Lectures 2

Topics:

Continuation of nephrotic syndrome, nephritic syndrome , and other clinical manifestations.

Anything added is written in italic
According to section 3 recording

Collapsing glomerulopathy

- a morphologic type of FSGS.
- poor prognosis.
- collapse of glomerular tuft and podocyte hyperplasia.
- It may be :
- 1-idiopathic .
- 2-associated with **HIV infection**.
- 3-drug-induced toxicities.

Membranous nephropathy or Membranous Glomerulonephritis (MGN)

- ***One of the important causes of nephrotic syndrome in adults , and as the name implies, there as an abnormality in the Basement membrane.***
- **Immune complex disease**
- **Types of Membranous glomerulonephritis :**
- **1- *primary* : Idiopathic (*most of the cases* →85% of cases).**
- **2-Secondary**

secondary Membranous glomerulonephritis :

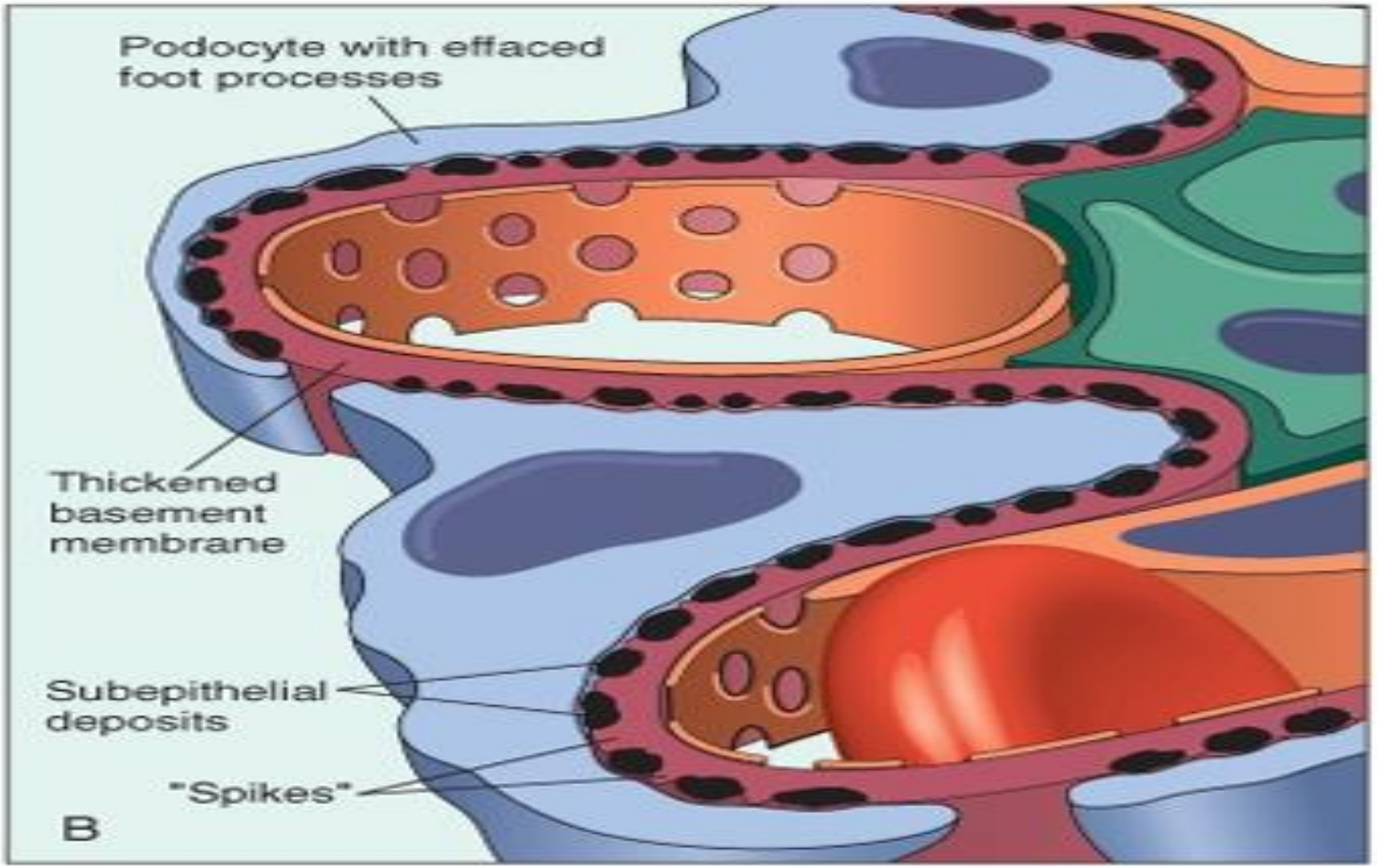
- **(1) infections (HBV, syphilis, schistosomiasis, malaria).**
- **(2) malignant tumors (lung, colon and melanoma).**
- **(3) autoimmune diseases as *systemic lupus erythromatus* SLE .**
- **(4) inorganic salts exposure (gold, mercury).**
- **(5) drugs (penicillamine, captopril,NSAID).**

- **Morphology**
- **LM**
- **diffuse thickening of the GBM .**
- **IF**
- **deposits** of immunoglobulins (IgG) and complement *(C3)* along the GBM
- **EM**
- **subepithelial deposits "spike and dome" pattern**.

Characteristic morphology

Domes are the immune complexes, and the spikes formed by building of material in the BM as a secondary reaction within the glomerular basement membrane (only seen in EM).

Remember:
Subepithelial means between the BM and the podocytes, see next slide.



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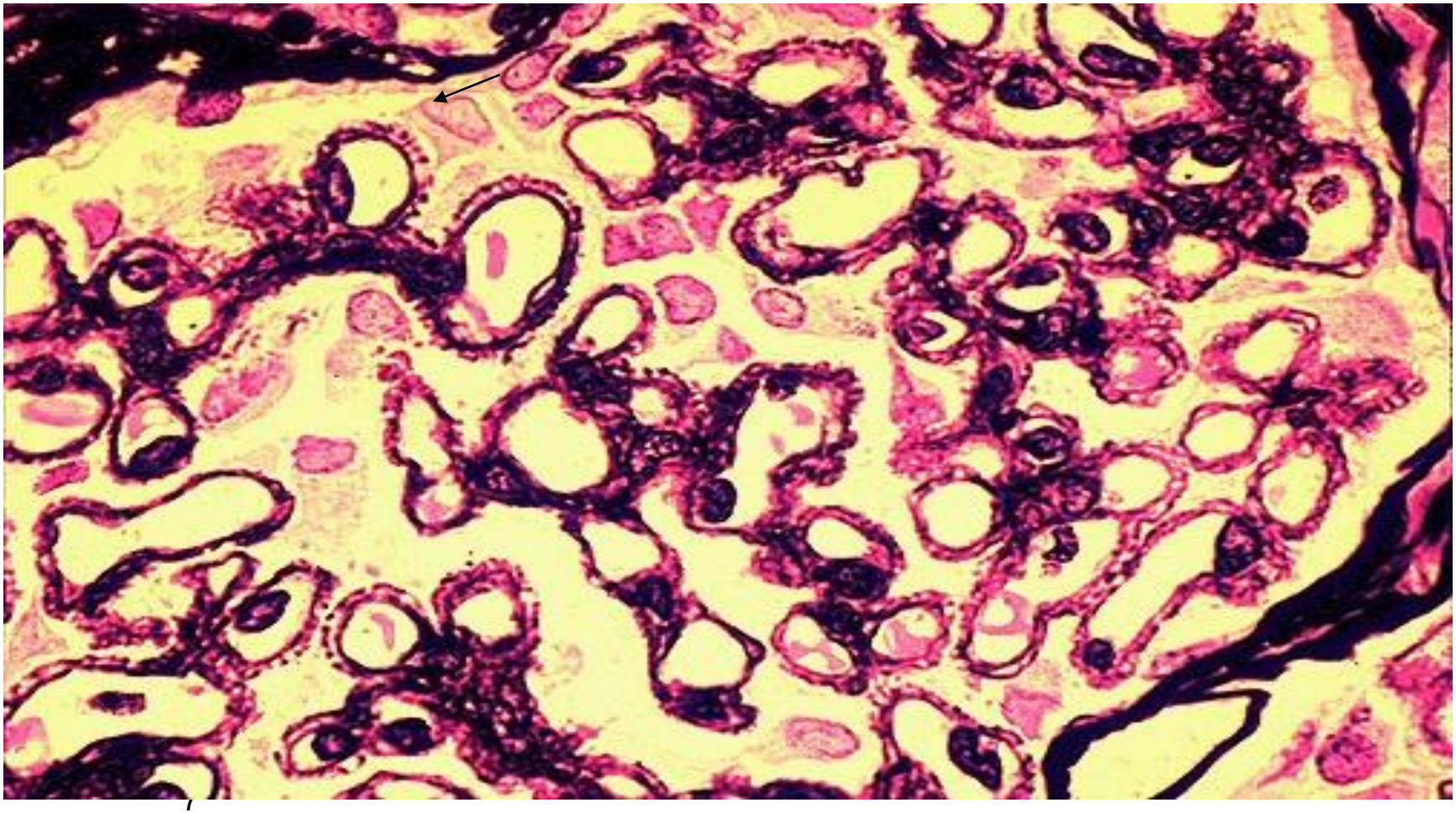
Membranous nephropathy.

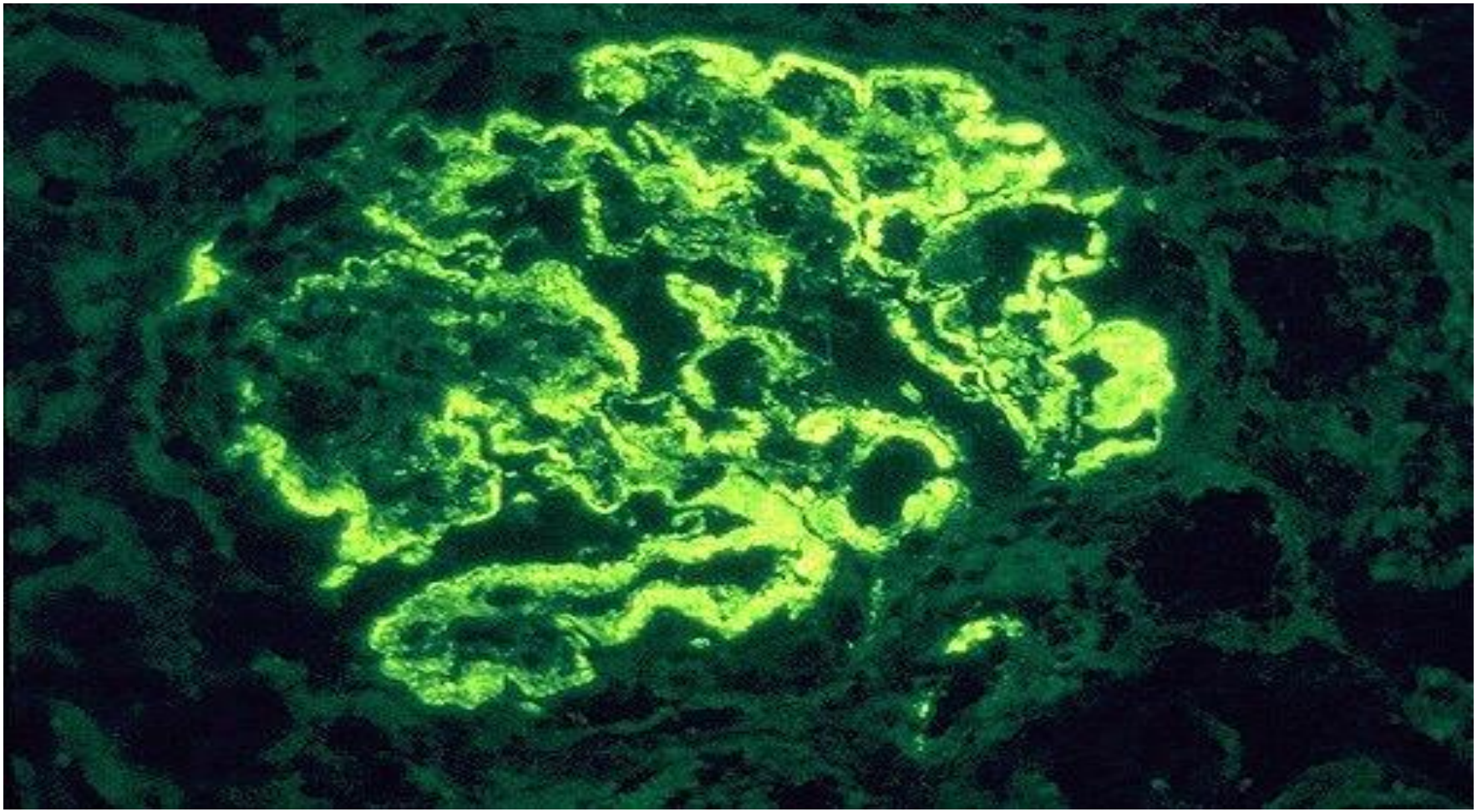
B ,Schematic diagram illustrating subepithelial deposits, effacement of foot processes, and the presence of "spikes" of basement membrane material between the immune deposits .

Silver stain dyes the basement membrane in black

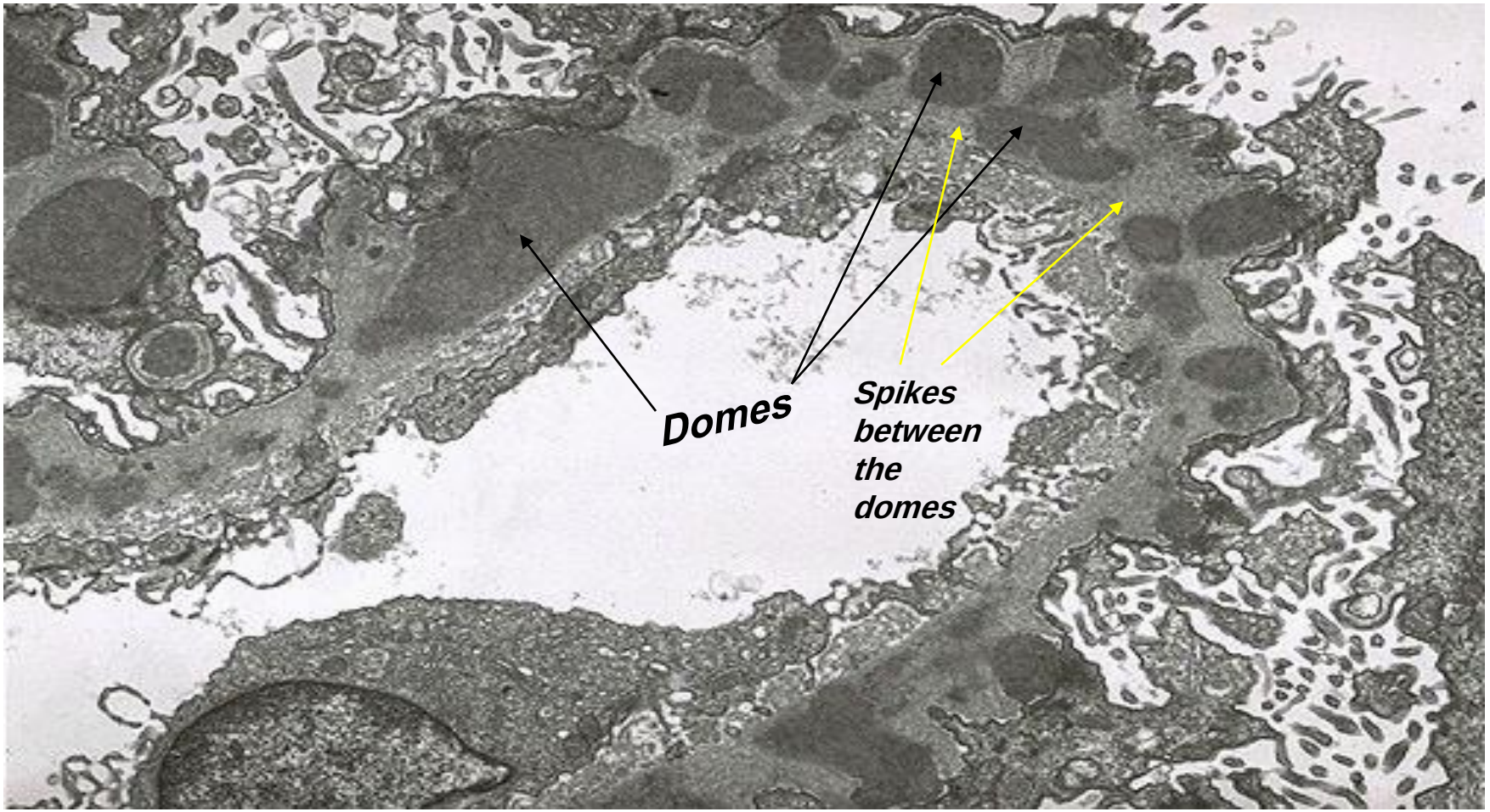
A silver stain (black). Characteristic "spikes" seen with membranous glomerulonephritis as projections around the capillary loops.



Membranous GN
IF: deposits of mainly IgG and complements *(C3)*



EM-the darker electron dense immune deposits are seen scattered within the thickened basement membrane .



Skipped, but doesn't mean its not included :P

- **Clinical Course**
- **nephrotic syndrome**
- **proteinuria nonselective.**
- **no response to corticosteroid therapy.**
- **60% of cases→ proteinuria persists**
- **~ 40%→ progressive disease and renal failure 2 to 20 yr.**
- **30% →partial / complete remission of proteinuria.**

Glomerular diseases- 2

- **Diseases leading to Nephritic syndrome**

The Nephritic Syndrome

- *-As said before, its one of the major renal syndromes, and its usually characterized by development of hematuria, hypertension, azotemia, fluid retention , edema ,and mild to moderate proteinuria.*
- *-Nephritic syndrome is related to **inflammation** inside the glomerulus, this inflammation will be associated with* "Pathogenesis" **proliferation of the cells in glomeruli & leukocytic infiltrate →**
- **Injured capillary walls *and damage to GBM* → escape of RBCs into urine *(hematuria)* → ↓ GFR → *activation of renin –angiotensin system* → oliguria, fluid retention, and azotemia.**

  Resulting in generalized edema
- **Hypertension (a result of both the fluid retention and some augmented renin release from kidneys).**

Extra :
Why does GFR decreases although the barrier (capillary wall) is breached ?
Because the inflammatory mediators will cause vasoconstriction to the afferent and efferent glomerular arterioles and the proliferated cells will block the capillary lumin.

1- Membranoproliferative Glomerulonephritis (MPGN)

As the name implies, in this disease we have a change and proliferation in the filtration membrane.

- **Abnormal proliferation of glomerular cells.**
- **Usually nephritic syndrome; others have a combined nephrotic-nephritic picture.**
- **Types of MPGN:**

1-type I (80% of cases)→ immune complex disease

2-type II → ***excessive complement activation***

Most of the nephritic syndrome causing diseases are due to immune complexes deposition, these immune complexes will lead to inflammation

Type I MPGN

- **circulating immune complexes**
- **Many associations :hepatitis B and C; SLE; infected A-V shunts.**

Type II MPGN (*dense-deposit disease*)

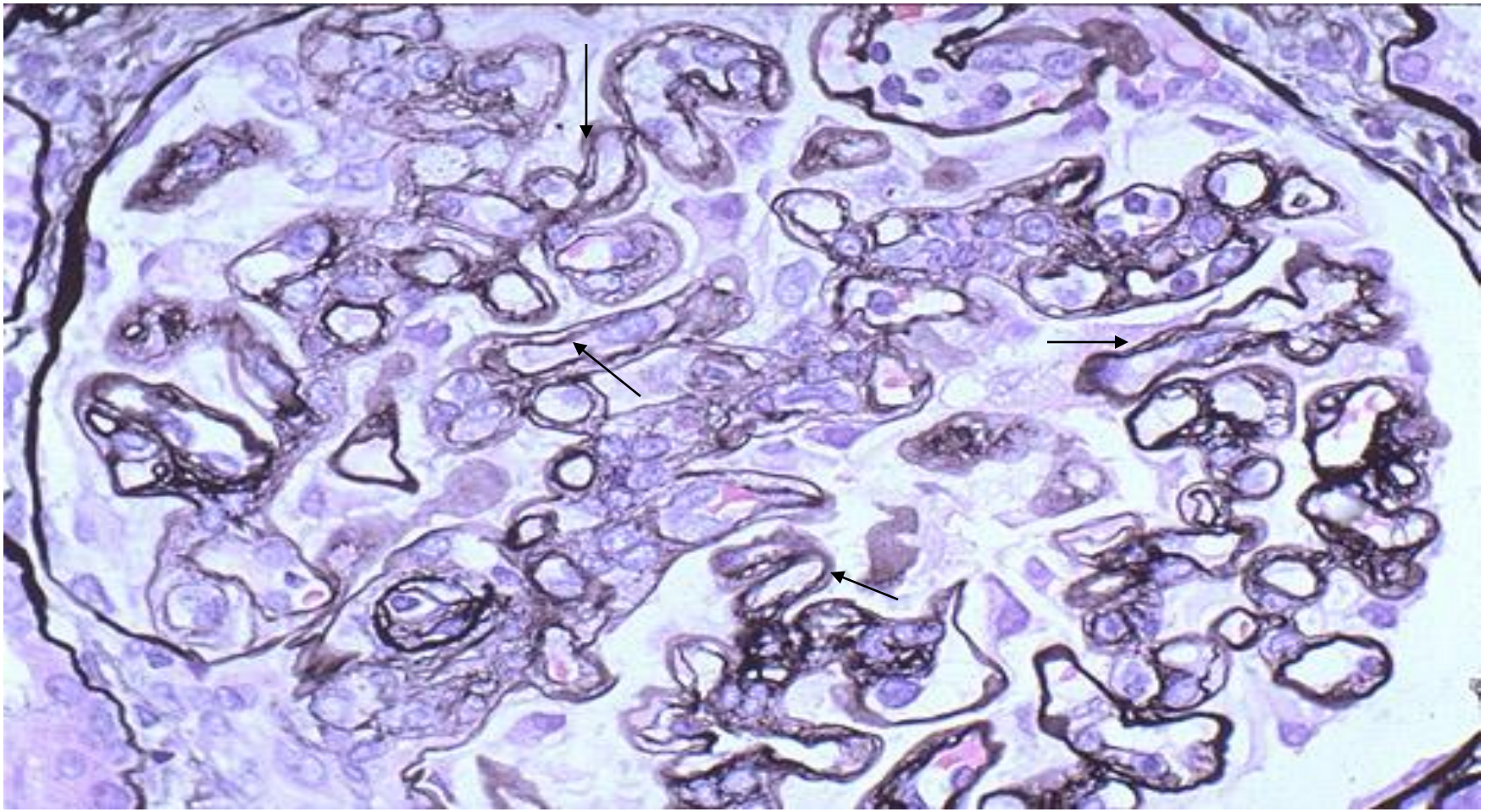
- **excessive complement activation**
- ***The reason is an*** **autoantibody against C3 convertase called C3 nephritic factor (it stabilizes *and activates* C3 convertase and lead to uncontrolled *continuous* cleavage of C3 and activation of the alternative complement pathway).**
- ***The result is*** **Hypocomplementemia,** ***because we are contiously cleaving them, and the activated C3 will reach the kidney and deposits inside the glomerulus***

- **Morphology**
- **LM**
- **both types of MPGN are similar by LM.**
- glomeruli are large with accentuated lobular appearance and show proliferation of mesangial and endothelial cells as well as infiltrating leukocytes
- **GBM is thickened (double contour or "tram track")**

Characteristic morphology

- **The tram track appearance is caused by "splitting" *and doubling* of the GBM**

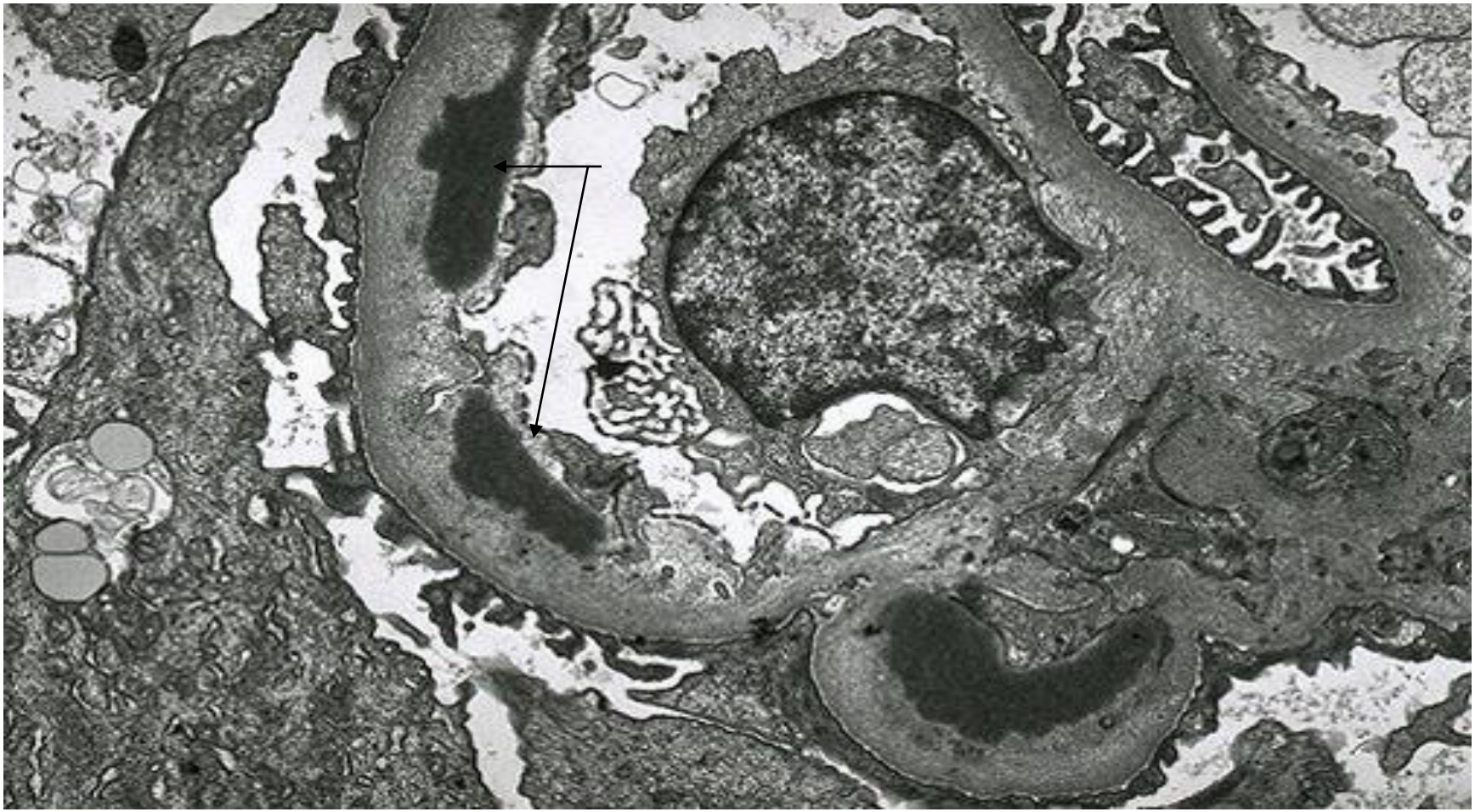
silver stain -double contour of the basement membranes("tram-track")that is characteristic of (MPGN)(arrows).



- IF
- **Type I MPGN** →subendothelial electron-dense deposits . (**IgG and early complement components (C1q and C4**)

- **Type II MPGN→ C3** is deposited in an irregular pattern.

EM-dense deposits in the basement membrane of MPGN type II in a ribbon-like mass of deposits *of C3* (arrows)



- ***Clinical Course***
- prognosis poor *(Poor response to treatment)*.
- No remission.
- 40% progress to end-stage renal failure.
- 30% had variable degrees of renal insufficiency.
- **Dense-deposit disease has a worse prognosis *than type I*.**
- **It tends to recur in renal transplant recipients**

2- Acute Postinfectious (Poststreptococcal) Glomerulonephritis (PSGN)

- *A very common condition in pediatric (usually the patient is a child or young adult)*
- *Related to inflammation and proliferation inside the glomerulus (as other diseases that lead to nephritic syndrome).*
- *Pathogenesis:*
- *After the recovery of an infection (not in the kidney but in the skin or pharyngitis streptococcal –as the name implies-) the body will produce antibodies against the bacteria, these antigens cross-react with antigens found in the glomerulus.*
- deposition of immune complexes +proliferation of glomerular cells and leukocytes (neutrophils).
- Not direct infection of the kidney
- Causes:
- poststreptococcal GN (most common).
- Infections by other organisms as pneumococci and staphylococci

Here the immune complexes circulate in the blood then get trapped in the glomeruli.
The doctor said this but it doesn't sound logical to me :/

Poststreptococcal GN

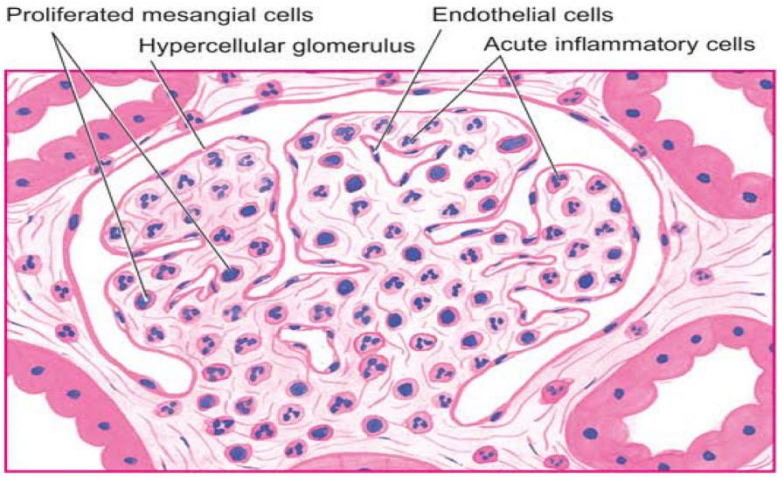
- It develops 1-4 wks after the individual recovers from a group A streptococcal infection.
- Only certain "nephritogenic" strains of β-hemolytic streptococci are capable of glomerular disease.
- In most cases pharynx or skin infection.

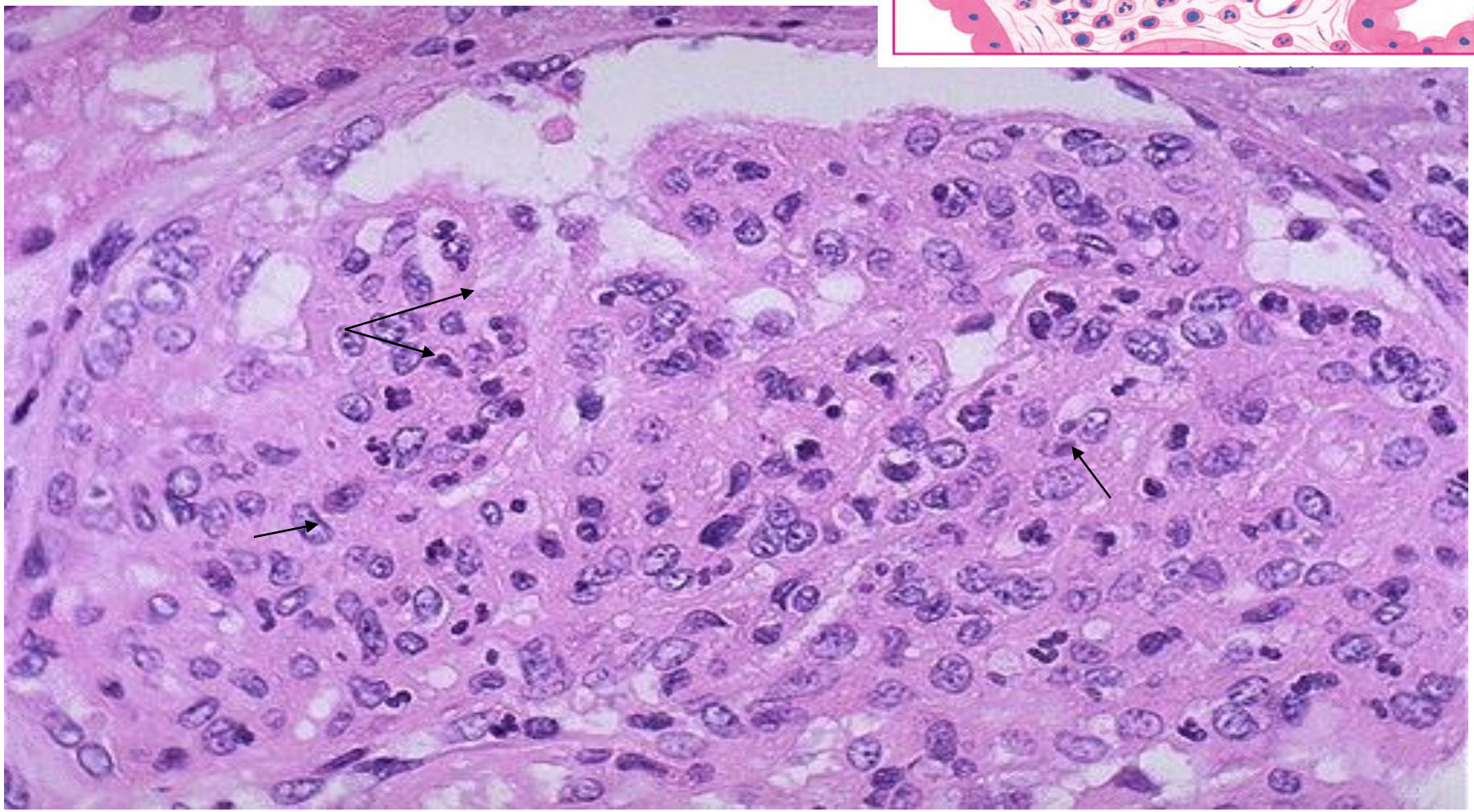
- **LM**
- **uniformly increased cellularity** of the glomerular tufts (proliferation of endothelial and mesangial cells and by a neutrophilic infiltrate).
- **IF**
- **deposits of IgG and complement** *(C3)* within the **capillary walls and mesangial areas.**
- **EM**
- immune complexes “**subepithelial "humps"** in GBM.

Post-streptococcal glomerulonephritis is due to increased numbers of epithelial, endothelial, and mesangial cells as well as neutrophils in and

around the capillary loops (arrows)

added





Clinical Course

- **acute onset .**
- **fever, nausea, and nephritic syndrome.**
- **gross hematuria.**
- **Mild proteinuria.**
- ***Hypertension, azotemia …etc (symptoms of nephritic syndrome)***
- **Serum complement levels are low during the active phase of the disease.**
- ***The only prove we have that these patient had a streptococcal infection is* ↑serum anti-streptolysin O antibody titers.**
- **Recovery occurs in most children *(good prognosis)*.**

3- IgA Nephropathy (Berger Disease)

- one of the most common causes of recurrent microscopic or gross hematuria
- children and young adults.
- episode of hematuria 1 or 2 days of nonspecific upper respiratory tract infection.
- hematuria lasts several days and then subsides and **recur** every few months.

Pathogenesis

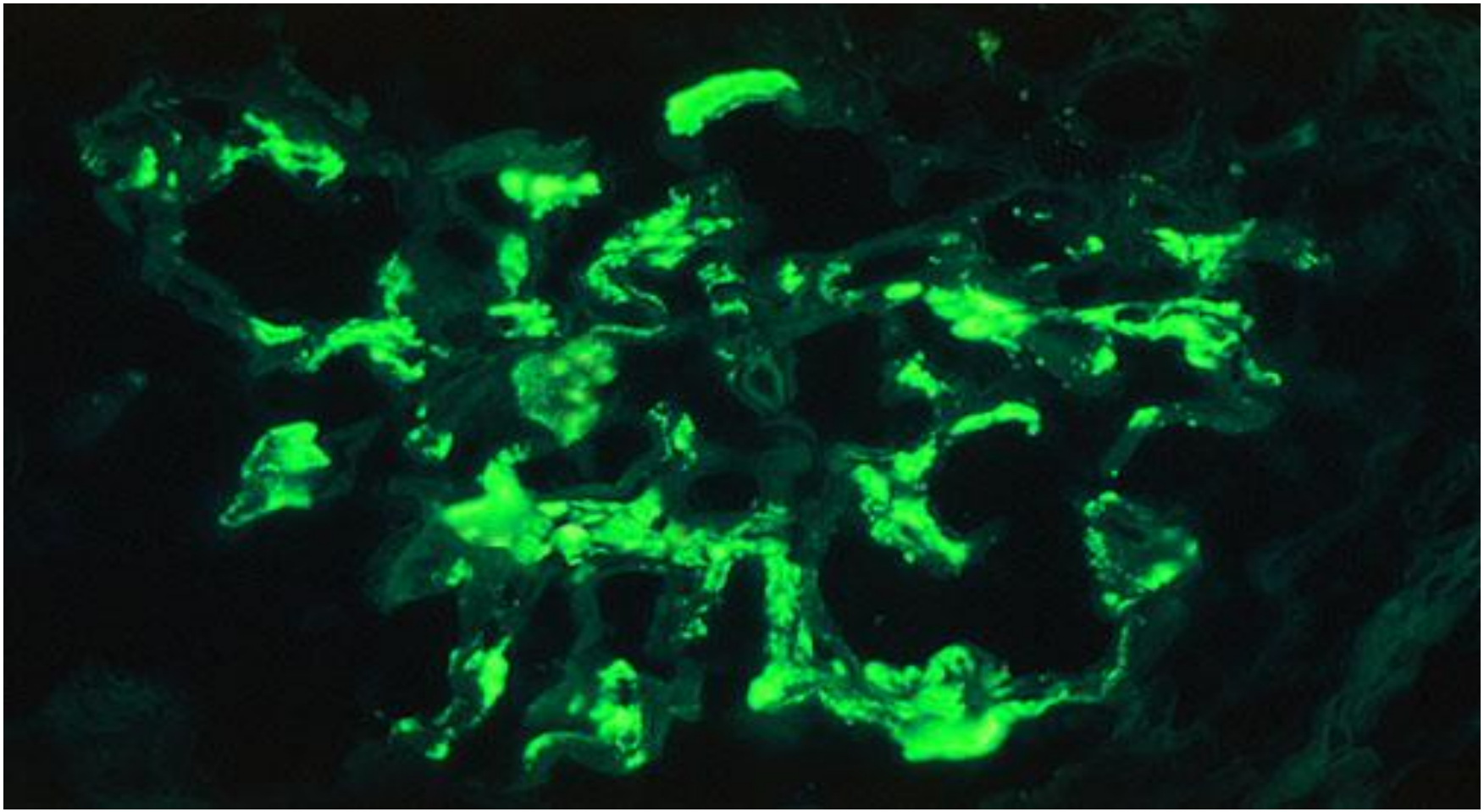
- **abnormality in IgA production, *activation and/or* clearance.**

- **LM: variable**
- **focal proliferative GN; diffuse mesangial proliferation or crescentic GN.**
- **IF**
- **mesangial deposition of IgA** with C3
- **EM**
- Electron-dense deposits in the **mesangium**

IF :IgA mesangial staining.

The diagnostic test is immunofluorescence for IgA complexes, because

this is the only disease with IgA deposition.



Rapidly Progressive (Crescentic) Glomerulonephritis

Remember :
Its a clinical picture in which the patient develops renal failure starting from normal kidney within a short period of time (days or weeks), similar to nephritic and nephrotic syndromes, its not caused by one disease, as more than one disease can lead to it.

Rapidly Progressive (Crescentic) Glomerulonephritis

In this disease, we are only required to know about crescents(قوس) and that there are 3 types, each of them with a certain etiology and immunofluorescence findings.
The next 3 slides are not required for the sake of the exam.

- characterized by the presence of crescents (crescentic GN).
- proliferation of the **parietal epithelial cells of Bowman's capsule** in response to injury and infiltration of monocytes and macrophages ,*and maybe fibroblasts. (all of this in response to inflammation)*
- **nephritic syndrome rapidly progresses to oliguria and azotemia.**

Not required

- ***Pathogenesis***
- **Type I (Anti-GBM Antibody):**
- **(12%)**
- linear deposits of IgG and, C3 on the GBM.
- Anti-GBM antibodies are present in the serum and are helpful in diagnosis.
- Plasmapheresis which removes pathogenic antibodies from the circulation is beneficial

Not required

- **Type II (Immune Complex) (**44%**):**
- Idiopathic
- E.g. SLE, Henoch-Schönlein purpura/IgA nephropathy, etc

- **Type III (Pauci-Immune) ANCA Associated (**44% **):**
- Idiopathic
- E.g. Wegener granulomatosis**;** Microscopic angiitis

Not required

- **IF**
- According to type:
- **Type 1→ linear IgG along GBM**
- **Type 2→ Igs and complements**
- **Type 3→ no deposits**
- **EM**
- **According to type:**
- **Type 1→ linear along GBM**
- **Type 2→ immune complexes**
- **Type 3→ no deposits**

Crescentic GN (PAS stain).
the collapsed glomerular tufts and the crescent-shaped mass of proliferating cells and leukocytes internal to Bowman's capsule.

This figure is important…
-whenever this morphology is seen, the patient is at high risk of losing his renal function in a short period

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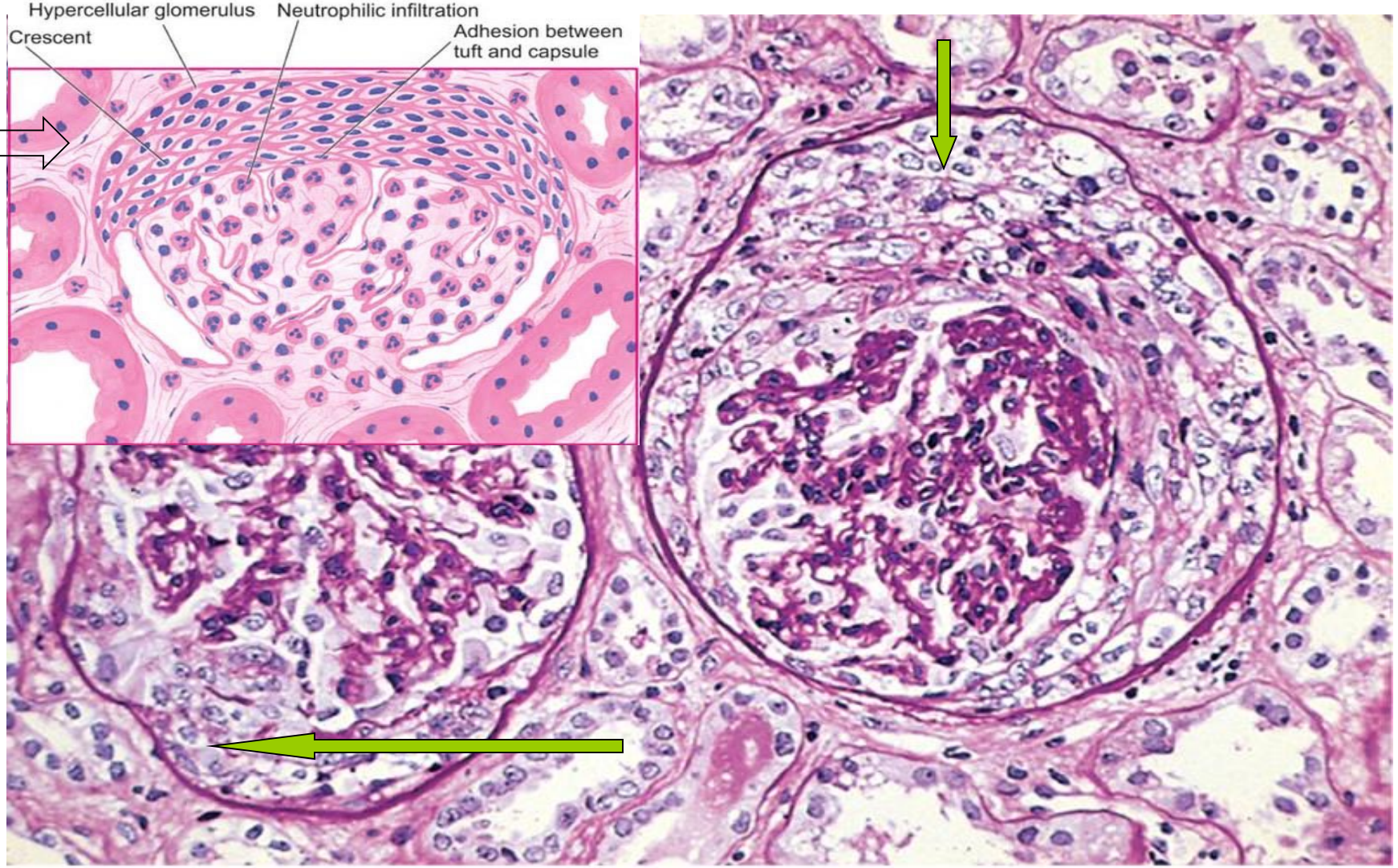

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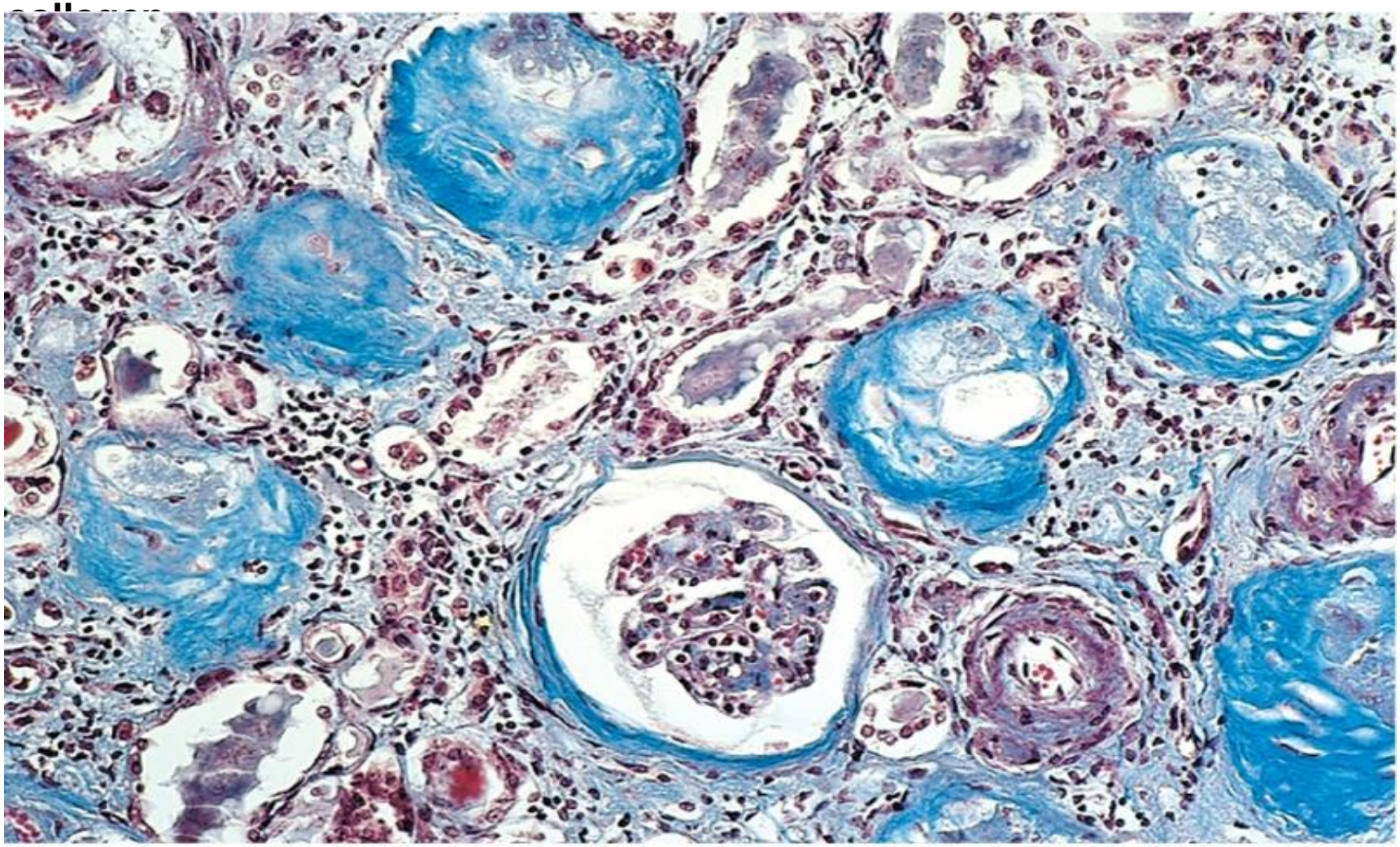
Chronic Glomerulonephritis

- *Here, we might not be able to know what is the underlining disease, but what we can see is end-stage kidney, meaning that function is lost in the kidney.*
- Among all chronic renal failure, 30% to 50% chronic GN.
- the end stage of any glomerular disease
- **Morphology = end-stage kidneys**
- kidneys are **symmetrically contracted.**
- **LM**
- **scarring of the glomeruli, interstitial fibrosis; tubular atrophy; thick walled, with narrowed blood vessles**

Chronic GN.

A MT stain shows complete replacement of virtually all glomeruli by blue-staining collagen.

Those blue circles used to be glomeruli, but as a result of an injury, fibrosis occurred in them.



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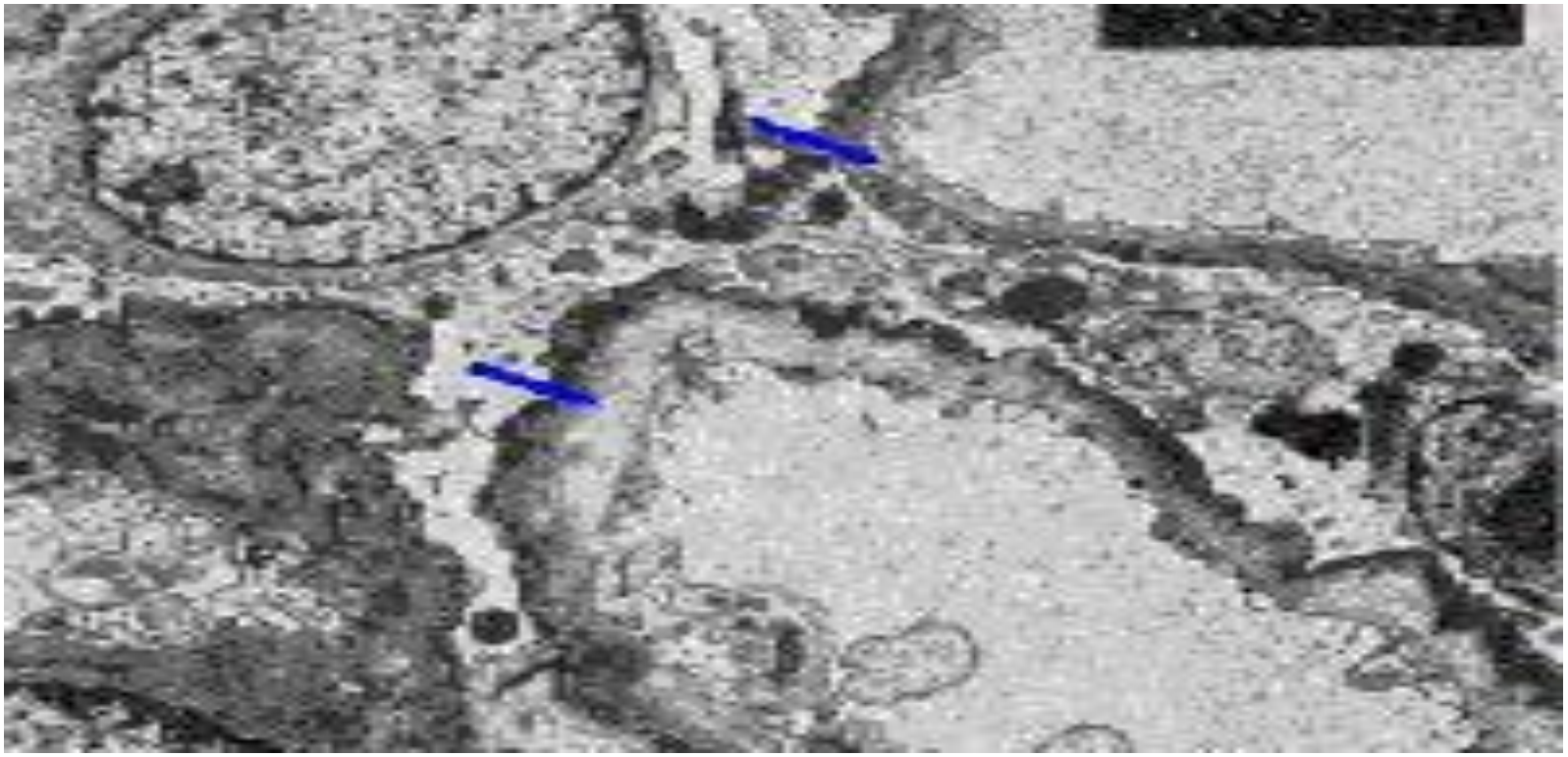
Hereditary Nephritis

- **a group of hereditary glomerular diseases caused by mutations in GBM proteins (most common** X-linked**.**
- **Most important type: Alport syndrome:**
- **= <u>nephritis + nerve deafness + eye disorders</u>, including lens dislocation, posterior cataracts, and corneal dystrophy.**
- <u>Pathogenesis:</u>
- Mutation of any one of the **<u>α chains of type IV collagen</u>**
- overt renal failure occurs between 20- 50 yrs of age

*Collagen type IV is a main component of the basement membrane **<u>in all of our body</u>** but the effect of the mutation above will be most visible in the eyes, middle ear and kidney. These patients will have defective glomerular basement membrane.*

- **EM**
- **GBM thin and attenuated *(weak)***
- **GBM later develops splitting and lamination "basket-weave" appearance**



Disease	Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Poor?
MNP	nephrotic	adults	Thickened GBM	IgG+C3 Granular capillary deposits	Sub-epithelial spikes and domes	Poor?
MPGN-type1	nephritic	adults	Tram track	Igs	Subendothelial deposits	poor
MPGN-type2	nephritic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropth	nephritic	Children, adults	variable	IgA capillary deposits	Subepithelial deposits	good±
PSGN	nephritic	children	Glomerular hypercellularity	IgG+ C3 capillary deposits	Subepithelial deposits	good
Alport syndrome	hematuria, hearing loss	children	variable	negative	Basket weave GBM	poor