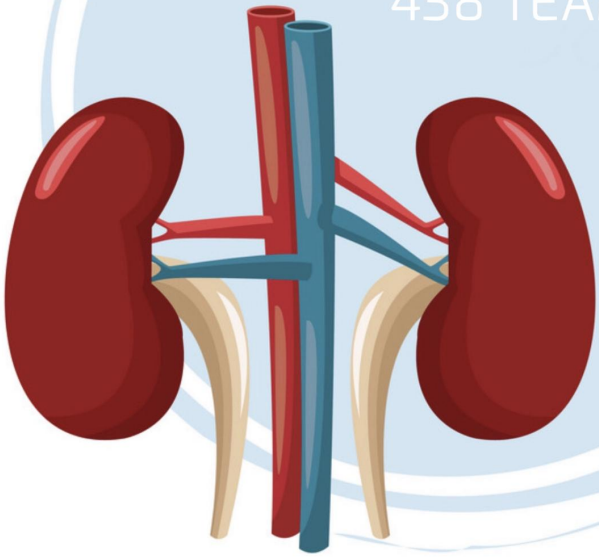
Editing file

Pathology

438 TEAM



Glomerular diseases

Objectives:

- Recognize the five major renal glomerular syndromes.
- Describe the main differential pathological diagnosis for each syndrome.
- Perform a clinico-pathological correlation.
- Describe the patterns of injury of each syndrome.

Content:
2 pages introduction.
14 pages main content
4 pages summary and quiz

Color index:

Black: original content.
Red: Important.
Light Purple: From Robbin's.
Blue: only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

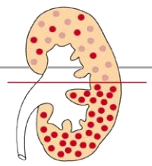
Pathology

Reviewed by: Rezan AlRabah & Ibrahim AlBabah

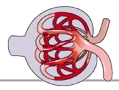
Introduction

Important terminologies

Focal:
Some of the glomeruli are involved

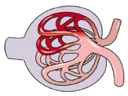


Global:
Involving the total glomerular tuft



Diffuse:
Majority of the glomeruli are involved

Segmental:
Only part of a glomerular tuft is involved



Pathogenesis of glomerular injury:

immunologic mechanisms

Antibody-mediated immune GN:
There are 3 major mechanisms of antibody-mediated inflammation in most forms of GN

Cell mediated immune GN:
sensitized T cells can also cause glomerular injury

Deposition of circulating complexes in glomerular capillary wall or mesangium

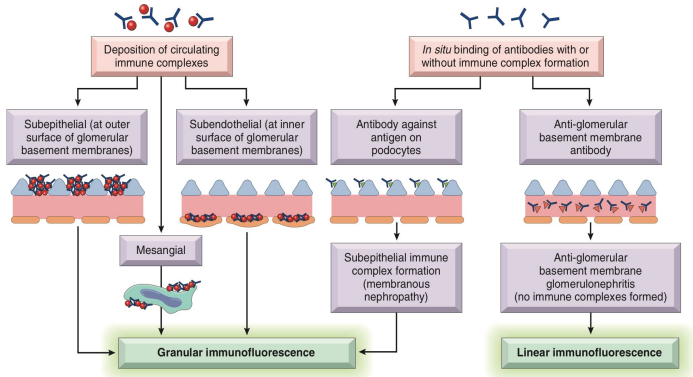
antigens released by bacteria or virus can bind to circulating antibodies → produce immune complexes → deposit in glomeruli → deposits attract inflammatory cells and activate complements → **glomerular injury**

In situ immune complex formation

Certain circulating antibodies react with certain antigens within glomeruli → formation of immune complexes in the glomeruli → deposits attract leukocytes and activate complement → **glomerular injury**.

Antineutrophil cytoplasmic autoantibodies (ANCAs)

Patients have circulating autoantibodies against antigens in the cytoplasm of neutrophils → activation and adhesion of the neutrophils to endothelial cells lining the capillaries especially the glomerular capillaries → The neutrophils release injurious products that promote vascular inflammation and GN → **Cause a severe GN**



All 3 initiate glomerular inflammatory injury by attraction and activation of leukocytes.

Introduction cont.

Most things here are already mentioned or will be mentioned in the lecture, this is just to give you an overview and a better understanding

Below is a brief summary of the various clinical manifestations and syndromes of renal diseases with their defining features.

	Nephrotic syndrome	Nephritic syndrome
Characteristics	• **Proteinuria**, with daily protein loss in the urine of 3.5 g or more in adults (said to be in the "*nephrotic range*") • **Hypoalbuminemia**, than 3 g/dL with plasma albumin levels less • **Generalized edema**, the most obvious clinical manifestations • **Hyperlipidemia** and **lipiduria**	• ***Hematuria*** (red cells and red cell casts in urine) • **Azotemia** • **Hypertension** • **Proteinuria** (usually in the *subnephrotic* range) with or without edema
Pathogenesis: **(Important)**	*The nephrotic syndrome has diverse causes that share a common pathophysiology:* Derangement in the capillary walls of the glomeruli → increased permeability to plasma proteins(leading to **proteinuria**)→With long-standing or heavy proteinuria, serum albumin is decreased → **hypoalbuminemia**→ decrease in plasma colloid osmotic pressure →leakage of fluid from the blood into extravascular spaces → Edema→decrease in blood volume→ decrease in RBF→RAAS activation→Salt and water retention → More edema(if unchecked may lead to the development of **generalized edema** (termed anasarca).	*Usually has an acute onset and is caused by inflammatory lesions of glomeruli.* proliferation of the cells within the glomeruli, often accompanied by an infiltrate of leukocytes → The inflammatory reaction injures the capillary walls → permitting blood to pass into the urine (Hematuria), and induces hemodynamic changes that lead to a reduction in the GFR(manifested clinically by **oliguria**, **fluid retention**, and **azotemia**.).
As result:	**They will have Hyperlipidemia and lipiduria. WHY?** **Hyperlipidemia:** Hypoalbuminemia triggers increased synthesis of lipoproteins in the liver, or massive proteinuria causes loss of an inhibitor of their synthesis. There also is abnormal transport of circulating lipid particles and impairment of peripheral breakdown of lipoproteins. **Lipiduria:** Reflects the increased permeability of the GBM to lipoproteins.	**They will have Hypertension. WHY?** **Hypertension:** Probably is a result of both the fluid retention and augmented renin release from the ischemic kidneys

Syndrome/ clinical manifestation	Defining features:
Asymptomatic hematuria &/or non-nephrotic proteinuria	A sign of mild glomerular abnormalities.
Rapidly progressive glomerulonephritis	Results from severe glomerular injury → loss of renal function within days or weeks → hematuria, dysmorphic red blood cells, red blood cell casts in urine sediments, mild to moderate proteinuria.
Acute kidney injury	Oliguria or anuria with recent onset of azotemia. It can result from glomerular injury (e.g. crescentic glomerulonephritis), interstitial injury, vascular injury (e.g. TMA) or acute tubular injury/necrosis.
Chronic kidney disease	Result of any chronic renal diseases that progresses to end stage kidney requiring dialysis and transplantationà characterized by prolonged symptoms and signs of uremia.
Urinary tract infection	Affect the kidney (pyelonephritis) or the bladder (cystitis) → bacteriuria and pyuria (bacteria and leukocytes in urine).
Nephrolithiasis (renal stones)	Renal colic, hematuria (without rbc casts).

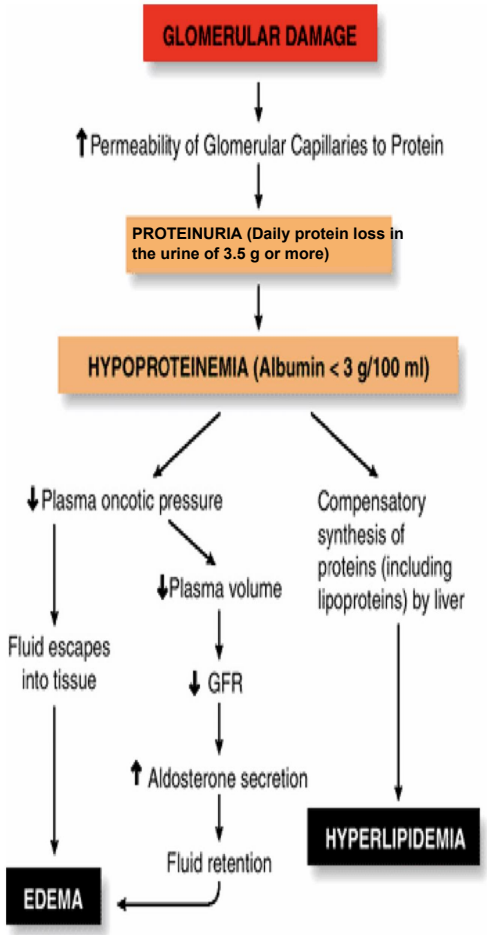
Nephrotic syndrome

Definition

The nephrotic syndrome has diverse causes that share a common pathophysiology, a derangement in the capillary walls of the glomeruli that results in Increased permeability to plasma proteins.

Clinical features

Massive proteinuria (we can differentiate between nephrotic and nephritic syndromes by the proteinuria).	The loss in the urine of >3.5 g of protein/day (said to be in the "nephrotic range"). This is due abnormal permeability of the glomerular capillary wall.
Hypoproteinemia / hypoalbuminemia	Plasma albumin levels <3g/dL (this due to the loss of plasma protein in the urine.)
Edema	Due to Hypoproteinemia causes reduced plasma colloid osmotic pressure.
Hyperlipidemia & lipiduria	Hypoalbuminemia causes compensatory increase in lipoprotein secretion by the liver leading to hyperlipidemia. The increased permeability of the GBM to lipoproteins leads to lipiduria.



Causes

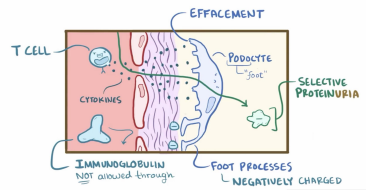
PRIMARY	SECONDARY
Minimal change disease (most common primary cause in children)	Diabetes mellitus (most common systemic causes)
Membranous GN (most common primary cause in Caucasian/Asian adults)	Amyloidosis
Focal segmental glomerulosclerosis (FSGS) (most common primary cause in black American adults)	Systemic lupus erythematosus (can also present as nephritic syndrome)
Membranoproliferative GN (can also present as nephritic syndrome)	Drugs (gold, penicillamine, "street heroin")

Minimal change disease

Primary nephrotic cause

Definition

- A relatively benign disorder, the most frequent cause of the nephrotic syndrome in children(mostly 1-7 years).
- Also known as lipoid nephrosis.



effacement of epithelial cell (podocyte) foot processes.

Pathogenesis

Unknown, but Involvement of the immune system has been postulated.

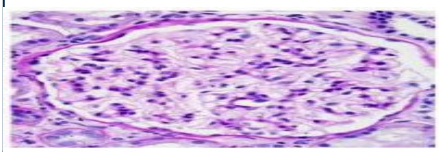
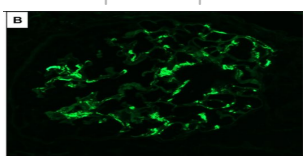
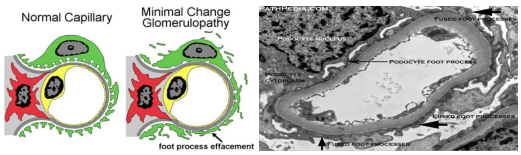
Manifestation

- abrupt development of the nephrotic syndrome.
- The protein loss usually is confined to smaller plasma proteins, chiefly albumin (selective proteinuria).

Characteristic

Morphology

Note that effacement occurs in all nephrotic cases not specific for MCD, what's specific is that LM appears normal.

Light Microscopy	Immunofluorescence	Electron Microscopy
- The glomeruli look **normal**. - The cytoplasm of the proximal convoluted tubular cells are often heavily laden with protein droplets and lipids, due to tubular reabsorption of lipoproteins passing through glomeruli. - There is no tubular atrophy or interstitial fibrosis. 	Is **negative** for immunoglobulins and complement. Why? Because its caused by cytokines production from T-cell not immune complexes deposition. 	- Characterized by diffuse fusion or **effacement** of the epithelial cell (podocyte) foot processes. - This effacement is due to the retraction of the foot processes as a result of extensive cell swelling. 

Treatment and prognosis

- Over 90% of children and few adults have complete remission within 8 weeks of corticosteroid therapy.
- In the absence of complications, the prognosis of MCD, especially in children is very good
- Some patients become steroid dependent i.e. after withdrawal of corticosteroids relapses occur.
- A small subgroup of patients has only partial remission.
- Less than 5% develop chronic renal failure

Focal and Segmental Glomerulosclerosis (FSGS)

Primary nephrotic cause

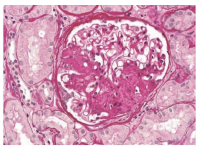
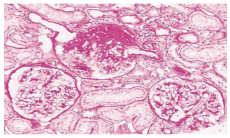
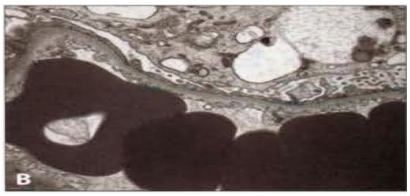
Definition

- Focal and segmental glomerulosclerosis (FSGS) is characterized by sclerosis of some glomeruli(focal) that involves only a part of each affected glomerolus (segmental).
- Most common nephrotic syndrome occurring in Hispanics and African Americans and occurs to older children and adults.
- Primary FSGS initially affects only the juxtamedullary glomeruli, with progression, eventually all levels of the cortex are affected.
- Unlike minimal change disease, the incidence of hematuria and hypertension is higher in individuals with FSGS. Also, FSGS-associated proteinuria is nonselective,

Etiology

- **Could be primary (idiopathic) or secondary to one of the following conditions:**
  - HIV infection (HIV nephropathy)
  - Heroin abuse (heroin nephropathy)
  - Mutations in cytoskeletal proteins and podocin, both of which are required for the integrity of podocytes.

Morphology

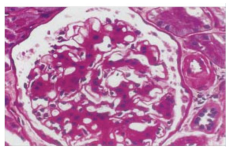
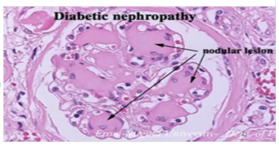
Light Microscopy	Immunofluorescence	Electron Microscopy
-**Focal and segmental sclerosis** of the glomerular tuft. -Adhesions and hyalinosis +/- (due to the entrapment of plasma proteins and lipids in foci of injury where sclerosis develops)  	-Sometimes igM and C3 are positive (in areas of scarring) but generally IF is usually **negative**	-Patchy **Effacement** of podocyte foot process, epithelial denudation. 

Diabetic Nephropathy

Secondary nephrotic cause

- Long standing poorly controlled DM → kidney disease.
- Is a common cause of secondary nephrotic syndrome.
- End result of diabetic nephropathy → end staged kidney.

Morphology

Light Microscopy Shows 2 types of lesions, both show diffuse thickening of the glomerular basement membrane	IF	Electron Microscopy
 • **Diffuse Glomerulosclerosis:** The glomeruli show increase in mesangial matrix and mesangial cell proliferation that ends sclerosis.	Negative	Diffuse Thickening of Glomerular Basement Membrane. (Without deposits).
 • **Nodular glomerulosclerosis (Kimmelstiel Wilson nodules):** There are nodules in the mesangium that are spherical and eosinophilic with a central acellular area.		

Membranous glomerulopathy/glomerulonephritis

Primary nephrotic cause

Characteristics

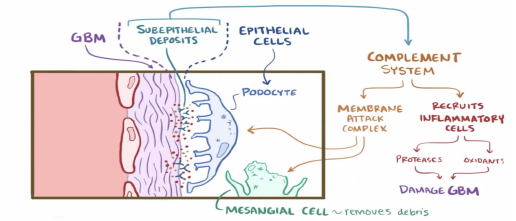
- Membranous glomerulopathy is characterized by **subepithelial** immunoglobulin-containing deposits along the glomeruli basement membrane.
- Early in the disease, the glomeruli may appear normal by light microscopy(as in PBL case), but well-developed cases show diffuse thickening of the capillary wall.
- Most common nephrotic syndrome occurring in Caucasians and Asians and occurs to adults between the ages of 30 to 60.
- The antigen-antibody immune complexes are formed either in the situ in the glomeruli or are performed in circulation and then deposited in the glomeruli.

Etiology

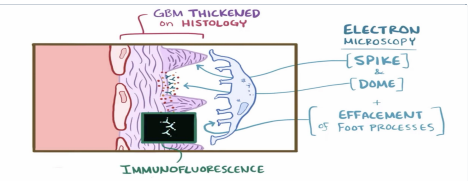
Patients should be investigated for secondary causes.

- **1- Primary/Idiopathic:** Up to 80% of cases of membranous nephropathy, caused by autoantibodies against podocyte antigens.
- **2- Secondary**: which Includes: Autoimmune(SLE) (Class 5)., Infectious(HBV), Therapeutic(Penicillamine) Neoplasms(Lung cancer), Exposure to inorganic salts(gold,mercury).

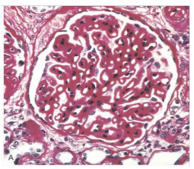
- Antibodies against the podocyte antigen phospholipase A2 receptor (PLA2R) are frequently present.
- Formation of subepithelial immune deposits leads to complement activation on the surface of podocytes and generates the membrane attack complex (C5-C9).

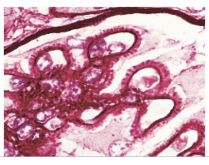


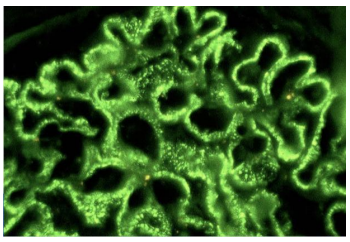
Morphology

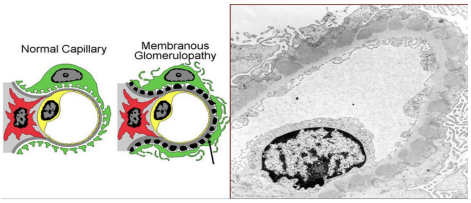


Light Microscopy	Immunofluorescence	Electron Microscopy
-The capillary wall of the glomeruli are diffusely **thickened** (due to subepithelial deposits in GBM). -The deposits are separated from each other by protrusions of GBM matrix called **Spikes** -As the disease progresses there is glomerular sclerosis and interstitial fibrosis.	-Granular positivity of **IgG** and complement **C3** along the glomerular Basement membrane.	-The immune complex appear in capillary walls in electron-dense deposits in the **subepithelial** space. -There is diffuse **effacement** of epithelial cell foot processes.









Clinical features:

- The proteinuria does not usually respond to corticosteroid therapy.
- Proteinuria persists in about half the patients.
- 10% to 30% have a more benign course with good prognosis, Some case progress to renal failure.

Nephritic syndrome

Nephritic syndrome

A group of clinical features characterized by acute onset that are the result of glomerular inflammation and bleeding (rupture of glomeruli).

Clinical features:

01

Hematuria (smokey brown color)

- Is a result of glomerular injury and inflammatory rupture of the glomerular capillaries with resultant bleeding into the Bowman's space → the RBCs collect in the tubules, mix with proteinaceous material in the tubules → forms RBC casts (which can be found in the urine).
- The hemodynamic changes caused by the rupture leads to a reduction in the glomerular filtration rate (GFR).

02

Oliguria

- Because of the decreased GFR

03

Azotemia

- Increased blood urea nitrogen and creatinine.
- It is also a result of reduced GFR.

04

Hypertension

- It is a result of the fluid retention and some augmented renin release from the ischemic kidneys.

NOTE: There may be mild proteinuria (limited proteinuria (<3.5 g/day) "usually in the *subnephrotic range*") and edema.

Examples of nephritic syndrome include:

- Membranoproliferative glomerulonephritis
- Post infectious glomerulonephritis
- Lupus nephropathy

Post-Infectious glomerulonephritis(PIGN)

Primary nephritic cause

Definition

- It's a type of **acute diffuse proliferative** GN caused by glomerular deposition of immune complexes resulting in proliferation of and damage to glomerular cells and infiltration of leukocytes, especially neutrophils.
- The typical case of poststreptococcal GN develops in a child 1 to 4 weeks after he or she recovers from a group A streptococcal infection, note that only certain "nephritogenic" strains of β-hemolytic streptococci evoke glomerular disease.
- In most cases the initial infection is in the:
  - Pharynx (pharyngitis)
  - Tonsils (tonsillitis)
  - Skin (impetigo, infected insect bite)
- Usually there is a latent period between the exposure and the occurrence of glomerulonephritis

Etiology

- The most common cause of post-infectious glomerulonephritis is infection with **group A, beta-hemolytic streptococci** and is therefore also called post-streptococcal glomerulonephritis
- Other infections include pneumococcal and staphylococcal infections and viral diseases (mumps, measles, chickenpox, hepatitis B and C.).

Epidemiology

- Acute PIGN was more common than in the past (because now we have antibiotics), but it still remains to be one of the common childhood renal diseases.

Pathogenesis:

It is not clear if immune complexes are formed mainly in the circulation or in situ.

01 — Infection

Infection by GAS which will lead to antibody production.

02 — Deposition

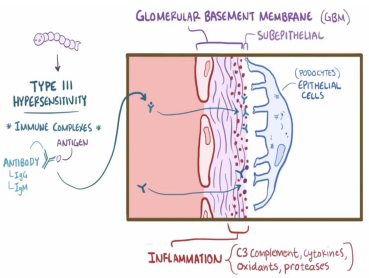
Antibody-antigen complexes form and are deposited in the glomeruli.

03 — Inflammation

These immune complexes initiate inflammation by activating complement.
(complement is used up leading to hypocomplementemia, so serum C3 is low during acute phase)

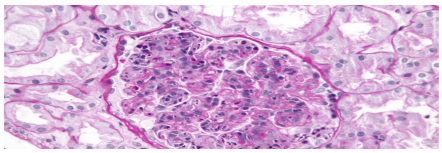
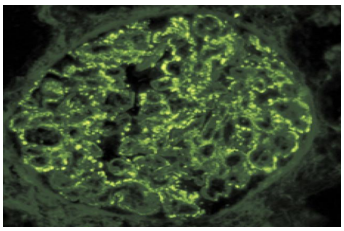
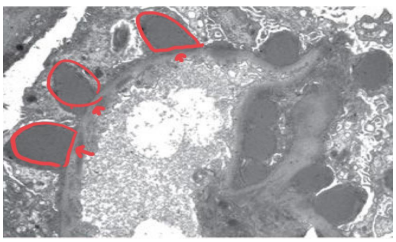
04 — Hypercellularity

The inflammatory mediators attract & activate neutrophils, and stimulate proliferation of endothelial and mesangial cells, causing glomerular hypercellularity resulting in diffuse **Proliferative** GN



Post-Infectious glomerulonephritis(PIGN) cont.

Morphology

Light Microscopy All histologic changes resolve completely in most patients after several months	Immunofluorescence	Electron Microscopy
- Diffuse glomerular enlargement & **hypercellularity**[1] (affects nearly all glomeruli). - There could be crescents. - Infiltration of the glomeruli by **neutrophils** and monocytes. - Occasionally there is necrosis of few glomeruli. 	Coarse granular **(lumpy bumpy)** appearance. (large deposits). IgG & C3 are positive along the GBM and mesangium. 	- **Subepithelial** electron dense deposits, they look like dome shaped **humps**. - Deposits clear up in 2 months. 

Clinical features of PIGN

1. Sudden onset of kidney disease
2. Serological rise of antibodies against streptococcal products. (ASO titre positive)
3. Rarely; adult progress to renal failure
4. Resolves in 90% of patients
5. Rarely; children develop rapidly progressive crescentic glomerulonephritis
6. Grossly: there are multiple punctate hemorrhagic spots on kidney surface
7. Gross hematuria & facial edema
8. Oliguria, facial edema, hypertension, & azotemia

1/The increased cellularity is caused both by proliferation and swelling of endothelial and mesangial cells and by infiltrating neutrophils and monocytes.

LUPUS NEPHROPATHY/ NEPHRITIS (LN)

Secondary nephritic/nephrotic cause

Definition

is an immune complex mediated disease in which there is the deposition of antigen antibody complexes in the glomeruli.

Background

- Patients with the autoimmune disease called systemic lupus erythematosus (SLE)[1] tend to have renal involvement and it is known as lupus nephritis (LN).
- It can present as nephrotic or nephritic syndrome.

Pathogenesis

1. There is the deposition of antigen antibody complexes in the glomeruli.
2. The deposits trigger an inflammatory response.
3. The inflammatory response in turn triggers the proliferation of the epithelial, endothelial and mesangial cells of the glomeruli, and can even lead to glomerular necrosis.

Chronic lesions

- Glomerular sclerosis
- Tubular atrophy
- Interstitial fibrosis

The kidney in LN can show active lesions or chronic lesions or a combination of both.

Active lesions

- Fibrinoid necrosis
- Endocapillary hypercellularity
- Subendothelial deposits
- Inflammation (glomerular or interstitial)
- Extracapillary proliferation (crescents)

1: SLE is an autoimmune disease involving multiple organs, characterized by a vast array of autoantibodies, particularly antinuclear antibodies (ANAs), in which injury is caused mainly by deposition of immune complexes and binding of antibodies to various cells and tissues.

LUPUS NEPHROPATHY / NEPHRITIS (LN) Cont.

The LN lesions have been classified into 6 classes by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). This classification helps give information regarding the activity, chronicity and the prognosis of the disease.
Dr. Note: classification is just additional, you don't have to memorize it. Just know that ISN/RPS classified lupus nephropathy and the fifth class is the membranous.

Class	Characteristics
Class I: Minimal mesangial LN	No active or chronic lesions.
Class II: Mesangial Proliferative LN	No active or chronic lesions.
Class III: Focal LN	Focal involvement of the glomeruli with active lesions, chronic lesions, or a combination of both.
Class IV: Diffuse LN	Similar to class III, however the involvement of the glomeruli is diffuse with active lesions, chronic lesions, or a combination of both.
Class V: Membranous LN	Similar to membranous glomerulopathy. It may co-exist with Class III or Class IV.
Class VI: Advanced sclerosing LN	Is end stage kidney with no activity.

Membranoproliferative glomerulonephritis (MPGN)

Primary nephritic cause

Definition

Membranoproliferative glomerulonephritis (MPGN) is a chronic progressive glomerulonephritis in older children and adults.

Histological Characteristics

- Mesangial **hypercellularity** with **lobulation** of glomerular tufts (lobular accentuation of glomeruli).
- Irregular **thickening** of the capillary wall due to the duplication or double contouring of the GBM (also called as tram track lesions).

Patients may present with:

- Nephrotic syndrome
- Asymptomatic proteinuria
- Nephritic syndrome

Main Types

- **MPGN type I** — Associated with Hepatitis B and C infections, SLE, infected ventriculoatrial shunts and others.
- **MPGN type II** — Also called as dense deposit disease (DDD).

Asymptomatic Hematuria

A separate clinical manifestation

IgA nephropathy (IgAN) / Berger's disease

Definition

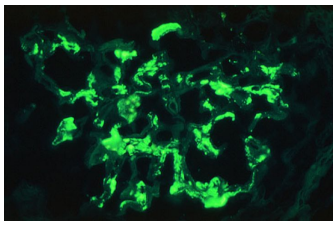
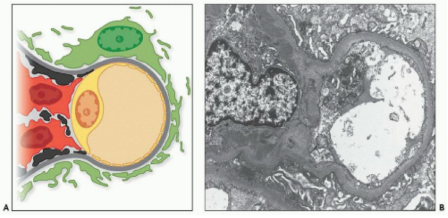
Asymptomatic hematuria or non-nephrotic proteinuria or a combination of the two is the typical clinical presentation of IgA nephropathy, Alport syndrome[1], or mild forms or early presentations of other glomerular diseases.

IgA nephropathy (IgAN)

- **One of the most common types of primary glomerulonephritis that presents as hematuria.**
- **characterized by the deposition of IgA immunoglobulin in the mesangium / paramesangium of glomeruli.**
- **Usually present as hematuria only and sometimes as nephritic syndrome.**
- **This condition usually affects children and young adults and begins as an episode of gross hematuria that occurs within 1 or 2 days of a nonspecific upper-respiratory tract infection.**

Note that when it occurs in combination with vasculitis (leukocytoclastic vasculitis) and multiorgan involvement (systemic) then is referred to as Henoch-Schonlein purpura, which involves the skin (purpuric rash), gastrointestinal tract (abdominal pain), and joints (arthritis).

Morphology

Light Microscopy Very variable (may or may not show):	Immunofluorescence	Electron Microscopy
- Mesangial hypercellularity, - Endocapillary hypercellularity, - Glomerular sclerosis, - Tubulointerstitial scarring.	- Dominant **IgA** stain positively in the mesangium, often with C3 and properdin and smaller amounts of IgG or IgM. - Early components of the classical complement pathway usually are absent. 	Immune complex deposits positive in the mesangium and para-mesangial area. 

1/ Alport syndrome is a genetic condition characterized by kidney disease, hearing loss, and eye abnormalities.

RAPID PROGRESSIVE GLOMERULONEPHRITIS/ CRESCENTIC GLOMERULONEPHRITIS (RPGN/CRGN)

A separate clinical manifestation

Definition

- It is a clinical syndrome and not a specific etiologic form of GN.
- Characterized by rapid and progressive loss of renal function within weeks to months.
- Patients usually present with acute renal failure, features of nephritic syndrome and severe oliguria (it is a mixture of nephritic syndrome & ARI), if untreated may lead to death due to renal failure(Poor prognosis)

- RPGN is commonly associated with severe glomerular injury (reversible stage) with necrosis (irreversible stage) and GBM breaks and subsequent proliferation of parietal epithelium (crescents).

What are Crescents?

Glomerular extracapillary parietal epithelium proliferations (i.e. proliferation outside the glomerular capillaries)

Crescents are formed by:

01 Proliferation of parietal epithelial cells that line the Bowman's capsule.

02 Migration of monocytes/macrophages into Bowman's space.

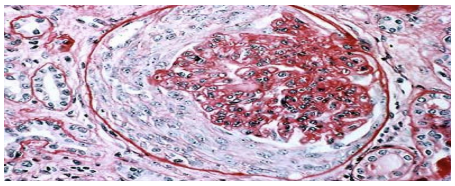
Morphology (Light microscopy)

- Histologically there is severe glomerular injury.
- The characteristic finding in RPGN is the presence of crescents.

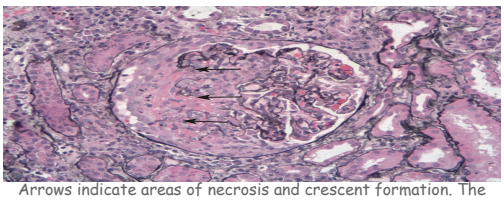
Segments of glomeruli may show necrosis.

Formation of many crescents, which will eventually fill the Bowman's space, compress the glomeruli and can even rupture the GBM

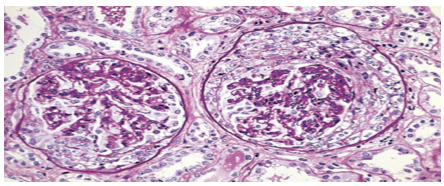
In time with healing the crescents undergo fibrosis/scarring.



Crescentic glomerulonephritis (silver stain).



Arrows indicate areas of necrosis and crescent formation. The segmental distribution in this case is typical of ANCA (anti-neutrophil cytoplasmic antibody)–associated crescentic glomerulonephritis.



Clinical features:

1 The onset of RPGN is much like that of the nephritic syndrome that can progress to ARF, except that the oliguria and azotemia are more pronounced.

2 Proteinuria sometimes approaching the nephrotic range may occur.

- Some affected individuals become anuric and require long-term dialysis or transplantation.
- The prognosis is roughly predicted by the fraction of involved glomeruli, as patients in whom crescents are present in less than 80% of the glomeruli have a more favorable prognosis than those in whom the percentage of crescents is higher

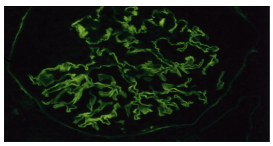
RPGN cont.

Based on etiology RPGN is divided into three types:

Types of RPGN

Type I RPGN (12%)
Anti-glomerular basement membrane antibody disease (Anti-GBM disease)

- Anti-GBM antibody disease is a rare autoimmune disorder. In it there are **autoantibodies directed against an antigen normally present in the glomerular basement membrane (GBM).**
- On IF: characteristic intense linear staining or positivity with IgG and C3 along the GBM.
- EM: negative
- ★ Patient's serum will have anti-GBM antibodies (helpful in diagnosis.)
- Patients have nephritic syndrome picture.
- Timely diagnosis of anti-GBM disease is important.
- Treatment: plasmapheresis, which removes pathogenic antibodies from the circulation.



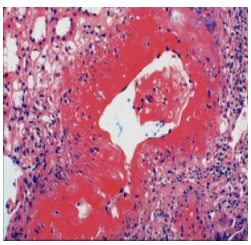
What's Goodpasture's syndrome?
It's when the anti-GBM antibodies also bind to **pulmonary alveolar capillary** basement membranes to produce the clinical picture of pulmonary hemorrhages(hemorrhagic pneumonitis) associated with renal failure. (In other words,it is the involvement of both the kidneys and lungs)

Type II RPGN (44%)
Immune complex mediated crescentic glomerulonephritis

- **Crescents can be a complication of any of the immune complex mediated GN e.g.**
  - poststreptococcal GN,
  - systemic lupus erythematosus,
  - IgA nephropathy and Henoch-Schönlein purpura.
- On IF there is presence of immune complexes (immunoglobulin and/or complement)
- On EM there are electron dense immune deposits.
- This disorder usually does not respond well to plasmapheresis (because there are no autoantibodies in this type).

Type III RPGN (44%)
Pauci-immune ANCA-associated GN (Wegener's granulomatosis with polyangitis.)

- **Patients have autoantibodies directed against antigens present in the cytoplasm of neutrophils called antineutrophil cytoplasmic autoantibodies (ANCAs).**
- **ANCA causes abnormal activation of neutrophil → adhesion of the neutrophils to endothelial cells lining the capillaries (esp. glomerular capillaries) → neutrophils promote vascular inflammation which leads to:**
  - Glomerular injury with crescent formation.
  - Necrosis (fibrinoid type) in the glomeruli and other blood vessels (arteries and arterioles).
  - Some blood vessels can show transmural full thickness inflammation and necrosis (photo A).
- Pauci-immune crescentic GN can be idiopathic or associated with systemic vasculitis like microscopic polyangiitis (P-ANCA) or Wegener granulomatosis (C-ANCA).



(A)

- ***Note: in pauci-immune GN there is:***
  - *NO anti-GBM antibody and NO immune complex deposition so the IF is negative/almost negative and there are no deposits on EM (hence-the name "pauci-immune" GN). (Pauci = few, little)*
- ***Note: RPGN type I and II are ANCA negative.***

CHRONIC RENAL FAILURE (CRF) OR CHRONIC KIDNEY DISEASE (CKD)

Definition

Chronic kidney disease describes the slow or gradual loss of kidney function, can be a consequence of irreversible acute disease or progressive scarring in any type of chronic renal disease.

Characteristics

- Patients need with dialysis or transplantation otherwise death from uremia will results(poor prognosis).
- Dialysis and kidney transplantation allow long-term survival.
- The end result is end stage kidney disease.*

*End-stage kidney disease:

- **There is scarring of all 4 renal compartments:** **(regardless of the primary site of injury.)**

- Glomerular sclerosis
- Tubular atrophy
- Interstitial fibrosis
- Arteriosclerosis

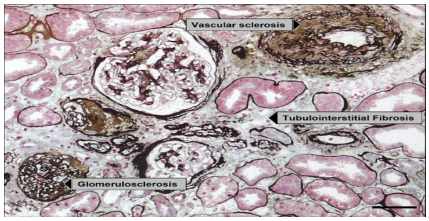
Etiology

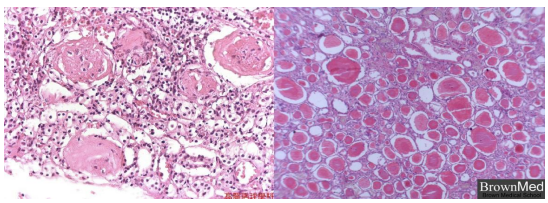
- Chronic glomerulonephritis like RPGN, membranous GN, membranoproliferative GN, FSGS, IgA nephropathy, etc.
- Diabetic Nephropathy (due to uncontrolled diabetes)
- Uncontrolled Hypertension and Polycystic kidney disease
- Reflux nephropathy in children
- Kidney infections & obstructions

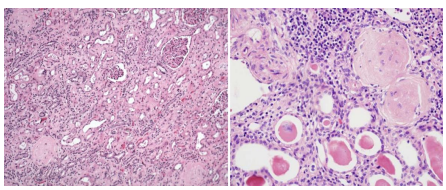
Morphology

Grossly	Microscopically
The kidneys are symmetrically contracted with red-brown and diffusely granular surface	1. Glomeruli: Glomerular sclerosis and scarring of majority of the renal glomeruli 2. Interstitium: Marked interstitial fibrosis with lymphocytic infiltrate 3. Tubules: Atrophy of the tubules in the cortex 4. Vessels: ○ Loss of portions of the peritubular capillary network ○ Thick walled arteries and arterioles with narrowed lumina

- Such markedly damaged kidneys are designated **"end-stage kidneys"**



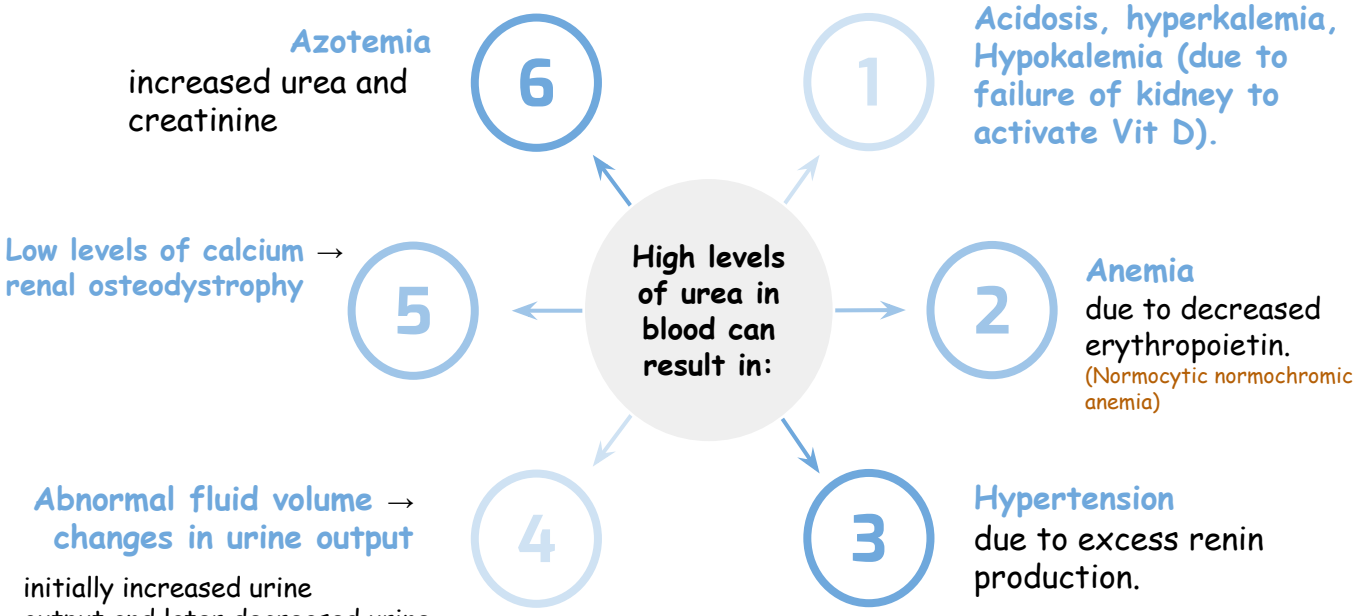




CHRONIC RENAL FAILURE (CRF) OR CHRONIC KIDNEY DISEASE (CKD)

Clinical features:

- In the early stages of chronic kidney failure → few signs or symptoms.
- Chronic kidney failure may not become apparent until your kidney function is significantly impaired.
- Some patients are oliguric and some patients are not oliguric.
- Gradual **rise in BUN** and serum creatinine.



Summary from Robbins

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

Summary

	Disease	Morphology			
		LM	IF	EM	Location
Nephrotic Syndrome	**Minimal Change Disease (MCD)/ Glomerulopathy** (Primary cause)	- Glomeruli looks normal. - Cytoplasm of the proximal convoluted tubular cells are heavily laden with protein droplets and lipids. - No tubular atrophy or interstitial fibrosis.	Negative for immunoglob-ulins and complement.	Characterized by diffuse fusion or effacement of the epithelial cell (podocyte) foot processes due to extensive cell swelling.	Epithelial cell (podocyte) foot processes.
	Focal and Segmental Glomerulosclerosis (FSGS) (Primary cause)	- Glomeruli at the juxtamedullary area are affected. - Some of the glomeruli are involved (focal). - Focal and segmental sclerosis of the glomeruli. - Adhesions and hyalinosis +/-.	Usually negative, but sometimes IgM positivity is present.	Patchy effacement of podocyte foot processes.	Epithelial cell (podocyte) foot processes.
	Membranous Glomerulopathy/ Glomerulonephritis (GN) (Primary cause)	- Capillary walls of the glomeruli are diffusely thickened - Deposits are separated from each other by protrusions of GBM matrix called spikes - With disease progression, there is glomerular sclerosis and interstitial fibrosis.	Granular positivity of immunoglob-ulin IgG and complement C3 along the GBM.	- Immune complexes appear in capillary walls as electron-dense deposits in the subepithelial space. - Diffuse effacement of epithelial cell foot processes	Subepithelial space & Epithelial cell (podocyte) foot processes.
	Diabetic Nephropathy (Secondary cause) **End result:** End-stage Kidney	- **2 types of lesions**, both show diffuse thickening of the glomerular basement membrane: 1) **Diffuse glomerulosclerosis** →↑mesangial matrix & proliferation 2) **Nodular glomerulosclerosis (Kimmelstiel Wilson nodules)** → in the mesangium	Negative.	Diffuse increase in the thickness of the glomerular basement membrane.	Glomerular basement membrane (GBM).

Summary

	Disease	Morphology			Location
		LM	IF	EM	
Nephritic Syndrome	Post-Infectious Glomerulonephritis (PIGN)	- Diffuse glomerular enlargement and hypercellularity due to proliferation of endothelial and mesangial cells. - Infiltration of the glomeruli by neutrophils and monocytes. - Occasional crescents may be present. - Occasional necrosis of few glomeruli. - All histologic changes resolve completely in most patients after several months.	Coarse granular (lumpy bumpy) IgG and C3 are positive along the capillary walls.	- Characteristic electron dense deposits are seen in the subepithelial area. - Look like dome shaped humps. - Deposits clear up over a period of about 2 months.	subepithelial area.
	Lupus Nephropathy (LN)/ Nephritis (Note: Patients may present with: nephrotic syndrome, nephritic syndrome)	- Proliferation of the epithelial, endothelial and mesangial cells of the glomeruli. - Can lead to glomerular necrosis. - Can show active lesions or chronic lesions or a combination of both: 1) Active lesions: endocapillary hypercellularity or extracapillary proliferation (crescents), inflammation (glomerular or interstitial), fibrinoid necrosis and subendothelial deposits. 2) Chronic lesions: glomerular sclerosis, tubular atrophy and interstitial fibrosis.			Epithelial, endothelial and mesangial areas.
	Membranoproliferative Glomerulonephritis (MPGN) (Note: Patients may present with: nephrotic syndrome, nephritic syndrome, asymptomatic proteinuria)	- **Membranoproliferative pattern:** **1)** mesangial hypercellularity with lobulation of glomerular tufts (lobular accentuation of glomeruli) **2)** Irregular thickening of the capillary wall due to the duplication or double contouring of the GBM (tram track lesions) - GBM splitting.	Granular IgG, C3 C1q & C4 along GBM and mesangium.	Subendothelial deposits.	Subendothelial area.
	IgA Nephropathy/ Berger's disease (**Hematuria**)	Very variable, may or may not show mesangial hypercellularity, endocapillary hypercellularity, glomerular sclerosis, tubulointerstitial scarring.	Dominant IgA stain positivity in the mesangium.	Immune complex deposits positive in the mesangium and paramesangial area.	Mesangial and paramesangial area.

Summary

Disease		Morphology			
		LM	IF	EM	Location
RPGN	**Type I RPGN:** Anti-glomerular basement membrane antibody disease (anti-GBM disease)	- Formation of many crescents. - Crescents fill Bowman's space, compress glomeruli and can rupture the GBM. - Segments of glomeruli may show necrosis. - With healing crescents undergo fibrosis.	Characteristic intense linear staining/ positivity with IgG along the GBM.		Glomerular basement membrane (GBM).
	Type II RPGN: Immune complex mediated crescentric glomerulonephritis		Presence of immune complexes (immunoglobulin and/or complement).	Electron dense immune deposits.	
	Type III RPGN: Pauci-immune ANCA-associated GN (Wegener's granulomatosis with polyangiitis)		Negative/almost negative, no immune complex deposition.	No deposits.	Cytoplasm of neutrophils called antineutrophil cytoplasmic autoantibodies (ANCAs).
Chronic Renal Failure (CRF)/ Chronic kidney disease (CKD) → **End result**: End-stage Kidney (Note: **Grossly**, kidneys are symmetrically contracted with red-brown and diffusely granular surface.)		- Glomerular sclerosis and scarring of most renal glomeruli. - Interstitial fibrosis with lymphocytic infiltrate. - Atrophy of the tubules in the cortex. - Loss of portions of the peritubular capillary network. - Thick walled arteries and arterioles with narrowed lumina.			

Quiz

Answer key: Answers Explanation File!

B) 1: D) 2: E) 3: D) 4: E) 5: C) 6

1) A 32-year-old man complains of recurrent hematuria since his youth. The hematuria typically occurs following upper respiratory tract infections. Vital signs are normal. Urinalysis shows proteinuria, hematuria, and a few red blood cell casts. Laboratory studies disclose normal levels of BUN and creatinine. The ANA and ANCA tests are negative. Which of the following is the most likely diagnosis?

A	Amyloid nephropathy
B	Berger disease (IgA nephropathy)
C	Hereditary nephritis (Alport syndrome)
D	Membranous glomerulopathy
E	Wegener granulomatosis

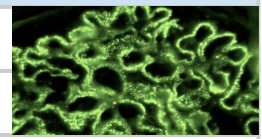
2) An 8-year-old boy presents with headaches, dizziness, and malaise. He was seen for a severe sore throat 2 weeks ago.Physical examination reveals facial edema. The blood pressure is 180/110 mmHg. A 24-hour urine collection demonstrates oliguria, and urinalysis shows hematuria. Which of the following best describes this patient's medical condition?

A	Hereditary nephritis
B	Membranous glomerulonephritis
C	Minimal change nephritic syndrome
D	Postinfectious glomerulonephritis
E	Thin glomerular basement membrane nephropathy

3) A 12-year-old girl complains of swelling of her eyelids, abdomen, and ankles. She had been in good health until several months ago, when she gained some weight and noted swelling of her lower legs. An X-ray film of the chest shows bilateral pleural effusions, without evidence of lung disease. Urinalysis reveals heavy proteinuria (8 g per 24 hours) without hematuria. A percutaneous needle biopsy of the kidney discloses no morphologic abnormalities by light microscopy. Which of the following best describes this patient's medical condition?

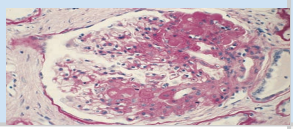
A	Amyloid nephropathy
B	Focal segmental glomerulosclerosis
C	Hereditary nephritis
D	Membranous glomerulopathy
E	Nephrotic syndrome

4) A 44-year-old man complains of swelling of his legs and puffiness around his eyes. His abdomen has become protuberant and he feels short of breath. Physical examination reveals generalized edema and ascites. Total serum protein is 5.2 g/dL (reference = 5.5 to 8.0 g/dL), and albumin is 1.9 g/dL (reference = 3.5 to 5.5 g/dL). Serum cholesterol is elevated at 530 mg/dL. There are 5 g of protein in a 24-hour urine collection. The urinary sediment contains many hyaline casts but no RBCs or inflammatory cells. A renal biopsy stained by direct immunofluorescence for igG is positive. Which of the following is the most likely diagnosis?



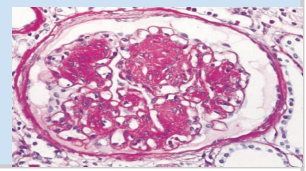
A	Amyloid nephropathy
B	Focal segmental glomerulosclerosis
C	Membranoproliferative glomerulonephritis type I
D	Membranous glomerulopathy
E	Minimal change disease

5) A 30-year-old man with a history of drug addiction presents with a 6-month history of progressive swelling in his ankles and abdomen. Urinalysis shows heavy proteinuria (>4 g per 24 hours) but no evidence of inflammatory cells or RBCs. Laboratory studies reveal hyperlipidemia and hypoalbuminemia. Serum creatinine level is normal. The blood test for ANCA is negative. The patient responds well to treatment with corticosteroids, but edema and proteinuria recur the following year. The steroid treatment is repeated with the same results. Upon the third recurrence of edema and proteinuria, the patient becomes steroid resistant. A renal biopsy is shown in the image. Which of the following is the most likely diagnosis for this patient's glomerulopathy?



A	Acute glomerulonephritis
B	Amyloidosis
C	Crescentic glomerulonephritis
D	Diffuse proliferative glomerulonephritis
E	Focal segmental glomerulosclerosis

6) A 52-year-old woman presents with swelling of her ankles of 6 weeks in duration. Physical examination reveals an obese woman (BMI = 32 kg/m2) with pitting edema of the lower extremities and periorbital edema. Laboratory studies show hyperlipidemia and hypoalbuminemia. Urinalysis discloses 3+ proteinuria and 3+ glucosuria but no evidence of inflammatory cells or RBCs. A kidney biopsy stained with PAS (shown in the image) displays a prominent increase in the mesangial matrix, forming nodular lesions, and thickening of capillary basement membranes. Which of the following is the most likely pathologic diagnosis?



A	Acute glomerulonephritis
B	Amyloid nephropathy
C	Diabetic glomerulosclerosis
D	Malignant nephrosclerosis
E	Membranoproliferative glomerulonephritis

Thank you

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- **Alwaleed Alsaleh**
- Faisal Almuhid
- Jehad Alorainy
- **Khalid Alkhani**
- **Mohammed Alhumud**
- Mohanad makkawi
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