Kidney and Urinary Tract Pathology

12

CONGENITAL

I. HORSESHOE KIDNEY

A. Conjoined kidneys usually connected at the lower pole (Fig. 12.1); most common congenital renal anomaly

B. Kidney is abnormally located in the lower abdomen; horseshoe kidney gets caught on the inferior mesenteric artery root during its ascent from the pelvis to the abdomen.

II. RENAL AGENESIS

A. Absent kidney formation; may be unilateral or bilateral

B. Unilateral agenesis leads to hypertrophy of the existing kidney; hyperfiltration increases risk of renal failure later in life.

C. Bilateral agenesis leads to oligohydramnios with lung hypoplasia, flat face with low set ears, and developmental defects of the extremities (Potter sequence, Fig. 12.2); incompatible with life

III. DYSPLASTIC KIDNEY

A. Noninherited, congenital malformation of the renal parenchyma characterized by cysts and abnormal tissue (e.g., cartilage, Fig. 12.3)

B. Usually unilateral; when bilateral, must be distinguished from inherited polycystic kidney disease

IV. POLYCYSTIC KIDNEY DISEASE (PKD)

A. Inherited defect leading to bilateral enlarged kidneys with cysts in the renal cortex and medulla (Fig. 12.4)

B. Autosomal recessive form presents in infants as worsening renal failure and hypertension; newborns may present with Potter sequence.

1. Associated with congenital hepatic fibrosis (leads to portal hypertension) and hepatic cysts

C. Autosomal dominant form presents in young adults as hypertension (due to increased renin), hematuria, and worsening renal failure.

1. Due to mutation in the *APKD1* or *APKD2* gene; cysts develop over time.
2. Associated with berry aneurysm, hepatic cysts, and mitral valve prolapse

V. MEDULLARY CYSTIC KIDNEY DISEASE

A. Inherited (autosomal dominant) defect leading to cysts in the medullary collecting ducts

B. Parenchymal fibrosis results in shrunken kidneys and worsening renal failure.

ACUTE RENAL FAILURE (ARF)

I. BASIC PRINCIPLES

A. Acute, severe decrease in renal function (develops within days)

B. Hallmark is azotemia (increased BUN and creatinine [Cr]), often with oliguria.

C. Divided into prerenal, postrenal, and intrarenal azotemia based on etiology

II. PRERENAL AZOTEMIA

A. Due to decreased blood flow to kidneys (e.g., cardiac failure); common cause of ARF
B. Decreased blood flow results in ↓ GFR, azotemia, and oliguria.
C. Reabsorption of fluid and BUN ensues (serum BUN:Cr ratio > 15); tubular function remains intact (fractional excretion of sodium [FENa] < 1% and urine osmolality [osm] > 500 mOsm/kg).

III. POSTRENAL AZOTEMIA

A. Due to obstruction of urinary tract downstream from the kidney (e.g., ureters)
B. Decreased outflow results in ↓GFR, azotemia, and oliguria.
C. During early stage of obstruction, increased tubular pressure "forces" BUN into the blood (serum BUN:Cr ratio> 15); tubular function remains intact (FENa < 1% and urine osm > 500 mOsm/kg).
D. With long-standing obstruction, tubular damage ensues, resulting in decreased reabsorption of BUN (serum BUN:Cr ratio< 15), decreased reabsorption of sodium (FENa > 2%), and inability to concentrate urine (urine osm < 500 mOsm/kg).

IV. ACUTE TUBULAR NECROSIS

A. Injury and necrosis of tubular epithelial cells (Fig. 12.5); most common cause of acute renal failure (intrarenal azotemia)
B. Necrotic cells plug tubules; obstruction decreases GFR.
   1. Brown, granular casts are seen in the urine.
C. Dysfunctional tubular epithelium results in decreased reabsorption of BUN (serum BUN:Cr ratio < 15), decreased reabsorption of sodium (FENa > 2%), and inability to concentrate urine (urine osm < 500 mOsm/kg).
D. Etiology may be ischemic or nephrotoxic.
   1. Ischemia - Decreased blood supply results in necrosis of tubules.
      i. Often preceded by prerenal azotemia
      ii. Proximal tubule and medullary segment of the thick ascending limb are particularly susceptible to ischemic damage.
   2. Nephrotoxic - Toxic agents result in necrosis of tubules.
      i. Proximal tubule is particularly susceptible.
      ii. Causes include aminoglycosides (most common), heavy metals (e.g., lead), myoglobinuria (e.g., from crush injury to muscle), ethylene glycol (associated with oxalate crystals in urine), radiocontrast dye, and urate (e.g., tumor lysis syndrome).
      iii. Hydration and allopurinol are used prior to initiation of chemotherapy to decrease risk of urate-induced ATN.

Fig. 12.1 Horseshoe kidney. (Courtesy of humpath,com)

Fig. 12.2 Potter sequence. (Courtesy of humpath. Allya com)

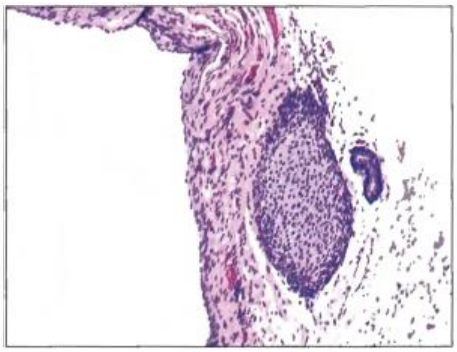


Fig. 12.3 Dysplastlc kidney. (Courtesy of Husain, MD)

E. Clinical features
   1. Oliguria with brown, granular casts
   2. Elevated BUN and creatinine
   3. Hyperkalemia (due to decreased renal excretion) with metabolic acidosis

F. Reversible, but often requires supportive dialysis since electrolyte imbalances can be fatal
   1. Oliguria can persist for 2-3 weeks before recovery; tubular cells (stable cells) take time to reenter the cell cycle and regenerate.

V. ACUTE INTERSTITIAL NEPHRITIS

A. Drug-induced hypersensitivity involving the interstitium and tubules (Fig. 12.6); results in acute renal failure (intrarenal azotemia)
B. Causes include NSAIDs, penicillin, and diuretics.
C. Presents as oliguria, fever, and rash days to weeks after starting a drug; eosinophils may be seen in urine.
D. Resolves with cessation of drug
E. May progress to renal papillary necrosis

VI. RENAL PAPILLARY NECROSIS

A. Necrosis of renal papillae
B. Presents with gross hematuria and flank pain
C. Causes include
   1. Chronic analgesic abuse (e.g., long-term phenacetin or aspirin use)
   2. Diabetes mellitus
   3. Sickle cell trait or disease
   4. Severe acute pyelonephritis

NEPHROTIC SYNDROME

I. BASIC PRINCIPLES

A. Glomerular disorders characterized by proteinuria (> 3.5 g/day) resulting in
   1. Hypoalbuminemia - pitting edema
   2. Hypogammaglobulinemia - increased risk of infection
   3. Hypercoagulable state - due to loss of antithrombin III
   4. Hyperlipidemia and hypercholesterolemia - may result in fatty casts in urine

II. MINIMAL CHANGE DISEASE (MCD)

A. Most common cause of nephrotic syndrome in children
B. Usually idiopathic; may be associated with Hodgkin lymphoma

Fig. 12,4 Polycystlc kidney disease. (Courtesy of Jamie Steinmetz, MD)

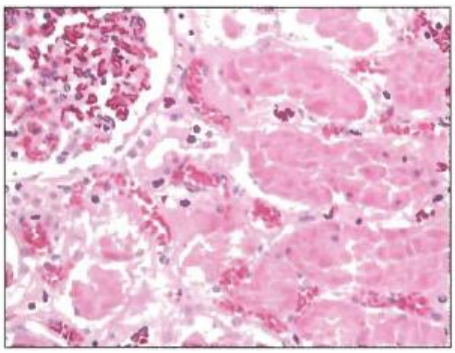


Fig. 12.5 Acute tubular necrosis.

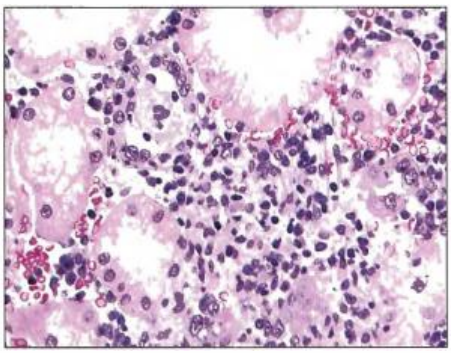


Fig. 12.6 Acute Interstitial nephritis.

C. Normal glomeruli on H&E stain (Fig. 12.7A); lipid may be seen in proximal tubule cells.
D. Effacement of foot processes on electron microscopy (EM, Fig. 12.7B)
E. No immune complex deposits; negative immunofluorescence (IF)
F. Selective proteinuria (loss of albumin, but not immunoglobulin)
G. Excellent response to steroids (damage is mediated by cytokines from T cells)

III. FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

A. Most common cause of nephrotic syndrome in Hispanics and African Americans
B. Usually idiopathic; may be associated with HIV, heroin use, and sickle cell disease
C. Focal (some glomeruli) and segmental (involving only part of the glomerulus) sclerosis on H&E stain (Fig. 12.8)
D. Effacement of foot processes on EM
E. No immune complex deposits; negative IF
F. Poor response to steroids; progresses to chronic renal failure

IV. MEMBRANOUS NEPHROPATHY

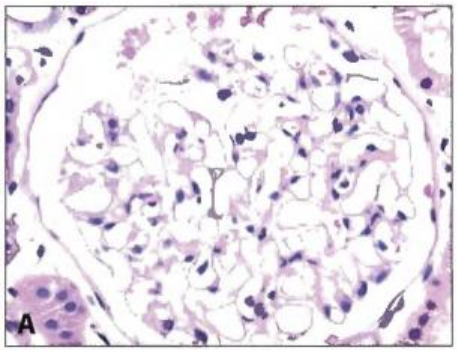
A. Most common cause of nephrotic syndrome in Caucasian adults
B. Usually idiopathic; may be associated with hepatitis B or C, solid tumors, SLE, or drugs (e.g., NSAIDs and penicillamine)
C. Thick glomerular basement membrane on H&E (Fig. 12.9A)
D. Due to immune complex deposition (granular IF, Fig. 12.9B); subepithelial deposits with 'spike and dome' appearance on EM (Fig. 12.9C)
E. Poor response to steroids; progresses to chronic renal failure

V. MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

A. Thick glomerular basement membrane on H&E, often with 'tram-track' appearance
B. Due to immune complex deposition (granular IF)
C. Divided into two types based on location of deposits
   1. Type I - subendothelial (Fig. 12.10); associated with HBV and HCV
   2. Type II (dense deposit disease) - intramembranous; associated with C3 nephritic factor (autoantibody that stabilizes C3 convertase, leading to overactivation of complement, inflammation, and low levels of circulating C3)
D. Poor response to steroids; progresses to chronic renal failure

VI. DIABETES MELLITUS

A. High serum glucose leads to nonenzymatic glycosylation of the vascular basement membrane resulting in hyaline arteriolosclerosis.



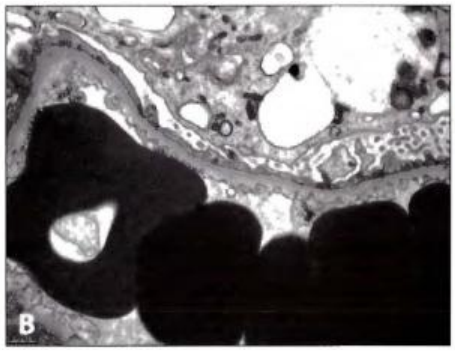


Fig. 12.7 Minimal change disease. **A,** Normal glomerulus. **B,** Effacement of foot processes on EM. (Courtesy of Tony Chang, MD)

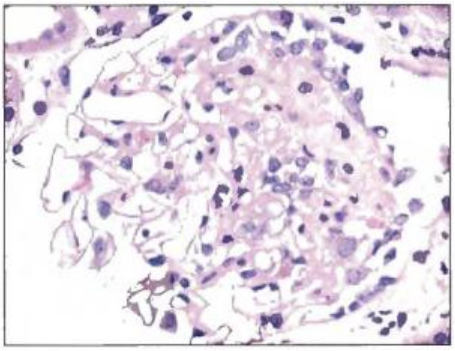


Fig. 12.8 Focal segmental glomerulosclerosis.

B. Glomerular efferent arteriole is more affected than the afferent arteriole, leading to high glomerular filtration pressure.
   1. Hyperfiltration injury leads to microalbuminuria.
C. Eventually progresses to nephrotic syndrome
   1. Characterized by sclerosis of the mesangium with formation of Kimmelstiel-Wilson nodules (Fig. 12.11)
D. ACE inhibitors slow progression of hyperfiltration-induced damage.

VII. SYSTEMIC AMYLOIDOSIS

A. Kidney is the most commonly involved organ in systemic amyloidosis.
B. Amyloid deposits in the mesangium, resulting in nephrotic syndrome.
C. Characterized by apple-green birefringence under polarized light after staining with Congo red

NEPHRITIC SYNDROME

I. BASIC PRINCIPLES

A. Glomerular disorders characterized by glomerular inflammation and bleeding
   1. Limited proteinuria (< 3.5 g/day)
   2. Oliguria and azotemia
   3. Salt retention with periorbital edema and hypertension
   4. RBC casts and dysmorphic RBCs in urine
B. Biopsy reveals hypercellular, inflamed glomeruli (Fig. 12.12).

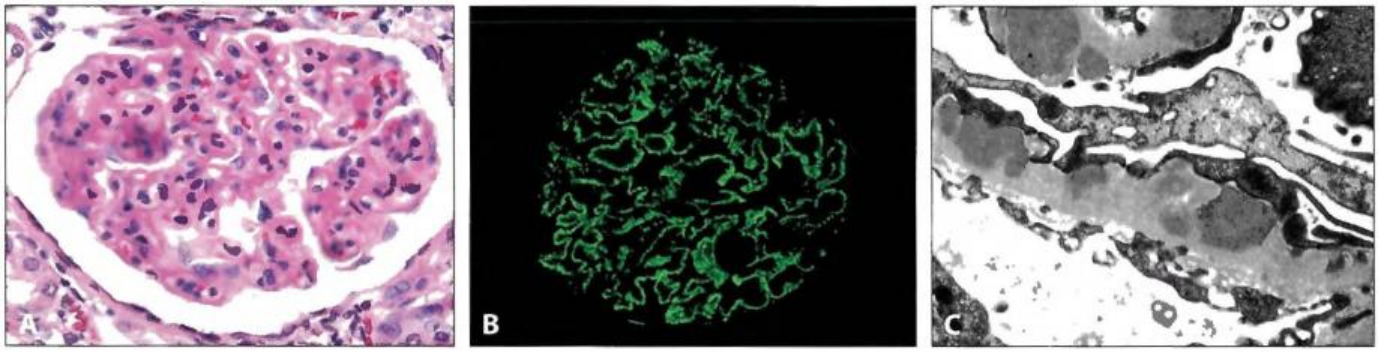


Fig. 12.9 Membranous nephropathy. **A.** Thick glomerular basement membranes. **B.** Granular IF. **C.** Subepithelial deposits with 'spike and dome' appearance. (Courtesy of Tony Chang, MD)

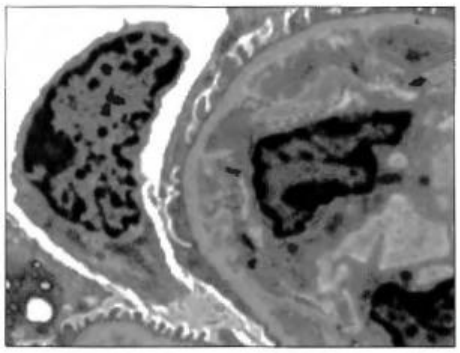


Fig. 12.10 Subendothelial deposits, membranoproliferative glomerulonephritis (type I). (Courtesy of Tony Chang, MD)

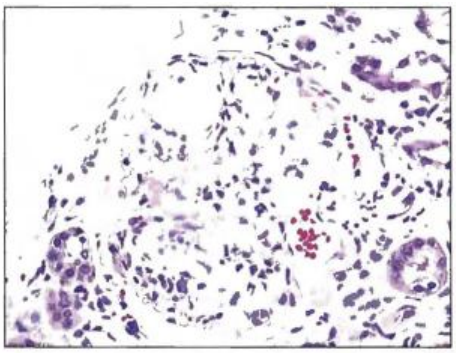


Fig. 12.11 Kimmelstiel-Wilson nodules, diabetic nephropathy.

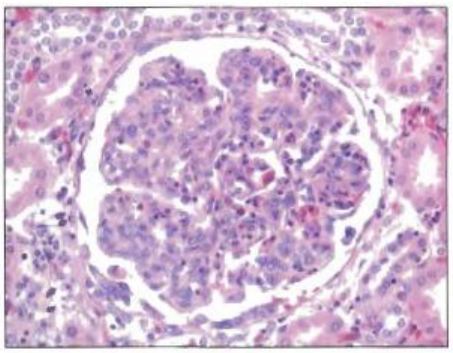


Fig. 12.12 Hypercellular, inflamed glomerulus, nephritic syndrome.

1. Immune-complex deposition activates complement; C5a attracts neutrophils, which mediate damage.

II. POSTSTREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

A. Nephritic syndrome that arises after group A β-hemolytic streptococcal infection of the skin (impetigo) or pharynx
   1. Occurs with nephritogenic strains
   2. May occur after infection with nonstreptococcal organisms as well
B. Presents 2-3 weeks after infection as hematuria (cola-colored urine), oliguria, hypertension, and periorbital edema
   1. Usually seen in children, but may occur in adults
C. Hypercellular, inflamed glomeruli on H&E
D. Mediated by immune complex deposition (granular IF); subepithelial 'humps' on EM (Fig. 12.13)
E. Treatment is supportive.
   1. Children rarely (1%) progress to renal failure.
   2. Some adults (25%) develop rapidly progressive glomerulonephritis (RPGN).

III. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

A. Nephritic syndrome that progresses to renal failure in weeks to months

Table 12.1: Immunofluorescence Findings in Rapidly Progressive Glomerulonephritis

IMMUNOFLUORESCENCE PATTERN	DISEASE	COMMENTS
Linear (anti-basement membrane antibody, Fig. 12.15)	Goodpasture syndrome	Antibody against collagen in glomerular and alveolar basement membranes; presents as hematuria and hemoptysis, classically in young, adult males
Granular (immune complex deposition)	PSGN (most common) or diffuse proliferative glomerulonephritis	Diffuse proliferative glomerulonephritis is due to diffuse antigen-antibody complex deposition, usually sub-endothelial; most common type of renal disease in SLE
Negative IF (pauci-immune)	Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome	Wegener granulomatosis is associated with c-ANCA; microscopic polyangiitis and Churg-Strauss are associated with p-ANCA. Granulomatous inflammation, eosinophilia, and asthma distinguish Churg-Strauss from microscopic polyangiitis.

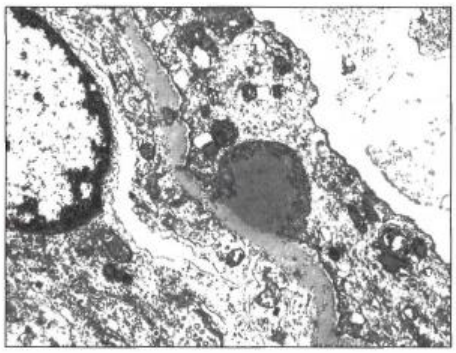


Fig. 12.13 Subepithellal 'humps,' PSGN. (Courtesy of Tony Chang, MD)

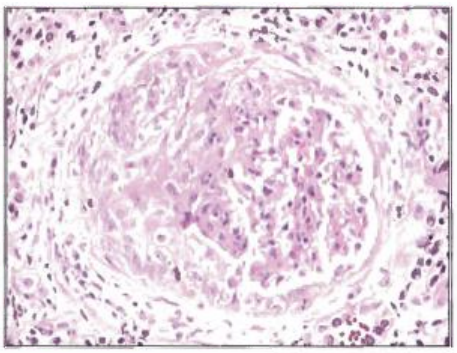


Fig. 12.14 Crescent formation, rapidly progressive glomerulonephrltls.

B. Characterized by crescents in Bowman space (of glomeruli) on H&E stain; crescents are comprised of fibrin and macrophages (Fig. 12.14).
C. Clinical picture and IF help resolve etiology (Table 12.1).

IV. IgA NEPHROPATHY (BERGER DISEASE)

A. IgA immune complex deposition in mesangium of glomeruli; most common nephropathy worldwide
B. Presents during childhood as episodic gross or microscopic hematuria with RBC casts, usually following mucosal infections (e.g., gastroenteritis)
   1. IgA production is increased during infection.
C. IgA immune complex deposition in the mesangium is seen on IF (Fig. 12.16).
D. May slowly progress to renal failure

V. ALPORT SYNDROME

A. Inherited defect in type IV collagen; most commonly X-linked
B. Results in thinning and splitting of the glomerular basement membrane
C. Presents as isolated hematuria, sensory hearing loss, and ocular disturbances

URINARY TRACT INFECTION

I. BASIC PRINCIPLES

A. Infection of urethra, bladder, or kidney
B. Most commonly arises due to ascending infection; increased incidence in females
C. Risk factors include sexual intercourse, urinary stasis, and catheters.

II. CYSTITIS

A. Infection of the bladder
B. Presents as dysuria, urinary frequency, urgency, and suprapubic pain; systemic signs (e.g., fever) are usually absent.
C. Laboratory findings
   1. Urinalysis - cloudy urine with > 10 WBCs/high power field (hpf)
   2. Dipstick - Positive leukocyte esterase (due to pyuria) and nitrites (bacteria convert nitrates to nitrites)
   3. Culture - greater than 100,000 colony forming units (gold standard)
D. Etiology
   1. *E coli* (80%)
   2. *Staphylococcus saprophyticus* - increased incidence in young, sexually active women (but *E coli* is still more common in this population)
   3. *Klebsiella pneumoniae*
   4. *Proteus mirabilis* - alkaline urine with ammonia scent

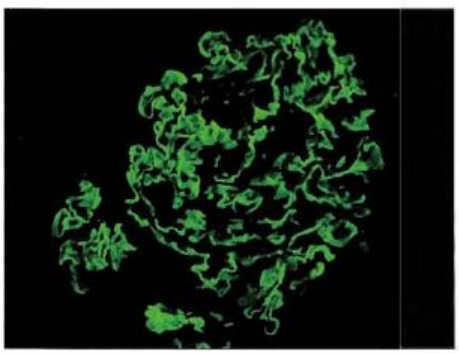


Fig. 12.15 Linear IF, Goodpasture syndrome. (Courtesy ofTony Chang, MD)

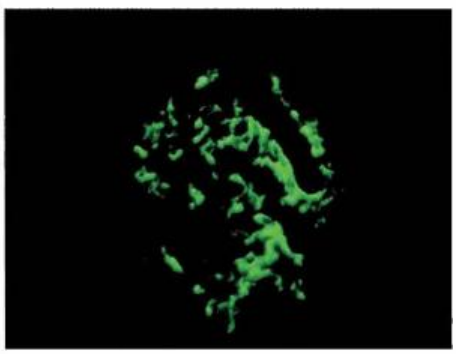


Fig. 12.16 IgA nephropathy. (Courtesy of Tony Chang, MD)

5. *Enterococcus faecalis*

E. Sterile pyuria is the presence of pyuria (> 10 WBCs/hpf and leukocyte esterase) with a negative urine culture.
   1. Suggests urethritis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* (dominant presenting sign of urethritis is dysuria)

III. PYELONEPHRITIS

A. Infection of the kidney
   1. Usually due to ascending infection; increased risk with vesicoureteral reflux

B. Presents with fever, flank pain, WBC casts, and leukocytosis in addition to symptoms of cystitis

C. Most common pathogens are
   1. *E coli* (90%)
   2. *Enterococcus faecalis*
   3. *Klebsiella* species

IV. CHRONIC PYELONEPHRITIS

A. Interstitial fibrosis and atrophy of tubules due to multiple bouts of acute pyelonephritis

B. Due to vesicoureteral reflux (children) or obstruction (e.g., BPH or cervical carcinoma)

C. Leads to cortical scarring with blunted calyces; scarring at upper and lower poles is characteristic of vesicoureteral reflux.

D. Atrophic tubules containing eosinophilic proteinaceous material resemble thyroid follicles ('thyroidization' of the kidney, Fig. 12.17); waxy casts may be seen in urine.

NEPHROLITHIASIS

I. BASIC PRINCIPLES

A. Precipitation of a urinary solute as a stone (Table 12.2)

B. Risk factors include high concentration of solute in the urinary filtrate and low urine volume.

C. Presents as colicky pain with hematuria and unilateral flank tenderness
   1. Stone is usually passed within hours; if not, surgical intervention may be required.

CHRONIC RENAL FAILURE

I. BASIC PRINCIPLES

A. End-stage kidney failure
   1. May result from glomerular, tubular, inflammatory, or vascular insults
   2. Most common causes are diabetes mellitus, hypertension, and glomerular disease.

B. Clinical features
   1. Uremia - Increased nitrogenous waste products in blood (azotemia) result in nausea, anorexia, pericarditis, platelet dysfunction, encephalopathy with asterixis, and deposition of urea crystals in skin.
   2. Salt and water retention with resultant hypertension
   3. Hyperkalemia with metabolic acidosis
   4. Anemia due to decreased erythropoietin production by renal peritubular interstitial cells

5. Hypocalcemia due to decreased 1-alpha-hydroxylation of vitamin D by proximal renal tubule cells and hyperphosphatemia
6. Renal osteodystrophy due to secondary hyperparathyroidism, osteomalacia, and osteoporosis

C. Treatment involves dialysis or renal transplant.
1. Cysts often develop within shrunken end-stage kidneys during dialysis, increasing risk for renal cell carcinoma.

RENAL NEOPLASIA

I. ANGIOMYOLIPOMA

A. Hamartoma comprised of blood vessels, smooth muscle, and adipose tissue
B. Increased frequency in tuberous sclerosis

II. RENAL CELL CARCINOMA

A. Malignant epithelial tumor arising from kidney tubules

Table 12.2: Features of Nephrolithiasis

COMPOSITION	FREQUENCY	CAUSES	TREATMENT
Calcium oxalate and/ or calcium phosphate	Most common type; usually seen in adults	Most common cause is idiopathic hypercalciuria; hypercalcemia and its related causes must be excluded. Also seen with Crohn disease	Treatment is hydrochlorothiazide (calcium-sparing diuretic).
Ammonium magnesium phosphate	Second most common type	Most common cause is infection with urease-positive organisms (e.g., *Proteus vulgaris* or *Klebsiella);* alkaline urine leads to formation of stone.	Classically, results in staghorn calculi in renal calyces (Fig. 12.18), which act as a nidus for urinary tract infections. Treatment involves surgical removal of stone (due to size) and eradication of pathogen (to prevent recurrence).
Uric acid	Third most common stone (5%); radiolucent (as opposed to other types of stones which are radiopaque)	Risk factors include hot, arid climates, low urine volume, and acidic pH. Most common stone seen in patients with gout; hyperuricemia (e.g., in leukemia or myeloproliferative disorders) increases risk.	Treatment involves hydration and alkalinization of urine (potassium bicarbonate); allopurinol is also administered in patients with gout.
Cystine	Rare cause of nephrolithiasis; most commonly seen in children	Associated with cystinuria (a genetic defect of tubules that results in decreased reabsorption of cysteine)	May form staghorn calculi; treatment involves hydration and alkalinization of urine.

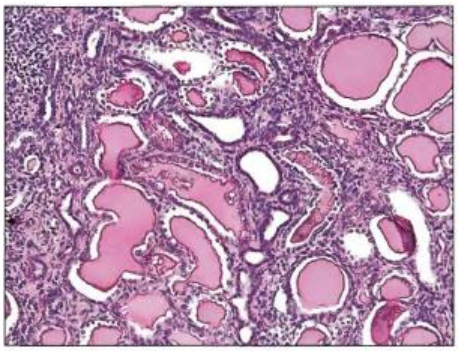


Fig. 12.17 'Thyroidization' of kidney, chronic pyelonephritis.

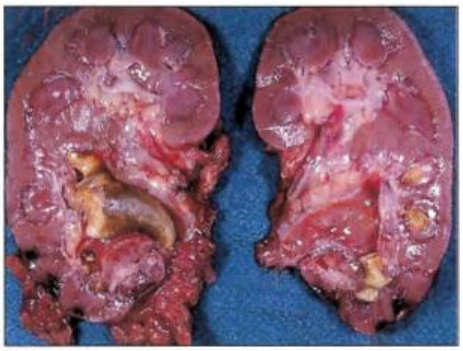


Fig. 12.18 Ammonium magnesium phosphate stone. (Courtesy of web pathology.com)

B. Presents with classic triad of hematuria, palpable mass, and flank pain
   1. All three symptoms rarely occur together; hematuria is the most common symptom.
   2. Fever, weight loss, or paraneoplastic syndrome (e.g., EPO, renin, PTHrP, or ACTH) may also be present.
   3. Rarely may present with left-sided varicocele
      i. Involvement of the left renal vein by carcinoma blocks drainage of the left spermatic vein leading to varicocele.
      ii. Right spermatic vein drains directly into the IVC; hence, right-sided varicocele is not seen.

C. Gross exam reveals a yellow mass (Fig. 12.19A); microscopically, the most common variant exhibits clear cytoplasm (clear cell type, Fig. 12.19B).

D. Pathogenesis involves loss of *VHL* (3p) tumor suppressor gene, which leads to increased IGF-1 (promotes growth) and increased HIF transcription factor (increases VEGF and PDGF).

E. Tumors may be hereditary or sporadic.
   1. Sporadic tumors classically arise in adult males (average age is 60 years) as a single tumor in the upper pole of the kidney; major risk factor for sporadic tumors is cigarette smoke.
   2. Hereditary tumors arise in younger adults and are often bilateral.
      i. Von Hippel-Lindau disease is an autosomal dominant disorder associated with inactivation of the *VHL* gene leading to increased risk for hemangioblastoma of the cerebellum and renal cell carcinoma.

F. Staging
   1. T-based on size and involvement of the renal vein (occurs commonly and increases risk of hematogenous spread to the lungs and bone)
   2. N- spread to retroperitoneal lymph nodes

III. WILMS TUMOR

A. Malignant kidney tumor comprised of blastema (immature kidney mesenchyme), primitive glomeruli and tubules, and stromal cells (Fig. 12.20)
   1. Most common malignant renal tumor in children; average age is 3 years.

B. Presents as a large, unilateral flank mass with hematuria and hypertension (due to renin secretion)

C. Most cases (90%) are sporadic; syndromic tumors may be seen with
   1. **WAGR** syndrome - **W**ilms tumor, **A**niridia, **G**enital abnormalities, and mental and motor **R**etardation; associated with *deletion* of *WT1* tumor suppressor gene (located at 11p13)
   2. Denys-Drash syndrome - Wilms tumor, progressive renal (glomerular) disease, and male pseudohermaphroditism; associated with *mutations* of *WT1*

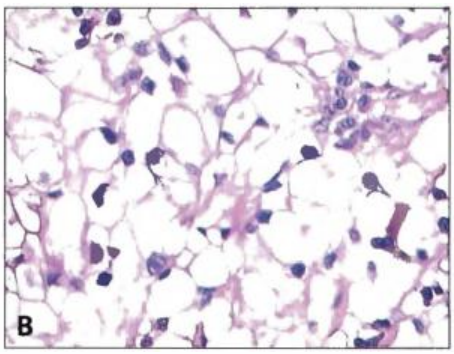


Fig. 12.19 Renal cell carcinoma. A, Gross appearance. B, Microscopic appearance.

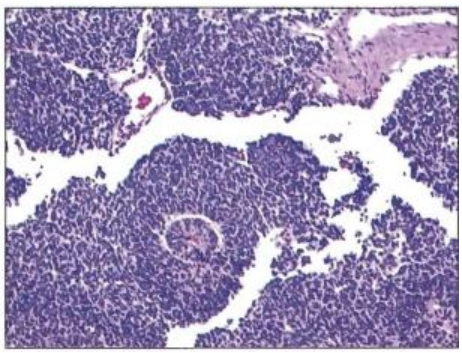


Fig. 12.20 Wilms tumor.

3. Beckwith-Wiedemann syndrome - Wilms tumor, neonatal hypoglycemia, muscular hemihypertrophy, and organomegaly (including tongue); associated with mutations in WT2 gene cluster (imprinted genes at 11p15.5), particularly IGF-2

LOWER URINARY TRACT CARCINOMA

I. UROTHELIAL (TRANSITIONAL CELL) CARCINOMA

A. Malignant tumor arising from the urothelial lining of the renal pelvis, ureter, bladder, or urethra
   1. Most common type of lower urinary tract cancer; usually arises in the bladder
B. Major risk factor is cigarette smoke; additional risk factors are naphthylamine, azo dyes, and long-term cyclophosphamide or phenacetin use.
C. Generally seen in older adults; classically presents with painless hematuria
D. Arises via two distinct pathways (Fig. 12.21)
   1. Flat - develops as a high-grade flat tumor and then invades; associated with early p53 mutations
   2. Papillary - develops as a low-grade papillary tumor that progresses to a high-grade papillary tumor and then invades; not associated with early p53 mutations
E. Tumors are often multifocal and recur ("field defect").

II. SQUAMOUS CELL CARCINOMA

A. Malignant proliferation of squamous cells, usually involving the bladder
B. Arises in a background of squamous metaplasia (normal bladder surface is not lined by squamous epithelium)
C. Risk factors include chronic cystitis (older woman), *Schistosoma haematobium* infection (Egyptian male), and long-standing nephrolithiasis.

III. ADENOCARCINOMA

A. Malignant proliferation of glands, usually involving bladder
B. Arises from a urachal remnant (tumor develops at the dome of the bladder), cystitis glandularis, or exstrophy (congenital failure to form the caudal portion of the anterior abdominal and bladder walls)

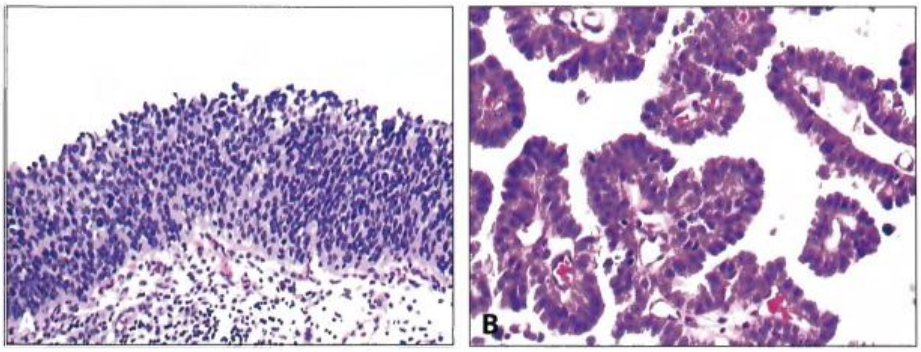


Fig. 12.21 Urothellal carcinoma. **A.** Flat. **B.** Papillary.