Renal

Kidney Diseases

Glomerular Disease

- Usually immune mediated
- Antibodies deposited

in situ antigen

1- intrinsic : good pasture antigens → BM / Heymann nephritis antigens → visceral epithelial cells
→ Produce linear immunofluorescence patterns

2- planted : BM deposition (exogenous / endogenous), Cationic proteins bind to glomerular anionic sites
→ Produce granular / lumpy staining by immunofluorescence

3- Circulating immune complexes : (endogenous / exogenous), localize within glomeruli and activate complement, mesangial or subendothelial deposition, resolve by macrophage phagocytosis

* Nephrotic Syndrome Diseases (Caused by primary Glomerular diseases)

- Nephrotic Syndrome
  - Proteinuria
  - hypoalbuminemia
  - edema
  - hyaline casts

① Minimal Change disease (Lipoid necrosis / nil disease / foot process disease)

- most common in Children (1-7 years old), good prognosis
- Diagnosis :-
  - normal glomeruli under light microscope
  - negative Immunofluorescence
  - * Electron microscope : 1) no immune deposits (no antibody deposits)
    2) uniform + diffuse effacement of podocytes foot processes
- injury to podocytes → proteinuria

Clinical Course

- no hypertension
- * Selective proteinuria (albumin)
- Treatment : Corticosteroids
- if in Adults :-
  - response is slower
  - relapses are more common

② Focal and Segmental Glomerulosclerosis (FSGS)

- Sclerosis involving some G ("focal") (focal involvement) and some segments of each affected G ("segmental")

* - Causes :
  - association with other conditions (HIV nephropathy / heroin nephropathy)
  - Secondary to other GN (IgA nephropathy)
  - maladaptation after nephron loss
  - inherited / congenital → mutations impacting cytoskeletal / related proteins in podocyte
    ex: nephrin (major component of slit diaphragms) (non-immune cause)
  - Primary / idiopathic → 20 - 30 % of nephrotic syndrome

* - **most common nephrotic syndrome in Adults**
- Clinical Course :-
  - **non-selective proteinuria** - hematuria - hypertension
  - **poor response to Corticosteroid therapy**
- Pathogenesis :-
  - Primary FSGS → unknown (non-immune injury to podocytes might be the initiating event)
  - permeability-increasing factors produced by lymphocytes have been proposed in both MCD+FSGS
  - deposition of hyaline masses in glomeruli represents the entrapment of plasma proteins and lipids in foci of injury where sclerosis develops
  - **IgM + Complement proteins commonly seen in lesion result from non-specific entrapment in damaged glomeruli**
- Effected glomeruli:
  - ↑ mesangial matrix (accumulation of matrix material) - endocapillary foam cells
  - hyalinosis + lipid droplets deposition - scaring + obliteration of capillary lumens
  - effacement of foot processes on electron microscope

*

Progression of FSGS, with time, leads to **global sclerosis** of the **G** with pronounced tubular atrophy & interstitial fibrosis, a picture difficult to differentiate from other forms of chronic **G** disease, with progression to RF occurring in 50% of FSGS patients after 10 years.

- Columbia University Classification of FSGS

Collapsing — hp-lesion — Cellular — Perihilar

- Collapsing → - Agressive type → worse prognosis - idiopatic or vius associated ....
  - At least 1 glomerulus with Capillary loop Collapse

* ③ Membranous GN (MGN) = Membranous Nephropathy (MN)
  * - Diffuse Capillary wall thickening (whole glomerulus involved)
  * - Subepithelial immunoglobulin-Containing deposits (inside the podocytes)
  - Form of Chronic immune Complex nephritis
  - most idiopathic MGN are induced by Antibodies reacting in situ to endogenous or planted glomerular Antigens
  - Types of MGN :-
    1) idiopathic (85 %)
       - most Common Cause of nephrotic syndrome in non-diabetic adults (second most Common after FSGS)
       * - diffuse subepithelial immune-Complex deposition, proteinuria, thickening of glomerular BM (Spike, silver stain)
       * - Anti-PLA2R autoantibodies
         ↳ autoantibodies bind to autoantigen (surface of podocytes) → in situ immune complex formation → activation of lectin Complement pathway → podocyte injury + proteinuria
       * - Target antigens :- ① PLA2R ② THSD7A
    2) Secondary
  - Morphology
    - LM : diffuse GBM thickening
    * - IF : Complement + immunoglobulin deposits along GBM (IgG) → finely granular staining for IgG (IgG4) in all G
    * - EM : 1- effacement of foot processes
      2- Spike and dome pattern
    - Grossly : Enlarged pale Kidney

- Clinical Course :-
  - insidious development of nephrotic syndrome , poor prognosis
  * - non-selective proteinia , poor response to corticosteroid therapy
  - Secondary causes should be ruled out
  * - Causes thrombosis in venous side (DVT, embolism, renal vein thrombosis)
    ↳ reason : blood reaching the vein is deficient in Anti-thrombin 3

* Nephritic Syndrome Diseases

Nephritic Syndrome :-
- PHAROH
  - Proteinuria
  - Hematuria
  - Azotemia
  - RBC Casts
  - Oliguria
  - HTN

(1) Acute Post Infectious (post streptococcal) Glomerulonephritis (PSGN)

- Caused by deposition of immune complexes ⟶ diffuse proliferation and swelling of resident glomerular cells (both kidneys + all Glomeruli)
- No direct kidney infection
- Prototypic exogenous pattern (PSGN, proliferative GN) ⟶ association with infections by other organisms
- Endogenous antigens : ex: SLE
- in Children 1-4 weeks after recovery from group A β-hemolytic streptococcal infection
  ↳ initial infection is in the pharynx or skin
- morphology :
  - LM : • diffuse uniform increased cellularity of glomerular tufts (due to swelling + proliferation of EC and mesangial cells and by a neutrophilic and monocytic infiltrate)
    Ominous features (very bad) :
    • Capillary wall necrosis ⟶ ↑ permeability ⟶ ↑ inflammatory cell infiltrate ⟶ proliferation of parietal cells
    • Crescents in urinary space due to severe inflammatory injury
  - IF : granular deposits of IgG + Complement (cleared within 2 months of treatment) ⟶ hypocomplementemia
  - EM : Subepithelial humps in GBM
- Clinical Course :-
  - Acute onset
  - gross hematuria
  - Recovery
  - Smoky brown urine
  - Mild proteinuria
  - low serum Complement levels (active)
  - ↑ serum Anti-Streptolysin O Antibody titer

→ Case : Sore throat before 3 weeks

② IgA Nephropathy (Berger Disease)

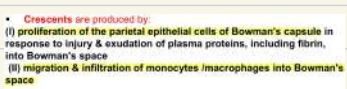
- Most common cause of recurrent microscopic or gross hematuria
- deposition of IgA in mesangium
- in children and young adults
- 50 % → gross hematuria (1-2 days of upper RTI, GIT infection, UT infection) lasts for several days → subsides only to returns every few months, loin pain
  40 % → microscopic hematuria, ± proteinuria
  10 % → develop acute nephritic syndrome
- Pathogenesis :-
  - IgA in mucosal secretions, low levels in normal serum
    ↳ ↑ IgA due to ↑ production in the bone marrow
  -
    - A **genetic influence** is suggested by it's occurrence in families & in HLA-identical siblings.
    - Studies suggest that ↑**IgA synthesis** in response to respiratory or GIT exposure to environmental agents (e.g., viruses, bacteria, & food proteins) may lead to deposition of IgA & IgA-containing immune complexes in the mesangium, where they activate the alternative complement pathway & initiate G injury.

    → abnormality in IgA production and clearance
- Morphology :
  - LM : normal G or mesangial widening (non-specific)
  - EM : deposits in mesangium
  - * IF : mesangial deposition of IgA with C3

③ Rapidly Progressive (Crescentic) Glomerulonephritis (RPGN)

- not specific etiologic form, its a clinical syndrome (any type of nephritis can become RPGN)
- rapid + progressive loss of renal function with features of nephritic syndrome, severe oliguria and death from RF within weeks to months (if untreated)
- Presence of Crescents filling Bowman's space (Bowman obliteration → no urine formation → oliguria)
  ↳ injury + infiltration of monocytes and macrophages → proliferation of parietal epithelial cells of Bowman's Capsule (immunologically mediated)
- Nephritic syndrome rapidly progressing to oliguria and azotemia
- Caused by different diseases (restricted to Kidney, Systemic) → classified into 3 groups (A, B, C) all have severe G injury, disease may be ① idiopathic
  ② associated with known, well defined renal, or extrarenal disease

- Group A :- (Anti-Glomerular BM Antibody ~> 12 %)
  - idiopathic - Anti-GBM Antibodies bind to renal GBM, without pulmonary lesion
  - Goodpasture syndrome - Anti-GBM Antibodies bind to GBM and pulmonary alveolar capillary BM causing pulmonary hemorrhages
  - linear IgG + C3 deposits
  - Anti-GBM Antibodies in serum
    ↳ patients benefit from plasmapheresis / Immunoadsorption (removes pathogenic Antibodies from circulation)
- Group B :- (immune complex mediated ~> 44 %)
  - Can be a complication of any immune complex nephritis or idiopathic
  - on IF → granular lumpy bumpy staining of GBM, mesangium for immunoglobulin, complement
  - Cannot be helped by plasmapheresis
- Group C (pauci-immune) :- (Antineutrophil cytoplasmic Antibody associated (ANCA) ~> 44 %)
  - lack of Anti-GBM Antibodies or significant immune complex deposition
  - Anti-neutrophilic Cytoplasmic Antibodies in serum, have some role in Vasculitis
    1- Systemic vasculitis : microscopic polyangiitis, Wegener granulomatosis
    2- Limited to kidney : idiopathic
  - IF : no immunoglobulin or complement deposits and no EM detectable deposits
- Morphology
  - grossly enlarged pale kidneys, cortical petechial hemorrhages
  - glomeruli show (histologically):
    - Segmental necrosis
    - GBM breaks
    - Crescents



- Clinical Course :-
  - nephritic Syndrome with severe oliguria and azotemia
  - Proteinuria sometimes approaching nephrotic range
  - some patients become anuric and require long term dialysis or transplantation

④ Hereditary Nephritis (Alport Syndrome) → not immunologically mediated

- mutations in GBM proteins (normally GBM is composed largly of type IV collagen, which is crucial for normal function of lens and cochlea)
- nephritis + nerve deafness and eye disorders (lens dislocation, Cataracts)
- Morphology
  - unremarkable until late course
  - interstitial cells take on foamy appearance due to accumulation of neutral fats (foam cells) and mucopolysaccharides as a reaction to proteinuria
  - progression : - glomerulosclerosis - tubular atrophy
    - vascular sclerosis - interstitial fibrosis
  - EM : - GBM thin and attenuated
    - later develops splitting and lamination "basket-weave apperance"
- Pathogenesis:
  - mutation of any one of the α-chains of type IV collagen
    - ↳ heterogeneous inheritance, most commonly X-linked due to mutation in gene encoding α5 type IV collagen (COL4A5)
      - → males tend to be more frequently and severely affected and more likely to develop RF
- Clinical Course :-
  - Ages 5-20 years old present with gross or microscopic hematuria and proteinuria
  - overt RF occurs between 20-50 years old

* Nephritic and Nephrotic

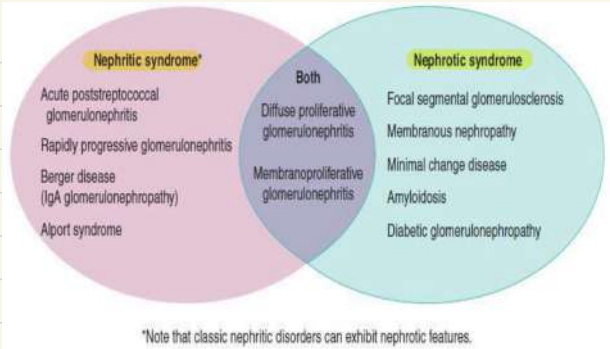
① Membranoproliferative GN (MPGN)

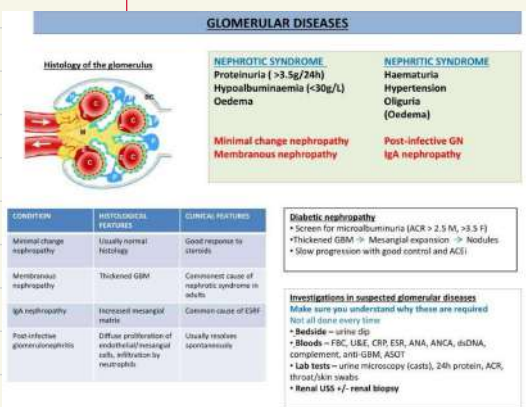
- hypercellularity and thickening of GBM, histologic lesion not specific entity
- * hypocomplementemic / lobular / mesangiocapillary nephritis
  - ↳ low complement level due to C3 convertase continous activity splitting C3 into C3b and C3A
- * - Essential features :-
  - hypercellularity
  - duplicating of GBM
  - mesangial and subendothelial deposits
  - idiopathic MPGN is diagnosis of exclusion

Clinical features
- Either immunoglobulin (polyclonal or monoclonal) mediated or complement mediated.
- **Immunoglobulin mediated:** due to infections, autoimmune diseases, paraproteinemias
- **Complement mediated:** dysregulation of alternative pathway due to genetic or acquired abnormalities in regulatory factors
- Traditional classification based on electron microscopy findings: MPGN type I (subendothelial and mesangial deposits), MPGN II (intramembranous dense ribbon-like deposits) and MPGN III (subendothelial and subepithelial deposits)
- **Newer classification based on immunofluorescence emphasizing pathophysiology:**
  Immune complex / monoclonal immunoglobulin mediated MPGN (activation of classic complement pathway) and C3 glomerulopathies (including dense deposit disease, C3 glomerulonephritis and CFHR5 nephropathy, activation of alternate complement pathway)
- **MPGN lesion due to immune complex now referred to simply as MPGN**
- Poor prognostic signs including nephrotic syndrome, an elevated serum creatinine and hypertension at presentation, crescents and tubulointerstitial disease on biopsy

- Pathogenesis ⟶ Different pathogenic mechanisms
- Type I (classical) :-
  * - Subendothelial and mesangial electron dense deposits
  - activation of classic complement pathway and some alternative complement pathway
    ⟶ immune complex deposition
  - * > 50% : nephrotic syndrome
    * 10 - 20 % : acute nephritis syndrome
    ~ 50% : low C3
  - recurs in ~30% of children 6-12 months after transplantation
  - IF : * C3 deposits in irregular granular pattern and IgG
    $C1_q$ + C4 present ⟶ indicating immune complex pathogenesis
- Type II (dense-deposit disease) :-
  * - due to excessive complement activation (only C3, no immune complex)
    ↳ autoantibody against C3 convertase (C3 nephritic factor) ⟶ hypocomplementemia
  * - intramembranous dense ribbon-like deposits of GBM ⟶ C3 glomerulonephropathies
  - Diagnosed at 14 years old, poorer prognosis than type I
  - renal insufficiency, hematuria, 33% nephrotic syndrome
  - deposits in BM of spleen, Choroid, retina
  * - C3 present in irregular and chunky and segmental linear Pas in BM
  * - IgG and early classical pathway complements are absent
- Morphology (Both)
  - LM : • large accentuated lobular Gl, proliferation of mesangial and endothelial cells (hypercellularity), irregular thickening of GBM
    * • double contour / train track appearance due to splitting of GBM
      ⟶ PAS or Silver Stain
    • Crescents (~20%) ⟶ indicating severe injury
- Clinical Course :-
  - 50% ⟶ nephrotic syndrome — 40% ⟶ progress to end stage RF
  - poor prognosis (type II has worse prognosis)
  - recur in renal transplant recipients

	MCG	FSGN
Hematuria	–	+
Hypertension	–	+
Proteinuria	Selective	Non-selective
Respond to corticosteroid therapy	Good	Poor





Disease	Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Poor?
MNP	nephrotic	adults	Thickened GBM	IgG+ C3+	Sub-epithelial spikes and domes	Poor?
MPGN-type1	Nephritic/ nephrotic	adults	Tram track	Ig s	Subendothelial deposits	poor
MPGN-Type2	Nephritic/ nephrotic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropth	nephritic	Children, young adults	variable	IgA+	Mesangial deposits	variable
PSGN	nephritic	children	hypercellularity	IgG+ C3+	Subepithelial deposits (humps)	good
Alport syndrome	hematuria, hearing loss	children	variable	negative	Basket weave GBM	poor

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

* Summaries *

* Chronic Glomerulonephritis

- Final outcome of various forms of Glomerular diseases
  ↳ it represents the end stage
- * Common (most common) and important cause of CRF
- 20% of Chronic GN cases arise with no history of symptomatic renal disease
- * Grossly :- - both kidneys are symmetrically contracted, red-brown surfaces
  - diffusely granular
- Histopathology :-
  - * Scaring and Glomerular obliteration
  - tubular atrophy in Cortex
  - Interstitial fibrosis, arteries are thick-walled and narrowed (due to HTN secondary to Chronic GN)
    → such markedly damaged kidneys : end-stage kidneys
  - masson-trichrome stain shows complete replacement of glomeruli by blue staining collagen

Chronic Glomerulonephritis

- Causes include repeated episodes of acute glomerular nephritis, hypertensive nephrosclerosis, hyperlipidemia, and other causes of glomerular damage.
- Symptoms vary; may be asymptomatic for years, as glomerular damage increases, before signs and symptoms develop of renal insufficiency/failure.
- Abnormal laboratory tests include urine with fixed specific gravity, casts, and proteinuria; and electrolyte imbalances and hypoalbuminemia.
- Medical management is determined by symptoms.

ASSESSMENT & DIAGNOSTIC FINDINGS

Urinalysis reveals a specific gravity of 1.010, proteinuria, and urinary casts.
BUN Elevation

As renal failure progresses the GFR falls below 50ml/min and the following changes occur:
Hyperkalemia
Metabolic Acidosis
Anemia
Hypoalbuminemia
Increased Serum Phosphorus
Decreased Serum Calcium
Mental Status Changes

C-xray reveal cardiac enlargement & pulmonary edema
ECG- normal or indicate Left ventricular hypertrophy
CT/MRI reveal reduced size of renal cortex

Tubular and Interstitial Diseases

- inflammatory involvement of the Tubules and Interstitium (interstitial nephritis)

-OR-

- ischemic / toxic Tubular injury → acute tubular necrosis and acute RF

Tubulointerstitial Nephritis (TIN) (primary inflammatory diseases)

- Causes :
1-bacterial infection.
2-drugs.
3-metabolic disorders
4-physical injury (irradiation).
5-immune reactions.

- Glomeruli may be spared or affected late in the Corse
- Pyelonephritis : TIN Caused by bacterial infection, with prominent renal pelvis involvement
- interstitial nephritis : TIN with non-bacterial sign
- divided into : 1- acute 2- chronic

① Acute Pyelonephritis

* 1- UTI (infectious)

* - Suppurative inflammation of the Kidney and renal pelvis

- most Commonly Caused by E. Coli
- Bacteria Reach by 2 ways :- 1- hematogenous (rare) 2- ascending (common)
  - F > M → urethra is short and close to rectum, trauma to vethra duig intercause
  - Bladder wine is steile • Antimicrobial propelties of bladder mucosa
    • periodic uoiding of wine
    • outflow obstruction / bladder dysfunction → UTI
    • Stasis → bacteria not flushed out → multiply undisturbed
- Common with individuals with UT obstruction (benign prostatic hyperplasia, Stones, uteine pulapse), also common in DM

* - incompetence of vesicoureteral orifice → bacteria ascends urete into pelvis
→ reflux of bladder wine into ureters (Vesicoureteral reflux = VUR)
↳ VUR → 20-40% young children with UTI (due to congenital defect)
* → acquired : flaccid bladder due to spinal chord injury and with neurogenic bladder dysfunction secondary to DM

- Morphology :

* - multiple abscesses, raised, discrete and yellowish on renal surface
- one or both Kidneys, can be normal or enlarged

- Microscopically :-
  - renal abscess formation within parenchyma
  - Early → Suppuration limited to interstitial tissue
  - Late → abscesses rupture into tubules, intratubular neutrophils extend into collecting ducts → * WBC granular Casts in urine + pus
  - glomeruli not affected

* Hyaline Casts → nephrotic syndrome
* RBC casts → nephritis
* WBC casts → infection

* 2- Papillary Necrosis (renal papillary necrosis) :-

Acute pyelonephritis develops to it

- Why in renal papillae → area with low blood perfusion so is subject to necrosis (tips of renal pyramids)
- Causes :-
  - * 1- Common among diabetics (who develop acute pyelonephritis)
    - ↳ treatment : hydration + broad spectrum antibiotic (until sensitivity test result → when result comes out → specific antibiotic)
  - 2- Complicate acute pyelonephritis when there is significant UT obstruction
  - * 3- chronic interstitial nephritis associated with analgesic (NSAID) abuse "Analgesic nephropathy"
  - 4- Sickle cell disease (occlusion of blood vessels → necrosis)
  - → Any condition involving ischemia → Renal papillary necrosis
    - ↳ ischemia → vasoconstriction → ↓ blood supply → necrosis
- Combination of : 1- Ischemic necrosis 2- Suppurative necrosis
- Macroscopically :- Sharply defined, grey white - yellow necrosis of apical 2/3 of 1, 2 or all pyramids papillae
- Microscopically :- Coagulative necrosis with surrounding neutrophilic infiltrate
- Symptoms / signs :- - Fever - painful / infrequent urination - urinary incontinence
  - Back pain - tissue pieces in urine - Cloudy urine
  - ↳ loin pain in CVA ↳ papillae exit in urine ↳ contains pus
- Pathophysiology :-
  - ↳ papillae are vunerable to ischemia because they are supplied by small caliber arteries → liable to obstruction → necrosis of papillae → sloughing into lumen → hematuria

- Clinically :- Sudden, pain at CVA, chills, fever, malaise, dysuria, frequency, urgency

- Diagnosis of Acute pyelonephritis
  ↳ finding pyuria (pus in urine) and bacteriuria in urinalysis and urine culture
- disease is usually unilateral
- recurrent or chronic ⟶ bilateral
- development of papillary necrosis indicates poor prognosis

(2) Malakoplakia (uncommon chronic granulomatous inflammatory condition)

- usually involves gram-negative bacteria
* - presents as: papule, plaque, or ulceration
* - result from the insufficient killing of bacteia by macrophages ⟶ partially digested bacteia accumulate in macrophages ⟶ deposition of iron and calcium
- Foamy macrophages with PAS+ granular cytoplasm
  ↳ due to: 1- phagosomes stuffed with bacterial debris
  2- Michaelis-Gutmann bodies
  ↳ rounded homogenous body containing calcium and iron, found within macrophages in the bladder wall

(3) Drug-Induced Interstitial Nephritis

* 1- Acute Drug-induced Interstitial Nephritis

- most commonly caused by: Synthetic penicillins
  other causes: Synthetic antibiotics, diuretics, NSAIDs, ...
- Pathogenesis
  ↳ drug acts as hapten ⟶ Covalently binds to some cytoplasmic or extracellular tubular cell component ⟶ becomes immunogenic ⟶ immunological IgE (type 1) or cell-mediated immune (type IV) reaction on tubular cells or BM ⟶ tubulointestitial injury
- Morphology: 1- edema 2- infiltration by large number of lymphocytes, macrophages, eosinophils, and neutrophils
  3- normal glomeruli (except in some cases caused by NSAIDs)
  4- non-necrotizing granulomas with giant cells (with some drugs: rifampin, thiazides, methicillin)

- Clinically :- * - begins 2-40 days (≈15) after drug exposure
  - fever, rash, eosinophilia, hematuria, mild proteinuria, leukocyturia
  - 50% → ↑ serum Creatinine or acute RF with oliguria ← Mostly older patients
  * - withdrawal of drug → recovery

* 2- Analgesic Nephropathy : Chronic drug induced

* - due to consuption of large quantities of analgesics over large periods
- may cause : 1- Chronic interstitial nephritis 2- renal papillary necrosis
- Common Causes : Aspirin and Acetaminophen → cell injury by Oxidative damage + Covalent binding
  * inhibit postraglandin synthesis → ↓ vasodilation by prostaglandins → ischemia of papillae
- papillary necrosis → interstitial nephritis in renal parenchyma
- Clinical course : - progressive renal impairment, CRF, HTN, anemia
  - Complication of analgesic abuse → increased incidence of transitional-cell carcinoma of the renal pelvis

Acute Tubular Necrosis (ATN)

- morphologically → damaged tubular epithelial cells
- Clinically → acute suppression of renal function with oliguria
- most common cause of acute renal failure (ARF)

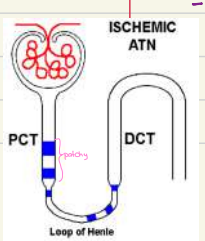
* Acute Tubular Necrosis / Acute Tubular Injury

- reversible condition if treated quickly and properly
- Clinical manifestations : - electrolyte abnormalities - acidosis - uremia
  - signs of fluid overload - oliguria
- proximal tubular epithelial cells are sensitive to hypoxiemia (anoxia) and toxins
- ATN can arise as one of 2 patterns :-

1- Ischemic ATN : · Caused by shock (hypotension + shock)

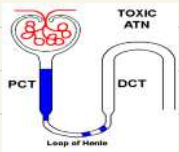
ex : * mismatched blood transfusions, hemolytic crisis, myoglobinuria

Patchy tubular involvement ← · distribution of areas of necrosis is more segmental



more common ← 2- Nephrotoxic ATN : • Caused by poisons (including heavy metals)

ex : CCl_4, drugs (gentamicin, antibiotics), radiographic contrast agents (ex : ones used in Angiogram)

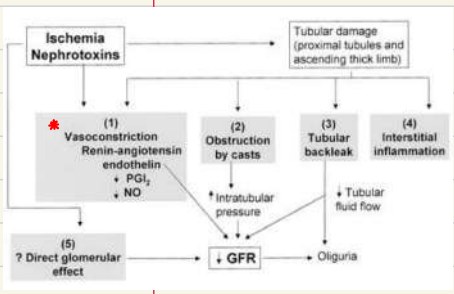


diffuse tubular involvement ← • distribution of areas of necrosis results in more proximal tubular injury

- Urine output will drop
- As tubular epithelium is regenerating concentration of urine is impaired and polyuria occurs
- pathogenesis : sloughing and necrosis → obstruction + ↑ intraluminal pressure → ↓ glomular filtration

Sloughed cells fall and accumulate in the tubule causing obstruction → ↑ intraluminal pressure → oliguria (necrosis and sloughing is in PCT, the glomeruli + DCT are preserved)

↳ with treatment of uremia → regeneration, but these cells in the begining don't function fully properly → don't absorb all substances → polyuria



Renal biopsy shows:

(1) Blebbing; vacuolization; **necrosis** & **detachment** of tubular cells from their underlying BM & their **sloughing** in the lumen

(2) **Proteinaceous casts** in the distal tubules & collecting ducts is a **striking** additional finding. They consist of **Tamm-Horsfall protein (secreted normally by tubular epithelium)** along with hemoglobin & other plasma proteins.

(3) When **crush injuries** have produced ATN, the casts are composed of **myoglobin** → Sere skeletal injuries

- ethylene glycol poisoning → tubular vacuolization and tubular dilation
- ATI management :-

1- repair and tubular regeneration
↳ gradual clinical improvement

2- Supportive Care
↳ patients who survive have a good chance of recovering renal function

3- pre-existing chronic renal disease
↳ complete recovery is less frequent

Diseases Involving the Blood Vessels

- All Kidney diseases involve the renal blood vessels secondarily

(1) Benign Nephrosclerosis (hyaline arteriolosclerosis) (BN)

- Chronic vascular damage, pressure-rising influence :- Sodium retention
- present at autopsy in persons > 60 years old
- ↑ frequency and severity when HTN or DM are present
- Can also be seen in response to some drugs (calcineurin inhibitors)
- Pathogenesis :- renal diseases that cause HTN
- Morphology :-
  - both kidneys symmetrically atrophic
  - finely granular surface (gain leather)
  - hyaline arteriolosclerosis
  - all kidney structures show ischemic atrophy
  - pink hyaline thickening → BV lumen narrowing → ↓ blood flow → ischemia
- Advanced cases :-
  - glomerular tufts become globally sclerosed with diffuse tubular atrophy and interstitial fibrosis
  - fibroelastic hyperplasia → to compensate ischemia
- BN alone rarely causes severe renal damage and with modern treatment we rarely see severe symptoms

(2) Malignant Hypertension + Malignant Nephrosclerosis (MA, MN)

less common than benign

- acute vascular damage, pressure-rising influence :- renin release
- Can arrise de novo (without pre-existing HTN) or suddenly appears in someone with mild HTN
- Pathogenesis
  - long standing HTN → injure arteriolar walls → 1- EC injury 2- ↑ permeability of small BVs to fibrinogen 3- platelet deposition → fibrinoid necrosis of arterioles and small arteries + intravascular thrombosis
  - mitogenic factors (from plasma and platelets) → SMCs hyperplasia of BV → hyperplastic arteriolosclerosis (onion skin lesion)
  - markedly ischemic kidneys + severe ischemia of renal afferent arterioles → stimulates renin-angiotensin system → angiotensin II causes intrarenal vasoconstriction → renal ischemia → ↑ renin secretion (elevated plasma renin) "vicious cycle"
  - ↑ Aldosterone + salt retention → ↑ BP → Consequences of that on BV → MA, MN

- Morphology :- - Normal Kidney sizes
  * - Pinpoint petechial hemorrhages → Flea-bitten appearance
- Microscopically :- - Fibrinoid necrosis of arterioles
  - Hyperplastic arteriolosclerosis → onion-skin appearance
- Clinically :- - ↑ diastolic BP
  - Fatal without treatment, 90% death → uremia, 10% death → CF or cerebral hemorrhage

Similar lesions seen in acute thrombotic microangiopathies

(3) Thrombotic Microangiopathies

- widespread thrombosis in microcirculation
- by: microangiopathic hemolytic anemia, thrombocytopenia, RF
- Causative diseases :- 1- Childhood HUS 2- Adult HUS 3- TTP

* 1- TTP

- Pathogenesis :- aquired defect in proteolytic cleavage of vWF multimers

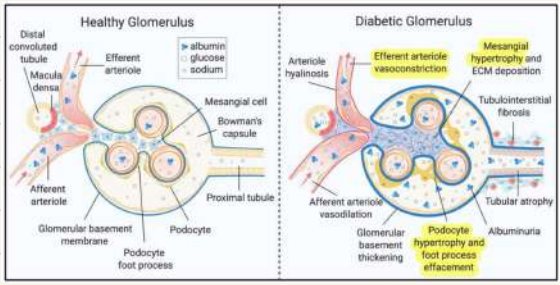
* 2- Childhood HUS

- follow intestinal infection with shiga toxin-producing E.Coli (ex: hamburgers) and infections with Shigella dysentery type 1
- Pathogenesis
  - Shiga toxin → Carried by neutrophils → target renal glomerular EC
  * - toxin effects :- 1- directly causes cell death
    2- in presence of cytokines (ex: TNF) → EC damage (due to inflammatory response)
    3- ↑ WBC adhesion → ↑ endothelin production + loss of EC nitric oxide → vasoconstriction → EC damage → thrombosis
- Morphology
  - Fibrinoid necrosis (similar to classic thrombotic microangiopathy), fibrin thrombi in G + arterioles + large arteries (severe cases)
  - Cortical necrosis (maybe)
- Clinically :- - Sudden onset
  * - after GIT infection
  - Severe oliguria
  - hematuria
  - microangiopathic hemolytic anemia (DIC)
  - if managed properly with dialysis → recovery in weeks

④ Diabetic Nephropathy (DN)

- Common complication of **type I + II DM**
  - ↳ not controlled DM → damage kidney BVs
- Histopathology :-
  - thickening of glomerular and tubular BM → proteinuria
  - ↑ mesangial matrix
  - microaneurysms
  - affecnt and effecnt arteiolar hyalinosis
  - Kimmelstiel - Wilson nodules
  - Capsular drop
- Risk factors :-
  - poor blood glucose control
  - long duration of diabetes
  - presence of diabetic complications
  - pre existing high BP
  - Family history : DN , HTN
  - Ethnicity : Asian , Pima indians

*



Cystic Diseases of the Kidney

- heterogenous group , important for :-
  1- Adult polycystic disese causes 10% of CRF cases
  2- Cysts are common , present diagnostic problems , can be confused with malignant tumors
- types of cysts :-
  1- Simple cysts
  2- Dialysis-associated aquired cysts
  3- Autosomal Dominant (Adult) polycystic Kidney Disease
  4- Autosomal Recessive (childhood) polycystic Kidney Disease
  5- Medullary Cystic Disease

(1) Simple Cysts

- multiple or single
- translucent filled with clear fluid + lined by grey glistening smooth membrane
- Confined to cortex
- no clinical significance, incidental discovery or due to hemorrhage and pain
- Importance: differentiate from kidney tumors

(2) Cysts associated with Chronic dialysis

- Patients with RF undergoing prolonged dialysis
- Cortex + medulla
- Complications: - hematuria
  - pain
  - * ↑ risk of renal carcinomas (x100)
  - renal adenomas / adenocarcinomas

* (3) Autosomal Dominant (Adult) Polycystic Kidney Disease

- multiple bilateral cysts
- destroy renal parenchyma
- Pathogenesis

  this gene encodes Polycystin-1

  * - 85-90% of families → PKD1 → encodes Polycystin-1
    ↳ defective gene is on short arm of c16
  * - 10-15% of families → PKD2 → encodes Polycystin-2
- Clinical presentation: - asymptomatic (until 4th decade)
  - flank pain, abdominal mass, heavy dragging sensation, hemorrhage, obstruction, intermittent gross hematuria
- morphology: - enormous size kidneys (4 kg each) → readily palpable
  - no intervening parenchyma
  - fluid filled cysts → clear / turbid / hemorrhagic
- Complications: - urinary infection
  - high incidence of subarachnoid hemorrhage
  - Saccular aneurysm of the brain circle of willis
  - uremia + HTN → cause of fatality
- treatment: renal transplantation

(4) Autosomal Recessive (Childhood) Polycystic Kidney Disease

- depends on time of presentation + presence of associated hepatic lesions
  - ↳ perinatal, neonatal, infantile, juvenile (subcategories)
* - mutations in PKHD1 gene → Codes fibrocystine (chromosome 6p)
  - ↳ involved in function of cilia in tubular epithelial cells
- morphology :-
  - bilateral
  * - Sponge like appearance
  - Cortex + medulla → replaced by dilated + elongated channels and cysts
  - Cysts originating from collecting tubules are lined by cuboidal cells
  * - multiple liver cysts and proliferation of portal bile ducts

(5) Medullary Cystic Disease

- 2 types :-

1- medullary Sponge Kidney
- Common, harmless, incurious condition

2- nephronophthisis - medullary cystic disease Complex
- always associated with renal dysfunction
- begins in childhood
* - most common genetic cause of end-stage renal disease in children and young adults
- 4 variants : * juvenile (most common), infantile, adolescent, adult
  - ↳ 5-20% have extra-renal manifestations, mostly as retinal abnormalities
- morphology : Kidneys are small and contracted
* - Histopathology : Cysts are at cortico-medullary junction
- Clinically :
  - polyuria and polydipsia (↓ tubular function)
  - RF
- difficult to diagnose because :
  - no serologic markers
  - cysts too small
  - cysts not apparent on biopsy
* - positive family history and unexplained CRF in young patients
  - ↳ Suspicion of nephronophthisis - medullary cystic disease Complex

Urinary Outflow Obstruction

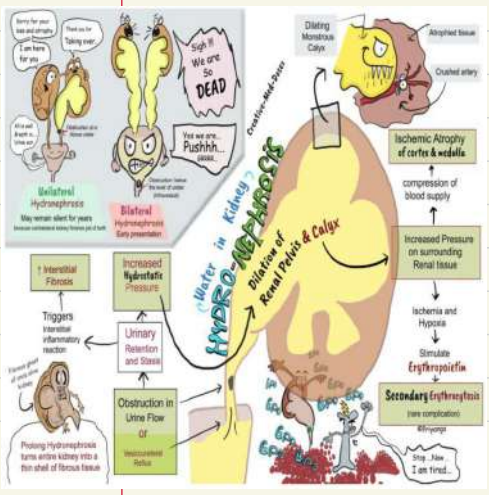
1. Renal stones (urolithiasis) ⇝ Stone formation at any level in the urinary collecting system
   - more commonly symptomatic in men
   - unilateral (80%), variable sizes
   - Stone = inorganic salt (98%) + organic matrix (2%)
   - Types according to organic salt :-
     1- Calcium oxalate / Calcium oxalate + Calcium phosphate (80%)
     2- Struvite (magnesium ammonium phosphate)
     3- Uric acid (6-7%)
     4- Cysteine stones (2%) → amino acid collection (genetic abnormality)
   - Causes :-
     1. increased urine concentration of stone's constituents exceeds solubility in urine (supersaturation)
        - 50% Calcium stone patients → hypercalciuria with no hypercalemia
        - 5-10% hypercalcemia and hypercalciuria due to hyperparathyroidism, Vit D intoxication, or Sarcoidosis
     2. Presence of a nidus
        - urates provide a nidus for calcium deposition
        - Desquamated epithelial cells
        - Bacterial colonies
     3. Urine PH
     4. infection

     } Alkaline urine → ↑ risk of infection → ↑ stone formation
   - Struvite stones
     * → Staghorn shaped stones
       → alkaline urine due to UTI → urea splitting bacteria (proteus vulgaris, Staphylococci)
   - Uric acid stones → form in acidic urine (PH < 5.5)
     → gout + diseases involving rapid cell turn over rate → ↑ uric acid levels in urine + uric acid stones
     → 50% → no hyperuricemia or urine urate but have unexplained persistent excretion of acidic urine
   - Cystine Stones : associated with a genetically dermined defect in renal transport of cysteine
   - Oxalate calculus : large, hard, spherical stone with rough spiny surface
     → hematuria + inflammation → scratches the ureter → fibrosis → stricture

② Hydronephrosis ⟶ Complication of Stones

- dilation of renal pelvis and calyces due to obstruction with atrophy of parenchyma
- Sudden / insidious , obstruction at any level from urethra to renal pelvis
  obstruction in ureter and above → unilateral - Obstruction below ureter → bilateral
- most common causes :
  1- Congenital , ex : - Atresia of urethra
  - Valve formations in ureter or urethra
  - Aberrant renal artery compressing ureter
  - Renal ptosis with torsion or Kinking of ureter ← Diet → ↓ Fat → Kidney kinks the ureter → obstruction
  2- Aquired , ex : - Foreign bodies - Calculi
  - necrotic papillae - tumors
  - Inflammation - Normal pregnancy

- Pathogenesis
  - even with Complete obstruction GF persists for some time → filtrate diffuses back into renal interstitium and perirenal spaces (continued filtration) → dilation of calyces and pelvis → ↑ pressure in renal pelvis → Compression of renal vasculature → venous stasis and Arterial insufficiency
  - most severe effects seen in papillae (subject to greatest ↑ in pressure)
  - Accordingly : 1- initial functional disturbances are largly tubular
    2- later does glomerular filtration begins to deminish



Renal Tumors

Benign

- cortical papillary adenomas
- interstitial cell medullary fibromas

→ no clinical significance

Malignant

- Renal cell carcinoma (RCC) (85%)
- Nephroblastoma = Wilm's tumor (10%)
- Carcinoma of renal calyces and pelvis (5%)

Malignant

(1) Renal cell carcinoma (RCC) / Renal Adenocarcinoma / Grawitz's Tumor ⇝ 85%

- 3rd most common GIT cancer and most fatal urology cancer → 2% of all cance deaths
- deived from renal tubular epithelium (PCT), so located in the cortex
- * most common from 6-7th decades, m > F (x2)
- ⅓ present with metastasis
- resistant to chemotherapy → development in effective molecular targeted therapies
- ↑ risk of RCC development → - smoking - obesity - hypertensive
  - occupational exposure to cadmium
  - aquired polycystic disease (from chronic dialysis) → 30 fold ↑
- RCC are classified into 3 forms :-

1. Clear cell RCC (80%)

- * mostly Sporadic (de novo), can occre in familial forms, or in association with Autosomal dominant VHL disease
- predesposition to tumors → hemangioblastomas of cerebellum and retina
- VHL → may experience tumors & cysts of up to 10 parts in the body
- * 40-60% VHL → hundreds of bilateral renal cysts + bilateral multiple clear cell RCC
- * VHL Syndrome → inheit a germline mutation of VHL gene on chromosome 3p25 and lose of the second allele by somatic mutation
- * mean age of onset = 26 years old, 97% of people with VHL gene mutation have symptoms by age of 65
- Grossly : - Solitary, spherical, large - in Cortex
  - Cystic necrosis + fresh / old hemhorage - yellow - orange

- loss of both copies of this tumor suppressor gene gives rise to clear cell RCC

- VHL protein is involved in limiting angiogenic responce to hypoxia
  ↳ absence may lead to angiogenesis and tumor growth

- As tumor enlarges it invades :-
  - renal vein as a solid column within it (can extend to IVC and right side of heart) ← most commonly
  - walls of calyces (→ hematuria), pelvis, ureter
  - into perinephric fat and adrenal gland
- Histologically (depends on amounts of lipid + glycogen) :-
  - Classically vacuolated, lipid-laden clear cells
  - .or.
  - Granular cells, granular pink cytoplasm
  - Some exhibit anaplasia, numerous mitotic figures, enlarged hyperchromatic pleomorphic nuclei
  - cells form tubules, chords, or disorganized masses, scant but vascularized stroma

2. Papillary RCC (15%) ⇝ papillary growth pattern

* multifocal and bilateral, familial and sporadic
* Cause : MET proto-oncogene on chromosome 7q31
  - ↳ trisomy of c7 → familial and sporadic, activating MET mutation → familial
* Grossly : - Papillary formation with fibrovascular cores
  - bilateral and multiple
  - cystic degeneration, necrosis, hemhorage
  - lower lipid content ⟶ less orange in colour (clear / pink cytoplasm)

3. Chromophobe RCC (5%) ⇝ from intercalated cells of collecting ducts

* Stain more darkly
- multiple losses of entire chromosomes → 1, 2, 6, 10, 13, 17, 21
* rarest, good prognosis
* Grossly : - mahogany brown (tan-brown)
  - Central scar
  - Clear flocculent cytoplasm
  - EM → many macrovesicles
  - nuclei surrounded by halos of cleared cytoplasm

- Clinically (Pain, Hematuria, mass) :-

1- hematuria → most common feature (50%)

2- Painful, palpable flank mass

3- metastasis → Tubule may remain silent → discovered after metastasis most commonly to → lungs, bones

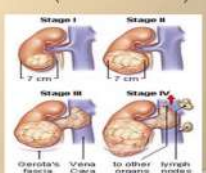
- Extra-renal non-specific manifestation of RCC :-
  - fever
  - polycythemia (5-10%) resulting from elaboration of erythropoietin by tumor cells
  - * paraneoplastic syndromes (uncommonly) → production of hormone-like substances resulting in : hypercalcemia (↑ PTH), HTN (↑ renin), Cushing Syndrome, Feminization / masculinization
- Immunohistochemical techniques in Renal neoplasms :-
  - renal neoplasm markers : Cytokeratins, vimentin, PAX2, PAX8, RCC marker, CD10
  - differential diagnosis of renal v.s non-renal neoplasms
- Staging (TNM) :-
  - T = size, extent
  - N = lymph nodes
  - M = metastasis

STAGING

Based on examination,imaging and biopsy
- AJCC (TNM) staging system:

T categories for kidney cancer:
- T0: No evidence of primary tumor
- T1: The tumor is only in the kidney and is 7cm or less across
  - T1a: The tumor is 4cm across or smaller
  - T1b: The tumor is larger than 4cm but not larger than 7cm
- T2: The tumor is larger than 7cm across but is still in the kidney
  - T2a: The tumor is more than 7cm but not more than 10
  - T2b: The tumor is more than 10cm across
- * T3: The tumor is growing into a major vein or tissue around the kidney but not into adrenals or beyond Gerota,s fascia
  - T3a: The tumor is growing into the main vein or into fatty tissue around the kidney
  - T3b: The tumor is growing into the venacava leading into the heart
  - T3c: The tumor has grown into the part of venacava that is within the chest or growing into the wall of that blood vessel
- T4: The tumor has spread beyond Gerota,s fascia. It may have grown into the adrenal gland

STAGING (CONTINUED)



STAGING (CONTINUED)

N categories for kidney cancer:
- N0: No spread to nearby lymph nodes
- N1: tumor has spread to nearby lymph nodes

M categories for kidney cancer:
- M0: There is no spread to distant lymph nodes or other organs
- M1: Distant metastasis is present ,distant lymph nodes and to organs like lungs, bone, brain and liver

(2) Nephroblastoma (Wilm's tumor) ⇝ 10%

- 3rd most common solid cancer in Children < 10 years old (more common in pediatric)
- mixed tumor, components all derived from mesoderm :-
  - ↳ Triphasic tumor :- - blastemal tissue - stromal cells - epithelial cells (permative tubule and glomeruli)
- Sporadic or Familial (AD)
- Clinical presentation :-
  - Abdominal mass → painless, palpable, non-tender, homogenous or incidental finding
  - Hematuria → tumor rupture and invade Collecting ducts
  - Hypertension → due to renin secretion - Fever - Anemia
- Diagnosis :-
  - Ultrasound (initially) - CT scan - MRI

(3) Tumors of Renal Calyces, Pelvis, Ureter, Urinary Bladder, and Urethra ~> 5%

- epithelial tumors assume transitional or urothelial patterns
- most common presentation is painless hematuria
  - ↳ hematuria → blood before urination → disease in urethra or prostate
    → blood with urination → disease in kidney
    → blood after urination → disease in bladder
- tumor in ureter → urinary outflow obstruction + hydronephrosis
- Renal pelvis papillary Transitional cell carcinoma (TCC)
  - 5% of kidney cancers (less frequent than bladder cancer)
  - Causes painless hematuria, if they cause obstruction → hydronephrosis + pain in CVA
  - infiltration of walls of calyces, pelvis, and renal vein worsens the prognosis

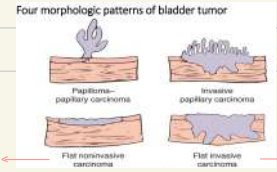
Bladder Tumors

Transitional (Urothelial) Carcinoma (TCCa)	Benign papillomas	papillary Urothelial Tumors
- papillary / flat	- very rare	- low malignant potential
- non invasive / invasive	- solitary	
- low / high grade	- non-invasive	
	- rarely recur	

↳ based on how tumor cells look under microscope
↳ low grade: look more like normal urothelial cells
high grade: abnormal looking cells, larger, darker, and less organized
: more likely to regrow after treatment, and spread to other parts of the body

* - 5% of bladder cancer (US) 50% elsewhere → associated with Schistosomal cystitis or true Squamous cell Carcinoma

- individuals with previous or simultaneous papillary or invasive tumors
  ↳ in-situ (pre-invasive) stage of bladder cancer can be recognised



* - Most common genetic abnormality (in Bladder Cancers)
  ↳ mutations on chromosome 9 → P16, P53, FGFR3
* - prognosis depends on depth of invasion and on histological grade
  ↳ Some bladder tumors invade prostate (use-ureter) → to decide the tumor origin we use an immune stain "Immune panel" for the prostate and bladder, the one that comes out positive → the origin of tumor (the other is invaded)
- except for benign papillomas, all bladder tumors tend to recur after removal
- invading ureteral or urethral orifices → UT obstruction
- prognosis is good → removal of low-grade shallow tumors
- prognosis is poor → deep penetration of bladder wall muscles (< 20% 5 year survival rate)

① Transitional (urothelial) carcinoma (TCCa)

1. low-grade (Grade I) carcinoma:

* - papillary, rarely invasive, may recur after removal
  - central atypia and anaplasia → papillary exophytic tumors → ↑ in size + invasion of the Submucosal
* - working for many years in the rubber industry

2. High grade (Grade II + III) Carcinoma:

* - papillary or flat, may cover larger areas
  - invade deeper into the muscular layer, may ulcerate, may show foci of squamous differentiation
  - Can infiltrate surrounding structures, spread to regional LN, occasionally metastize
  - fibrovascular core

*