Pathology

-Lec (1 & 2)

La Medica Academy

Study Smarter Not Harder

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Renal Diseases

Important Terminology:

- **Azotemia:** (without clinical manifestations)

  ↑ blood urea nitrogen creatinine levels ↓ glomerular filtration rate

- **Uremia:** (clinical manifestations & systemic biochemical abnormalities)

  -Failure of renal excretory function + metabolic & endocrine alterations

  ↑ blood urea nitrogen كلاهما ←(Azotemia & Uremia)

- **Urinary tract infection** (UTI):

  -bacteriuria & pyuria (bacteria and leukocytes in the urine).
  -Symptomatic or asymptomatic.
  -Affect the kidney (pyelonephritis) or the bladder (cystitis) only.

- **Nephrolithiasis:**

  -formation of stones in the collecting system.
  -Manifested by renal colic & hematuria.

- **Acute kidney injury:**

  -abrupt onset of renal dysfunction (acute increase in serum creatinine) often ass/w oliguria or anuria

- **Chronic kidney disease:**

  -progressive scarring in the kidney of any cause

  -Metabolic & electrolyte abnormalities

  -asymptomatic until the most advanced stages → symptoms of uremia develop

- **End-stage renal disease** (ESRD):

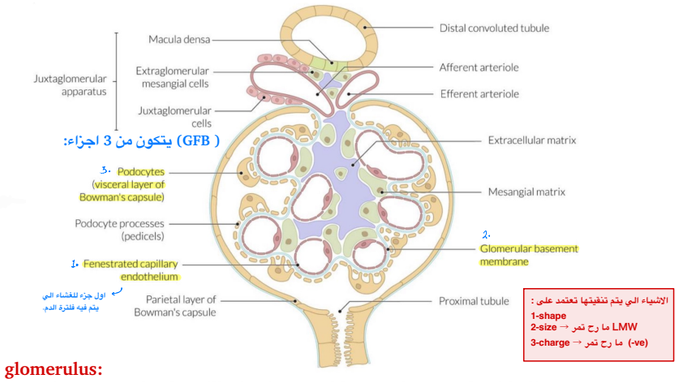
  -is irreversible loss of renal function

  requiring → dialysis or transplantation due to severe progressive scarring in the kidney

(Diseases of the kidney)

- Kidneys carry out many functions that require a high degree of structural complexity.
- Renal diseases are responsible for a great deal of morbidity & mortality.
- Four basic morphologic components: glomeruli, tubules, interstitium, blood vessels.

توضيح :



-The glomerulus:
anastomosing network of capillaries invested by two layers of epithelium:

1-~~The visceral epithelium~~ (composed of podocytes) is part of the capillary wall.
2-~~the parietal epithelium~~ encircles Bowman space (urinary space), the cavity in which filtrate of plasma collects.

- **Primary**: kidney is the only or predominant organ.
- **Secondary**: Injured in the course of a systemic diseases.

  مثلاً عنده SLE وأثر على الkidney

-are major problems in nephrology

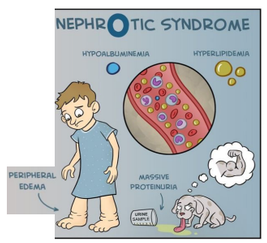
-Chronic glomerulonephritis is one of the most common causes of chronic kidney disease

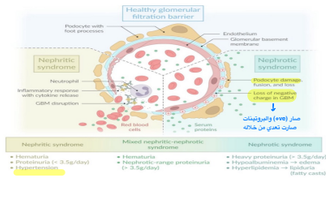
-Immune mechanisms: (most types of primary diseases & many of the secondary)
1-Deposition of circulating antigen-antibody complexes in the glomerular capillary wall or mesangium.

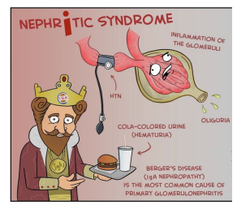
2-Antibodies reacting in situ within the glomerulus, either with fixed (intrinsic) glomerular antigens or with extrinsic molecules that are planted in the glomerulus.

*The two most common syndromes associated with glomerular diseases :

Nephrotic syndrome	Nephritic syndrome
• Massive Proteinuria (Normal = 0.150) daily protein loss in the urine of = > 3.5 g	• Proteinuria (sub nephrotic range) with or without edema
• Hypoalbuminemia with plasma albumin < 3 g/dL	• Hematuria (red cells & red cell casts in urine)
• Generalized edema the most obvious clinical manifestation	• Azotemia: ↑ blood urea nitrogen creatinine levels ↓ glomerular filtration rate
• Hyperlipidemia and lipiduria (الجسم خسر proteins بكميات كبيرة ، الكبد رح يحاول يعوض ويصنع بروتينات اكثر، lipid transporter (بروتينات تحمل الlipid بزيادة)	• Hypertension





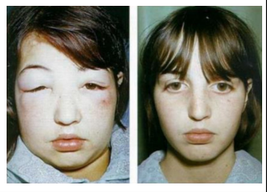
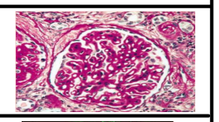
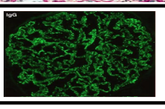
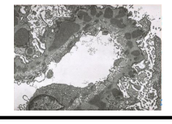
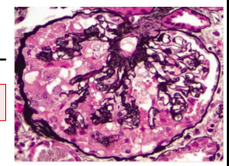


Mnemonic ⟹ "PALE"
massive Proteinuria
hypoAlbuminemia
hyperLipidemia
Edema

Nephrotic syndrome

In children → associated with primary kidney lesion

In adult → associated with systemic disease (2ry)
(diabetes, amyloidosis, SLE)

	Minimal-Change Disease (MCD)	Focal segmental glomerulosclerosis (FSGS)	Membranous Nephropathy
	-benign disorder -most common in children (at 1-7 years of age)	sclerosis of some (but not all) glomeruli; involves only a part of each affected glomerulus -highest prevalence in adults	-Antibodies reacting in situ to endogenous antigens / planted glomerular antigens -most common in older adult
Pathogenesis	-T-cell dysfunction → release factors that damage podocytes & efface foot processes.	-Injury to podocytes → entrapment of plasma proteins & lipids in foci of injury → Hyaline deposition in the glomeruli → sclerosis	-Chronic immune complex glomerulonephritis.
Clinical symptoms	-abrupt nephrotic syndrome in an otherwise healthy child -No hypertension, & renal function is often preserved selective proteinuria With long-standing or heavy proteinuria → ↓ serum albumin→ hypoalbuminemia → a drop in plasma colloid osmotic pressure → leakage of fluid from the blood into extravascular spaces. 	-Hematuria -Hypertension proteinuria is nonselective . primary (idiopathic) or secondary (HIV infection (5-10% of HIV patients), Heroin abuse, other forms of GN (IgA nephropathy), nephron loss.	Sudden onset full-blown nephrotic syndrome proteinuria is nonselective •Primary (idiopathic): -75% of cases -Antibodies against the podocyte antigen phospholipase A2 receptor (PLA2R) •Secondary:(should always be ruled out) -Infections: chronic HBV, malaria, syphilis -Autoimmune diseases: particularly SLE -Malignancies: Ca. of lung & colon,melanoma -Exposure to inorganic salts (gold, mercury) -Drugs (penicillamine, captopril, NSAIDs)
(LM)	Normal glomeruli	Sclerosis in some glomeruli not all of them & in a segment not all of the affected glomerulus	The main histologic feature is diffuse thickening of the capillary wall (GBM) on routine H&E stains. 
(IF)	negative	negative or nonspecific trapping of immunoglobulins	granular deposits contain both immunoglobulins & complement. 
(EM)	The only obvious glomerular abnormality is the diffuse effacement of the foot processes of the podocytes	as in minimal-change disease	subepithelial deposits (spike & dome pattern) 
silver stain			(black) of the GBM → appears with characteristics spikes (projections in capillary loops)
Prognosis	The response to corticosteroid therapy is excellent > 90% of children respond to a short course of corticosteroid therapy. Adults with also respond to steroid therapy, but slower & relapses are more common. Less than 5% develop chronic kidney disease after 25 years.	The response to corticosteroid therapy is poor 50% develop renal failure in 10 years • Collapsing glomerulopathy- FSGS morphologic variant: -Collapse glomerular tuft & epithelial cell hyperplasia. -severe form with worse prognosis. -Can be: idiopathic, ass/with HIV infection, or drug-induced toxicities. 	-fails to respond to corticosteroid therapy • Variable prognosis: ➢ Proteinuria persists in > 60% of patients ➢ ~ 40% progress to renal failure over 2 to 20 years. ➢ 10-30% benign course → partial or complete remission of proteinuria.

نميز الفرق باللون النهدي

Nephritic syndrome

-inflammation in the glomeruli → injury in capillaries → permeable to RBCs & other contents → hematuria

-proliferation of the cells in glomeruli

-leukocytic infiltrate

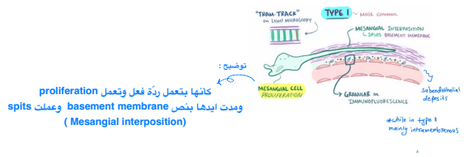
↓↓ GFR → augmented Renin/aldosterone (fluid retention & ↑↑ plasma volume) → Hypertension

Membrano-proliferative Glomerulonephritis (MPGN)

-pattern of immune mediated injury rather than a specific disease.
(Alterations in the GBM & mesangium & proliferation of glomerular cells).

-Mixed Glomerulonephritis

begin as acute nephritis or as mild proteinuria —50% of cases→ nephrotic syndrome

MPGN type I Subendothelial deposits	Dense Deposit Disease (MPGN type 2) intramembranous deposits
80% of cases (MC type)	Less common
Immune complex activates both classical &alternative complement pathways. The antigens Mostly are proteins derived from infectious agents e.g., hepatitis C & B viruses	Excessive complement activation. • Complement dysregulation •C3 nephritic factor (Autoantibody) —against→ C3 convertase
(either planted antigens or preformed immune complexes deposited from the circulation)	• Ab It stabilizes the enzyme → uncontrolled cleavage of C3 & activation of the alternative complement pathway
On IF: C3 is deposited in an irregular granular patterns IgG and (C1q &C4)	On IF: Only C3 is present in irregular foci in the GBM (not within the dense deposits)
EM Marked thickening of the glomerular capillary wall by immune deposits by interposition of mesangial cell processes	EM dense homogeneous deposits within the basement membrane. Ribbon-like appearance of subendothelial & intramembranous material
LM double contour or "tram track" appearance, especially evident with use of silver	

The prognosis generally is poor (No complete remission)

40% progressed to renal failure

60% → 30% (renal insufficiency); 30% had persistent nephrotic syndrome without renal failure

Acute Postinfectious (Poststreptococcal) Glomerulonephritis

Subepithelial deposits

-Glomerular deposition of immune complexes (containing streptococcal antigens & specific antibodies)

↓

activate complement system

→ proliferation of & damage to glomerular cells

→ infiltration of leukocytes (esp. neutrophils)

-initial infection in pharynx or skin

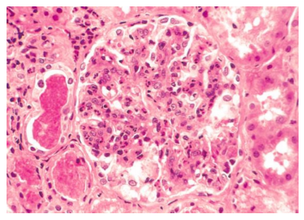
Classic pattern/most common → poststreptococcal GN

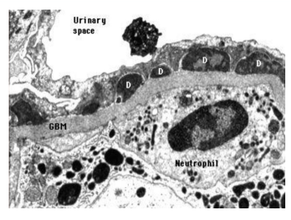
but → ass/w other organisms; viral or bacterial

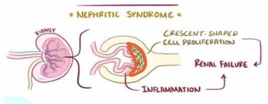
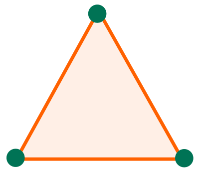
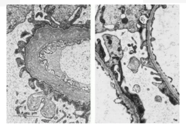
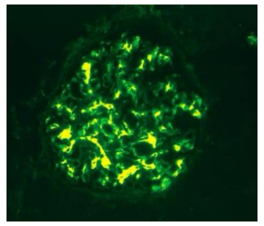
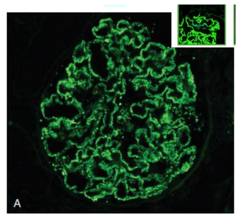
Typical history :
child 1-4 weeks after he/she recovers from a group A streptococcal infection.

- clinically:
- Most commonly present as acute nephritic syndrome.
- Fever, nausea, gross hematuria, & mild proteinuria.
- Serum complement levels are low during the active phase of the disease.
- Serum anti–streptolysin O antibody titers are elevated in poststreptococcal cases.
- Recovery occurs in most children with poststreptococcal disease.

LM	EM	IF
increased cellularity of all glomeruli → caused by: (1) proliferation & swelling of endothelial & mesangial cells (2) by infiltrating neutrophils & monocytes.	subepithelial "humps" (on the epithelial side of GBM) (Without spikes)	scattered granular deposits of IgG & complement within the capillary walls





	IgA Nephropathy (Berger Disease) Not IgM or IgG	Rapidly Progressive (Crescentic) Glomerulonephritis	Hereditary Nephritis (Alport Syndrome)
pathogenesis	genetically susceptible individual + URTI or GIT exposure to microbial ↓ ↑↑↑ IgA synthesis ↓ deposition of IgA & immune complexes in the mesangium.	presence of crescents (crescentic GN)  Formed by: → proliferation of epithelial cells → migration of monocytes/ macrophages into Bowman's space in response to injury	Mutation of any one of the α chains ↓ defective heterotrimer assembly ↓ manifestations of Alport syndrome
characteristics	-children & young adults (20-30 years old) (Acute Postinfectious (5-15 years old) كانت) -most common causes of recurrent microscopic or gross hematuria (chronic). -An episode of gross hematuria → lasts days & subsides, but it recurs periodically (within 1-2 days of a nonspecific URTI) → (1-4 weeks) كانت Acute Postinfectious - Similar IgA deposits are present in a systemic disorder of children, Henoch Schonlein purpura. → احد انواع vasculitis IgA يترسب فيB.V بأغلب اماكن الجسم ويعمل Extrarenal menifestation+ IgA Nephropathy -Renal manifestations occur in one third of patients. (same deposition pattern as IgA nephropathy)	-Associated with number of diseases: a. Anti-GBM antibody–mediated crescentic GN (Goodpasture disease) b. Any of the immune complex nephritides c. Pauci-immune RPGN Serum ANCA **RPGN –Goodpasture disease :** - anti-GBM antibodies bind to pulmonary alveolar capillary BM to produce the clinical picture of pulmonary hemorrhages ass/w renal failure → Goodpasture syndrome. يهاجم → Glomerular, Pulmonary -Anti-GBM Abs are in the serum → Diagnosis. -It is important to recognize Goodpasture disease → benefit from plasmapheresis → removes pathogenic antibodies from the circulation.	-a group of heterogeneous familial renal diseases ass/ w mutations in collagen genes & manifest primarily with glomerular injury -Inherited as an X-linked trait in ~ 85% of cases GBM is composed of → type IV collagen → heterotrimers of α3, α4, & α5 type IV collagen → is crucial for function of the lens, cochlea, & glomerulus Alport Syndrome (Classic triad)  various eye disorders: lens dislocation, corneal dystrophy, posterior cataracts
LM	-Different findings but whatever the histologic lesions	-Collapsed glomerular tufts and crescent-shaped mass of proliferating parietal epithelial cells & leukocytes internal to Bowman capsule	**EM** Early → GBM is thin & attenuated Later → develops irregular foci of thickening, splitting and lamination, "basket-weave" appearance 
IF	-the pathognomonic feature → is the deposition of IgA and C3, in the mesangial region. (diagnostic) 	(Goodpasture disease) → linear deposits of IgG in GBM 	
Mnemonic	**IgA in mesAngium**		**Alport** (Classic triad) حرف A زي المثلث