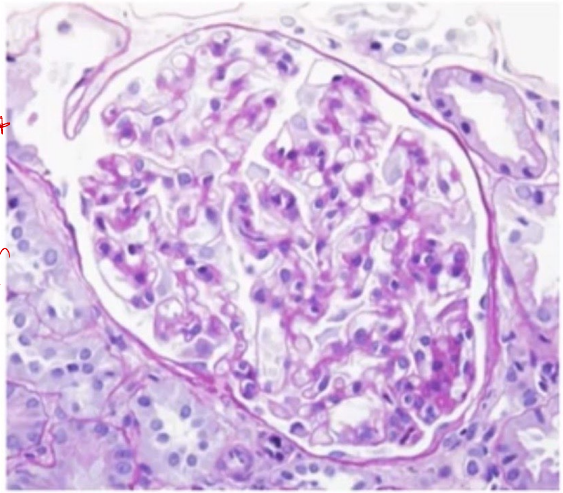
Membranoproliferative GN (MPGN)

- Underlying diseases
  - Hep C
- Pathology
  - Membrane: Double contours – tram track appearance
  - Proliferative: Mesangio-proliferative
- Treat underlying disease



Hereditary nephritis (Alport syndrome)

- Mimics: IgA
- Manifestation: recurrent hematuria
- Hereditary:
  - X-linked, Autosmmal recessive)
- Collagen defect
- Affects primarily BM
  - Thining/thickening
  - Basket weaving
  - Foamy tubular cells
- Associated: hearing defects, eye involvement



Hereditary nephritis (Alport syndrome)