Ist Year

30 pages

No 4

PATHOLOGY OF THE KIDNEY AND URINARY SYSTEM

- ACUTE KIDNEY INJURY -

BY

DR. AMMAR C. AL-RIKABI, PROFESSOR M.O. ALSOHAIBANI

AND DR. HALA KASSOUF KFOURY

DEPARTMENT OF PATHOLOGY

KING KHALID UNIVERSITY HOSPITAL

LECTURE ONE:

- **NORMAL ANATOMY AND HISTOLOGY OF THE KIDNEY.**
- **PATHOLOGY OF CONGENITAL AND CYSTIC RENAL DISEASES.**
- **ACUTE RENAL FAILURE.**

The kidneys are retroperitoneal organs. Each adult kidney weighs 120 to 150 grams and is covered by a thin capsule of connective tissue and a layer of perinephric fat. Through the hilus of each kidney pass a renal artery and vein, lymphatics, a nerve plexus and the renal pelvis which divides into three major and several minor calyces.

On cut section, the kidney reveals two sections: the reddish brown cortex and the lighter medulla. The medulla is formed into medullary rays and 10 to 20 pyramids whose most distal ends is called the papillae which project into the calyces of the upper collecting system.

NEPHRON

Each kidney is composed of approximately 1 million nephrons, the basic functional unit of the kidney. The nephron components are as follows:

1. The glomerulus with its afferent and efferent arterioles, consists of a tuft of capillary loops that protrude into Bowman's capsule. The glomerular tuft has several components.
   (a) The mesangium is a supporting structure composed of cells and matrix.
   (b) The glomerular capillary loops are endothelial-lined tubes, which are covered with basement membrane and visceral epithelium and held in place by the mesangium.
   (c) The glomerular basement membrane (GBM) and visceral epithelial cells together comprise the ultrafiltration barrier necessary for urine formation.

2. The renal tubule begins as Bowman's capsule and consists of the proximal convoluted tubule. Loop of Henle, distal convoluted tubule and collecting duct (the last of which conveys urine to the renal pelvis and ureter).

3. The interstitium is a connective tissue consisting of reticular fibers and interstitial cells, lymphatics, blood vessels and nerves.

There are two distinct types of nephrons:

(1) Cortical nephrons: they are the predominant type and have glomeruli situated in the outer cortex.
(2) Juxtamedullary nephrons: have glomeruli located at the corticomedullary junction. These nephrons have long loops of Henle penetrating deep into the medulla.

URINARY TRACT STRUCTURE

The urinary tract connects to the kidney at the renal pelvis and consists of the ureters, urinary bladder and urethra.

CONGENITAL AND CYSTIC RENAL DISEASES

Learning Objectives:

You should:

- Have a working knowledge of the embryology of the kidney and urinary tract.
- Be able to apply this to the more common abnormalities.

There are numerous possible congenital abnormlaties of the kdieny from non-formation of one kidney (unilateral agenesis), which is compatible with a normal life (and may only be discovered incidentally at autopsy) to congenital absence of both kidneys, which usually leads to death in utero. Sometimes the upper or lower poles of the kidneys are fused (forming a so-called "horseshow kidney). This type of kidney malformation may be found in fetuses/children who have chromosomal abnormalities such as Turner's syndrome (45x). Congenital cystic disease of the kidney is clinically very important and include:

(1) Cystic renal dysplasia
- ❖ Commonest cystic renal disease in children.
- ❖ Caused by disorganized renal development.
- ❖ Can be unilateral or bilateral.
- ❖ Often associated with poorly formed ureter.
- ❖ Rarely part of a syndrome.

(2) Autosomal dominant polycystic kidney disease
- ❖ Progressive distention of kidney by enlarging cysts.
- ❖ 1-2 cases per 1000 live births.
- ❖ Usually present in adults.
- ❖ Caused by mutation in two genes PKD1 (85% of cases: chromosome 16) and PKD2 (155 of cases, chromosome 4) (? also PKD3 in rare cases).
- ❖ 10% new mutations.
- ❖ Maybe associated with cysts in liver, pancreas, spleen and cerebral/coronary artery and aneurysms.
- ❖ About 10% require dialysis/transplantation.

(3) Autosomal recessive polycystic kidney disease
- ❖ Rare, 1 case per 20,000 live births.
- ❖ Gene on chromosome 6.

- ❖ Liver also always affected.
- ❖ Large kidneys at birth (may cause death soon after birth due to renal failure).

(4) Medullary sponge kidney
- ❖ Dilated collecting ducts give "spongy" appearance.
- ❖ ? 1 case per 5000 populatioan.
- ❖ May present with renal infections in adult life.
- ❖ No obvious genetic link.

ACUTE TUBULAR NECROSIS – is the most common cause of **acute renal failure (acute renal shutdown).**

Acute renal failure is manifested clinically by oliguria or anuria (no urine flow) with recent onset of azotemia (elevated urea and creatinine). The condition is mainly manifested by acute tubular necrosis. Acute renal failure can be caused by prerenal, renal or postrenal causes.

1. This condition is reversible. Necrotic renal tubular cells are replaced by new cells in approximately 2 weeks, with complete return of renal function to normal if the patient is maintained on dialysis. Proper medical management results in complete recovery, otherwise the syndrome is potentially fatal.
2. This condition can also lead to cardiac standstill from hyperkalemia, most often during the initial oliguric phase. Oliguria from acute tubular necrosis must be distinguished from oliguria due to prerenal causes: such as reduced blood volume or dehydration.
3. **Causes and predisposing factors**: The acute condition is most frequently precipitated by **renal ischemia**, which is often caused by prolonged hypotension or shock, most often induced by gram-negative sepsis, trauma or hemorrhage. Another associated condition is crush injury with myglobinuria. Myoglobinuria also can be observed after intense exercise, but this is not of clinical consequence.

   Other causes may include direct injury to the proximal renal tubules from mercuric chloride, gentamicin, and several other toxic substances. Ethylene glycol (antifreeze) is extremely toxic when ingested and can result not only in acute tubular necrosis but also in renal oxalosis with massive intratubular oxalate crystal deposition that can be visualized under polarized light.

LECTURE TWO: PATHOLOGY OF THE INFECTIONS OF THE UPPER AND LOWER URINARY TRACT

BY

DR. AMMAR C. AL-RIKABI, PROFESSOR M.O. ALSOHAIBANI

AND DR. HALA KASSOUF KFOURY

DEPARTMENT OF PATHOLOGY

KING KHALID UNIVERSITY HOSPITAL

URINARY TRACT OBSTRUCTION

A. This obstruction may occur anywhere in the urinary system.

B. In children, the condition is most often due to congenital malformations (associated with reflux or other causes).

C. In adults, the condition is most often acquired and usually occurring as a consequence of renal stones or benign prostatic hyperplasia.

D. **Clinical manifestations** include:

1. Renal colic, which is an excruciating pain caused by acute distention of the ureter, usually due to the transit (movement) of a stone.
2. Hydronephrosis, which is progressive dilation of the renal pelvis and calyces.
3. Infection, which is localized proximal to the site of obstruction and may lead to infection of the renal parenchyma.

INFECTIONS OF THE URINARY TRACT AND KIDNEY (PYELONEPHRITIS AND CYSTITIS)

A. General considerations

1. The incidence of infection of the urinary tract and kidney is greatly increased in women, presumably because of the shorter length of the female urethra and the incidence is increased during pregnancy (because of pressure by the uterus).

2. This condition can be caused by hematogenous bacterial dissemination to the kidney or by external entry of organisms through the urethra into the bladder and in this case infection can spread upward from the bladder into the ureters (vesicounreteral reflux)and through the ureters to the kidney (ascending infection).

3. Most frequently, the infection involves or is caused by the normal flora of the colon, most often Escherichia coli.

B. **Predisposing factors**

1. Obstruction of urinary flow, such as that occurring with urethral obstruction in benign prostatic hyperplasia

2. Surgery on the kidney or urinary tract.

3. Catheters inserted the urethra into the bladder

4. Gynecologic abnormalities

C. **Clinical manifestations**

1. Urinary frequency: a compelling necessity to void small amounts of urine at frequent intervals.

2. Dysuria: painful, burning sensation on urination

3. Pyuria: large numbers of neutrophils in the urine

4. Haematuria: blood in the urine; urinary red cells are a nonspecific finding in urinary tract infection.

5. Bacteriuria: usually defined as more than 10^5 organisms per milliliter of urine: it must be distinguished from contamination of urine specimen by external flora.

D. **Additional diagnostically significant findings in acute pyelonephritis (acute infection of the renal parenchyma).**

1. Fever, leukocytosis, flank tenderness, urinary white cells, and **white** cells casts in the urine (this latter finding is pathognomonic of acute pyelonephritis).

2. Greatly increased frequency in women, especially during pregnancy.

E. **Cystitis: Characteristics include pyuria and often hematuria, but urinary white cell casts are not found.**

TUBULAR AND INTERSTITIAL DISORDERS OF THE KIDNEY

A. **Acute drug-included interstitial nephritis**

1. Most often the trigger is penicillin derivatives, such as methicillin, and other drugs, such as nonsteroidal anti-inflammatory drugs and diuretics.

2. The disease is most likely of immune etiology.

3. Acute interstitial renal inflammation including many eosinophils is characteristic.

4. The nephritis resolves on cessation of exposure to the inciting drug.

B. **Renal papillary necrosis(necrotizing papillitis) is ischemic necrosis of the tips of the renal papillae.**

1. This form of necrosis is most often associated with **diabetes mellitus**, in which it is related to renal infection and coexisting vascular disease. It is occasionally a catastrophic consequence of acute pyelonephritis.

2. Renal papillary necrosis is also associated with long-term persistent abuse of **phenacetin**; most often when phenacetin in is used association with aspirin and other analgesics. This can lead to chronic analgesic nephritis, a chronic inflammatory change characterized by loss and atrophy of tubules and interstitial fibrosis and inflammation. Phenacetin is no longer approved for over-the-counter analgesia preparations (not allowed to be sold by pharmacies without prescriptions).

Chronic pyelonephritis.

1. Coarse, asymmetric corticomedullary scarring and deformity of the renal pelvis and calyces occurs; these findings are essential for the diagnosis.

3. Characteristics include interstitial inflammatory infiltrate in the early stages and later by interstitial fibrosis and tubular atrophy; atrophic tubules often contain eosinophilic proteinaceous casts,resulting in an appearance reminiscent of thyroid follicles (thyroidization of the kidney).

3. Causes almost always include chronic urinary tract obstruction and repeated bouts (attacks) of acute inflammation.

4. Consequences include renal hypertension and end-stage renal disease.

UROLITHIASIS

This condition is characterized by the formation of calculi (stones) in the urinary tract. The incidence is increased in men.

A. **Calcium stones** account for 80% -85% of urinary stones.

1. The stones consist of calcium oxalate or calcium phosphate, or both.

2. They are radiopaque (can be seen by using x-rays).

4. They are associated with hypercalciuria, which is caused by:

a. Increased intestinal absorption of calcium.

b. Increased primary renal excretion of calcium

c. Hypercalcemia, which may be caused by:

(1) Hyperparathyroidism leads to nephrocalcinosis (calcification of the kidney), as well as urolithiasis.

(2) Malignancy leads to hypercalcemia because of osteolytic metastases or ectopic production of parathyroid hormone (often by a squamous cell carcinoma of the lung).

(3) Other causes include sarcoidosis, vitamin D intoxication, and the milk-alkali syndrome.

B. **Ammonium magnesium phosphate stones** are the second most common form of urinary stones.

1. These stones are formed in alkaline urine, which is caused most often by ammonia producing or "splitting" (urease-positive) organisms, such as proteus vulgaris or staphylococcus.

2. They are radiolucent.

3. They can form large staghorn (struvite) calculi (casts of renal pelvis and calyces).

C. **Uric acid stones** are associated with hyperuricemia in approximately half of the patients; hyperuricemia can be secondary to gout or to increased cellular turnover, as in the leukaemias or myeloproliferative syndromes.

D. **Cystine stones** are almost always associated with cystinuria or genetically determined aminoaciduria.

LECTURES THREE AND FOUR

PATHOLOGY OF THE NEPHROTIC, NEPHRITIC

AND CHRONIC KIDNEY DISEASE

BY

DR. AMMAR AL RIKABI, PROFESSOR M.O. ALSOHAIBANI

AND DR. HALA KFOURY

DEPARTMENT OF PATHOLOGY

KING KHALID UNIVERSITY HOSPITAL

EVALUATION OF GLOMERULAR DISEASE

1] **Terminology**: The following terms are used to describe the extent of glomerular injury:

(a) Diffuse	-	all glomeruli are affected.
(b) Focal	-	some glomeruli are affected.
(c) Segmental	-	part of one glomerulus is affected.
(d) Global	-	the entirety of one glomerulus is affected.

2] **Techniques used for studying of glomerular diseases:**

(a) Light microscopy: using routine (haematoxylin and eosin) and special stains.
(b) Immunofluorescence: antibodies tagged (labelled) with a fluorchrome are used to localize immunoreactants in the glomerulus.
(c) Electron microscopy: ultrastructural studies of the glomerulus are used to features like the position and location of immune complex, basement membrane reactions and epithelial cell changes.

GLOMERULAR DISEASES (See table 1)

A] **Nephrotic syndrome** includes a group of conditions characterized by increased basement membrane permeability, permitting the urinary loss of plasma proteins, particularly low-weight proteins such as albumin.

(1) **Classical manifestations**:
(a) Massive proteinuria is generally characterized by excretion of more than 4 grams of protein per day. Unlike disorders with greater disruption of the glomerular structure, proteinuria in the nephrotic syndrome is not accompanied by increased urinary red cells or white cells.
(b) Hypoalbuminemia results from proteinuria and is often marked by a serum concentration of less than 3 g/100 ML.
(c) Generalized edema results from decreased plasma colloid or oncotic pressure.
(d) Hyperlipidemia and hyperchomsterolemia are caused by increased hepatic lipoprotein synthesis.

(2) **Minimal change disease** (lipoid nephrosis) is seen most often in young children but can also occur in older children and adults. It is the prototype of the nephrotic syndrome.

TABLE 1: SUMMARY OF GLOMERULAR DISEASES

TYPES	MORPHOLOGIC FINDINGS
A] Disorders manifest by the nephrotic syndrome	
Minimal change disease (lipid nephrosis)	No visible basement membrane changes; fused epithelial foot process; lipid accumulation in renal tubular cells.
Focal segmental glomerulosclerosis	No visible basement membrane changes; segmental sclerosis of scattered juxtamedullary glomeurli.
Membranous glomerulonephritis	Basement membrane markedly thickened by intramembranous and epimembranous (subepithelial) immune complex deposits; granular immunofluorescence, "spike and dome" appearance.
Diabetic nephropathy	Basement membrane markedly thickened; diffuse or nodular mesangial accumulations of basement membrane-like material.
Renal amyloidosis	Amyloid protein identified by special stains (e.g. Congo Red) with birefringence under polarized light, or electron microscopy "criss-cross" fibrillary pattern.
Lupus nephropathy	Immune complex deposition in subendothelial location may manifest as membranous glomerulonephritis.
B] Disorders manifest by the nephritic syndrome	
Post-streptococcal glomerulonephritis rapidly progressive (crescentic) glomerulonephritis	Subepithelial electron-dense "humps"; lumpy-bumpy" immunofluorescence, crescents formation, antineutrophil cytoplasmic antibody (ANCA) – negative forms with immune complexes or antiglomerular basement membrane antibodies; ANCA-positive (pauci-immune) form with Wegener granulomatosis.
Goodpasture syndrome	Linear immunofluorescence antibody deposition caused by antiglomerular basement membrane antibodies.
Alport syndrome	Split basement membrane due to hereditary nephritis.
C] Other glomerular disorders	
IgA nephropathy (Berger disease)	Mesangial IgA deposits.
Membranoproliferative glomerulonephritis	Tram-track appearance; deposits of C3 and dense deposits in one variant.

(a) Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells) particularly in cells of proximal convoluted tubules.
(b) Light microscopy demonstrates normal-appearing glomeruli.
(c) Electron microscopy is normal except for the disappearance or fusing of epithelial foot processes.
(d) Most often, this condition responds well to corticosteroid therapy.

3] **Focal segmental glomerulosclerosis** is clinically similar to minimal change disease but occurs in somewhat older patients. It is characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution.
(a) Focal distribution is involvement of some, but not all of the glomeruli.
(b) Segmental distribution is involvement of only a part of the glomerulus.

4] **Membranous glomerulonephritis** is an immune complex disease of unknown etiology.
(a) This disease is a major primary cause of the nephrotic syndrome.
(b) Incidence is highest in teenagers and young adults.
(c) The diagnosis should be suspected when the nephrotic syndrome is accompanied by azoemia (increased concentrations of serum urea nitrogen and creatinine).
(d) Morphologic characteristics include greatly thickened capillary walls which are visible by light microscopy and visible by electron microscopy as a 5- to 10-fold thickening of the basement membrane.
(e) Ultrastructural findings include numerous electron-dense immune complexes in intramembranous and epimembranous (epithelial) locations within and on the basement membrane. This immune complex disease can be mimicked in an animal model resulting from multiple repeated injections of foreign protein.
(f) With special stains, a "spike and dome" appearance resulting from the extension of basement membrane between and around the immune deposits is seen; the spikes are basement membrane material and the domes are immune complex deposits.
(g) Granular deposits of immunoglobulin G (IgG) or C3 are apparent on immunofluorescence. Granular immunofluorescence is a general characteristic of immune complex disease.
(h) Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.
(i) It (membranous glomerulonephritis) is seen in 10% of patients with systemic lupus erythematosus (SLE) and other associations sometimes include hepatitis B, syphilis, or malaria infection; drugs, such as gold salts or penicillamine or malignancy.
(j) The disorder sometimes causes renal vein thrombosis, which was previously thought to be an etiologic factor.

5] **Diabetic nephropathy**

(a) Often, this disease is clinically manifested by the nephrotic syndrome.

(b) Electron microscopy demonstrates striking increase in thickness of the glomerular basement membrane. Thickening of vascular basement membranes observable by electron microscopy is one of the earliest morphologic changes in diabetes mellitus.

(c) An increase in mesangial matrix results in two characteristic morphologic patterns:

(1) Diffuse glomerulosclerosis is marked by a diffusely distributed increase in mesangial matrix.

(2) Nodular glomerulosclerosis is marked by nodular accumulations of mesangial matrix material (Kimmelstiel-Wilson nodules).

6] **Renal amyloidosis**

(a) This condition is another cause of the nephrotic syndrome.

(b) Predominantly subendothelial and mesangial amyloid deposits are characteristic.

(c) The amyloidosis can be identified by reactivity of amyloid with special stains (e.g. Congo Red, crystal violet, thioflavin T) and by birefringence under polarized light. It is also demonstrated by a characteristic criss-cross fibrillary pattern of amyloid by electron microscopy.

(d) Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumours such as multiple myeloma.

7] **Lupus nephropathy**

(a) This is the renal component of SLE; the severity of the renal lesion often determines the overall prognosis in patients with SLE. It is often manifest as the nephrotic syndrome but many cases also have major nephritic features.

The pathogenesis of all forms of glomerulonephritis in SLE involves deposition of DNA and anti DNA complexes within the glomeruli. This causes an inflammatory responses that may cause proliferation of the endothelial, mesangial and/or epithelial glomerular cells and in severe cases necrosis of the glomeruli.

The World Health Organization has divided SLE glomerular disease into five classes:

Class one: Normal by light, electron and immunofluorescence microscopyc. (This is seen in less than 5% of SLE patients).

Class two: Mesangial lupus glomerulonephritis is seen in 10 to 25% of cases and is associated with mild clinical symptoms and immune complex deposits in the mesangium.

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

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

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

B] **Nephritic syndrome** is characterized by inflammatory rupture of the glomerular capillaries, with resultant bleeding into the urinary space; proteinuria and edema may be present but usually are mild.

(1) **Clinical findings**:
   (a) Oliguria
   (b) Azotemia (which is elevation of blood urea nitrogen and creatinine levels due to decreased glomerular filtration rate/GFR).
   (c) Hypertension
   (d) Haematuria results from leakage of red cells directly from glomerular capillaries into the Bowman space. Many of the red cells are aggregated into the shape of the renal tubules and embedded in a proteinaceous matrix forming red cells casts that can be observed in the urine. The

(e) patient often reports having "smoky brown urine". Red cell casts can degenerate and become pigmented granular casts.

(2) **Posstreptococcal glomerulonephritis** (acute proliferative glomerulonephritis) is the prototype of the nephritic syndrome. It is immune complex disease with the antigen being of streptococcal origin.
   (a) This disorder most often follows or accompanies infection (tonsillitis, streptococcal impetigo, infected insect bites) with nephritogenic strains of group A B-hemolytic streptococci.
   (b) Complete recovery in almost all children and many adults follow. A very minority develop rapidly progressive glomerulonephritis.
   (c) Several laboratory abnormalities are characteristic, including urinary red cells and red cell casts, azotemia, decreased serum C3 and increased titers of anticationic proteinase as an evidence of recent streptococcal infection.
   (d) An intense inflammatory reaction involving almost all glomeruli in both kidneys result in:
      1. Innumerable punctuate hemorrhages on the surface of both kidneys.
      2. Enlarged, hypercellular, swollen, blood less glomeruli with proliferation of mesangial and endothelial cells and sometimes neutrophilic infiltration.
      3. Glomerular basement membrane of normal thickness and uniformity despite the extensive inflammatory changes.
      4. Characteristic electron-dense "humps" on the epithelial side of basement membrane with subepithelial localization.
      5. 'Lumps-bumpy" immunofluorescence (extremely coarse granular immunofluorescence for IgG or C3).

(3) **Rapidly progressive (crescentic) glomerulonephritis (RPGN).**
   (a) RPGN usually presents with the nephritic syndrome that progresses rapidly to renal failure within weeks or months. The disorder is histologically defined by the formation of crescents between the Bowman capsule and the glomerular tuft which result from deposition of fibrin in the Bowman space and from proliferation of parietal epithelial cells of the Bowman capsule. Cells of monocytic origin are often involved.
   (b) The etiology is poststreptococcal in approximately 50% of cases with immune complex deposition; other immune complex forms of RPGN include, among others, lupus nephropathy and IgA nephropathy.
   (c) Antiglomerular basement membrane antibodies (non streptococcal) are characteristic in approximately 10% of cases; these cases often present clinically as **Goodpasture syndrome.**

(d) RPGN can also be of the pauci-immune type. This mean that in these cases RPGN is without immune complex deposition or antiglomerular basement membrane antibodies. This third type of RPGN is associated with antineutrophilic cytoplasmic antibodies (ANCAs), in contrast to the immune complex or antiglomerular basement membrane forms of RPGN, which are ANCA-negative. The ANCA-negative forms of RPGN are designated type I when RPGN is of the antiglomerular basement membrane antibody type and type II when it is of the immune complex type. The ANCA-positive pauci-immune form of RPGN is designated type III.

(4) **Good pasture syndrome** (antiglomerula basement membrane disease).

(a) The cause is the formation of antibodies (antiglomerular basement membrane antibodies) which are directed against antigen in the glomerular and pulmonary alveolar basement membranes.

(b) Flourescent antibody studies for Igg demonstrate positive linear immunofluorescence.

(c) Clinical manifestations include:

1. Nephritic syndrome.
2. Pneumonitis with hemoptysis (hemorrhagic pneumonitis).
3. Peak incidence in men in their mid-20s.
4. RPGN crescentic morphology with linear immunofluorescence.
5. Alport syndrome.
   a. This disease is a hereditary nephritis associated with nerve deaflines and ocular disorders, such as lens dislocation and cataracts.
   b. Clinical characteristics include the nephritic syndrome, often progressing to end stage renal disease by 30 years of age.
   c. The causes is mutation in the gene for the 5 chain of type IV collagen.
   d. Irregular glomerula basement membrane thickening with foci of splitting of the lamina densa are seen by electron microscopy.

C] **Other glomerular diseases**

(1) **IgA nephropathy** (Berger disease) is an extreme common entity defined by deposition of IgA in the mesangium.

(a) Most frequently, the disease is characterized by benign recurrent hematuria in children, usually following an infection, lasting 12 days, and usually of minimal clinical significance.

(b) Focal glomerulonephritis may be the presenting feature.

(c) IgA nephropathy can be a component of the Henoch-Schonlein vasculitis disease.

(2) Membranoproliferative glomerulonephritis

(a) Clinical characteristics include slow progression to chronic renal disease.

(b) Histological characteristics include both basement membrane thickening and cellular proliferation.

(c) The disease is marked by reduplication of the glomerular basement membrane into two layers due to expansion of the mesangial matrix into the glomerular capillary loops; this results in a characteristic tram-track appearance best seen with silver stains.

(d) Disease occurs in two forms:

1. **Type I is an immune complex nephritis** associated with an unknown antigen. It has a striking tram-track appearance.
2. **Type II (dense deposit disease)** has a tram-track appearance that is not as apparent as that of type I.
   a. Irregular electron-dense material deposited within the glomerular basement membrane is characteristic. C3 is demonstrable adjacent to but not within the dense deposits and serum C3 is characteristically markedly reduced.
   b. The possible cause is an IgG autoantibody (C3 nephritic factor) with specificity for the C3 convertase of the alternate complement pathway.

RENAL FAILURE

A] General considerations

(1) Renal failure can be acute or chronic and can result from any of the glomerular or tubulointerstitial lesions diseased in the preceeding sections.

(2) Azotemia (elevated urea and creatinine) of renal origin is always an associated feature.

(3) In advanced stages, renal failure results in uremia; the term uremia denotes the biochemical and clinical syndrome characteristic of symptomatic renal disease.

B] Major clinical characteristics of uremia

(1) Azotemia (elevated urea and creatinine)

(2) Acidosis resulting from the accumulation of sulfates, phosphates and organic acids.

(3) Hyperkalemia.

(4) Abnormal control of fluid volume.

(a) An early characteristic is the inability to concentrate urine, a later manifestation is the inability to dilute urine.

(b) Sodium and water retention can result in congestive heart failure.

(5) Hypocalcemia caused by failure to synthesize the active form of Vitamin D, hypocalcemia can lead to renal osteodystrophy.
(6) Anemia caused by decreased secretion of erythropoietin.
(7) Hypertesnion caused by hyperproduction of rennin.

C] **Other clinical characteristics of uremia** include anorexia, nausea and vomiting; neurologic disorders, ranging from diminished mental function to convulsions and come; bleeding caused by disordered platelet function; accumulation in the skin of urochrome and other urinary pigments and fibrinous pericarditis.

NON-RENAL CAUSES OF AZOTEMIA

A] **Pre-renal azotemia.** This condition results from decreased renal blood flow due to blood loss, decreased cardiac output, systemic hypovolemia (as in massive burns), or peripheral pooling of blood due to marked vasodilatation (as in grame-negative sepsis). It is characterized by increased tubular reabsorption of sodium and water, resulting in oliguria, concentrated urine and decreased urinary sodium excretion.

(1) Measurement of urinary sodium is diagnostically significant in the delineation of the oliguria of shock.
  (a) Oliguria may be caused by decreased renal blood flow with consequent decreased glomerular filtration rate, in which case tubular reabsorption of sodium is maximaly increased and urinary sodium is low.
  (b) Oliguria may be a manifestation of acute tubular necrosis, in which case tubular reabsorption is greatly impaired and urinary sodium is not decreased.

(2) The BUN: creatinine ratio is characteristically greater than 15 due to a combination of both decreased glomerular filtration and increased tubular reabsorption of urea.

B] **Post-renal azotemia** results from mechanical blockage (obstruction) of urinary flow.

- BUN is an abbreviation of Blood Urea Nitrogen.

LECTURE FIVE: PATHOLOGY OF TUMOURS

OF THE KIDNEY AND URINARY TRACT

BY

DR. AMMAR C. AL-RIKABI, PROFESSOR M.O. ALSOHAIBANI

AND DR. HALA KASSOUF KFOURY

DEPARTMENT OF PATHOLOGY

KING KHALID UNIVERSITY HOSPITAL

A. Benign tumors of the Kidney

1. Adenoma

a. This tumor is most often small and asymptomatic. It is derived from renal tubules.

b. It may be a precursor lesion to renal carcinoma.

2. Angiomyolipoma

a. It is often associated with the tuberous sclerosis syndrome.

B. Malignant tumors of the Kidney

1. Renal cell carcinoma

a. This cancer is the most common renal malignancy.
b. It is more common in men, occurs most often from 50-70 years of age and has a higher incidence in cigarette smokers.
c. In some instances, it is associated with gene deletions in chromosome 3; renal cell carcinoma can also be associated with von Hippel-Lindau disease, which is caused by alterations in a gene localized to chromosome 3.
d. The carcinoma originates in renal tubules. Most often, it arises in one of the renal poles, frequently the upper pole. (This is why it was called hypernephroma).
e. Frequently the tumor invades renal veins or the vena cava and can extend up the vena cava. Early hematogenous dissemination may occur.
f. Histologic characteristics include polygonal clear cells, sometimes with vestigial (primitive) tubule formation.
g. Presenting features may include the triad of flank pain, palpable mass and hematuria. Hematuria is the most frequent presenting abnormality. Renal cell carcinoma may be manifest clinically by any of the following additional findings:
    1. Fever
    2. Seconadry polycythemia (results from erythropoietin production)
    3. Ectopic production of various hormones or hormone-like substances (e.g., ACTH, prolactin, gonadotropins, and renin.) Paraneoplastic parathyroid-like hormone can also cause hypercalcemia.

2. Wilms tumor (nephroblastoma)

a. This cancer is the most common renal malignancy of early childhood.
b. Incidence peaks in children 2-4 years of age.
c. Wilms tumor originates from primitive metanephric tissue.
d. Histologic characteristics are varied with immature stroma, primitive tubules and glomeruli, and mesenchymal elements such as fibrous connective tissue, cartilage bone, and rarely striated muscle.
e. Most often, the presenting feature is a palpable flank mass (often huge).
f. Wilms tumor is often associated with deletions of the short arm of chromosome 11. The WT-1 and WT-2 genes localized to this chromosome are cancer suppressor genes.
g. The disease can be part of the AGR (or WAGR) complex (Wilms tumor, Aniridia (absence of the choroid layer in the eye), Genitourinary malformations, and mental-motor Retardation). This set of anomalies is associated with deletion of the **WT-1 tumor suppressor gene** and other nearby genes.
h. It can also be associated with hemihypertrophy (gross asymmetry due to unilateral muscular hypertrophy), macroglossia, organomegaly, neonatal hypoglycemia and various embryonal tumors. This set of anomalies along with Wilms tumor is collectively referred to as the Beckwith-Wiedemann syndrome and is associated with deletion of the WT-2 gene.

C. Transitional cell carcinoma

1. This cancer is **the most common tumor of the urinary collecting system** and can occur in renal calyces, pelvis, ureter, or bladder. It is often multifocal in origin.
2. In the renal pelvis, transitional cell carcinoma has been asscociated with phenacetin abuse.
3. This carcinoma is likely to recur after removal.
4. Most often, the presenting feature is **hematuria.**
5. There is a tendency to spread by local extension to surrounding tissues.
6. Associated toxic exposures may sometimes be involved, including the following:
   a. Industrial exposure to benzidine or β-naphthylamine which is an aniline dye.
   b. Cigarette smoking.
   c. Long-term treatment with cyclophosphamide.

D. Squamous cell carcinoma constitutes a minority of urinary tract malignancies.

1. This cancer may result from chronic inflammatory processes, such as chronuic bacterial infection or *Schistosoma haematobium* infection.
2. It can also be associated with renal calculi.

Malignant tumors of the bladder

By far the commonest malignant tumour of the bladder in adults is the urothelial-delivered transitional cell carcinoma (TCC).

However, in the paediatric age group a common malignant tumour of the bladder is the rhabdomyosarcoma

Transitional cell carcinoma-in-situ is believed by many authorities to precede the development of TCC in some patients (as evidenced by the presence of TCCis in the majority of cases of TCC), TCCis is characterised by flat and thickened or gently undulating full-thickness dysplastic urothelium (nuclear pleomorphism, abnormal mitoses and apoptotic figures are seen). Often appearing as a red patch, the disease may be multifocal within the bladder.

TCC accounts for about 5% of all malignancies in adults in the U.K. Most patients are over 50 years of age and there are definite risk factors for development of TCC, the most important of which are mentioned in Box I. The tumour may present with haematuria, frequency or urgency. TCC may be multifocal within the bladder or the urinary tract.

As in other parts of the urothelium-lined urinary tract, the tumour can have a very varied appearance, both macroscopically (fronded and seaweed-like to solid) and microscopically (well differentiated and papillary to poorly differentiated and widely muscle-invasive). The grading and staging system for bladder TCC is shown in Box II, together with prognosis.

Numerous cytogenetic and molecular alterations have been found in TCC, including monosomy or deletions of the short (p) or long (q) arm of chromosome 9 and deletions of 17p (which involves the p53 gene).

Squamous metaplasia of the urothelium can occur in a variety of circumstances, for example as a response to bladder stones, indwelling catheters and infection by *Schistosoma* (schistosomiasis is endemic in countries such as Egypt). Under these

circumstances, squamous cell carcinoma of the bladder can develop. Often this tumour has invaded the bladder wall at time of presentation.

Box I. Confirmed or suspected risk factors for transitional cell carcinoma

Smoking	Increases risk up to five times
Analgesics	Mainly associated with renal pelvis transitional cell carcinoma, but also bladder tumours.
Occupation	Workers in aniline dye, rubber and chemical industries due to exposure to β-naphthylanine (which in the liver is converted to a carcinogen that must be activated in the bladder). These workers need regular bladder checks.
Cyclophosphamide	Can cause bladder cancer in the long term (although used for cancer treatment)
Schistosomiasis	Causes chronic inflammation and metaplasia (squamous) of the bladder mucosa (leading to squamous cell carcinoma)
Chronic infections/inflammation	Some authorities believe that any chronic inflammatory process may predispose to cancer

Box II. Grading and staging of bladder transitional cell carcinoma (TNM)

GRADE	DEFINITION
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated/undifferentiated
STAGE	**DEFINITION**
Tis	In situ carcinoma
Ta	Non-invasive, papillary tumour
T1	Tumour invades subepithelial connecticve tissue
T2	Tumour invades muscularis propia
T3	Tumour invades beyond muscularis propia
T4	Tumour invades prostate, uterus, vagina or pelvic wall/abdominal wall
N1	Single lymph node metastasis (≤ 2 cm)
N2	Single metastases (>2 cm) or multiple metastases (≤ 5 cm)
N3	Multiple metastases (> 5 cm)

- The prognosis of TCC of the bladder depends largely on the grade and stage of tumour but most patients with metastatic bladder TCC die within five years of diagnosis.

LECTURE SIX: PATHOLOGY OF RENAL TRANSPLANTATION

BY

DR. AMMAR C. AL-RIKABI, PROFESSOR M.O. ALSOHAIBANI

AND DR. HALA KASSOUF KFOURY

DEPARTMENT OF PATHOLOGY

KING KHALID UNIVERSITY HOSPITAL

The major barrier to transplantation of organs from one individual to another of the same species (called allografts) is immunological **rejection** of the transplanted tissue.

The word allograft refers to transplantation of organs within the same species while xenografts refer to transplantation between different species.

Rejection is a complex phenomenon involving both cell and antibody mediated hypersensitivity reactions directed against the histocom-patibility molecules on the foreign graft.

The key to successful transplantation has been the development of therapies (drugs) that prevent or minimize rejection.

Mechanisms of graft (renal allograft) rejection:

Donor class I and class II major histocompatibility antigens on antigen-presenting cells in the graft (donor) are recognized by host (recipient) CD8+ and cytotoxic or suppressor T cells and CD4 + herper T cells respectively. CD4 + cells proliferate and produce cytokines (like interferon gamma γ) which induce tissue damage to renal blood vessels and tubules by a local hypersensitivity reaction.

In addition, graft antigen are taken by the antigen presenting cells in the host (recipient). These APC's activate CD4 + cells which damage the graft (renal transplant) by a local delayed hypersensitivity reaction and stimulate B lymphocytes to produce antibodies.

Renal allograft transplant rejections are divided into:

A] **Hyperacute rejection**: occurs within minutes to a few hours after transplantation in a presensitized host and is typically recognized by the surgeon just after the vascular anastomosis is completed. Grossly, the kidney becomes cyanotic. Microscopically, there is widespread acute arteritis and arteriolitis, vessel thrombosis and ischemic necrosis.

B] **Acute rejection**: acute rejection may occur within days to weeks of transplantation and sometimes after months or years later. This rejection is divided into:

(1) Cellular rejection: interstitial oedema and mononuclear (lymphocytic) infiltration of the renal interstitium.

(2) Humoral rejection: associated with vasculitis.

C] **Chronic rejection**: patients usually presents late after transplantation (months to years) with a progressive rise in serum creatinine levels. Chronic rejection is dominated by vascular changes, interstitial fibrosis and loss of renal parenchyma. Chronic rejection does not respond to standard immunosuppression treatment.