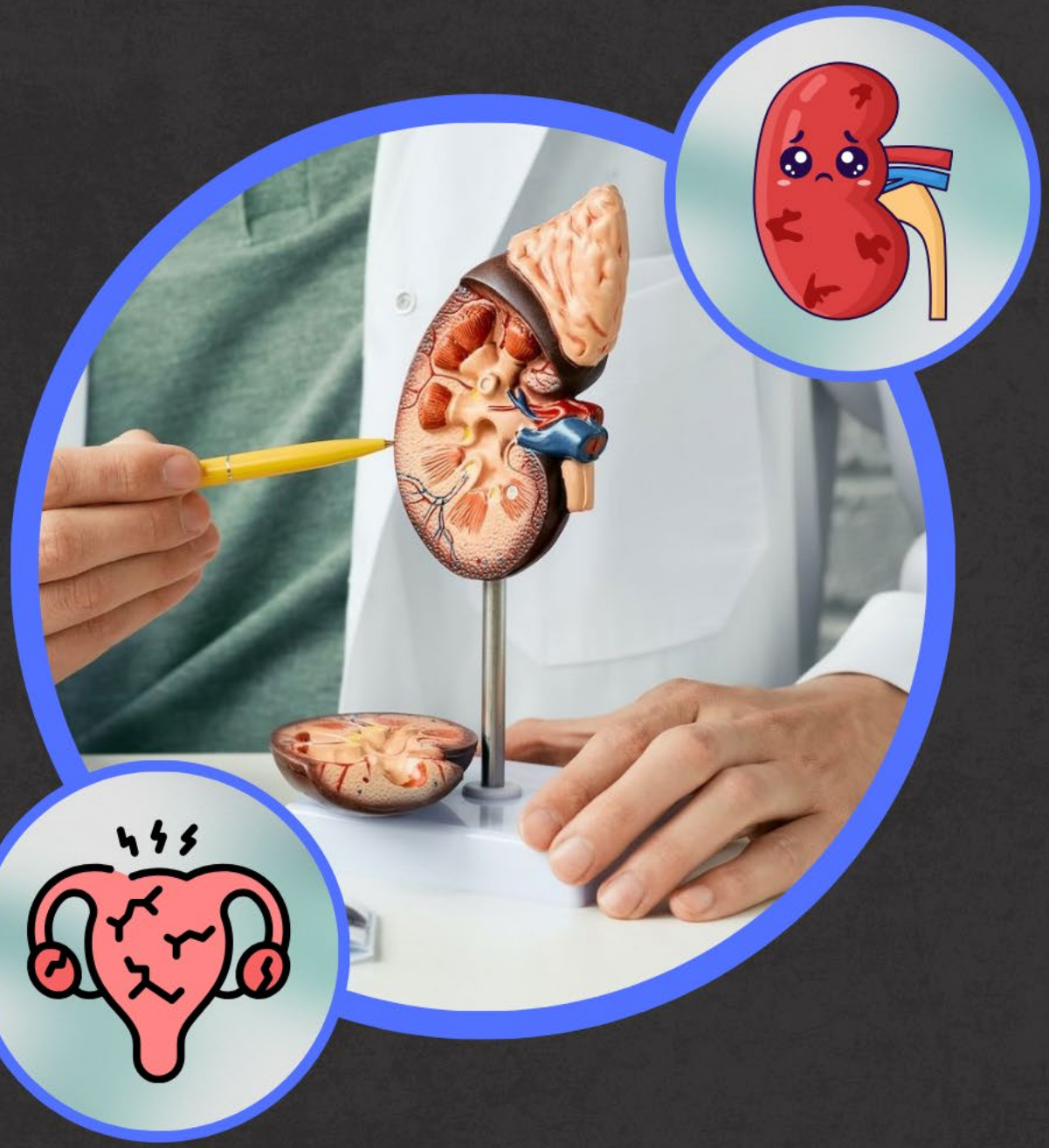


PATHO

MODIFIED NO. 3

الكُتّاب: اسماعيل العارضة وميس

المدققين: ليث الخزاعلة

الدكتور/ة: نسرين شاهين

Nephritic syndrome

Color code
Slides
Doctor
Additional info
Important

Dr. Nisreen Abu Shahin

Nephritic Syndrome: Presentation

- **PHAROH**
- ***P**roteinuria*
  - *<3.5g/1.73m2/day*
- ***H**ematuria*
  - *Abrupt onset*
- ***A**zotemia*
  - *Increased creatinine and urea*
- ***R**BC Casts*
- ***O**liguria*
- ***H**TN*

Peripheral Edema/Puffy Eyes

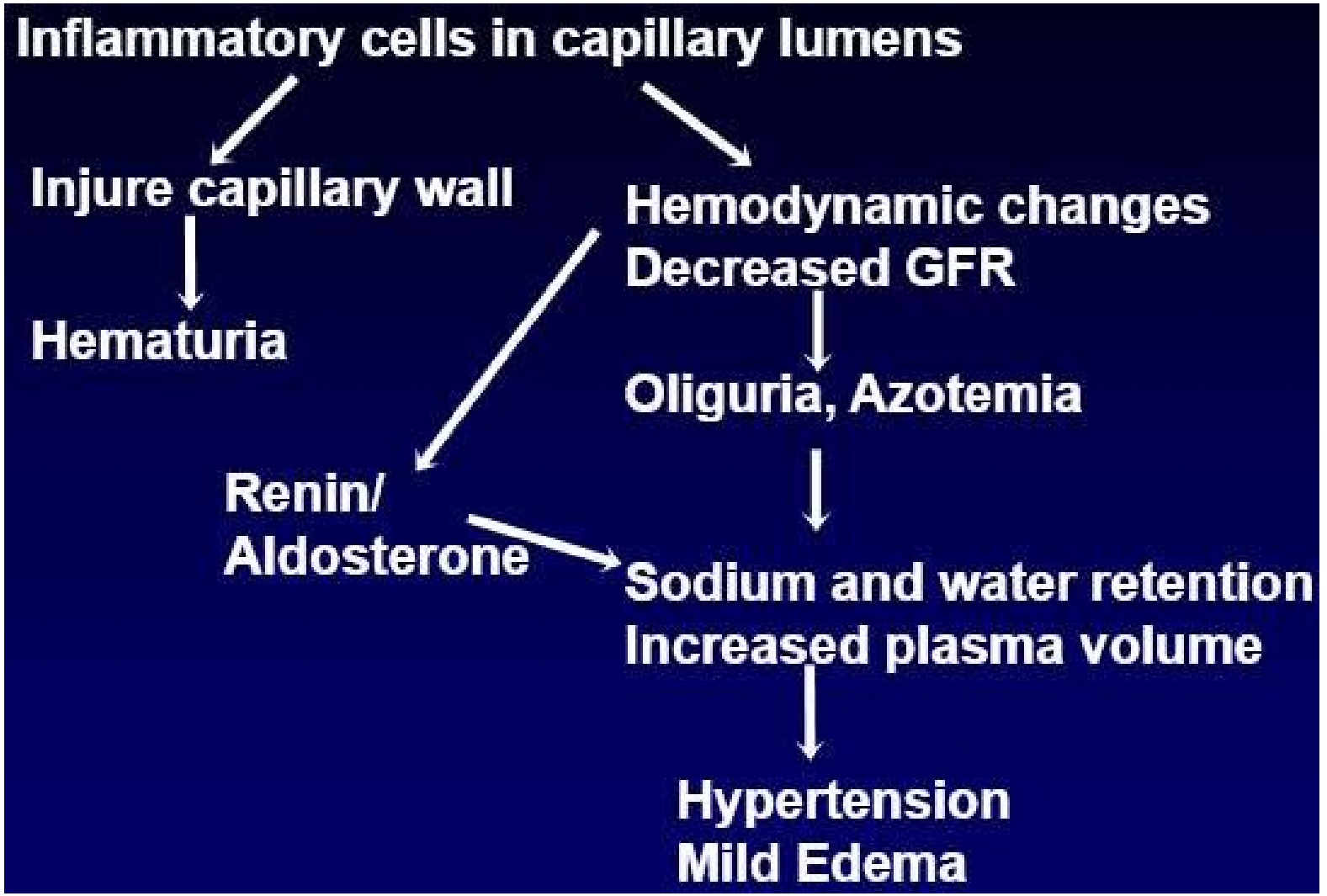
Two urine samples showing gross and microscopic hematuria: in Nephritic Syndrome

- Proteinuria in nephritic syndrome isn't as heavy as the proteinuria we've in nephrotic syndrome, it's usually non-nephrotic range proteinuria meaning that it's less than 3.5g/day.
- Hematuria is the presence of RBC in urine.
- RBC casts are indication of a glomerular origin of hematuria.
- Oliguria is a decrease in urine output also as a manifestation of renal impairment.
- Hypertension (HTN) is related to the fluid retention and azotemia.

The Nephritic Syndrome

- Pathogenesis: inflammation (in the glomerular).
- **leukocytes infiltration** that produce different kinds of chemicals that will stimulate **proliferation of cells in glomeruli.**
- **Injury of capillary walls → escape of RBCs into urine (hematuria & RBC casts)**
- ↓ **GFR** (glomerular filtration rate) → **oliguria, fluid retention (edema), and azotemia** (impairment of the renal clearance of toxic substances).
- **Hypertension (result of both fluid retention and ↑renin release from kidneys).**
- **May have some proteinuria**

Pathogenesis

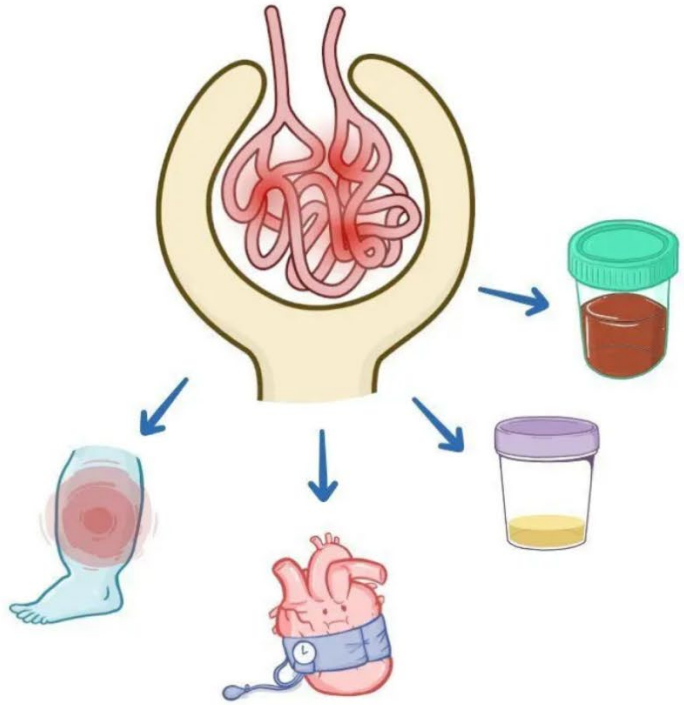


- Recap: regarding the pathogenesis of nephritic syndrome, it begins by the production of inflammation inside the glomerular capillary lumina and this inflammation and the presence of inflammatory cells will lead to both injury of the capillary walls and so the escape of RBCs producing hematuria and RBC casts and on the other hand, they will lead to hemodynamic changes that will eventually lead to decreased GFR which will produce oligouria and azothemia.
- Together with renin and aldosterone access augmented work, this will lead to sodium and water retention, increased plasma volume which will all produce hypertension and edema.

- Extra

NEPHRITIC SYNDROME

* GLOMERULONEPHRITIS
* INFLAMMATION and DAMAGE to KIDNEY'S GLOMERULI
* UNDERLYING CONDITIONS:
  - INFECTIONS
  - GENETIC CONDITIONS
  - AUTOIMMUNE DISEASES



- Extra

RENAL SYNDROMES

NEPHROTIC vs. NEPHRITIC

NEPHROTIC
a·k·a non-proliferative

↳ Sx are all about loss of prOtein

- Oedema
- frOthy
- prOteinuria
- hypOalbuminaemia

(+ hyperlipidaemia)

NEPHRITIC
a·k·a proliferative

↳ All about Inflammation + proliferation

- haematuria → RBC casts & dysmorphic RBCs
- oligouria
- ↑BP (due to Na^+ + H_2O retention)

(+ some proteinuria)

HUMERUS HACKS

To learn more check out episode #16: "Glomerul-You'll-Know-Nephritis"

Glomerular diseases mostly presenting with Nephritic syndrome

1 Membranoproliferative Glomerulonephritis (MPGN)

- **Abnormal proliferation of glomerular cells** as well as inflammation.
- **Usually nephritic syndrome; some have a combined nephrotic-nephritic picture.**
- **<u>Types of MPGN:</u>**

1 type I (80% of cases)→ immune complex disease (The inciting antigen is not known).

2 type II → ***excessive complement activation*** (called dense deposit disease).

Type I MPGN

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

- Certain circulating immune complexes travel through the circulation, reach the kidney and get deposited there inside the glomeruli when theyare deposited inside the glomeruli, they will elicit an inflammatory reaction.
- This inflammation will begin the cascadeof different changes that will give us the pathogenesisof nephritic syndrome.

Type II MPGN (*dense-deposit disease*)

- ***Cause*: excessive complement activation**
- **autoantibody against C3 convertase called *C3 nephritic factor* (it stabilizes the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway).**

- **Result: Hypocomplementemia**

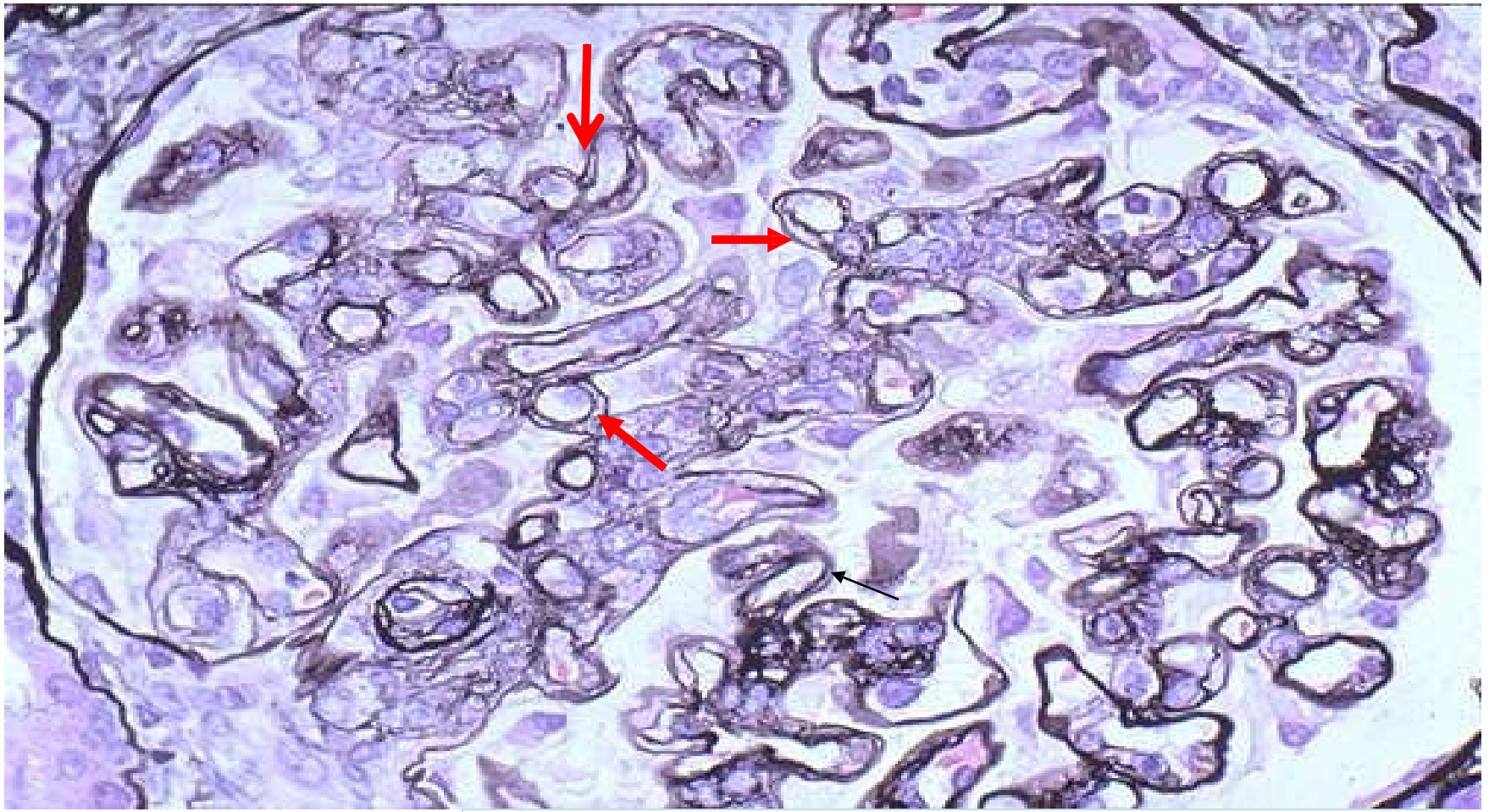
> - The activated C3 particles will travel in the circulation, they will reach the glomeruli and get deposited.

- **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** because the inflammation as well as the injury that happens inside the glomerular membrane and deposition of immune complexes (**double contour** or **"tram track").**
- The **tram track** appearance is caused by **"splitting" of the GBM.**

“tram-track“ appearance

2 parallel lines in the basement membrane instead of one

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



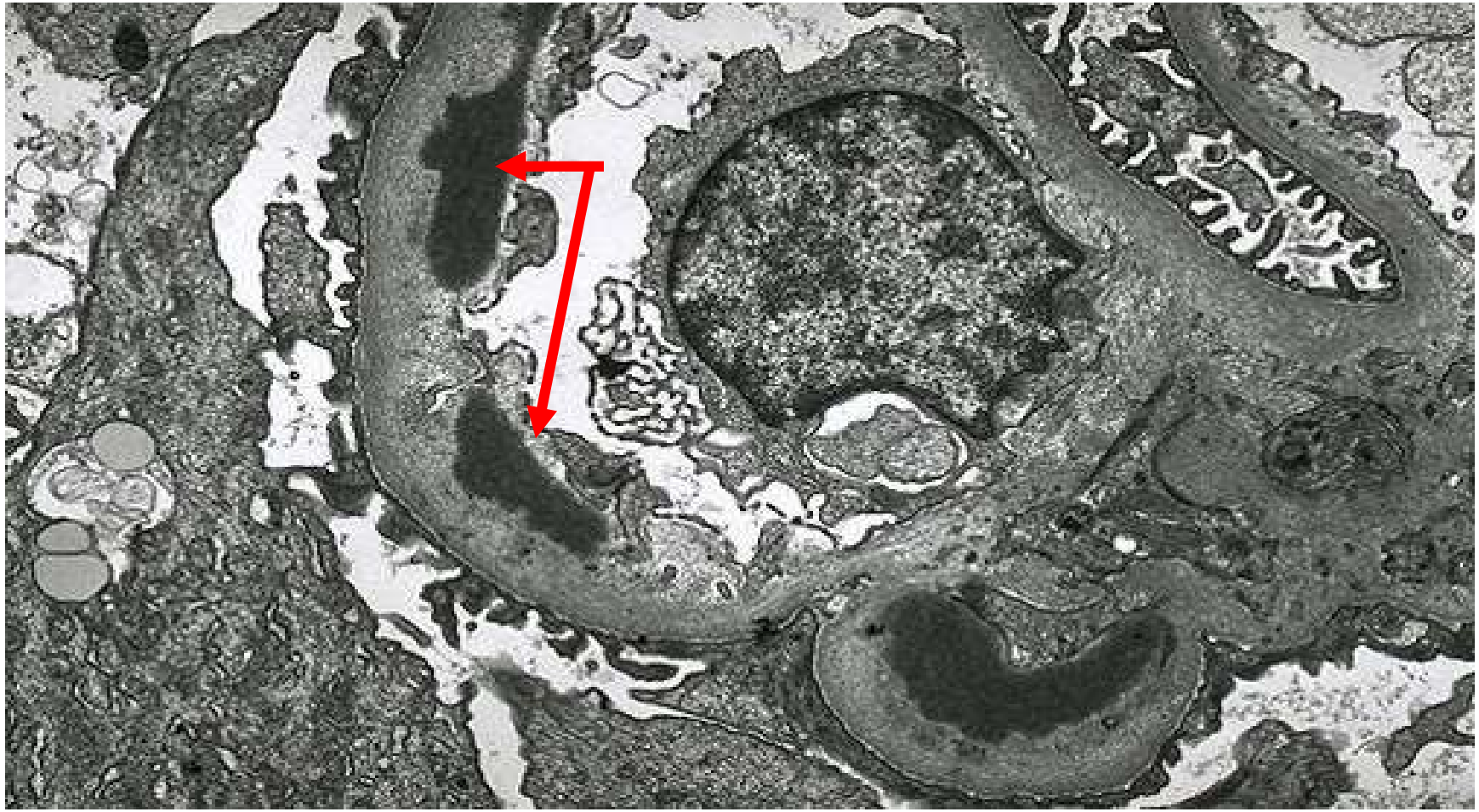
silver stain: stains basement membranes black

- The black color represents the glomerular basement membrane (GBM), silver stain is used to show us the elastic fibers inside the basement membrane.
- The red arrow show us a double lines of basement membrane instead of the normal single line of the basement membrane.
- And there is a double contour or the tram-tracking appearance, so the presence of double contour or tram-track appearance in the light microscope is actually characteristic of this disease in MPGN.

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

- **Type II MPGN→ C3 alone in GBM** because the pathogenesis is related to excessive and abnormal C3 complement activation.

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



- The red arrows show us some immune deposited within the basement membrane in this case of type II MPGN.
- Because the color of these deposits is very dark and dense, it was called dense deposited disease.
- These deposits are composed of C3 without immunoglobulins.

- ***Clinical Course***
- prognosis poor.
- No remission.
- 40% progress to end-stage renal failure.
- 30% had variable degrees of renal insufficiency.
- **Dense-deposit disease (type II) has a worse prognosis.**
- **It tends to recur in renal transplant recipients** because the problem is within the immune system of the patient, not inside the glomeruli.

2- Acute Postinfectious (Poststreptococcal) Glomerulonephritis (PSGN)

- deposition of **immune complexes** + proliferation of glomerular cells and leukocytes (neutrophils).
- Not direct infection of the kidney (it is a post infectious process).

- Cause: an immune-mediated reaction to a previous infection of pharynx or skin.
- most commonly, Post-streptococcal infection.
- Infections by other organisms also possible as pneumococci and staphylococci.

The clinical presentation

- 1-4 wks after recovery from a group A β-hemolytic streptococci infection **(pharynx or skin)**, patient will start develop clinical manifestations related to the kidney glomeruli.

- A few strains (3%)of **β-hemolytic streptococci** are capable of this.

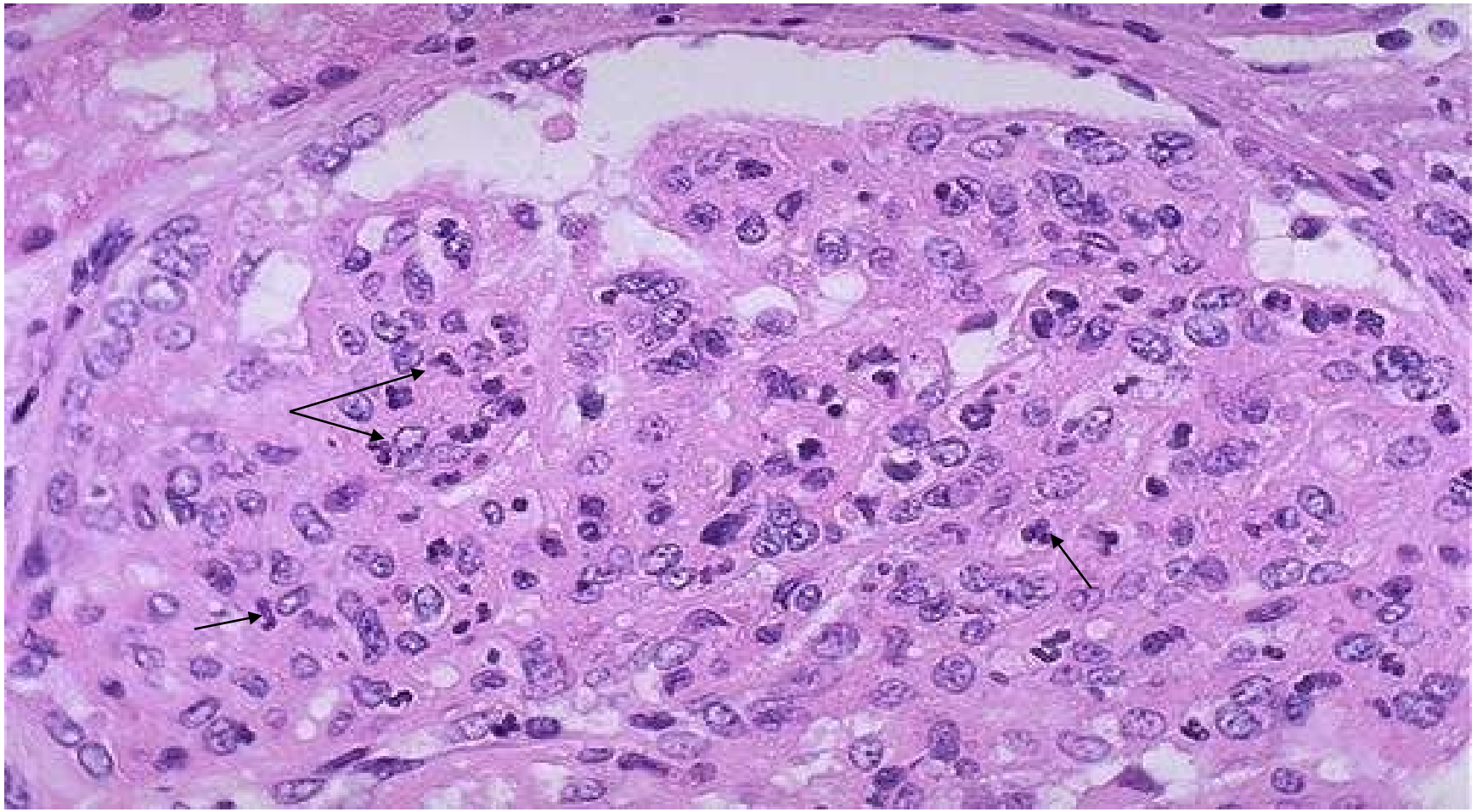
- **Mechanism:**

1. Binding of immune complexes that formed against streptococcal antigens and these complexes will be deposited within the GBM proteins.

2. Antibodies to bacterial antigens "planted" in the GBM.

This will lead to activation of the inflammatory cascade inside the glomeruli and this will give us the picture of Nephritic Syndrome.

PSGN: <u>increased epithelial, endothelial, and mesangial cells as well as neutrophils in and around the capillary loops</u> (arrows)

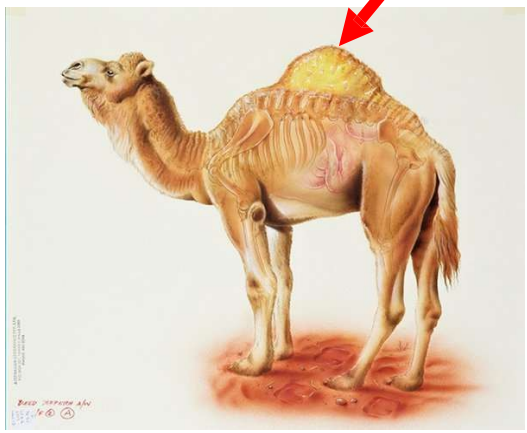


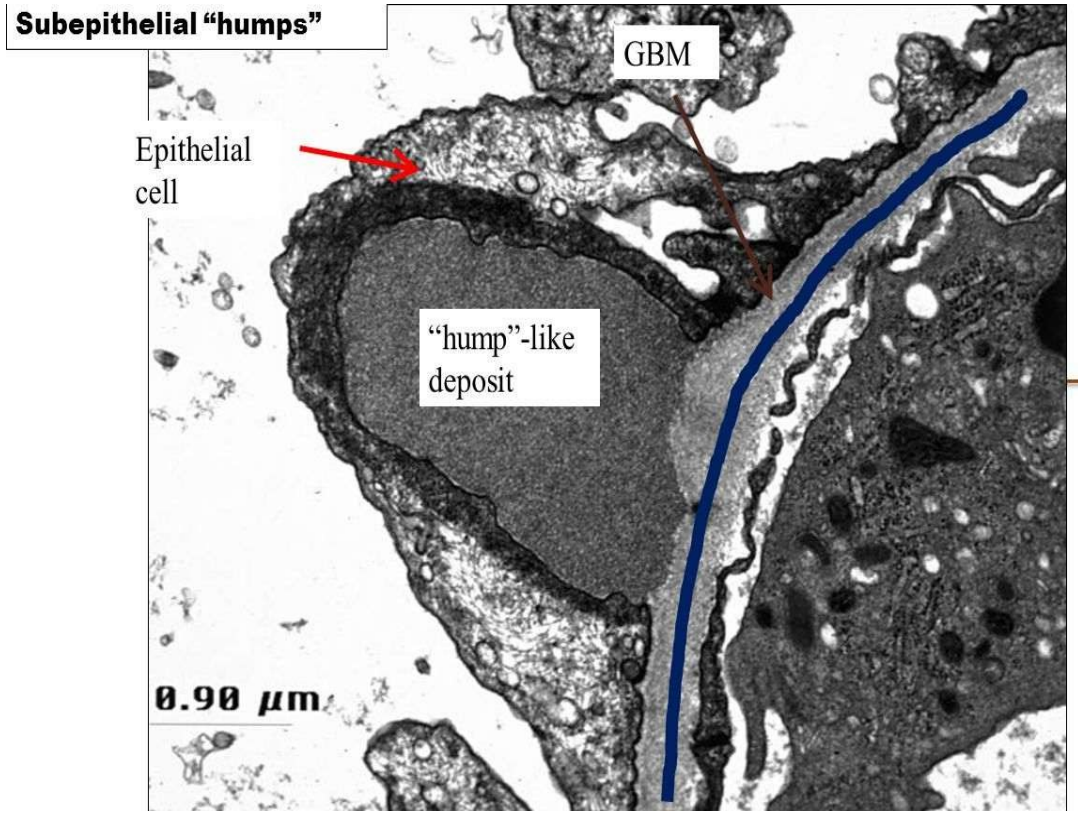
The presence of all these cells in the glomeruli will cause crowding within the glomerular tuft and occlusion of the capillary lumina.

- **LM** (light microscopy)
- Proliferation of endothelial and mesangial cells and neutrophilic infiltrate.

- **IF (**immunofluorescence)
- Because the pathogenesis involves inflammation and the formation and deposition of immune complexes within the glomeruli, the immunofluorescence (IF) will be positive.
- Deposits of IgG and complement within the capillary walls.

- **EM** (electron microscopy)
- Immune complexes forming "**subepithelial "humps"** in GBM.





- So this is an electron microscopic picture from a case of poststreptococcal glomerulonephritis and it shows us these sub-epithelial humps. These are the humps, and as you can see why they were called humps, they look like the hump of a camel, and they are present just beneath the podocytes on this side of the glomerular basement membrane, so they are sub-epithelial indication.

- This finding is the characteristic of post-infectious glomerulonephritis. Now, these deposits, if we are talking about immunofluorescence tests, they will be positive for immunoglobulins , mainly immunoglobulin G, as well as complements mainly C3.

PSGN- Clinical Course

- Acute onset .
- Many of patients are children
- fever, nausea, and nephritic syndrome.
- gross hematuria.
- Mild proteinuria.
- Serum complement levels are low during the active phase of the disease.

  (If we examine the blood of those patients, we will find serum hypocomplementemia, which means low levels of complements, mainly complement C3, inside the serum during the active phase of the disease. This is an indication of activation of the alternative pathway of complement system).

- **↑ Serum anti-streptolysin O antibody titers.**

- Now, to confirm that this case we are dealing with is poststreptococcal glomerulonephritis , we need to have a confirmation that this patient had a prior infection with streptococci, and this is done using a serum test against streptococcal antigens, or antibodies. So, high serum levels of anti-streptolysin or antibody titers is regarded as an evidence of a prior infection with streptococci, and by that we can confirm that the case we are dealing with is poststreptococcal glomerulonephritis.

- **Recovery occurs in most children.**

- Because the pathogenesis of this condition is all related to a hormone process inside the immune system and the production of those antibodies, these antibodies can be cleared from the circulation within a period of time, and with clearance of these antibodies from the circulation, the patient will go into recovery. So, recovery following poststreptococcal glomerulonephritis is usually the mainstay, and it happens in most cases.

3- IgA Nephropathy

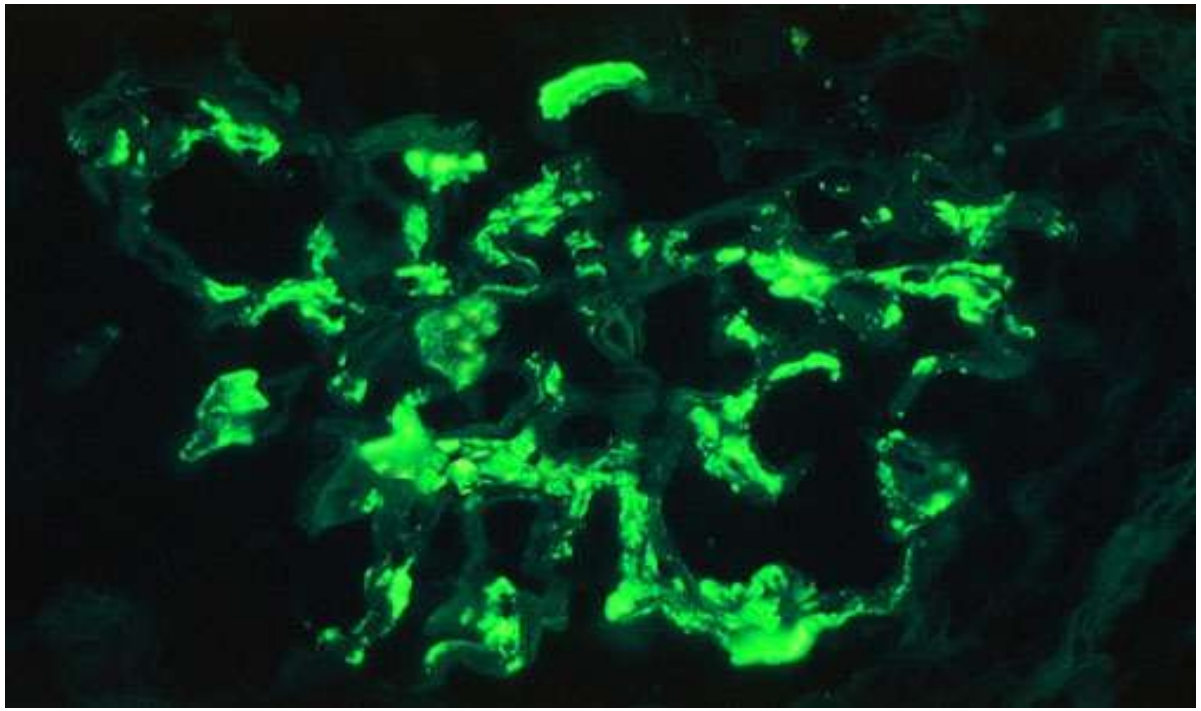
- one of the **most common causes** of recurrent microscopic or gross hematuria.
- children and young adults.
- hematuria 1 or 2 days after **nonspecific** upper respiratory tract infection.
- hematuria lasts several days and then subsides and then recur every few months.
- So the clinical scenario, as you can see, is recurrent or episodic hematuria.

Pathogenesis

- Abnormality in IgA production and clearance.

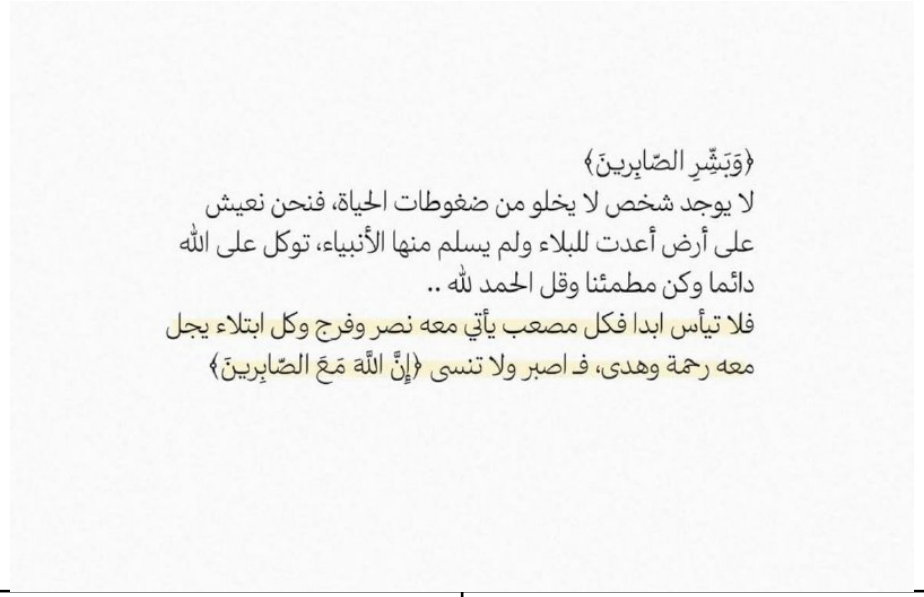
- **LM: variable.**
- **IF:** is very characteristic, and the one that we need to memorize here, which is **mesangial deposition of IgA with C3.**
- **EM: deposits in the mesangium.**
- So here the main injury is inside the mesangium. The deposition here is by immunoglobulin A.

IF : IgA mesangial staining.



- This is an immunofluorescence picture showing us a case of IgA nephropathy. The fluorescent areas here represent the mesangium inside this glomerulus. So this is a glomerulus, and these areas represent the mesangium. The mesangium, as you can see, is positive. It is fluorescent. It gives us this fluorescent color when we use an antibody against IgA. This finding is very characteristic and actually diagnostic of IgA nephropathy.

Disease	Usual Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Progressive
MNP	nephrotic	adults	Thickened GBM	IgG+ C3+	Sub-epithelial spikes and domes	Progressive
MPGN-type1	Nephritic/ nephrotic	adults	Tram track	Ig s	Subendothelial deposits	poor
MPGN-type2	Nephritic/ nephrotic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropthy	nephritic	Children, young adults	variable	IgA+	Mesangial deposits	variable
PSGN	nephritic	children	hypercellularity	IgG+ C3+	Subepithelial deposits (humps)	good



VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

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