Objectives

- Recognise the clinical manifestations of renal diseases
- Describe the pathophysiology of common renal diseases, particularly the effects of hypertension and diabetes mellitus on the kidney
- Have an awareness of well-recognised congenital and cystic diseases of the kidney
- Describe the pathology of common kidney tumours

Outline

I. Clinical Manifestations of Renal Diseases

a. **Azotemia and Uremia**
b. **Nephritic and Nephrotic syndrome**
c. **Asymptomatic hematuria / proteinuria**
d. **Acute kidney injury, Chronic kidney disease and End-stage renal disease**

II. Glomerular Diseases

a. **Normal structure of the glomerulus**
b. **Pathologic response of the glomerulus to injury:** *Hypercellularity, Basement membrane thickening, Hyalinosis, Sclerosis*
c. **Pathogenesis of glomerular injury:** *Antibody-associated injury, Cell-mediated immunity, Alternative complement pathway activation, Progression of glomerular injury*
d. **Major primary glomerulonephritides:** *Post-infectious glomerulonephritis, Rapidly progressive glomerulonephritis, Membranous nephropathy, Minimal change disease, Focal segmental glomerulosclerosis, Membranoproliferative glomerulonephritis, IgA nephropathy*
e. **Glomerular lesions associated with systemic diseases:** *Hypertensive nephrosclerosis, Diabetic nephropathy, Lupus nephritis, Amyloidosis*

III. Tubular and Interstitial Diseases

a. **Acute tubular injury (ATI) / necrosis:** *Ischaemic vs nephrotoxic*
b. **Tubulointerstitial nephritis:** *Pyelonephritis (acute vs chronic), Drugs and toxins-induced*
c. **Other tubulointerstitial diseases:** *Urate nephropathy, Nephrocalcinosis, Light-chain cast nephropathy*

IV. Vascular Diseases

a. **Nephrosclerosis:** *strongly associated with hypertension*
b. **Renal artery stenosis**
c. **Thrombotic microangiopathies**
d. **Other vascular disorders:** *Atherosclerotic ischaemic renal disease, Atheroembolic renal disease, Sickle cell nephropathy, Renal infarcts*

V. Congenital and Developmental Anomalies

a. **Agenesis of kidney**
b. **Hypoplasia**
c. **Ectopic kidneys**
d. **Horseshoe kidney**

VI. Cystic Diseases of the Kidney

a. **Autosomal dominant (adult) polycystic kidney disease (ADPKD)**
b. **Autosomal recessive (childhood) polycystic kidney disease (ARPKD)**
c. **Medullary cystic diseases:** *Medullary sponge kidney, Nephronophthisis*
d. **Multicystic renal dysplasia**
e. **Acquired cystic disease**
f. **Simple cysts**

VII. Hydronephrosis and Urolithiasis

a. **Hydronephrosis**
b. **Urolithiasis**

VIII. Neoplasms

a. **Benign neoplasms:** *Renal papillary adenoma, Angiomyolipoma, Oncocytoma*
b. **Malignant neoplasms:** *Renal cell carcinoma, Urothelial carcinoma of the renal pelvis, Nephroblastoma (Wilms tumour)*

References

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WHO Classification of Tumours Editorial Board. *Urinary and male genital tumours.* Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8).

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. CLINICAL MANIFESTATIONS OF RENAL DISEASES

Early manifestations of diseases affecting each renal morphologic component (glomeruli, tubules, interstitium and blood vessels) tends to be distinct. However, due to their functional and anatomic interdependence, damage to one component usually subsequently affects other components, which can ultimately culminate in end-stage renal disease.

Common clinical presentations are:

- **Azotemia: biochemical** anomaly referring to raised blood urea nitrogen and creatinine, usually due to a decreased glomerular filtration rate (GFR)
  Uremia: **azotemia + clinical signs and symptoms**, which may include systemic manifestations e.g. metabolic and endocrine alterations, GI system, peripheral nerves and heart

Systemic manifestation of uremia	
Fluid and electrolytes	Dehydration, oedema, hyperkalemia, metabolic acidosis
Calcium, phosphate and bone	Hyperphosphatemia, hypocalcemia (later may be hyper), secondary hyperparathyroidism, renal osteodystrophy
Haematologic	Anaemia, bleeding diathesis
Cardiopulmonary	Hypertension, congestive heart failure, cardiomyopathy, pulmonary oedema, uremic pericarditis
Gastrointestinal	Nausea and vomiting, bleeding, oesophagitis, gastritis, colitis
Neuromuscular	Myopathy, peripheral neuropathy, encephalopathy
Dermatologic	Sallow colour, pruritus, dermatitis

- **Nephritic syndrome**: acute onset of haematuria (grossly visible or microscopic) associated with azotemia, mild-moderate proteinuria and hypertension
  - Due to glomerular disease characterized by inflammation, which severely injures capillary walls, permitting blood to pass into urine and inducing haemodynamic changes that lead to GFR reduction
  - **Rapidly progressive glomerulonephritis**: form of nephritic syndrome with rapid GFR decline
- **Nephrotic syndrome**: heavy proteinuria (>3.5 g/24hr), hypoalbuminaemia, severe edema, hyperlipidaemia and lipiduria
  - Due to glomerular disease whereby derangement in glomerular capillary walls results in increased permeability to plasma proteins, resulting in proteinuria and resultant hypoalbuminaemia. The decreased intravascular colloid osmotic pressure plus sodium and water retention then cause oedema. The genesis of hyperlipidaemia is most complex. Lipiduria then follows hyperlipidaemia as lipoproteins leak across glomerular capillary walls
  - **Complications**: infections (likely due to loss of immunoglobulins), hypercoagulability (due to loss of anticoagulants) e.g. renal vein thrombosis
- **Asymptomatic hematuria / proteinuria**: usually due to subtle/mild glomerular abnormalities
- **Acute kidney injury**: rapid decline in GFR with dysregulation of fluid and electrolyte balance, retention of metabolic waste products normally excreted by the kidney (azotemia), oligura or anuria (reduced or no urine flow). Can result from disease in all compartments

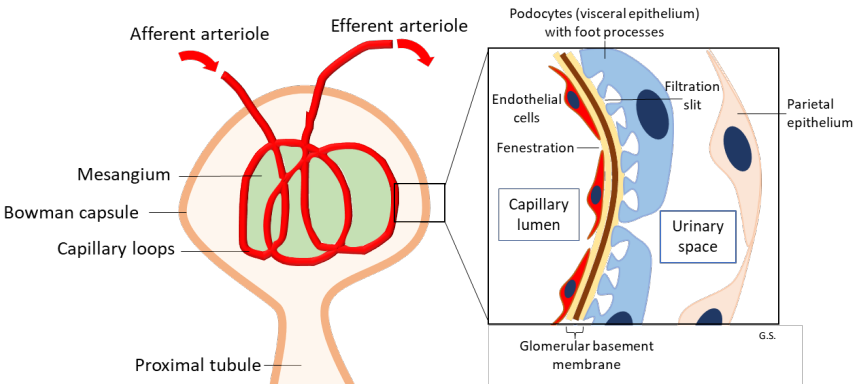
  - Can be **pre-renal** (hypoperfusion of kidneys due to hypotension, haemorrhage, severe dehydration, heart disease, liver failure), **renal** (kidney parenchymal damage e.g. glomerulonephritis, acute tubular necrosis, acute interstitial nephritis) or **post-renal** (e.g. acute urinary obstruction, acute bladder atonia/hypotonia)
- **Chronic kidney disease**: decreased GFR (<60ml/min/1.73 m^2) for at least 3 months and/or persistent albuminuria
  - Due to any cause, and end-result of all chronic renal parenchymal diseases (most commonly **diabetes** and **hypertension**). Major cause of death from renal disease
  - May be a clinically silent decline in renal function or with symptoms and signs of uremia - urine volume may be near-normal initially or polyuria (due to lack of concentrating ability by tubules), to eventual oliguria
  - Bilateral small contracted kidneys with widespread glomerulosclerosis, tubular atrophy and interstitial fibrosis
- **End-stage renal disease**: GFR <5% of normal – terminal stage of uremia

Investigations for renal disease include blood tests (renal panel: urea, creatinine, electrolytes), urine analysis (protein, red and white blood cells, haemoglobin, myoglobin), imaging studies (ultrasound kidney/ureter/bladder, intravenous or CT urogram, CT/MRI) and renal biopsy. Pathologic assessment of renal diseases with renal biopsy typically requires light microscopy (LM), immunofluorescence microscopy (IF) and electron microscopy (EM) evaluation

II. GLOMERULAR DISEASES

- **Primary glomerulonephritis / nephropathy**: kidney is the only or predominant organ involved
- **Secondary glomerular diseases**: systemic diseases or hereditary conditions that involve the glomerulus e.g. diabetes, SLE, Alport syndrome

Normal structure of glomerulus



- Glomerulus comprises an anastomosing network of **capillaries** lined by fenestrated endothelium, and is invested by 2 layers of epithelial cells – 1. visceral epithelium aka **podocytes**, and 2. **parietal epithelium** on the Bowman capsule. The space between the 2 layers is the **urinary space** in which plasma filtrate from blood first collects. The **mesangium** is the tissue between capillaries supporting

the entire glomerular tuft, and comprises **mesangial matrix** within which **mesangial cells** are embedded

- The glomerular capillary wall acts as the **glomerular filtration barrier**, and consists of:
    - Fenestrated endothelial cells (fenestra are 70-100nm in diameter)
    - Glomerular basement membrane (GBM): thick electron-dense central layer (lamina densa) and thinner electron-lucent peripheral layers (lamina rara interna and externa) comprising type IV collagen, polyanionic proteoglycans and other components with biochemical properties important in the filtration barrier function
    - Visceral epithelial cells (podocytes): possess interdigitating processes embedded in and adherent to the lamina rara externa. Adjacent foot processes are separated by filtration slits (20-30nm wide) bridged by a thin diaphragm, which provide size selection. Podocytes also help synthesize GBM components

  The structure of the capillary wall results in the glomerular filtration barrier being **size- and charge-dependent**, allowing only protein molecules of certain size and charge (smaller, cationic) to be permeable while larger anionic molecules e.g. albumin are excluded from the plasma filtrate
- Because of this filtration function, diseases of the glomerulus usually present with **nephrotic syndrome**, **nephritic syndrome**, **microscopic hematuria**, **acute renal failure** or **chronic renal failure**

Pathologic response of the glomerulus to injury

Glomerulopathies usually show one or more of 4 basic tissue reactions, which can further classified based on their distribution as **diffuse** vs **focal** (involving > or <50% of all the kidney glomeruli), **global** vs **segmental** (involving > or <50% of a single glomerulus), or **capillary loop** vs **mesangial** regions:

- **Hypercellularity**: increase in number of cells in the glomerular tufts, which may result from
    (1) Proliferation of mesangial or endothelial cells
    (2) Infiltration of leukocytes. (1)+(2) = **endocapillary proliferation**
    (3) **Crescent formation** = proliferation of glomerular epithelial cells + infiltrating leukocytes
- **Basement membrane thickening**: best seen with PAS on light microscopy (LM). On electron microscopy (EM), can be further distinguished as:
    (1) **Deposition of electron-dense material**: usually immune complexes, or other proteins
    (2) **Increased synthesis of basement membrane proteins**
    (3) **Formation of additional layers of basement membrane**
- **Hyalinosis**: seen on LM as accumulation of homogeneous and eosinophilic material, comprising plasma proteins insudated from the circulation usually due to endothelial or capillary wall damage
- **Sclerosis**: due to deposition of extracellular collagenous matrix

Pathogenesis of glomerular injury

Most primary and secondary glomerular diseases are immunologically mediated, which are mostly antibody-mediated but also can have a component of cell-mediated immune reactions

(I) Antibody-associated injury can result from:

1. **Antibodies reacting in-situ** within the glomerulus (more common):
   (1) Binding to insoluble intrinsic glomerular antigens or extrinsic molecules planted within the glomerulus, forming **in-situ immune complexes**
      - Classic condition: Membranous nephropathy
      - IF findings: **Granular** pattern of immune deposition
      - EM findings: **Discrete** electron-dense deposits (made up of immune reactants)
   (2) Binding to normal components of the GBM
      - Classic condition: Anti-GBM antibody-induced glomerulonephritis
      - IF findings: **Diffuse** linear staining pattern of immune deposition
      - EM findings: No discrete deposits seen
2. **Deposition of circulating antigen-antibody complexes** in the glomerulus: these trapped immune complexes have no specificity for glomerular constituents and are only trapped because of their physicochemical properties and hemodynamic factors of the glomerulus. Antigens can be endogenous (e.g. in SLE glomerulonephritis) or exogenous (e.g. post-infections glomerulonephritis implicating microbial antigens). Inciting antigen often unknown. However, these trapped immune complexes can initiate further in-situ complex formation

- Antigen-antibody complexes either formed or deposited in the glomerulus elicit a **local inflammatory reaction** including complement activation and engaging of Fc receptors on leukocytes and other cells, resulting in leukocytic infiltration and proliferation of mesangial and endothelial cells. These inflammatory mediators release proteases, oxygen-derived free radicals / reactive oxygen species, arachidonic acid metabolites, growth factors, cytokines, chemokines and various other biologically active molecules that cause tissue injury and activate the coagulation system
- Once deposited, immune complexes may be eventually degraded with resolution of the inflammatory reaction (short limited course e.g. post-streptococcal glomerulonephritis). Alternatively, if there is prolonged repeated deposition of immune complexes, many cycles of injury lead to a more chronic membranous or membranoproliferative type of glomerulonephritis (e.g. SLE)
- The immune complexes may be **subendothelial** (between endothelial cells and GBM), **subepithelial** (between GBM and podocytes) and/or **mesangial.** Their localization depends on the molecular **charge and size** of these reactants:
  - Cationic reactants tend to cross the GBM and reside in a subepithelial location, while anionic macromolecules are not nephritogenic or trapped subendothelially without crossing the GBM. Neutral charge molecules tend to reside in the mesangium
  - Large circulating complexes are usually cleared by the mononuclear phagocyte system and not nephritogenic
- **Their localization determines the injury response and key histologic features** e.g. mesangial and subendothelial deposits are accessible to the circulation and more likely involved in inflammatory processes with circulating leukocytes, while subepithelial deposits are typically noninflammatory

(II) Cell-mediated immunity: sensitized T cells most likely can also cause injury and progression of some glomerulonephritides but is not the primary mechanism

(III) Alternative complement pathway activation: complement activation resulting from defective regulation of the complement system rather than from antibody/immune complex deposits. The main mechanism in **C3 glomerulonephropathies** and **dense-deposit disease** (membranoproliferative glomerulonephritis type II)

Both immune and non-immune mediated primary or secondary glomerular diseases can result in **podocyte injury**; if this is the predominant feature, they are termed "podocytopathies", and are characterized by proteinuria. Morphologically, podocyte injury includes effacement of foot processes, vacuolization, cell detachment and retraction from the GBM. Podocytes have limited capacity for replication and repair

Progression of glomerular injury: depends on both host and disease factors. However, once any renal disease (glomerular or not) destroys functional nephrons and reduces the GFR to ~30-50% of normal, progression to end-stage renal failure proceeds at a steady rate independent of the original insult or activity of the underlying disease as compensatory changes lead to further glomerular injury. Morphologically, this is seen as:

- **Glomerulosclerosis**: Sclerosis involving parts of some glomeruli (e.g. secondary focal segmental glomerulosclerosis); may develop even in non-glomerular diseases. In secondary FSGS due to loss of renal tissue, compensatory hypertrophy of the remaining unaffected glomeruli initially maintains renal function but is accompanied by glomerular hemodynamic changes including increases in glomerular blood flow, filtration and transcapillary pressure, causing endothelial and visceral cell injury in these glomeruli, increased protein permeability, proliferation of mesangial cells, increased accumulation of extracellular matrix and eventual segmental and global sclerosis, setting up a vicious cycle of continuing glomerulosclerosis
- **Tubular damage and interstitial inflammation/fibrosis**: Degree correlates with decline in renal function. May result from ischaemia of tubular segments downstream from sclerotic glomeruli, interstitial acute and chronic inflammation, damage/loss of peritubular capillary blood supply, direct injury from proteinuria/other filtered proteins (e.g. haemoglobin) causing activation of tubular cells and secretion of inflammatory mediators that contribute to interstitial fibrosis

Major primary glomerulonephritides

Disease	Pathogenesis / Clinical features	LM	IF	EM
Nephritic syndrome				
Post-infectious glomerulonephritis *e.g. post-streptococcal, post-viral* Usu. children 6-10yo	Immune complex mediated (e.g. exogenous streptococcal antigens planted in subendothelial location with in-situ immune complex formation and subsequent migration and reformation on the subepithelial side of the GBM)	Hypercellular; Global and diffuse endocapillary proliferation. Severe cases have crescent formation	Granular IgG and C3 in GBM and mesangium	Subepithelial humps (subendothelial deposits in early stage)

	Post-streptococcal GN appears 1-4 weeks after strep infection of pharynx or skin (impetigo) >95% of children recover with conservative therapy. <1% develop RPGN. Few progress to chronic GN			
Rapidly progressive glomerulonephritis (crescenteric)	Clinical syndrome that may be seen in various diseases but in most cases is immune mediated. Classified according to the IF pattern: 1. **Anti-GBM** antibody-mediated disease. If associated with pulmonary haemorrhage = **Goodpasture syndrome** 2. Diseases caused by **immune complex deposition** e.g. postinfectious GN, lupus nephritis 3. **Pauci-immune crescentic GN** (usu. ANCA related e.g. systemic vasculitis or limited to kidneys) Requires immunosuppressive therapy, otherwise will progress to renal failure	Extracapillary proliferation with crescents; necrosis	1. Linear IgG±C3 in GBM 2. Granular deposits 3. IF-negative	GBM ruptures 1. No deposits 2. Immune complexes at various locations 3. No deposits
Nephrotic syndrome*: causes differ based on age group*				
Membranous nephropathy *Primary 75%* *Secondary 25% e.g. drugs, malignancy, SLE, infections*	Immune complex-mediated (endogenous or exogenous antigens in secondary causes; PLA_2R (phospholipase A_2 receptor at the basal surface of the glomerular epithelial cell) antigen in most cases of primary disease) Variable disease course but generally indolent. 40% have complete or partial remission	Diffuse capillary wall thickening	Diffuse granular IgG and C3	Subepithelial deposits Effacement of podocyte foot processes
Minimal change disease (MCD) Most frequent cause of nephrotic syndrome in children; less common in adults	Unknown, not immune complex-mediated but still likely immunologic basis. Podocyte injury May sometimes follow a respiratory infection or routine immunization. Highly selective proteinuria (mostly albumin). Relatively benign, responds well to steroids/ immunosuppressives	Normal-appearing glomeruli Proximal tubular epithelium laden with lipid	Negative	Effacement of podocyte foot processes

Focal segmental glomerulosclerosis (FSGS) Most frequent cause of nephrotic syndrome in adults in US	Can be **primary** (idiopathic) or **secondary** (associated with other conditions e.g. HIV-associated nephropathy, as a result of scarring or previously active necrotizing lesions e.g. in IgA nephropathy, or as an adaptive response to loss of renal tissue due to various causes). Some cases of primary FSGS have a genetic basis or are due to an unknown circulating factor May sometimes also be associated with microscopic haematuria, azotemia and hypertension. Non-selective proteinuria Poor response to steroids – 50% develop ESRD in 10 years	Focal and segmental sclerosis and hyalinosis	Focal; IgM+C3 in sclerotic areas / mesangium	Effacement of podocyte foot processes; epithelial denudation
Nephritic/nephrotic syndrome				
Membranoproliferative glomerulonephritis (MPGN) (type I) 10% of nephrotic syndrome in children and young adults	Pattern of immune-mediated injury rather than a specific disease Can be **primary** (unknown aetiology) or **secondary** (e.g. chronic immune complex disorders e.g. SLE, Hep B/C, malignancy). Immune complexes activate both classical and alternative complement pathways Usually slowly progressive unremitting course – 50% develop CRF in 10 years	Mesangial proliferative or membrano-proliferative patterns. GBM thickening / duplication	Granular IgG and C3 ±early complement components C1q and C4	Subendothelial deposits
Dense deposit disease (MPGN type I) Mostly children and young adults	Acquired or genetic abnormalities resulting in excessive activation of the alternative complement pathway. Decreased serum C3. Poor prognosis - >50% progress to ESRD		Granular or linear C3 in GBM and mesangium. No IgG, C1q or C4	Dense deposits in the GBM (not seen in other C3 glomerular diseases)
Recurrent haematuria ± proteinuria				
IgA nephropathy	Usually isolated renal disease but similar features seen in **Henoch-Schönlein purpura**. Also can be secondary in patients with liver and intestinal disease. Likely 'multi-hit' aetiology, including aberrantly glycosylated IgA	Variable; Focal mesangial proliferation and widening, focal proliferation	IgA ±IgG, IgM and C3 in mesangium	Mesangial and paramesangial deposits

Most common primary glomerulonephritis worldwide; usually older children and young adults	Most present with gross/ microscopic haematuria ± proteinuria after infection of respiratory/GI/urinary tract. Disease course is highly variable	or rarely, crescents		

Glomerular lesions associated with systemic diseases

Hypertensive nephrosclerosis

Glomeruli show ischaemic glomerular obsolescence. Main changes are in the arterioles (hyalinosis +/- muscular thickening) and arteries (arteriosclerosis). *(see section IV. Vascular Diseases – Nephrosclerosis)*

Diabetic nephropathy

Renal lesions are extremely common in diabetes, mostly in association with poor control of blood glucose levels which leads to non-enzymatic glycosylation of collagen and other proteins and formation of advanced glycation end-products (AGEs). Renal lesions include: 1. **Glomerular lesions** 2. **Renal vascular lesions** 3. **Pyelonephritis** (both acute and chronic, including necrotizing papillitis). Diabetes is the commonest cause of ESRD in Singapore, and frequently presents with proteinuria (mild in early stages, can be nephrotic-range in advanced disease).

Glomerular lesions include:

- **Capillary basement membrane thickening**: Part of diabetic microangiopathy
- **Diffuse mesangial sclerosis**: Diffuse increase in mesangial matrix due to PAS+ deposits. Can progress onto nodular glomerulosclerosis
- **Nodular glomerulosclerosis**: Often laminated PAS-positive matrix nodules (Kimmelstiel-Wilson) within the mesangium in the periphery of the glomerulus, which may be surrounded by dilated capillary loops (microaneurysms)
- **Hyalinosis**: Due to protein insudation

Both glomerular and vascular lesions (hyaline arteriolosclerosis) cause renal ischaemia, subsequent tubular atrophy and interstitial fibrosis.

Lupus nephritis

Up to 50% of SLE patients have clinically significant renal involvement, mainly glomerulonephritis and tubulointerstitial nephritis. There are 6 patterns of glomerular disease, which are due to immune complex deposition on the glomerular basement membrane, in the mesangium and sometimes the entire glomerulus. The patterns can overlap or evolve over time:

- **Class I**: Minimal mesangial lupus nephritis (least common)
- **Class II**: Mesangial proliferative lupus nephritis
- **Class III**: Focal lupus nephritis

- **Class IV**: Diffuse lupus nephritis (most common and severe)
- **Class V**: Membranous lupus nephritis
- **Class VI**: Advanced sclerosing lupus nephritis (i.e. end-stage renal disease)

Amyloidosis

Renal amyloidosis usually occurs either in patients with plasma cell dyscrasias (AL amyloid – Ig light chains) or chronic inflammatory diseases/neoplasms (AA amyloid – amyloid A protein), and often manifests as proteinuria (nephrotic-range). Amyloid deposits may be seen in glomeruli, interstitium and blood vessel walls and appears as extracellular accumulation of fibrillary proteins that are positive on Congo red stain and apple-green birefringence under polarized light examination.

III. TUBULAR AND INTERSTITAL DISEASES

Tubular and interstitial disorders are frequently caused by toxic or infectious agents, which mainly manifest as acute tubular injury/necrosis or tubulointerstitial nephritis

Acute tubular injury (ATI) / necrosis

- **Reversible** process characterized by **acute renal failure** (most common cause) and usually morphologic evidence of tubular injury
- Caused by a variety of conditions that usually have in common either/both:
  (1) **Ischaemia (ischaemic ATI)**: Due to decreased or interrupted blood flow e.g. hypotensive /hypovolemic shock, microangiopathies
  (2) **Direct toxic injury to the tubules (nephrotoxic ATI)**: Due to **endogenous** agents (e.g. hemoglobin, myoglobin, monoclonal light chains) or **exogenous** agents (e.g. drugs, radiographic contrast agents, organic solvents, heavy metals)
- **Pathogenesis**: Regardless of cause, tubular cell injury and persistent severe disturbances in blood flow are critical events:
  (1) **Tubular cell injury**: Tubular epithelial cells (esp. proximal tubules) are especially sensitive to ischaemia and also vulnerable to toxins. Ischaemia causes structural and functional abnormalities including loss of cell polarity resulting in abnormal ion transport and increased sodium delivery to distal tubules, which via tubuloglomerular feedback incites vasoconstriction and resultant decreased GFR. The ischaemic tubular epithelial cells also incite an inflammatory response. Eventually, the injured cells slough off and cause luminal obstruction, increased intratubular pressure and further GFR decrease. The damaged tubules also allow backleak of glomerular filtrate into the interstitium, causing interstitial oedema, increased interstitial pressure and further tubular damage
  (2) **Blood flow disturbances**: **Intrarenal vasoconstriction** occurs via several pathways including renin-angiotensin system, and sublethal endothelial injury leading to increased release of the vasoconstrictor endothelin and reduced production of vasodilators endothelin and prostacyclin. This results in both reduced glomerular blood flow and hypoxia of the thick ascending limb and straight segment of the proximal tubule in the outer medulla

If the precipitating cause is resolved, re-epithelialisation and repair can occur due to the patchiness of the injury and maintenance of basement membrane integrity. This is mediated by growth factors and cytokines produced by tubular cells and/or inflammatory cells

- **Clinical features**: 3 classic phases (although can be variable) -
  (1) **Initiation** (~36 hrs): Mild oliguria, mostly due to transient decrease in blood flow and GFR
  (2) **Maintenance**: Sustained oliguria with hyperkalemia, rising urea and creatinine, metabolic acidosis and other manifestations of uraemia
  (3) **Recovery**: steady increase in urine volume (as the tubules are still damaged and unable to resorb much water, sodium and potassium) with hypokalaemia and risk of infection. Eventually, there is recovery of renal tubular function and concentrating ability

  Prognosis depends on magnitude and duration of injury.
- **Morphology**: Casts within tubular lumina, and tubular epithelial injury (patchy with skip areas in ischaemic type, more often continuous in toxic ATI) which may be accompanied by basement membrane rupture and interstitial oedema. There may be epithelial regeneration in later stages. Not associated with necrosis of glomeruli or adjacent renal cortex (ddx: zonal kidney infarction, renal cortical necrosis)

<u>Tubulointerstitial nephritis</u>

- Group of diseases causing inflammation and damage to the tubules and interstitium, which can be **acute** (rapid clinical onset with interstitial oedema) or **chronic** (interstitial fibrosis and tubular atrophy). Glomerular and vascular abnormalities may be seen in advanced stages, while chronic tubulointerstitial damage can also be a consequence of progression in glomerular diseases (secondary)
- **Primary causes**: **infections** (acute or chronic pyelonephritis), **toxins** (drugs, acute hypersensitivity, analgesics, heavy metals), **metabolic diseases** (e.g. urate or oxalate nephropathy), **physical factors** (chronic urinary obstruction, neoplasms, myeloma), **immunologic** (transplant rejection), **vascular diseases** or **idiopathic**
- **Clinical features**: Principal manifestation = azotemia ± defects in tubular function (e.g. defects in concentrating ability manifest as polyuria/nocturia, salt wasting, metabolic acidosis). Unlike glomerular diseases, no nephritic or nephrotic syndrome

Infectious - Pyelonephritis and urinary tract infection

- Pyelonephritis = Inflammation affecting the tubules, interstitium and renal pelvis
  - **Acute**: associated with urinary tract infection (UTI), generally caused by bacteria
  - **Chronic**: other factors (e.g. obstruction) on top of bacterial infection predisposing to repeat episodes of acute pyelonephritis
- **Pathogenesis**: >85% of UTI are caused by gram-negative bacilli that are normal inhabitants of the intestinal tract e.g. *E.coli, Proteus, Klebsiella, Enterobacter*. Mycobacterial and fungal organisms can also infect and cause granulomatous inflammation, while viral infections (e.g. polyoma virus, cytogemegalovirus) can cause renal infection in immunocompromised patients (e.g. transplant). Most infections usually remain localized in the bladder. Pathways of infection include:

- **Ascending infection** (from lower urinary tract): Most common cause
  - Coliform bacteria colonizes the distal urethra (and introitus in females), and spread to the bladder. Risk factors include:
    - **Instrumentation** (e.g. long term catheterization)
    - **Female** (shorter urethra, hormonal changes affecting bacterial adherence to mucosa, pregnancy, absence of antibacterial properties found in prostatic fluid etc.)
  - From bladder to kidney. Risk factors include:
    - **Urinary tract obstruction and urinary stasis** (facilitating bacterial multiplication)
    - **Vesicoureteral reflux** (VUR) (i.e. incompetence of the one-way vesicoureteral valve) allowing bacteria to ascend the ureter into the renal pelvis. VUR is mostly congenital (1-2% of normal children), and also can be acquired in children/ adults e.g. by bladder infection affecting ureteral contractility, or persistent bladder atony caused spinal cord injury
    - **Intrarenal reflux**: urine is propelled deep into the renal parenchyma through open ducts at papillae tips. Most common in upper and lower poles of the kidney where papillae tend to have flattened/concave tips
- **Hematogenous** (through bloodstream): Less common
  - Kidneys seeded by bacteria during septicaemia or localized infection e.g. infective endocarditis. More likely debilitated or immunosuppressed patients

	Acute pyelonephritis	Chronic pyelonephritis
Clinical features	Frequently associated with above risk factors as well as pre-existing renal lesions, **diabetes** (neurogenic bladder dysfunction, increased risk of infection), immunosuppression and immunodeficiency. **Presentation**: Sudden onset of loin pain, systemic evidence of infection i.e. fever, chills and often lower urinary tract symptoms (dysuria, frequency, urgency) **Treatment**: Antibiotics if bacterial **Complications**: • **Papillary necrosis**: diabetics, sickle cell disease, urinary tract obstruction, drugs. Usually bilateral, involving one or all of the tips/distal parts of kidney pyramids • **Pyonephrosis**: when total obstruction, where pus cannot drain and fills the pelviureteric system • **Perinephric abscess**: suppuration extends through the renal capsule • **Sepsis**	Anatomic anomalies resulting in urine **reflux** or urine outflow **obstruction** are important risk factors **Presentation**: Asymptomatic or similar to acute recurrent pyelonephritis (e.g. back pain, fever, pyuria). Gradual onset of renal insufficiency and hypertension. Polyuria and nocturia (loss of tubular function). Some develop secondary FSGS with significant proteinuria, usually several years after scarring and in the absence of continued infection → poor prognosis due to likely progression to ESRD
Morphology	**Gross**: Discrete focal abscesses or large wedge-like greyish-white areas	**Gross**: Irregular kidney scarring (asymmetric if bilateral) with coarse, discrete corticomedullary scars overlying dilated

	Microscopy: Patchy interstitial suppurative inflammation, intratubular aggregates of neutrophils, neutrophilic tubulitis and tubular injury. Glomeruli are relatively uninvolved unless extensive disease. Papillary necrosis shows ischaemic coagulative necrosis	blunted or deformed calyces and blunting of the renal papillae (usually upper and lower poles where intrarenal reflux occurs more frequently). Calyceal involvement important **Microscopy**: tubular atrophy/hypertrophy. Thyroidization of tubules (dilated tubules with flattened epithelium filled with casts). Varying degrees of chronic interstitial inflammation and fibrosis. Glomeruli largely normal except for ischaemic changes, or secondary FSGS in advanced stages **Xanthogranulomatous pyelonephritis**: accumulation of foamy macrophages with other inflammatory cells, often associated with *Proteus* infections and obstruction. Grossly large yellow-orange nodules that mimic renal cell carcinoma

Drugs and toxins-induced acute tubulointerstitial nephritis

- 2nd most common cause of acute kidney injury (after pyelonephritis)
- Drugs can injure the kidneys by 1. triggering an interstitial immunologic reaction (e.g. acute hypersensitivity nephritis induced by methicillin), 2. causing ATI (see above), 3. causing subclinical but cumulative tubular injury that takes years to result in chronic kidney disease – the latter may be unrecognized until renal damage is irreversible
    - E.g. NSAIDs can cause several forms of renal injury including acute kidney injury (due to decreased synthesis of vasodilatory prostaglandins, usually in the setting of other renal disease/conditions causing volume depletion), acute hypersensitivity interstitial nephritis, acute interstitial nephritis and minimal change disease, membranous nephropathy
- **Pathogenesis**: Drug-induced acute interstitial nephritis is likely due to an **idiosyncratic immune mechanism** i.e. not dose-related. Most likely, drugs function as haptens and covalently bind to tubular cells, resulting in immunogenic modified self antigens. IgE (type I) or T cell-mediated (type IV) **hypersensitivity reaction** towards these tubular cells or their basement membranes then occurs. Common drugs include antibiotics, diuretics and NSAIDs
- **Clinical features**: Fever, eosinophilia (may be transient), +/-rash and renal abnormalities (hematuria, mild proteinuria, leukocytouria, rising serum creatinine) 2-40 days after drug exposure. Reversible with withdrawal of the offending drug, if discovered early enough. However, ~30-40% of acute interstitial nephritis have no identifiable offending drug/mechanism.
- **Morphology**: Interstitial oedema and mononuclear cell infiltrate (mostly lymphocytes and macrophages +/- other inflammatory cells), and tubulitis (infiltration of tubules by lymphocytes) with variable tubular injury and regeneration. Glomeruli normal except in NSAIDs. Papillary necrosis can be seen in analgesic nephropathy (likely caused by ischemia from compression/obstruction of small medullary blood vessels e.g. by interstitial oedema)

Other tubulointerstital diseases

Urate nephropathy: Precipitation of uric acid crystals in renal tubules, leading to obstruction and acute renal failure (**acute uric acid nephropathy**, usually in tumour lysis syndrome) or precipitation in tubular lumens and interstitium, evoking a mononuclear response (tophus), cortical atrophy and scarring (**chronic urate nephropathy**, in chronic hyperuricemia e.g. gout). Uric acid stones (**nephrolithiasis**) are also seen in patients with gout or secondary hyperuricemia

Nephrocalcinosis: Deposition of calcium in the kidney and calcium stones can be seen in various disorders associated with **hypercalcemia** (e.g. hyperparathyroidism, multiple myeloma, metastatic cancer). Extensive nephrocalcinosis can lead to chronic tubulointerstitial disease and renal insufficiency

Light-chain cast nephropathy ('Myeloma kidney'): Bence-Jones (light-chain) proteinuria is intrinsically toxic to tubular epithelial cells and can also combine with urinary glycoproteins to form large tubular casts that obstruct the lumen and induce an inflammatory reaction. May be associated with amyloidosis, light-chain deposition disease (glomerulopathy), nephrocalcinosis

IV. VASCULAR DISEASES

Nearly all kidney diseases will secondarily involve renal blood vessels. Systemic vascular diseases (e.g. vasculitis) and hypertension also affect renal vessels

Nephrosclerosis

- Term used for the renal pathology associated with sclerosis of renal arterioles and small arteries. Strongly associated with hypertension (can be both cause and consequence)
- **Pathogenesis**: Combination of 2 processes – **medial and intimal thickening** (a response to hemodynamic changes, aging, genetics) and **hyalinization of arteriolar walls** (due to extravasation of plasma proteins through injured endothelium, and increased deposition of basement membrane matrix). The resulting thickened wall causes luminal narrowing and focal parenchymal ischaemia, leading to glomerulosclerosis and chronic tubulointerstitial injury
- **Clinical features**: Uncomplicated nephrosclerosis seldom causes renal insufficiency / uraemia, unless there are risk factors (e.g. concomitant disease like diabetes, severe blood pressure elevations and African descent). May present with proteinuria (usually low grade, may be nephrotic-range with secondary FSGS). ~5% of hypertensive persons have **malignant hypertension** – severe pressure elevations associated with renal failure (malignant nephrosclerosis, which may overlap with thrombotic microangiopathies), retinal haemorrhages and exudate +/- papilledema
- **Gross**: Normal or shrunken kidneys with a finely granular cortical surface
- **Microscopy**: **Hyaline arteriolosclerosis** (thickened hyalinized walls) of arterioles and small arteries, with narrowed lumens) and **fibroelastic hyperplasia** of the interlobular and arcuate arteries (medial hypertrophy, replication of the internal elastic lamina and increased intimal myofibroblastic tissue). Patchy ischemic atrophy results in **microscopic subcapsular scars** (with tubular atrophy, interstitial fibrosis, sclerotic glomeruli/periglomerular fibrosis and GBM collapse)

Renal artery stenosis

- Unilateral; Potentially surgically correctable condition that accounts for 2-5% of hypertension cases
- **Pathogenesis**: causes hypertension by increased production of renin from the ischaemic kidney (renin-angiotensin system), which may be further potentiated by sodium retention. Most common cause (70%) is due to an **atheromatous plaque** at the origin of the renal artery (M>F, older); 2nd most common cause is **fibromuscular dysplasia** of the renal artery (F>M, younger)
- **Morphology**: The ischaemia kidney is shrunken with sings of diffuse ischaemic atrophy. The arterioles in the ischemic kidney are relatively protected from the effects of high pressure due to the renal artery stenosis and show only mild arteriolosclerosis vs the contralateral non-ischaemic kidney

Thrombotic microangiopathies

Spectrum of clinical syndromes including thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), which are caused by various injuries leading to thrombi in capillaries/arterioles of various tissue beds, including the kidneys, resulting in tissue ischaemia and organ dysfunction, as well as red cell hemolysis and consumptive thrombocytopenia

Other vascular disorders

Atherosclerotic ischaemic renal disease: bilateral renal artery disease is fairly common in older individuals, sometimes in the absence of hypertension, causing chronic ischaemia

Atheroembolic renal disease: embolization of fragments of atheromatous plaques from the aorta/renal artery into intrarenal vessels. Frequently of no clinical significance unless pre-existing renal injury/numerous emboli

Sickle cell nephropathy: accelerated sickling in the hypertonic hypoxic milieu of the renal medulla can cause patchy papillary necrosis, hematuria, diminished concentrating ability and proteinuria

Renal infarcts: kidneys are common sites for infarcts due to the extensive blood flow to the kidney (1/4th of cardiac output) and limited collateral circulating from extrarenal sites. Most are due to embolism (e.g. from cardiac atrial thrombi) and less commonly due to thrombosis and acute vasculitis of renal arteries. Usually clinical silent. **Gross:** sharply demarcated pale yellow-white wedge-shaped areas, frequently rimmed by hyperemia. With time, the ischemic necrosis undergoes fibrous scarring, forming depressed pale grey-white cortical scars

V. CONGENITAL AND DEVELOPMENTAL ANOMALIES

~10% of people are born with significant urinary system malformations. Congenital renal disease is more often an acquired developmental defect during gestation but can also be hereditary. Structural kidney anomalies are uncommon except for horseshoe kidney

Agenesis of kidney: Bilateral agenesis is incompatible with life; unilateral agenesis can be compatible with normal life if no other abnormalities exist, although some patients may eventually develop chronic kidney disease due to compensatory hypertrophy and progressive glomerulosclerosis

Hypoplasia: Failure of kidneys to develop to normal size (reduced number of lobules and calyces). Usually unilateral, rarely bilateral (resulting in renal failure in early childhood). Seen in low birth weight infants

Ectopic kidneys: Abnormal location of normal/ slightly smaller kidneys usually either just above the pelvic brim or within pelvis. Complications include kinking/tortuosity of ureters causing urinary obstruction and increased risk of bacterial infection

Horseshoe kidney: Fusion of the upper (10%) or lower (90%) poles of the kidney so that the kidney is continuous across the midline anterior to the great vessels. Complication includes renal calculi

VI. CYSTIC DISEASES OF THE KIDNEY

Cystic kidney disease are a heterogenous group (hereditary, developmental or acquired) and relatively common. Some forms can result in chronic kidney disease

Autosomal dominant (adult) polycystic kidney disease (ADPKD)

- Hereditary disorder characterized by bilateral multiple renal cysts that gradually enlarge and ultimately destroy renal parenchyma and cause renal failure
- **Pathogenesis**: Susceptibility to develop this disease is inherited as an autosomal dominant trait, but both alleles of the involved genes have to be nonfunctional to develop the disease
    - Genes involved include ***PKD1*** (85%) and ***PKD2*** (polycystin-1 and -2), each with a wide range of different possible mutations. It is thought that mutations in *PKD1* or *2* alters intracellular Ca2+ levels via the cilia-centrosome complex of tubular epithelial cells, which thus affects many downstream signaling events including cellular proliferation, apoptosis, secretory functions and interaction with the extracellular matrix
    - Both genetic (e.g. *PKD2* less severe than *PKD1*) and environmental factors influence disease severity
- **Clinical features**: Relatively common (1 in 400-1000 live births, ~5-10% of ESRD cases requiring transplantation or dialysis). **Presentation**: Patients usually asymptomatic until ~30-40 yo as cysts increase in size and number. Some may experience pain as cysts enlarge or bleed, or renal colic due to excretion of blood clots. Renal function is generally retained initially; when progressive chronic kidney disease sets in, patients experience hematuria, proteinuria, polyuria and hypertension. **Associated extrarenal congenital anomalies**: Polycystic liver disease (40%), intracranial berry aneurysms, mitral valve prolapse and other cardiac valvular anomalies (20-25%). **Disease course**: Prolonged course (patients may survive many years with azotemia slowly progressing to uremia). 40% of adult patients die of coronary or hypertensive heart disease, 25% of infection, 15% of intracranial haemorrhage (ruptured berry aneurysm or hypertensive)

- **Gross**: Bilateral kidney enlargement comprising a mass of cysts with no/minimal intervening kidney parenchyma. Cysts are filled with clear serous fluid (may be turbid or brown / haemorrhagic)
- **Microscopy**: Cysts are lined by varying epithelium type (depending on the part of the renal tubule they arise from)

Autosomal recessive (childhood) polycystic kidney disease (ARPKD)

- Can be subcategorized into perinatal, neonatal, infantile and juvenile depending on the time of presentation and associated hepatic lesions
- **Pathogenesis**: Mostly caused by varying ***PKHD1*** mutations (fibrocystin)
- **Clinical features**: Perinatal and neonatal subtypes are most common and may have serious manifestations at birth. Infantile and juvenile subtypes may have congenital hepatic fibrosis
- **Gross**: Enlarged kidneys with smooth outer surface. Cut surface has spongelike appearance due to numerous small cysts and dilated elongated channels perpendicular to cortical surface. Liver has cysts associated with portal fibrosis and portal bile duct proliferation (congenital hepatic fibrosis)
- **Microscopy**: Cylindrical (less commonly, saccular) dilation of collecting tubules

Medullary cystic diseases

Medullary sponge kidney: Relatively common, adults. Renal function usually normal

Nephronophthisis: Most common genetic cause of ESRD in children and young adults. Progressive renal disorder with shrunken kidneys and cysts concentrated at the corticomedullary junction. Eventual renal insufficiency (in 5-10 years) results from cortical tubulointerstitial damage

Multicystic renal dysplasia

- Sporadic disorder, unilateral or bilateral, often associated with other lower urinary tract anomalies. Due to abnormal metanephric differentiation, with persistence of primitive / abnormal structures
- **Clinical features**: If unilateral, other kidney functions normally – good prognosis. If bilateral, can result in renal failure
- **Gross**: Kidney is usually enlarged, irregular and multicystic
- **Microscopy**: Lobar disorganization with characteristic presence of undifferentiated mesenchyme, cartilage and immature collecting ducts amongst normal nephrons. Cysts lined by flattened epithelium

Acquired cystic disease: Cysts may develop in ESRD patients who have undergone prolonged dialysis, likely due to obstruction of tubules by interstitial fibrosis or oxalate crystals. 100x increased risk of renal cell carcinoma

Simple cysts: Single or multiple, often cortical. Often no clinical significance but can mimic tumours

VII. HYDRONEPHROSIS AND UROLITHIASIS

Hydronephrosis

- Dilatation of the renal pelvis and calyces associated with progressive kidney atrophy due to urinary outflow obstruction. Obstruction can occur at any level of the urinary tract from various causes (See "Study Notes on Male Genitourinary Tract")
- **Pathogenesis**: The high pressure in the pelvicalyceal system from urinary obstruction transmits back through the collecting ducts into the cortex, causing renal atrophy and also compressing the medullary renal vasculature. This leads to medullary functional disturbances (first presenting as impaired concentrating ability) before GFR starts to fall. Obstruction also triggers interstitial inflammation and eventually interstitial fibrosis
- **Clinical features:** Early symptoms are mostly due to the underlying cause e.g ureteric colic from calculi, bladder symptoms from BPH, or pain from distension of the collection system/ renal capsule. **Unilateral or partial hydronephrosis** often clinically silent and only incidentally detected on imaging as overall renal function unaffected, while **bilateral partial obstruction** may manifest with polyuria and nocturia (impaired concentrating ability), and hypertension. **Complete bilateral obstruction** presents with oliguria or anuria. After relief of the obstruction, post-obstructive diuresis results. **Investigations**: Ultrasound kidney, ureter and bladder.
- **Gross:** Sudden complete obstruction leads to only mild pelvicalyceal dilatation, while subtotal / intermittent obstructions causes progressive dilation resulting in hydronephrosis (marked cortical thinning and obliteration of pyramids) +/- dilation of bladder and ureter depending on the level of obstruction
- **Microscopy:** Often interstitial inflammation and dilated tubules and Bowman's spaces. Chronic cases show cortical tubular atrophy with marked diffuse interstitial fibrosis

Urolithiasis

- Formation of a calculus or calculi (stones) anywhere in the urinary tract; most arise in the kidney
- **Pathogenesis**: Primarily due to **supersaturation** i.e. increased urinary concentration of the stones' constituents such that it exceeds their solubility. Other contributing factors include low urine volume, change in urinary pH, presence of bacteria, presence of foreign body (e.g. indwelling catheter) and possibly due to some deficiency in inhibitors of crystal formation in urine e.g. citrate, glycosaminoglycans. Familiar and hereditary predisposition contributes (e.g. inborn errors of metabolism e.g. cystinuria, primary hyperoxaluria)
  4 main types of calculi:
  1. **Calcium oxalate (65-70%)**: Radiopaque. 55% have **hypercalciuria** (without hypercalcemia) e.g. due to absorptive hypercalciuria (intestine), renal hypercalciuria (renal tubular reabsorption defect); also seen in 5% of patients with **hypercalcemia and hypercalciuria** (e.g. hyperparathyroidism), in association with **increased uric acid secretion** (hyperuricosuric calcium nephrolithiasis) with nucleation of uric acid crystals, **hyperoxaluria**, **hypocitraturia** or **idiopathic**.

2. **Magnesium ammonium phosphate (15%)**: Usually large stones (e.g. staghorn calculi in the renal pelvis). Formed after infection by urea-splitting bacteria e.g. *Proteus* that convert urea to ammonia, causing alkalinization of urine and resulting in precipitation of magnesium ammonium phosphate salts
3. **Uric acid (5-10%)**: Radiolucent. Common in patients with hyperuricemia (e.g. gout, acute leukemia) but most uric acid stones form in patients without hyperuricemia/ hyperuricosuria, likely because of acidic urine (pH less than 5.5)
4. **Cystine (1-2%)**: caused by cystinuria (due to genetic defects in renal reabsorption of amino acids)

- **Clinical features**: M>F, 20-30yo peak incidence. Can be asymptomatic, produce renal colic / abdominal pain, renal damage or hematuria. **Complications**: Urinary stasis, ulceration, bleeding, pain, infection (due to obstruction and the induced trauma), fistula formation
- **Gross**: 80% unilateral, mostly within renal pelvicalyceal system and bladder. Those within renal pelvis tend to be small (2-3mm) but can grow to form a cast of the pelvicalyceal system (staghorn calculus)

VIII. NEOPLASMS

Benign neoplasms

Renal papillary adenoma: <15 mm cortical unencapsulated tumours which are often incidental findings and histologically appear similar to low grade papillary renal cell carcinoma (distinguished by size)

Angiomyolipoma: Most common mesenchymal kidney tumour; can also be seen in other sites e.g. liver, lungs. May be sporadic or seen in 25-50% of patients with tuberous sclerosis. Comprises vessels, smooth muscle and fat originating from perivascular epithelioid cells. Can be complicated by haemorrhage. Fat content usually allows accurate diagnosis on CT imaging.

Oncocytoma: Can be familial. Well-encapsulated tan-brown tumours, classically with central scar

Malignant neoplasms

Renal cell carcinoma

- 85% of renal cancers in adults; arises from tubular epithelium
- **Risk factors**: Tobacco, obesity (particularly in women), hypertension, unopposed oestrogen therapy, exposure to asbestos/heavy metals, pre-existing renal disease (ESRD/ chronic kidney disease, acquired cystic disease), tuberous sclerosis
- **Clinical features**: usually 50-60 yo, M>F. Most are sporadic, but familial forms occur e.g. in von Hippel Lindau syndrome (clear cell RCC), hereditary leiomyomatosis and renal cell cancer syndrome, Birt-Hogg-Dube syndrome. **Presentation**: Classic triad of costovertebral pain, palpable mass and hematuria seen only in 10%. May be associated with constitutive symptoms e.g. weight loss, fever, as well as mimic other diseases due to paraneoplastic syndromes (e.g. hypercalcemia). Often asymptomatic until large (>10cm) and therefore increasingly detected as incidental imaging finding.

Prognosis: Tends to metastasize widely (most commonly lungs and bones) before becoming symptomatic, therefore affecting survival. Metastasis may be late. **Treatment**: Partial/radical nephrectomy, anti-VEGF therapy as adjunct for metastatic disease

- **Pathologic classification**: based on correlative cytogenetic, genetic and histologic findings. Main subtypes include:

Histologic type	Genetic changes	Morphology
Clear cell carcinoma (70-80%) - 95% sporadic, 5% familial	3p del (*VHL* gene)	**Gross:** Solitary unilateral lesion with bright yellow variegated appearance **Micro**: Nests of polygonal cells with abundant clear cytoplasm, separated by delicate fibrovascular septa. Tendency to invade renal vein
Papillary carcinoma (10-15%) - both sporadic and familial	Trisomy 7 Also trisomy 17 and loss of Y if sporadic	**Gross**: Can be multifocal and bilateral. Typically haemorrhagic and cystic esp. when large **Micro**: Papillary arrangements of cuboidal to low columnar cells
Chromophobe carcinoma (5%)	Multiple chromosome losses and extreme hypodiploidy	**Gross**: Mostly circumscribed unencapsulated tumour **Micro**: Solid sheets of cells with distinct cell membranes, pale eosinophilic cytoplasm and perinuclear haloes
***TFE3*-rearranged renal cell carcinomas** (subtype of molecularly defined renal carcinomas)	Xp11.3 fusion translocation (*TFE3* gene)	**Gross**: Not distinctive **Micro**: Papillary neoplasm comprising epithelioid clear cells with abundant psammoma calcifications
Collecting duct carcinoma (<1%)	Several chromosomal losses and deletions	**Gross**: Grey white firm tumours based in the medulla with haemorrhage and necrosis **Micro**: Malignant glands and papillae lined by highly atypical hobnailed cells within a fibrotic stroma

Urothelial carcinoma of the renal pelvis

- 5-10% of primary renal tumours. Usually presents while small and with hematuria due to their location, but prognosis not good as they often infiltrate the pelvicalyceal wall. Can also cause urinary obstruction with hydronephrosis and flank pain
- Can be metachronous / synchronous with bladder urothelial tumours. Increased incidence in Lynch syndrome patients.
- Histology similar to bladder urothelial tumours

Nephroblastoma (Wilm's tumour)

- Most common primary renal tumour in children (usu. 2-5 yo) and can involve bilateral kidneys
- **Pathogenesis / genetics**: 90% sporadic. 10% of cases show increased risk with at least 3 recognisable groups of congenital malformations associated with distinct chromosomal loci (syndromic WT):
    - **WAGR syndrome**: germline deletion of 11p13 (*WT1*)
    - **Denys-Drash syndrome**: germline WT1 abnormalities

  - **Beckwith-Wiedemann syndrome**: possibly due to loss of imprinting leading to overexpression of IGF2 protein, an embryonal growth factor
- **Clinical features:** Usually presents with large abdominal mass +/- hematuria, pain, fever. Pulmonary metastases may also be present at time of diagnosis. **Treatment**: Usually combination of surgery and chemotherapy. **Prognosis**: Mostly good even for tumours that spread beyond kidney; anaplasia and other chromosomal changes are markers of adverse prognosis. Patients who survive may develop second primary tumours as a consequence of radiation therapy
- **Gross:** Large solitary well-circumscribed mass with soft, homogeneous tan-gray surface in the cortex
- **Microscopy:** Attempts to recapitulate different stages of nephrogenesis with classic triphasic combination of **blastemal** (sheets of small blue cells), **stromal** (spindle cells) and **epithelial** (abortive tubular and glomeruloid structures) components. 5% of tumours have anaplasia (marked nuclear atypia and abnormal mitoses – correlates with *TP53* mutations and chemotherapy resistance)