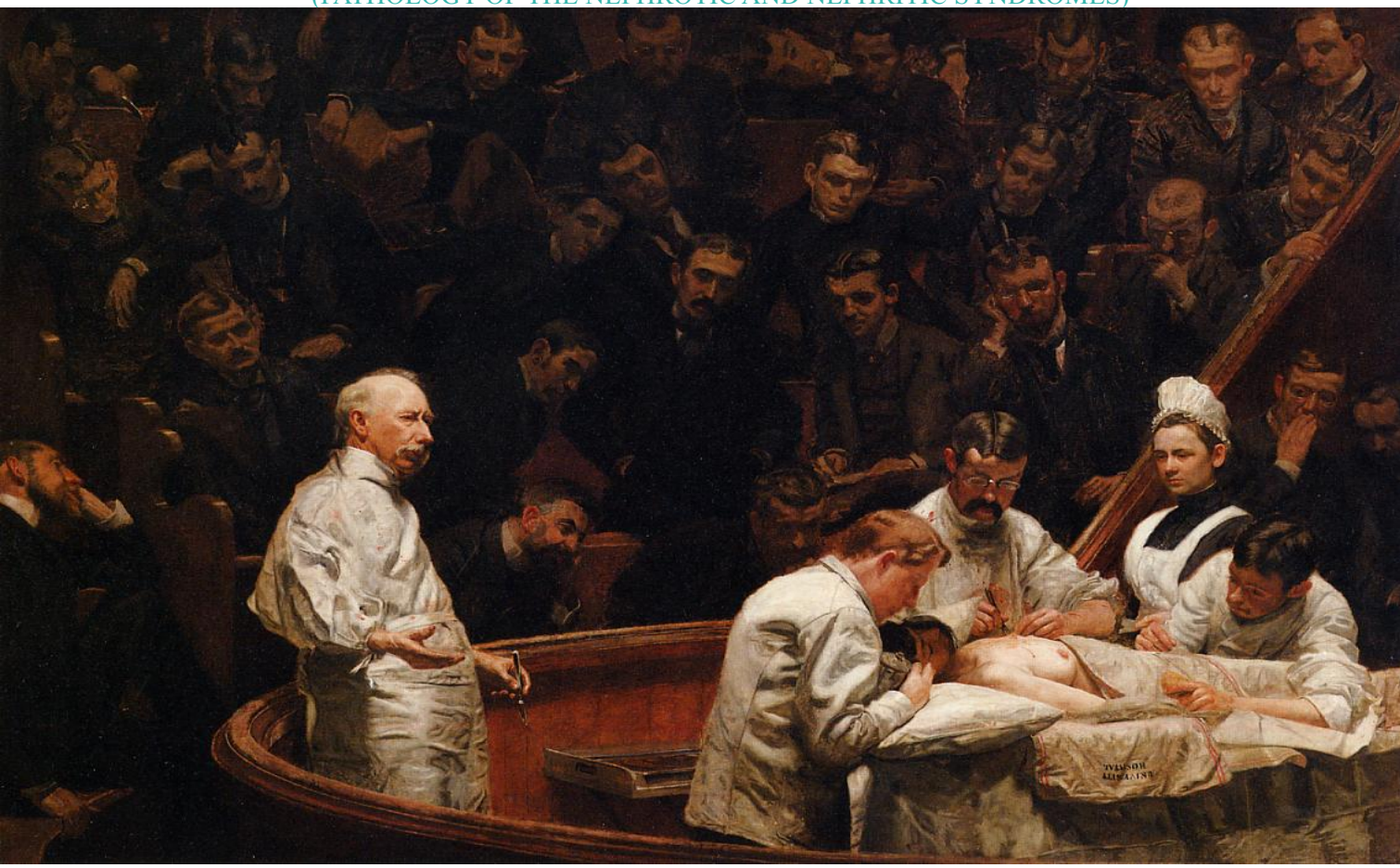
GLOMERULAR DISEASES

(PATHOLOGY OF THE NEPHROTIC AND NEPHRITIC SYNDROMES)



"If we win here we will win everywhere. The world is a fine place and worth the fighting for."

-Ernest Hemingway

تحت المراجعة
غيداء آل مصمم
&
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Objectives

-Recognize the five major renal clinical syndromes.

-Describe the pathology

-Describe the main differential pathological diagnosis for each syndrome.

-Perform a clinico-pathological correlation.

-Describe the patterns of injury of each syndrome.

*Important *Doctor notes

MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Introduction

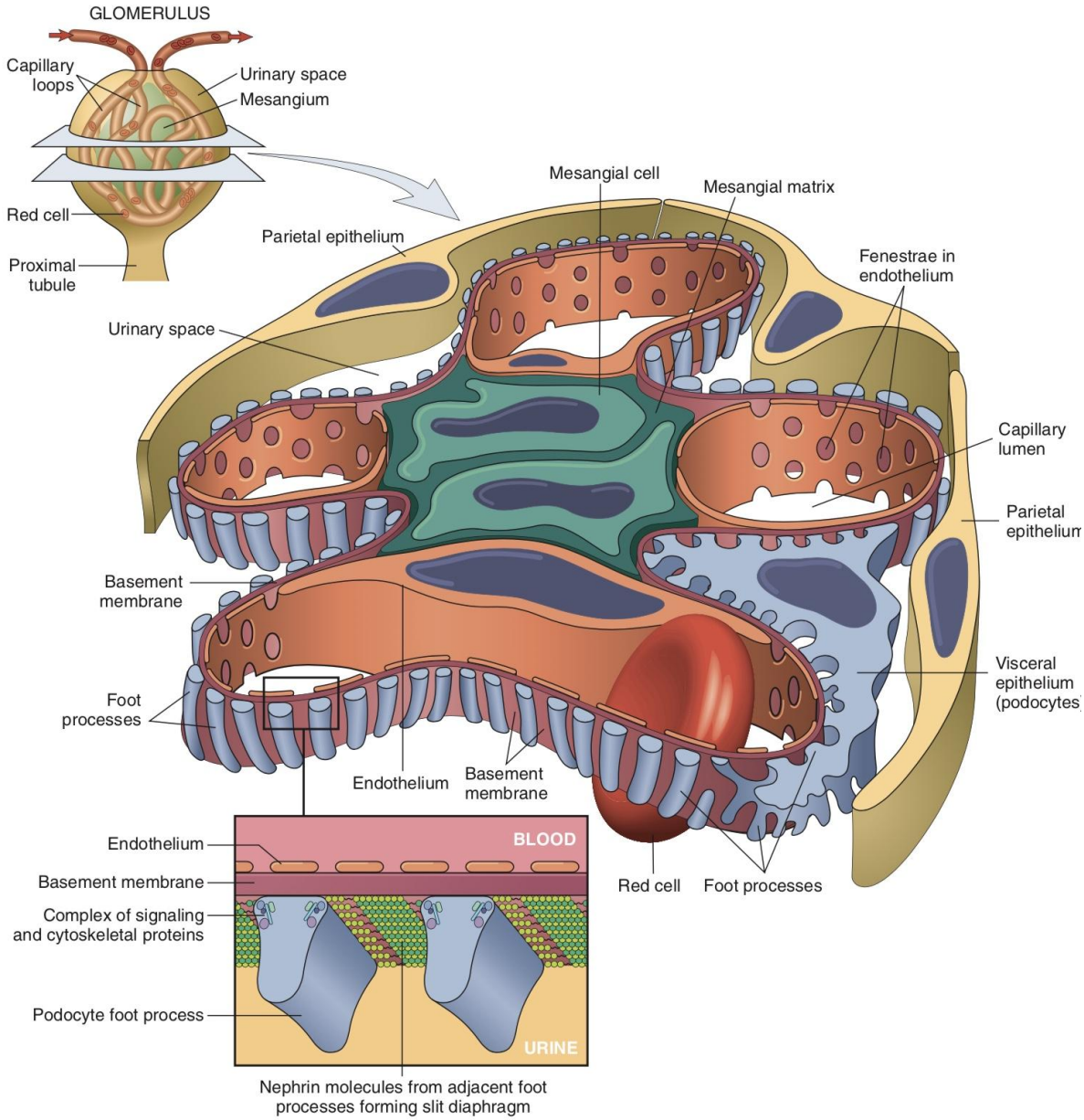
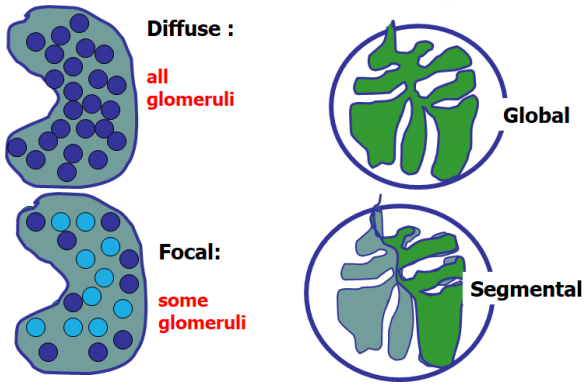


Figure 13–1 Schematic diagram of a lobe of a normal glomerulus.



Terminology:- The following terms are used to describe the extent of glomerular injury:

- Diffuse: All glomeruli are affected
- Focal: Some glomeruli are affected
- Segmental: Part of the glomerulus is affected
- Global: The entity of one glomerulus is affected

Overview


CRESCENTIC GLOMERULONEPHRITIS:
Type I, anti-GBM disease
Type II, immune complex-mediated
Type III, pauci immune (ANCA-associated)
creatinine is jumping
Rapidly progressive GN syndrome
global scelorosis
And interstitial fibrosis
Chronic nephritic syndrome
Chronic Renal Failure
end stage renal failure
Asymptomatic hematuria/proteinuria syndrome
Renal clinical syndromes
A- minimal change disease
B- Focal Segmental Glomerulosclerosis (FSGS)
C- Membranous nephropathy
1- Alport syndrome
2- IgA nephropathy
Primary cause:
Nephrotic syndrome
loss of protein in urine less
than 3.5/ day – hematuria
loss of protein in urine
more than 3.5 g/day
Nephritic syndrome
A- diabetic neuropathy
B- Amyloidosis
C- Lupus nephritis (class V)
1- Acute post-infectious GN
Secondary cause:
(To systemic disease)
2-Membranoproliferative
glomerulonephritis
A) MPGN type I.
B) MPGN type II Dense deposit disease (DDD)
ultrastructural studies of the glomerulus
are used to features like the position and
location of immune complex, basement
membrane reactions and epithelial changes.
3- Electron microscopy
1- Light microscopy
using routine (haematoxylin and eosin)
and special stains.
Techniques used for studying
of glomerular diseases
2- Immunofluorescence
antibodies tagged (labeled) with
fluorochrome are used to localize
immune reactants in the glomerulus.

Glomerular diseases

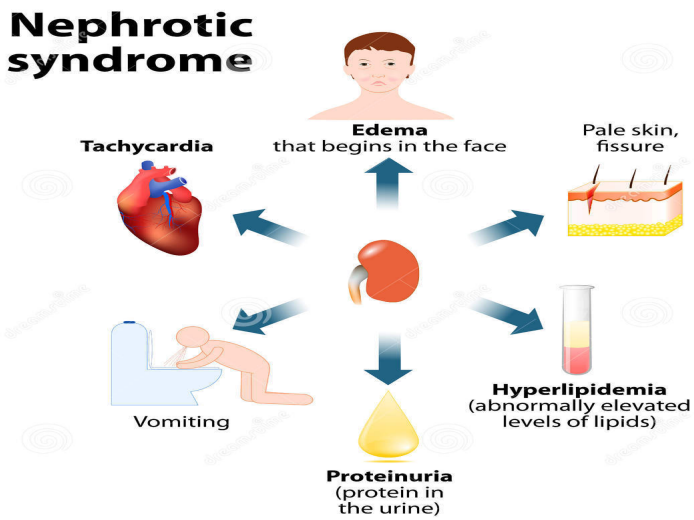
Nephrotic syndrome

Includes a group of conditions characterized by increased basement membrane permeability, permitting the urinary loss of plasma proteins, particularly **low-weight proteins** such as **albumin**.
*the conditions that without it you can't have proteinuria foot process will be flat in the electron microscope

Clinical manifestations:

In all diverse causes of the nephrotic syndrome there is a *derangement* in the capillary walls of the glomeruli that results in *increased* permeability to *plasma proteins* → allows protein to escape from the *plasma* into the *glomerular filtrate* →**extremely *heavy proteinuria***, serum albumin is decreased→ *hypoalbuminemia* and a drop in plasma colloid osmotic pressure. → Increased release of *renin* from renal juxtaglomerular cells → Renin in turn stimulates the angiotensin aldosterone axis→ promotes the retention of salt and water by the kidney. At the onset, there is little or no *azotemia, hematuria*, or *hypertension*.

- Heavy proteinuria = proteins in urine = loss of 3,5 g/day.
- Not accompanied by increased urinary red cells or white cells. (No increased cells or no cells).
- Hypoalbuminemia is often marked by Serum concentration of less than 3g/ 100 ML
- Generalized edema results from decreased plasma colloid or oncotic pressure.
- Hyperlipidemia and hypercholesterolemia are caused by increased hepatic lipoprotein synthesis.



Primary Nephrotic syndrome

1.Minimal change disease (lipoid nephrosis)

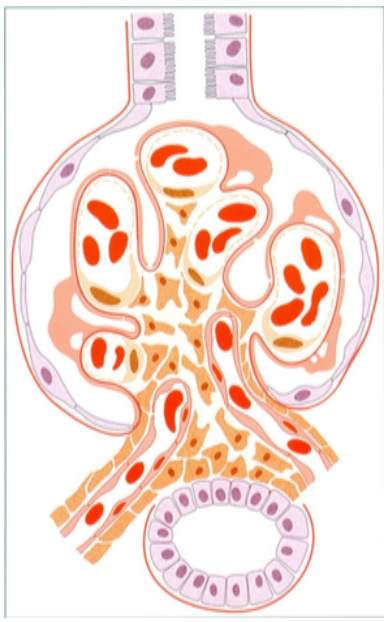
Diffuse Epithelial Cell Disease

Seen most often in young children but can also occur in older children and adults. It is the prototype of the nephrotic syndrome.

Pathogenesis: T cell release cytokines "for unknown reason" into the foot process which is lead to destroy them.

- Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells) particularly in cells of proximal convoluted tubules.
- **Light microscopy:** normal-appearing glomeruli.
- **Electron microscopy:** normal except for the diffuse effacement of epithelial foot processes.
- **Immunofluorescence microscopy (IF):** **Negative**
- Most often this condition responds well to corticosteroid therapy. More than 90% of children.
- Benign disorder, the most frequent cause of the nephrotic syndrome in children (most commonly between the ages of 1 – 7 yrs).
- The protein loss usually is confined to the smaller plasma proteins, chiefly albumin (selective proteinuria). Only albumin will go so it is selective.

The glomeruli are normal by LM, but with diffuse effacement of foot processes by EM.



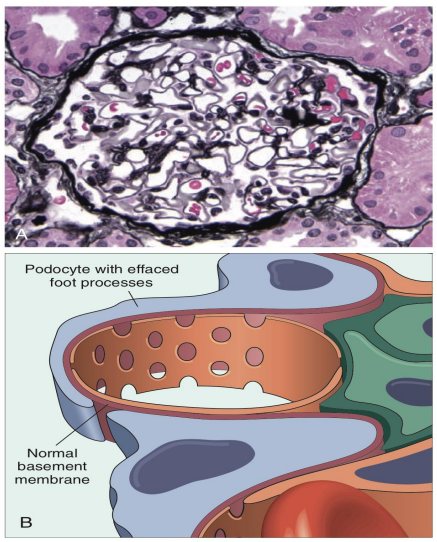
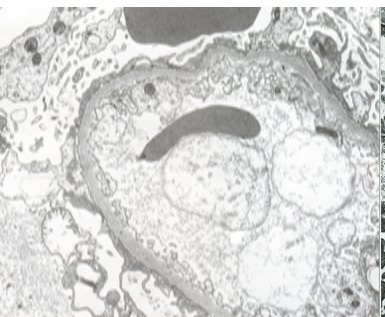
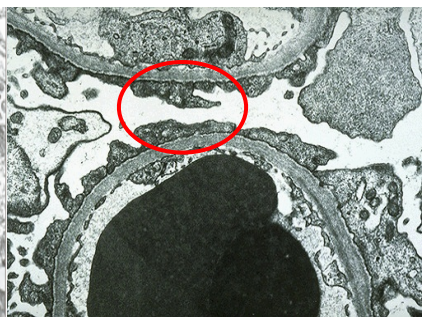


Fig. 14.5 Minimal-change disease. (A) When viewed with a light microscope, the silver methenamine–stained glomerulus appears normal, with a delicate basement membrane. (B) Schematic diagram illustrating diffuse effacement of foot processes of podocytes with no immune deposits.

Minimal change disease **EM**:
1- Extensive foot process effacement.
2- microvillous transformation of visceral epithelial





Minimal change disease **EM**:
1- Extensive foot process effacement.
2- microvillous transformation of visceral epithelial cells in MCD.

2.Focal segmental glomerulosclerosis(FSGS):

Clinically similar to minimal change disease but occurs in somewhat older patients It is characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution. Defined as obliteration[1] of capillary loops and increased matrix, without deposits and with diffuse foot process effacement[2] by EM. Adhesions can also be present.

- Injury to the podocytes is thought to represent **the initiating event of primary FSGS.**
- The incidence of hematuria and hypertension is higher in persons with FSGS than in those with minimal-change disease.
- **Proteinuria is nonselective**; and in general the response to corticosteroid therapy is **poor**.
- FSGS may be :

  1- primary (idiopathic)

  2- secondary: to one of the following conditions:

  - In association with other conditions, such as **HIV nephropathy** or **heroin nephropathy** or **sickle cell disease.**
  - As a secondary event in other forms of GN (e.g., IgA nephropathy).
  - As a maladaptation to nephron loss.
  - In inherited or congenital forms. **Autosomal dominant** forms are associated with mutations in cytoskeletal proteins and podocin, both of which are required for the integrity of podocytes. In addition, a sequence variant in the apolipoprotein L1 **gene (APOL1)** on chromosome 22 appears to be strongly associated with an increased risk of FSGS and renal failure in individuals of **African descent.**

1.obliteration : محو أو إبادة

2.effacement : محو

3. if they are treating minimal change and treatment is not effective they will take another biopsy to check for Focal segmental

Techniques that used in (FSGS)

Immunofluorescence microscopy (IF): often reveals nonspecific trapping of immunoglobulins, usually **IgM**, and complement. "Negative"
Electron microscopy(EM): the podocytes exhibit effacement of foot processes, as in minimal- change disease.[3]
Light microscopy(LM): Focal (some glomeruli) and segmental (involving only part of the glomerulus) sclerosis.

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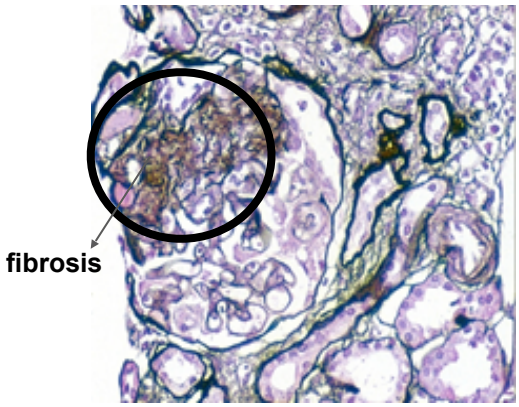
<td> 
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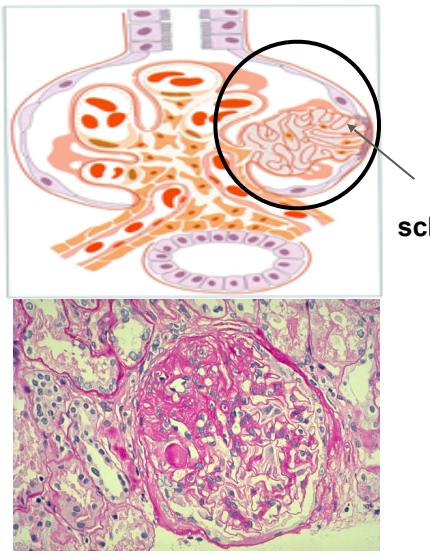
<td> 
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<td>FSGS. The typical segmental sclerotic lesion in FSGS is characterized by increased matrix and obliteration of capillary lumina, frequently with hyalinosis and adhesions, as illustrated here.</td>
<td>FSGS. There is sharply defined segmental sclerosis, defined as obliteration of capillary loops and increased matrix, without deposits and with diffuse foot process effacement by EM. Adhesions can also be present.</td>
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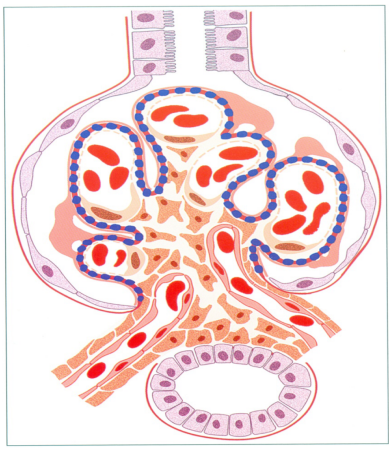
3.Membranous glomerulonephritis[4]

An immune complex disease of unknown etiology.



- This disease is a major primary cause of the nephrotic syndrome. Incidence is high in adults between 30-60 years old.
- Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.
- The diagnosis should be suspected when the nephrotic syndrome is accompanied by azotemia[5] .
- The disorder sometimes causes **renal vein thrombosis.**
- Induced by antibodies reacting in situ to endogenous or planted glomerular antigens.

1. In about **85%** of cases, membranous nephropathy is caused by autoantibodies that cross-react with antigens expressed by podocytes.
2. In the remainder (secondary membranous nephropathy), it occurs secondary to other disorders, including:

- Infections (chronic hepatitis B, syphilis, schistosomiasis, malaria)
- Malignant tumors, particularly carcinoma of the lung and colon and melanoma
- Systemic lupus erythematosus and other autoimmune conditions(class 5)
- Exposure to inorganic salts (gold, mercury)
- Drugs (penicillamine, captopril, nonsteroidal anti- inflammatory agents)

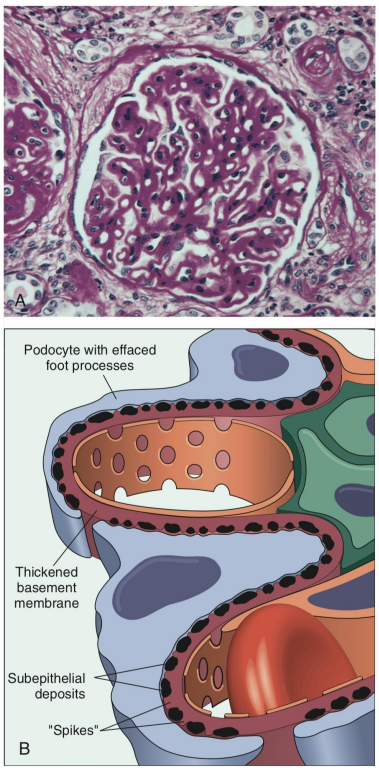


Figure 13–8 Membranous nephropathy. **A,** Diffuse thickening of the glomerular basement membrane (periodic acid–Schiff stain). **B,** Schematic diagram illustrating subepithelial deposits, effacement of foot processes, and the presence of *spikes* of basement membrane material between the immune deposits.

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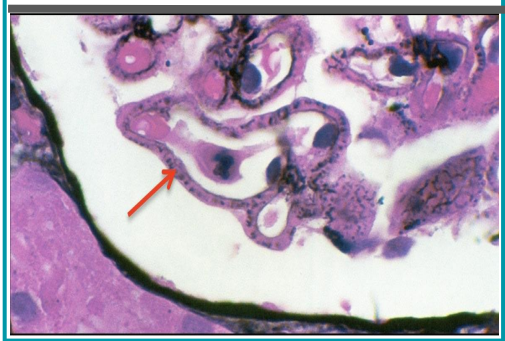
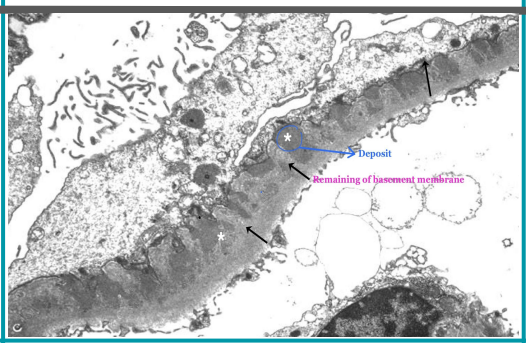
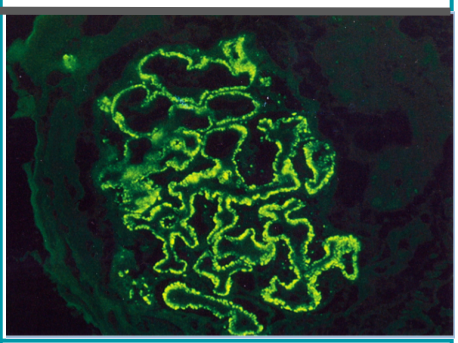
4. When you see the word membranous in Diseases you should think of thickening of basement membrane **5.azotemia:** increased concentrations of serum urea nitrogen and creatinine.

Morphological characteristic:

- There is no evident proliferation by light microscopy (LM), with global **subepithelial deposits**, which may be visualized by light microscopy by the glomerular basement membrane spike reaction on **silver stain.**
- With special stains, "spike and dome" appearance resulting from the **extension of basement membrane** between and around the immune deposits is seen; the spikes are basement membrane material and the dome are immune complex deposits.
- Granular deposits of **immunoglobulin G (IgG)** or **C3** are apparent on immunofluorescence. Granular immunofluorescence is a general characteristic of immune complex disease.
- **Greatly thickened capillary walls**, which are visible by **light microscopy** and visible by electron microscopy as 5- to 10- fold thickening of the basement membrane.
- Include numerous electron-dense **immune complexes** in **intramembranous and epimembranous (epithelia)** locations within and on the basement membrane.

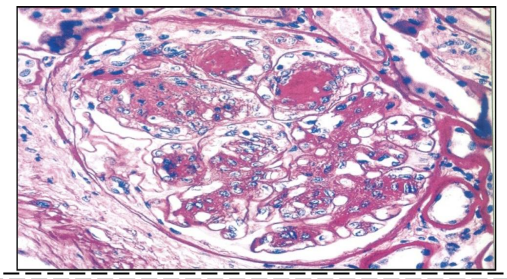
Silver stain (LM)	Electron microscopy	Immunofluorescence
		
LM: Membranous glomerulopathy. There are well-developed spikes and holes in tangential sections in stage-2 membranous glomerulopathy. "**Silver stain** colored the membrane & the deposit within the base membrane. So you will see **spikes** and **dome**".	**EM**: you'll see it directly (The dots)we can see subepithelial deposits which is the cause of thickening of the capillary wall. The subepithelial deposits is separated by small spike-like protrusion of GBM matrix. + the podocytes show effacement of foot processes.	**IF**: There is an evenly distributed granular capillary loop pattern of positively in membranous glomerulopathy. "In **IF** you will see the opposite, you will not see the membrane but you will see the dots".

1.Diabetic nephropathy

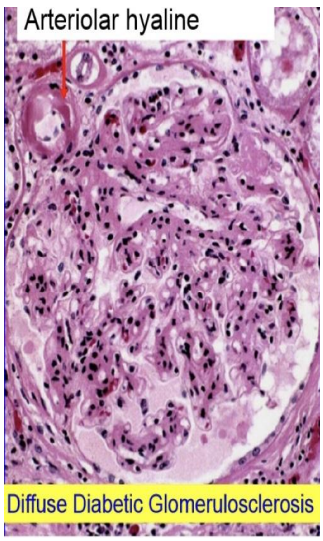
- Often,this disease is clinically manifested by the nephrotic syndrome.
- **Electron microscopy** demonstrates striking increase in **thickness of the glomerular basement membrane.** Thickening of vascular basement membrane is one of the earliest morphologic changes in diabetes mellitus.
- An increase in mesangial matrix results in two characteristic morphologic patterns:

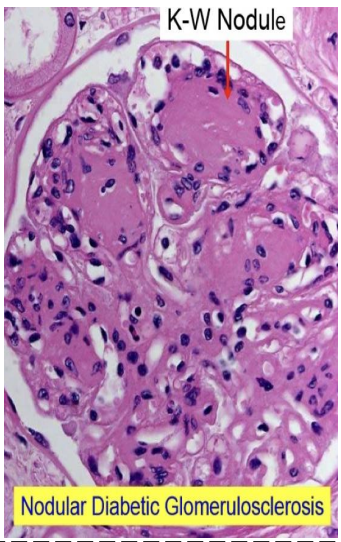
1. **Diffuse glomerulosclerosis** is marked b a diffusely distributed increase in mesangial matrix.
2. **Nodular glomerulosclerosis** is marked by nodular accumulations of mesangial matrix material **(Kimmelstiel-Wilson nodules)**.

Diabetic nephropathy may manifest either as diffuse mesangial increase, or with nodular glomerulosclerosis as in this case.

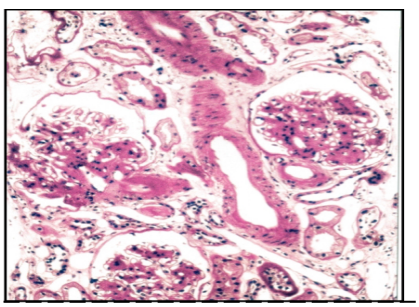


Diabetic nephropathy.The lamellated appearance of the Kimmelstiel-Wilson nodule characteristic of the nodular sclerosis form of diabetic nephropathy is shown, along with arteriolar hyalinization and surrounding tubulointerstitial fibrosis.



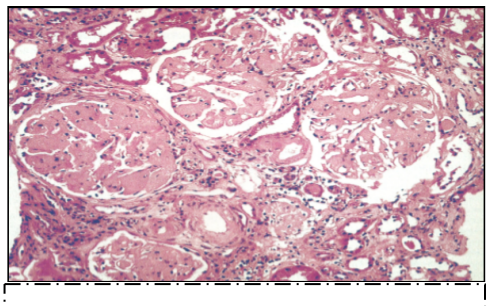


The lesions in diabetic nephropathy are characterized by arteriolar hyalinization, mesangial matrix expansion and glomerular basement thickening.



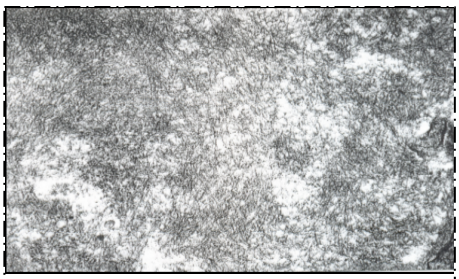
2- Renal amyloidosis[6]:

- This condition is another cause of nephrotic syndrome.
- Predominantly subendothelial and mesangial amyloid deposits are characteristic.
- The amyloidosis can be identified by reactivity of amyloid with special stains (e,g, Congo Red, crystal violet, thioflavin T) and by birefringence under polarized light. It is also demonstrated by a characteristic criss cross fibrillary pattern of amyloid by electron microscopy.
- Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumors such as multiple myeloma. .

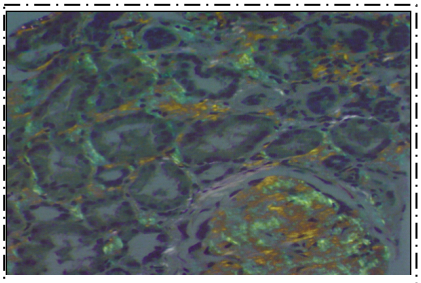


L/mMassive amyloid deposits are present in glomeruli and arterioles

Congo Red Stain gold standard



EM/ Randomly oriented, **8-10nm** fibrils, typical of amyloid within the mesangium.

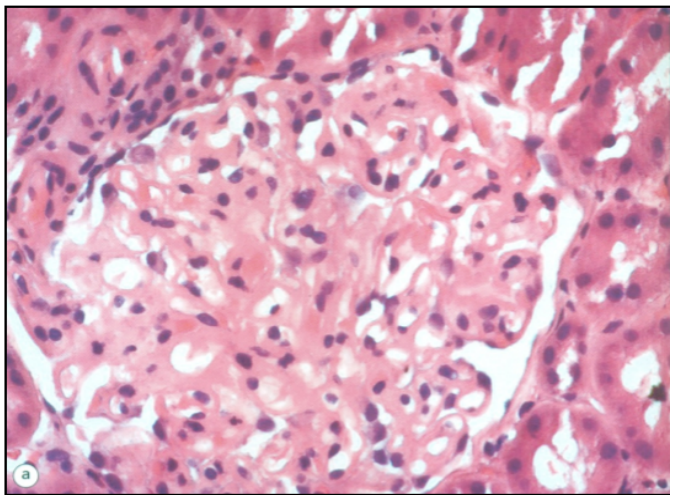


Tubular involvement with amyloid is verified by **apple-green** birefringence under polarized light.

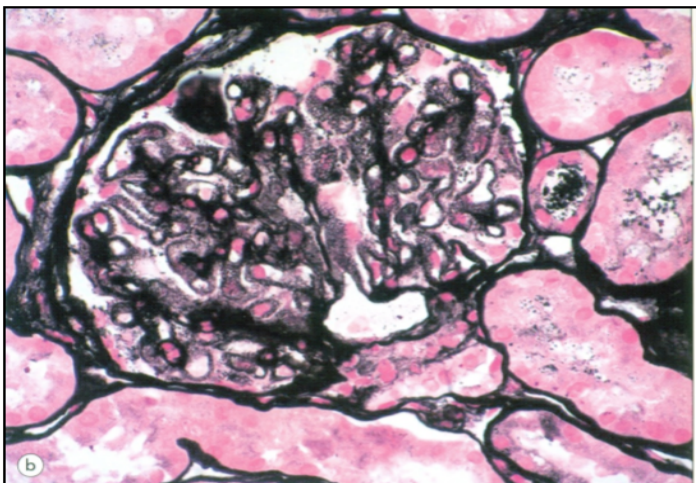
6.It effect all part of the body but we talk about it when it present in the kidney

3-Lupus nephropathy:

- This is the renal component of SLE, the severity of the renal lesion often determines the overall prognosis in patients with SLE. It is often manifest as the nephrotic syndrome but many cases also have major nephritic features. EM/LM finding is the same as membranous nephropathy, But IF here is showing "Full House" which shows that all immunoglobulin is positive.In the exam how will you differentiate they have to mention lupus
- The pathogenesis of all forms of glomerulonephritis in SLE involves deposition of DNA and anti DNA complexes within the glomeruli (subendothelial). This causes an inflammatory response that may cause proliferation of the endothelial, mesangial and/or epithelial glomerular cells and in severe cases necrosis of the glomeruli.



a) **Class V** lesion or lupus membranous glomerulopathy. There is diffuse thickening of the peripheral capillary walls associated with an increase in mesangial matrix.



(b) Silver methenamine (jones) stains reveal a spike and dome pattern to be present along the peripheral capillary loops where the wall of the capillaries cut tangentially; **there is a moth-eaten appearance of the capillary wall.**

The world health organization has divided SLE glomerular disease into five classes:

Class one: (seen less than 5% of SLE patients). **Normal** by light, electron and immunofluorescence microscopy.

Class two: (seen in 10 to 25% of cases) **Mesangial lupus glomerulonephritis** and it's associated with mild clinical symptoms and immune complex deposits in the mesangium.

Class three: (seen in 20 to 35% of patients) **Focal proliferative lupus glomerulonephritis**. Here one or two foci within an otherwise normal glomerulus show swelling and proliferation of endothelial and mesangial cells with neutrophilic infiltration or fibrinoid deposits and capillary thrombi.

Class four: (seen in 35% to 60% of SLE patients) In **diffuse proliferative lupus glomerulonephritis**. The histological features are similar to the one described in class 3 but are more diffuse. In this condition, immune complexes depositions create an overall thickening of the capillary walls, which resembles rigid "wire loops" on light microscopy.

Class five: (occurs in 10 to 15% of cases) **Membranous lupus glomerulonephritis**. In class 5, the patients have severe nephrotic syndrome and there is thickening of the capillary walls due to deposition of basement membrane like material as well as immune complex.

Table 13–2 Causes of Nephrotic Syndrome

Cause	Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	5	30
Minimal-change disease	65	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis	10	10
IgA nephropathy and others	10	15
Systemic Diseases with Renal Manifestations		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Ingestion of drugs (gold, penicillamine, "street heroin")		
Infections (malaria, syphilis, hepatitis B, HIV infection)		
Malignancy (carcinoma, melanoma)		
Miscellaneous (bee sting allergy, hereditary nephritis)		

*Approximate prevalence of primary disease is 95% of the cases in children, 60% in adults. Approximate prevalence of systemic disease is 5% of the cases in children, 40% in adults.
HIV, human immunodeficiency virus.

Nephritic syndrome

Characterized by inflammatory rupture of the glomerular capillaries, with resultant bleeding into the urinaryspace; proteinuria and edema may be present but usually are mild.

Clinical manifestations: :

- Inflammation → severe injury to the capillaries → filtration of blood cells → red blood cells casts in urine = grossly visible hematuria.
- GBM is blocked by inflammatory cells, RBC's & proteins →less filtration → oliguria → fluid retention → hypertension & azotemia.
- loss of proteins is less than in nephrotic syndrome because of the blockage of the GFM → **less edema.**
- Because of the decreased filtration →activation of RAAS system → even more hypertension

Clinical findings :

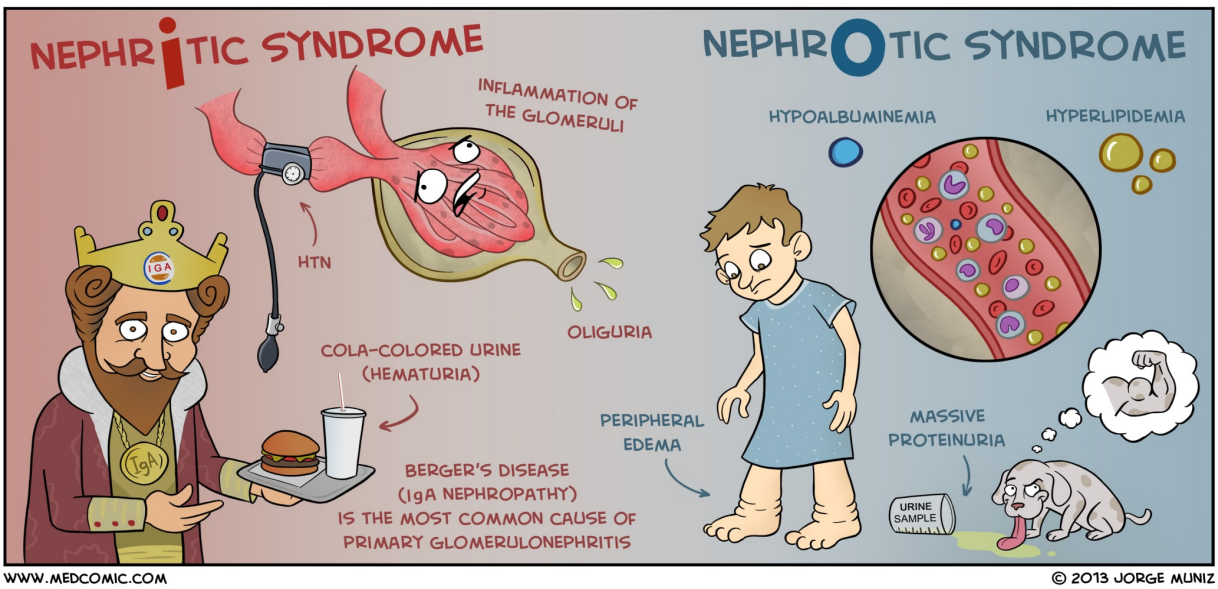
-**Hematuria.**

- Dysmorphic RBCs + **red cells cast.**
- Smoky brown color (tea color).

-**Oliguria and Azotemia.**

-**Hypertension**: Due to fluid retention and renin release .

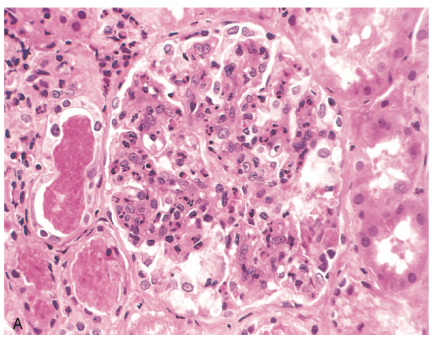
-Mild edema and Proteinuria.

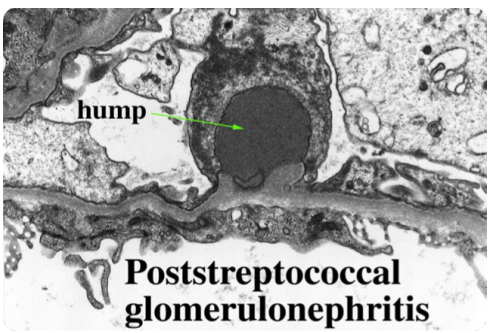


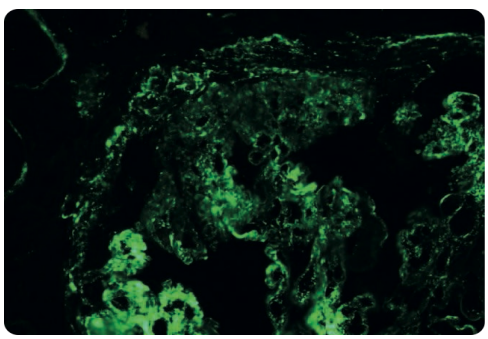
Primary Nephritic syndrome

1- Acute post-infectious (post-streptococcal) glomerulonephritis:

- One of the frequently occurring glomerular disorders. It caused by glomerular deposition of immune complexes resulting in proliferation of glomerular cells and infiltration of leukocytes, especially neutrophils and endocapillary proliferation
- **The classic case of post-streptococcal GN develops in a child**:
- 1 to 4 weeks after they recover from a group A streptococcal infection (e.g **pharyngitis**). Only certain "nephritogenic" strains of B-Hemolytic streptococci evoke glomerular disease.
    - In most cases the initial infection is localized to the pharynx or skin.
    - sometimes it's due to endogenous antigen like in case of SLE class 3 or 4.







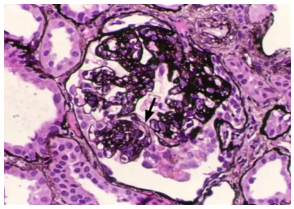
EM: Sub-epithelial Hump.
LM: Increased cellularity* caused by proliferation and swelling of endothelial and mesangial cells and by infiltrating neutrophils and monocytes. (Sometimes there is necrosis of capillary wall).
Immunofluorescence studies: reveal scattered granular deposits of IgG and complement c3 within the capillary walls and mesangial areas.

7.HYPERCELLULAR: Seen only in post-infection and lupus nephritis class 3 &4

2-MembranoProliferative GlomeruloNephritis (MPGN):

This Group can present as Nephrotic and/or Nephritic Syndromes. Microscopic finding: hematuria (red cell casts), proteinuria <1 gram/24 hours, normal renal function.

Type 1 MPGN

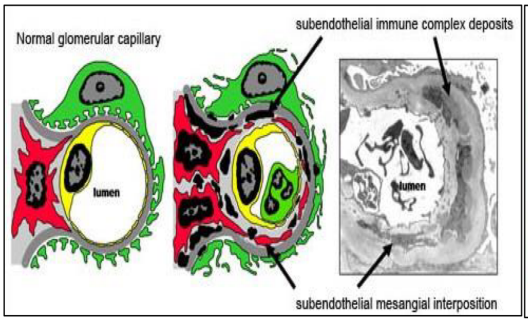


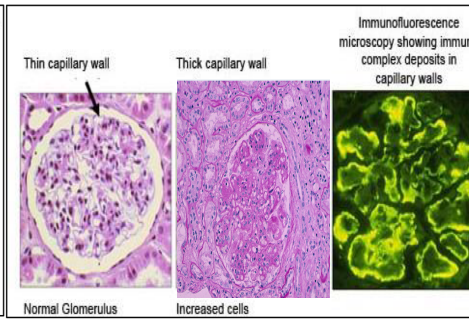
Tram track

Most common type of MPGN: nephrotic presentation (60% of cases) some cases have nephritic presentation. Association: **HBV, HBC and SLE**

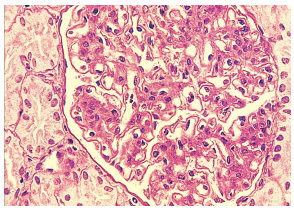
MORPHOLOGY:

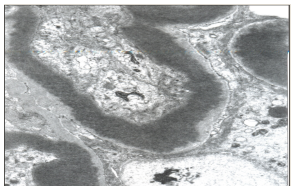
1: glomerular are large with lobular appearance.
2: EM: **sub-endothelial** immune complexes (deposits).
3:IF: **granular IgG + C3**
4.LM :thickening of the capillary wall+Mesangium proliferation
5: GBM is **thickened**.
6: proliferation of the mesangium causes tram track-use silver stain-double contour, by splitting of the GBM.
- Does not respond to corticosteroid & majority progress to Chronic renal failure.



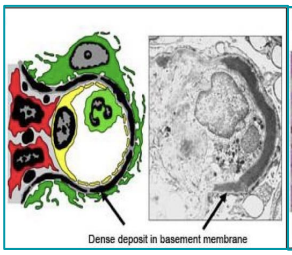


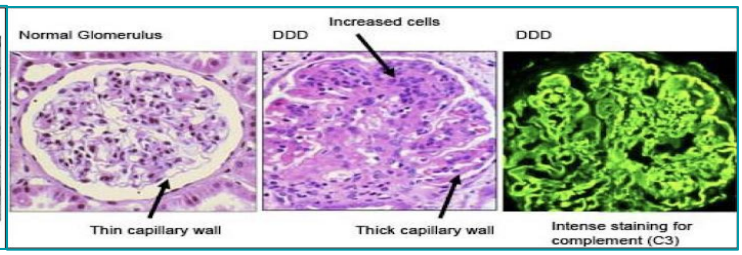
Type 2 MPGN





Associate with C3 nephritic factor (C3NeF) < (autoantibody that bind to C3 convertase prevent the degradation of C3 Convertase, causing sustained activation of the C3 alternative pathway, resulting in very low c3 level)
Diffuse intramembranous deposits (dense deposit disease) iDDD:
- EM shows tram tracks. LM shows **dense ribbon-like deposits** are found along the basement membranes of the glomeruli, tubules, and Bowman's capsule.
Does not respond to corticosteroid. Majority progress to Chronic renal failure.
- Granular C3 is present NO IgG.





Type 3MPGN

Rare and doesn't include in our objectives

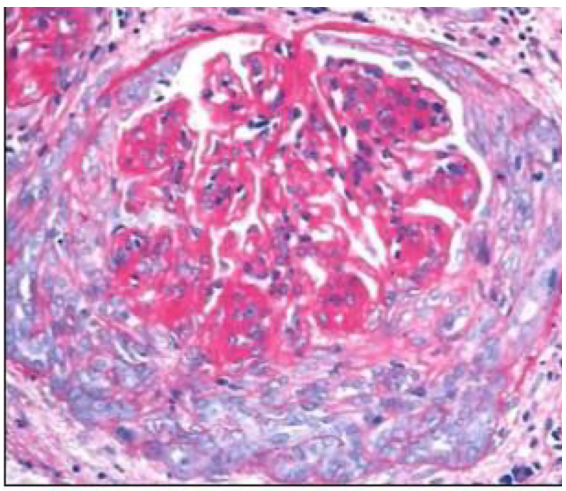
Rapidly Progressive Glomerulonephritis*:

It is rapid deterioration of renal function which severe renal failure develops rapidly within weeks and months. It can be Idiopathic (primary) or glomerulonephritis.
Laboratory findings typical of the nephritic syndrome.
- Prognosis is poor with rapid progression to renal failure.

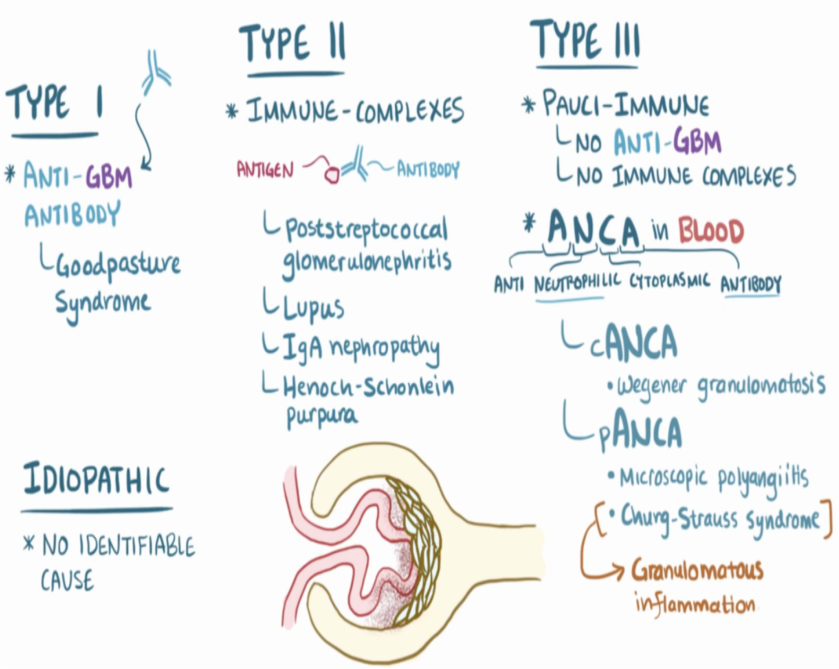
What is glomerular crescent?

Proliferation of parietal epithelial cells lining Bowman's capsule in the kidney; may protrude into Bowman's space and eventually lead to destruction of the glomerulus. **Crescent: proliferative parietal cells + macrophages.**
***Notice here is extra capillary where streptococcal endocapillary**

There are 3 Groups that cause RPGN. Mostly Autoimmune Diseases:



1. hypercellular of glomeruli.
2. crescent formation of bowman space.

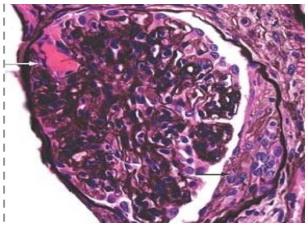


*clinically patient come loss his kidney + jumping on creatinine

Type I
Anti-Glomerular Basement Membrane (Anti-GBM) Antibody-Mediated Crescentic Glomerulonephritis

- Characterized by **linear** deposition of **IgG** and **C3** on the GBM.
- **Hemoptysis** associated with lung Disease (**GoodPasture Syndrome**) and you can see necrosis and **crescent formation.**

Antibodies bind also in the pulmonary alveolar capillary basement membranes leading to bleeding from the lungs.

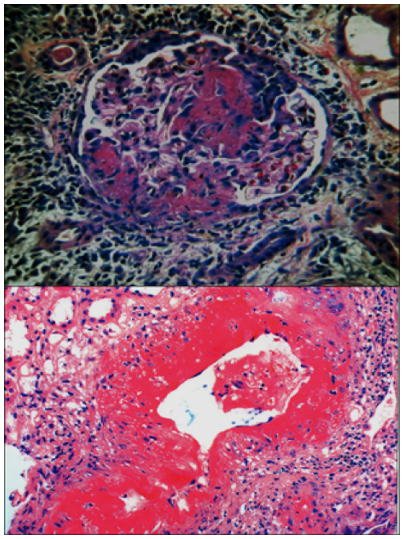


Type ll
Immune Complex-Mediated Crescentic Glomerulonephritis:

- **Associated with:** Post Streptococcal, SLE and IgA Nephropathy.
- Characteristic by granular (**lumpy-bumpy**) pattern of staining of the GBM for immunoglobulin & complement.

Type lll
Pauci immune (ANCA associated)

- The lack of **anti-GMB** antibodies and usually associated with **ANCA** (anti-neutrophil cytoplasmic antibody) such as Vasculitis.
- (ANCA associated): microscopic form of polyarteritis nodosa, wegener's granulomatosis, Chung Strauss syndrome, drug induced vasculitis
- **Wegener's granulomatosis:**



Glomerulus demonstrating focal and segmental necrosis with adhesion to Bowman's capsule and proliferation of parietal epithelium.

Vessel with transmural necrosis involving the vessels circumferentially with a significant inflammatory infiltrate with mixed polymorphonuclear leukocytes and mononuclear cells.

RPGN: Clinical Features

	Clinical Signs	Serology	Biopsy
Immune-complex	Infection or lupus or IgAN history	↓ C3 (except IgAN) ANA+ if lupus	IgG & C3 deposits (or IgA deposits in IgAN)
Anti-GBM	Pulmonary hemorrhage 'Goodpastures'	Anti-GBM antibody	Linear IgG deposits
Pauci-immune	Skin rash, Pulm hemorr, upper respiratory granuloma 'Wegeners' (GPA)	ANCA antibody	No immune deposits

Asymptomatic hematuria/proteinuria

1- Hereditary Nephritis (Alport syndrome):

- **Alport syndrome** or **hereditary nephritis** is a genetic disorder characterized by glomerulonephritis, end-stage kidney disease, and **hearing loss**. Alport syndrome can also affect the eyes, causing eye abnormalities. They have problem in hearing.
    - GBM is composed of collagen IV, this collagen type is mutated in Alport syndrome.

- In the glomeruli there is alternating areas of extreme **thinning** of the glomerular basement membrane (~120 nm) with thick, irregular areas with **basket weaving** are shown.

2- IgA Nephropathy:

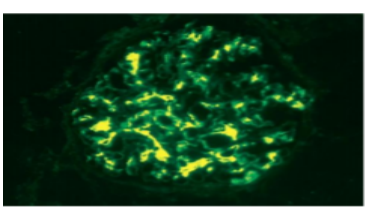
- This condition usually affects children and young adults and begins as episode of gross hematuria that occurs within 1 or 2 days of nonspecific upper respiratory tract infection.
- IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria and is the most common granular disease revealed by renal biopsy worldwide.

- Hallmark of the disease: deposition of IgA in the mesangium.

- The lesions in IgA nephropathy vary a lot →glomeruli may be normal or may show mesangial cells and matrix increase 'widening' and segmental inflammation.

- The characteristic immunofluorescence picture is of mesangial deposition of **IgA**, often with C3 and properdin and smaller amounts of **IgG** or **IgM**

- EM confirms the presence of electron dense deposits in the mesangium. The deposits may extend to the **subendothelial** area of adjacent capillary wall.



Chronic nephritic syndrome:

- **Azotemia**.
- Active urine sediment (variable).
- Proteinuria (variable).
- Past history of RPGN, nephrotic syndrome, nephritic syndrome.
- **Hypertension**

Chronic Renal Failure: (Global sclerosis + interstitial fibrosis)

Chronic kidney disease (End stage renal disease - ESRD) is the result of progressive **scarring** resulting from any type of kidney disease.

- Kidney disease → function of the remaining intact nephrons are maladapted to such changes occurred by the disease → Chronic Renal Failure (ESRD)[8] → uremia.

Uremic syndrome manifestation:

1. Skin manifestations → pruritus, uremic "frost"(صقيع) skin.
2. Cardiac manifestations → uremic pericarditis **fluid around the pericardium**
3. Neurological manifestations → peripheral neuropathy (lethargy)
4. Pulmonary complications → pneumonitis and hemorrhage.
5. Hematopoietic manifestations → anemia, bleeding diathesis.
6. Skeletal abnormalities → renal osteodystrophy (secondary hyperparathyroidism)
7. Others → metabolic imbalances (acid-base disorders)

Pathogenesis of uremic syndrome: toxins that cannot be removed
Uremic "Toxins" → Middle molecules[1]→ The "Trade off" hypothesis[2].

Treatment of End Stage Renal Disease:

- Supportive therapy.
- Dialysis.
- Renal transplantation.

Chronic renal failure is characterized by: Symmetrically contracted kidneys, diffusely granular surfaces, tubular atrophy, arteriolar sclerosis, obliteration of the glomeruli and interstitial fibrosis.

Clinical course: the patient presents with proteinuria, hypertension, azotemia. Death to uremia is the role unless the patient has treated with dialysis or transplantation.

8.chronic renal failure will reach to thyroidization of tubules
9.any molecule with an atomic mass between 350 and 2000 daltons. These molecules accumulate in the body fluids of patients with uremia.
10.provides an explanation for some of the disorders of the uraemic syndrome.

Summary Histopathology Of GLOMERULAR DISEASES

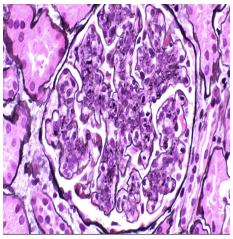
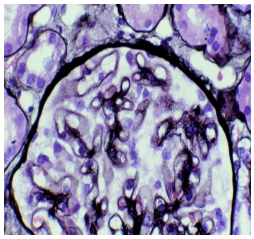
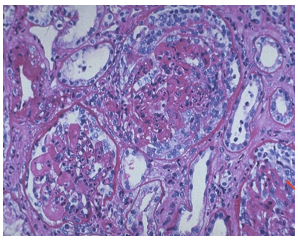
Disease	Acute post-streptococcal glomerulonephritis	Membranous glomerulonephritis	Rapid progressive glomerulonephritis
Picture			
Prominent Features	**Hypercellularity** Due to increased number of 1-epithelial cells 2-endothelial cells 3-mesingeal cells 4-Neutrophils (cause it's acute)	The **thickened** capillary wall shows nemours holes which indicates the deposits (deposits does not take the silver stain).	**Crescent** formation which is composed of 1-epithelial cells 2-macrophages In severe cases fibrin also contribute
Notes/ Comparisons	The basement membrane does NOT show spikes or splitting. Silver stain is used to show the basement membrane as seen in the picture above.	The changes in this disease are thickened capillary wall due to deposition. (NOT hypercellularity) Ultrastructural findings Include numerous electron-dense immune complexes in intramembranous and epimembranous (epithelia) locations within and on the basement membrane.	

Table 14.2 Summary of Major Primary Glomerular Diseases

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Minimal-change disease	Nephrotic syndrome	Unknown; podocyte injury	Normal	Negative	Effacement of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; nonnephrotic range proteinuria	Unknown: reaction to loss of renal mass; plasma factor?	Focal and segmental sclerosis and hyalinosis	Usually negative; IgM and C3 may be present in areas of scarring	Effacement of foot processes; epithelial denudation
Membranous nephropathy	Nephrotic syndrome	In situ immune complex formation; PLA2R antigen in most cases of primary disease	Diffuse capillary wall thickening and subepithelial "spike" formation	Granular IgG and C3 along GBM	Subepithelial deposits
Membranoproliferative glomerulonephritis (MPGN) type I	Nephrotic/nephritic syndrome	Immune complex	Membranoproliferative pattern; GBM splitting	Granular IgG, C3, C1q and C4 along GBM and mesangium	Subendothelial deposits
C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis)	Nephrotic/nephritic syndrome; nonnephrotic proteinuria	Activation of alternative complement pathway; antibody-mediated or hereditary defect in regulation	Mesangial proliferative or membranoproliferative patterns	C3	Mesangial, intramembranous and subendothelial electron-dense or "waxy" deposits
Acute postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 along GBM and mesangium	Primarily subepithelial humps
IgA nephropathy	Recurrent hematuria or proteinuria	Immune complexes containing IgA	Mesangial or focal endocapillary proliferative glomerulonephritis	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits
Anti-GBM disease (e.g. Goodpasture syndrome)	Rapidly progressive glomerulonephritis	Autoantibodies against collagen type IV α3 chain	Extracapillary proliferation with crescents; necrosis	Linear IgG and C3; fibrin in crescents	No deposits; GBM disruptions; fibrin
Pauci-immune glomerulonephritis	Rapidly progressive glomerulonephritis	Anti-neutrophil cytoplasmic antibody	Extracapillary proliferation with crescents; necrosis	Fibrin in crescents	No deposits; GBM disruptions; fibrin

GBM, Glomerular basement membrane; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M.

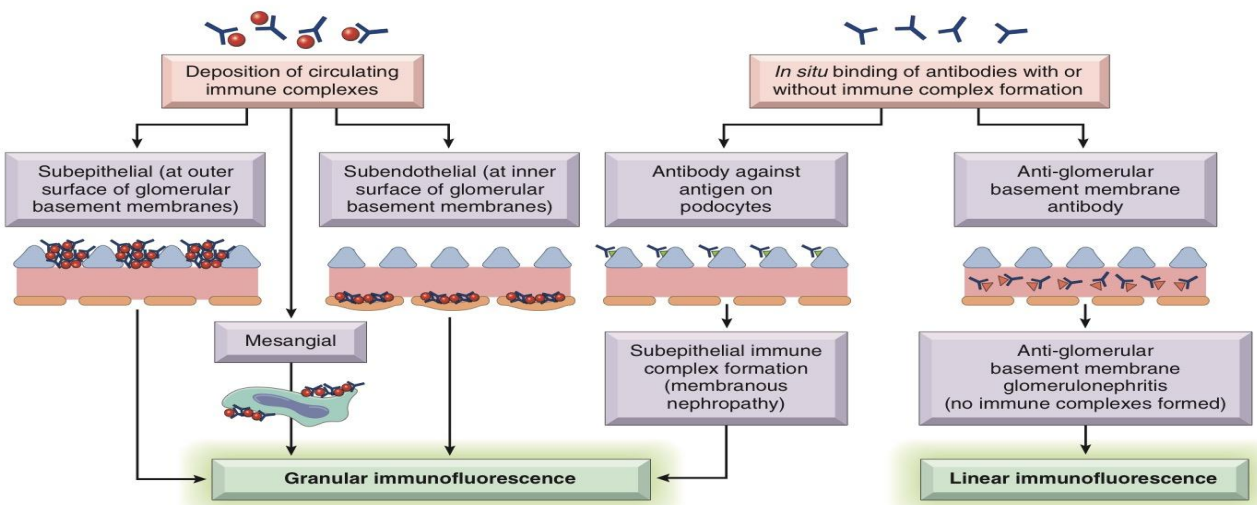


Fig. 14.3 Antibody-mediated glomerular injury. Injury can result either from the deposition of circulating immune complexes or from antibody-binding to glomerular components followed by formation of complexes in situ. Deposition of circulating immune complexes gives a granular immunofluorescence pattern. Anti-glomerular basement membrane (anti-GBM) antibody glomerulonephritis is characterized by a linear immunofluorescence pattern; there is no immune deposit formation in this disease.

Mnemonics

Features of Nephrotic syndrome – NAPHROTIC

- **N**a+ decrease (Hyponatremia)
- **A**lbumin decrease (Hypoalbuminemia)
- **P**roteinuria >3.5 g/day
- **H**yperlipidemia
- **R**enal vein thrombosis
- **O**rbital edema
- **T**hromboembolism
- **I**nfection (due to loss of Immunoglobulins in urine)
- **C**oagulability (due to loss of Antithrombin III in urine)

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POST-STREPTOCOCCAL GLOMERULONEPHRITIS (PSG)

PSG = 3 Letters

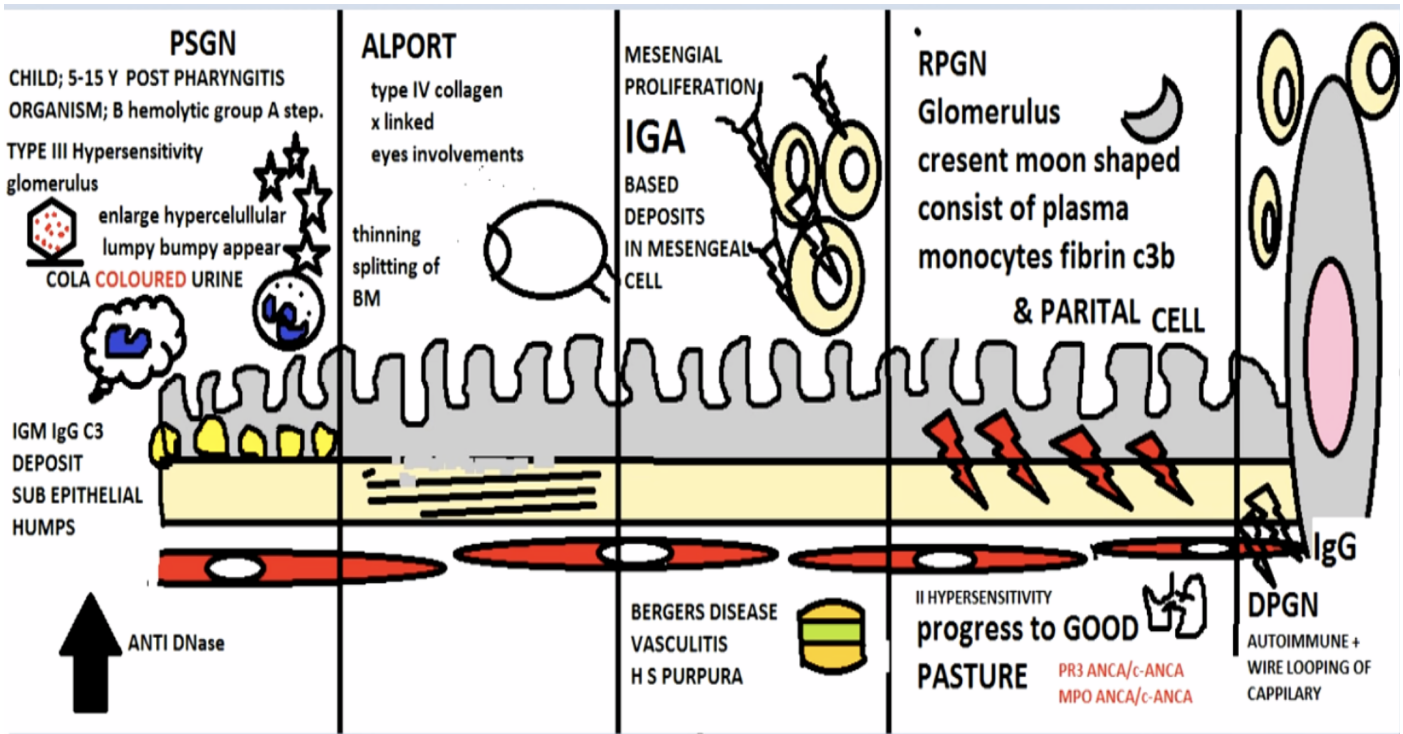
1. *Lump3-Bump3*
2. *C3*
3. *3 weeks post-strep*
4. *Type-3 Reaction*

nephrOtic

hypOalbuminemia

prOteinuria

hyperlipidemia



Summary-pathoma

NEPHROTIC SYNDROME

BASIC PRINCIPLES

Glomerular disorders characterized by proteinuria**(> 3.5 g/day)** resulting in

l. Hypoalbuminemia-pitting edema

2. Hypogammaglobulinemia-increased risk of infection

3. Hypercoagulable state-due to loss of antithrombin III

4. Hyperlipidemia and hypercholesterolemia-may result in fatty casts in urine

MINIMAL CHANGE DISEASE (MCD)

A. Most common cause of nephrotic syndrome in **children**

B. Usually **idiopathic**; may be associated with Hodgkin lymphoma

C. **Normal glomeruli on H&E stain** lipid may be seen in proximal tubule cells.

D. **Effacement** of **foot processes** on electron microscopy

E. No immune complex deposits; negative immunofluorescence (IF)

F. **Selective proteinuria** (loss of albumin, but not immunoglobulin)

G. Excellent response to steroids (damage is mediated by cytokines from T cells)

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

A. Most common cause of nephrotic syndrome in Hispanics and African Americans

B. Usually idiopathic; may be associated with **HIV**, heroin use, and **sickle cell disease**

C. **Focal (some glomeruli) and segmental (involving only part of the glomerulus) sclerosis on H&E stain**

D. **Effacement of foot processes on EM**

E. No immune complex deposits; negative IF

F. Poor response to steroids; progresses to chronic renal failure

NEPHROTIC SYNDROME

MEMBRANOUS NEPHROPATHY

A. Most common cause of nephrotic syndrome in **Caucasian adults**

B. Usually idiopathic; may be associated with **hepatitis B or C, solid tumors, SLE, or drugs (e.g., NSAIDs and penicillamine)**

C. **Thick glomerular basement membrane on H&E**

D. Due to immune complex deposition (granular IF); **subepithelial deposits with 'spike and dome'** appearance on EM

E. Poor response to steroids; progresses to chronic renal failure

DIABETES MELLITUS (Diabetic Nephropathy)

A. High serum glucose leads to nonenzymatic glycosylation of the vascular basement membrane resulting in **hyaline arteriolosclerosis**

B. Glomerular **efferent arteriole is more affected than the afferent arteriole,** leading to high glomerular filtration pressure.

1. Hyperfiltration injury leads to microalbuminuria.

C. Eventually progresses to nephrotic syndrome

1. Characterized by sclerosis of the mesangium with formation of Kimmelstiel-Wilson nodules

D. ACE inhibitors slow progression of hyperfiltration-induced damage.

SYSTEMIC AMYLOIDOSIS

A. Kidney is the most commonly involved organ in systemic amyloidosis.

B. **Amyloid deposits in the mesangium,** resulting in nephrotic syndrome.

C. Characterized by **apple-green birefringence under polarized light after staining with Congo red**

NEPHRITIC SYNDROME

BASIC PRINCIPLES

A. Glomerular disorders characterized by glomerular inflammation and bleeding

1. Limited proteinuria**(< 3.5 g/day)**

2. Oliguria and azotemia

3. Salt retention with periorbital edema and hypertension

4. **RBC casts and dysmorphic RBCs in urine**

B. Biopsy reveals hypercellular, inflamed glomeruli

1. Immune-complex deposition activates complement; C5a attracts neutrophils, which mediate damage.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

A. Nephritic syndrome that arises **after group A streptococcal infection of the skin (impetigo) or pharynx**

1. Occurs with nephritogenic strains (which carry theM protein virulence factor)

2. May occur after infection with nonstreptococcal organisms as well

B. **Presents 2-3 weeks after infection as hematuria (cola-colored urine),** oliguria, **hypertension**, and periorbital edema l. Usually seen in **children**, but may occur in adults

C. **Hypercellular**, inflamed glomeruli on H&E

D. Mediated by immune complex deposition (granular IF); **subepithelial 'humps' on EM**

E. Treatment is supportive.

l. Children rarely (1 %) progress to renal failure.

2. Some adults (25%) develop rapidly progressive glomerulonephritis (RPGN).

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

A. **Thick glomerular basement membrane** on H&E, often with '**tram-track**' appearance

B. Due to immune complex deposition (granular IF)

C. Divided into two types based on location of deposits

1. Type 1- subendothelial ; associated with HBV and HCV

2. Type 2 (dense deposit disease)-intramembranous; associated with C3 nephritic factor (autoantibody that stabilizes C3 convertase, leading to overactivation of complement, inflammation, and low levels of circulating C3)

D. Poor response to steroids; progresses to chronic renal failure

Asymptomatic hematuria/proteinuria

ALPORT SYNDROME

A. Inherited defect in type IV collagen; most commonly X-linked

B. Results in **thinning and splitting of the glomerular basement membrane**

C. Presents as isolated **hematuria, sensory hearing loss, and ocular disturbances**

IgA NEPHROPATHY (BERGER DISEASE)

A. IgA immune complex **deposition in mesangium of glomeruli**; most common nephropathy worldwide

B. Presents during childhood as episodic **gross or microscopic hematuria with RBC casts, usually following mucosal infections (e.g., gastroenteritis)**

1. IgA production is increased during infection.

C. IgA immune complex deposition in the mesangium is seen on IF}.

D. May slowly progress to renal failure

NEPHRITIC SYNDROME

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

A. Nephritic syndrome that progresses to renal failure in weeks to months

B. **Characterized by crescents in Bowman space (of glomeruli)** on H&E stain; **crescents are comprised of fibrin and macrophages**

C. Clinical picture and IF help resolve etiology

Table: **Immunofluorescence Findings** in Rapidly Progressive Glomerulonephritis

IMMUNOFLUORESCENCE PATTERN	DISEASE	COMMENTS
Linear (anti-basement membrane antibody, Fig. 12.15)	Goodpasture syndrome	Antibody against collagen in glomerular and alveolar basement membranes; presents as hematuria and hemoptysis, classically in young, adult males
Granular (immune complex deposition)	PSGN (most common) or diffuse proliferative glomerulonephritis	Diffuse proliferative glomerulonephritis is due to diffuse antigen-antibody complex deposition, usually sub-endothelial; most common type of renal disease in SLE
Negative IF (pauci-immune)	Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome	Wegener granulomatosis is associated with c-ANCA; microscopic polyangiitis and Churg-Strauss are associated with p-ANCA. Granulomatous inflammation, eosinophilia, and asthma distinguish Churg-Strauss from microscopic polyangiitis.

CHRONIC RENAL FAILURE

I. BASIC PRINCIPLES

A. End-stage kidney failure

1. May result from glomerular, tubular, inflammatory, or vascular insults 2. **Most common causes are diabetes mellitus, hypertension, and glomerular disease.**

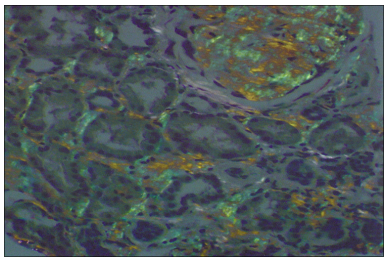
B. Clinical Features

1. **Uremia**-Increased nitrogenous waste products in blood (azotemia) result in nausea, anorexia, pericarditis, platelet dysfunction , encephalopathy with asterixis, and deposition of **urea crystals in skin.**
2. Salt and water retention with resultant hypertension
3. **Hyperkalemia** with metabolic acidosis
4. **Anemia due to decreased erythropoietin** production by renal peritubular interstitial cells
5. **Hypocalcemia** due to decreased !-alpha-hydroxylation of vitamin D by proximal renal tubule cells and **hyperphosphatemia 6.** Renal osteodystrophy due to secondary hyperparathyroidism, osteomalacia, and osteoporosis

C. Treatment involves **dialysis or renal transplant.**

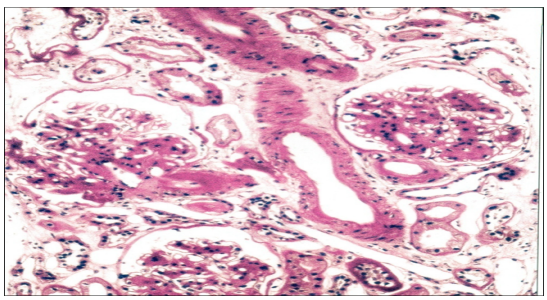
l. Cysts often develop within shrunken end-stage kidneys during dialysis, increasing risk for renal cell carcinoma

Questions -practical



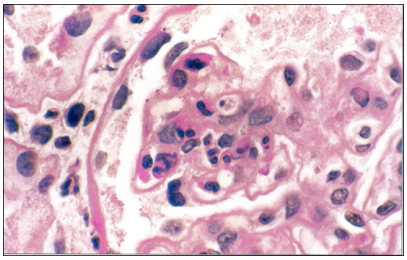
1In this picture, we can see tubular involvement which verified by apple-green birefringence under polarized light. This description belongs

A-Focal segmental glomerulosclerosis
B-Amyloidosis
C-Diabetic nephropathy
D-Membranous glomerulopathy



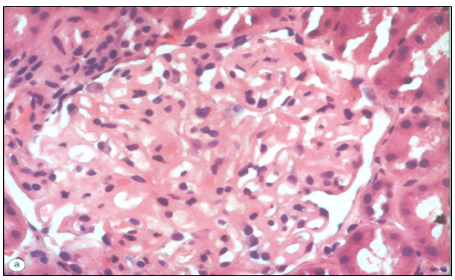
3A patient complains of excessively frothy urine when he uses the toilet in the morning. **Thickening of the glomerular basement membrane** and **Kimmelstiel-Wilson** lesions are seen on light microscopy.

A. Recent streptococcal infection
B. SLE
C. Antibodies to the glomerular and alveolar basement membranes
D. Poor control of glucose levels



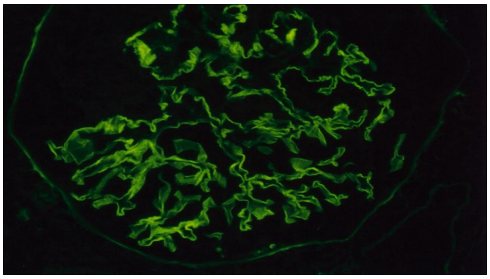
? 2A 7 y.o child came to the hospital with edema and hypertension, after taking his history we got the information that he was recently recovered from pharyngitis. Based on these information's what is the possible diagnosis

A- Wegener's granulomatosis
B- Anti-GBM-antibody mediated glomerulonephritis
C- Membranoproliferative glomerulonephritis
D- Acute post-infectious glomerulonephritis.



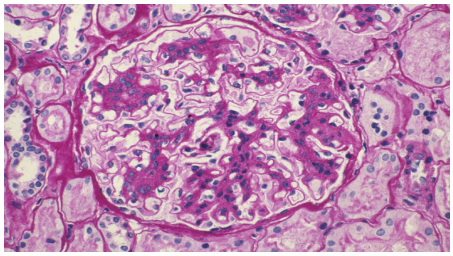
4A woman with a history significant for **lupus** is found to have 3.7 grams of protein in her urine each day. In the investigation you find wire looping of the capillaries on light microscopy. Which of the following tops your differential?

A. Focal segmental glomerulosclerosis
B. Rapidly progressive Glomerulonephritis
C. Diffuse proliferative glomerulonephritis
D. IgA nephropathy



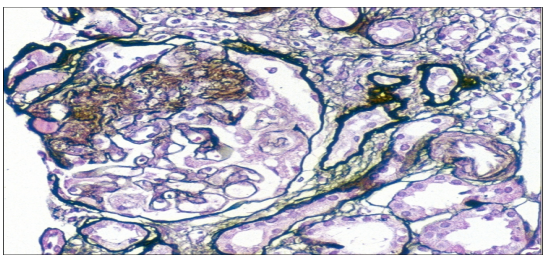
5A 42-year-old man has experienced increasing malaise for the past month. He is bothered by increasing swelling in the hands and legs. On physical examination, there is generalized edema. Urinalysis shows a pH of 6.5, 4+ proteinuria and no blood, glucose, or ketones. The 24-hour urine protein level is 4.2 g. A renal biopsy specimen is obtained, and **immunofluorescence staining with antibody to the C3** component of complement produces the pattern shown in the figure. Which of the following underlying disease processes is most likely to be present?

A. A. Chronic hepatitis B
B. B. AIDS
C. C. Multiple myeloma
D. D. Recurrent urinary tract infection



6A patient, who is known to have hepatic failure, came to the clinic complaining from hematuria after she getting a respiratory infection. During investigation after taking a renal biopsy, the lab found a deposition of **IgA antibody** and **matrix increase**, **with mesangial deposits.** what is most likely the diagnosis?

A. Nephritic syndrome
B. Glomerulonephritis
C. Renal failure
D. IgA nephropathy



7A 12-year-old girl has experienced increasing malaise for the past 2 weeks. On physical examination, she has periorbital edema. The child is afebrile. Laboratory findings show proteinuria on dipstick urinalysis. A renal biopsy is done; the biopsy specimen shows that approximately **50% of the glomeruli in the specimen are affected** by the lesion shown in the figure. What is the most likely diagnosis?

A. Focal segmental glomerulosclerosis
B. Membranoproliferative glomerulonephritis type I
C. Postinfectious glomerulonephritis
D. Rapidly progressive glomerulonephritis

1.b/2.d/3.D/4.C/5.A/6.D/7.A

1-A 65 year old patient came to the clinic with edema in his foot, examination shows presence of protein in urine. Which of the following syndrome does the patient has?
A-chronic renal failure
B-nephrotic syndrome
C-nephritic syndrome
D-rapidly progressive GN

2-A 5 year old boy is brought to the hospital with a fever. His blood pressure was slightly elevated also there was some swelling in his hands, his mother reported that he was having a sore throat but he started getting better 2 days ago. What is the most likely diagnosis?
A-dense deposit disease
B-wegner granulomatosis
C-diabetic nephropathy
D-post infectious glomerulonephritis

3-abnormalities can be detected in minimal change disease by using?
A-LM
B-IF
C-EM
B-none of the above

4-what disease will have tram track appearance?
A-membranoproliferative glomerulonephritis
B-anti glomerular basement membrane disease
C-IgA nephropathy
D-alport syndrome

5-which of the following is an evidence for rapid progressive glomerulonephritis diagnosis?
A-fibrinoid necrosis
B-hump shaped sub epithelial deposition
C-crescent development
D-all of the above

6-In IgA nephropathy under IF we see a deposition of IgA often with:-
A-C3
B-C2b
C-C1a
D-C4

7-In which disease the immune complex deposition will be in subendothelial location?
A-diabetic nephropathy
B-FSGS
C-minimal change disease
D-MPGN

8-a 55 year old women with an uncontrolled diabetes and proteinuria. A renal biopsy reveals hyaline arteriosclerosis along with kimmelstiel-wilson lesions. What is the diagnosis?
A-minimal change disease
B-FSGS
C-nodular glomerularsclerosis
D-membranous glomerulonephritis

9-which of the following disease can be treated with corticosteroids?
A-minimal change disease
B-FSGS
C-MPGN1
D-MPGN2

10-Which of the following diseases characterized by a mutation in Collagen IV?
A-membranous glomerulonephritis
B-alport syndrome
C-IgA nephropathy
D-MPGN

11
A 51 years old male patient came to the hospital and he was diagnosed with Nephrotic Syndrome.
The most common cause of Nephrotic syndrome
in his age group is:
A-Minimal change disease/ glomerulonephritis.
B-Focal segmental glomerulosclerosis
C-Membranous glomerulopathy
D-Acute post-infectious glomerulonephritis.

12
Which one of these conditions tend to be the most common cause of recurrent microscopic or gross Hematuria?
A- Acute post-infectious glomerulonephritis
B-IgA Nephropathy
C-Asymptomatic hematuria/proteinuria
D-Membranoproliferative glomerulonephritis

1.b/2.d/3.c/4.a/5.c/6.a/7.d/8.c/9.a/10b/ 11:C / 12/B

قُلْ هَلْ يَسْتَوِي ٱلَّذِينَ يَعْلَمُونَ وَٱلَّذِينَ لاَ يَعْلَمُونَ سورة الزمر الآية ٩ «

القادة

فاطمة بالشرف **عبدالله العمر**

الأعضاء

ريناد الغريبي
منيرة المسعد
شوق القحطاني
رزان الزهراني
بتول الرحيمي
فاطمة الديحان
الجوهرة الشنيفي
نورة القاضي
غادة الحيدري
بلقيس الراجحي
غرام جليدان
آلاء الصويغ
الفهدة السليم
شيرين حمادي
رناد الفرم
نورة الحربي
ميعاد النفيعي
مجد البراك

عبدالجبار اليماني
عبدالله المعيذر
معن شكر
سيف المشاري
عبدالعزيز الجهني
محمد العمر
خالد المطيري
عبدالعزيز العبدالكريم
ماجد الجهني
منصور العبرة
أنس السيف
راكان الغنيم
فايز الدرسوني
خالد العقيلي
بندر الجماز
طارق العلوان
سلطان بن عبيد
تركي الشمري
محمد الأصقه
أحمد الصبي
سعد الفوزان