DISEASES OF THE URINARY TRACT 2

EVALS 6

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Trans Group: 5A, 6A

OUTLINE

I. Renal Vascular Diseases
- A. Nephrosclerosis
  - 1. Benign Nephrosclerosis
  - 2. Malignant Nephrosclerosis
- B. Renal Artery Stenosis
  - 1. Fibromuscular Dysplasia
- C. Thrombotic Microangiopathies
  - 1. Typical Hemolytic Uremic Syndrome (HUS)
  - 2. Atypical Hemolytic Uremic Syndrome (Atypical HUS)
  - 3. Thrombotic Thrombocytopenic Purpura (TTP)

II. Renal Congenital Diseases
- A. Renal Agenesis
- B. Renal Hypoplasia
- C. Ectopic Kidneys
- D. Horseshoe Kidneys

III. Renal Cystic Diseases
- Pathogenesis Of Hereditary Cystic Diseases
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- B. Autosomal Dominant Polycystic (ADPKD)
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  - Mutations
  - Pathogenesis
  - Cyst And Anomalies In Other Organs
- C. Autosomal Recessive Polycystic (ARPKD)
- D. Cystic Diseases Of The Medulla

IV. Obstructive Uropathy
- A. Causes Of Obstruction
- B. Hydronephrosis

V. Urolithiasis
- A. Types Of Stones
  - 1. Calcium Oxalate Stones (70%)
  - 2. Magnesium Ammonium Phosphate Stones (5-10%)
  - 3. Uric Acid Stones (5-10%)
  - 4. Cystine Stones (1-2%)

VI. Tumors Of The Kidney
- A. Benign Tumors
  - 1. Renal Papillary Adenoma
  - 2. Renal Fibroma
  - 3. Angiomyolipoma
  - 4. Renal Oncocytoma
- B. Malignant Tumors
  - 1. Renal Cell Carcinoma
  - 2. Urothelial Carcinoma

Diseases Of Lower Urinary Tract

I. Ureters
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  - 1. Double Ureters
  - 2. Ureteropelvic Junction Obstruction
  - 3. Diverticula
  - 4. Vesicoureteral Reflux
- B. Tumors And Tumor-Like Lesion
  - 1. Fibroepithelial Polyp
  - 2. Leiomyoma
  - 3. Urothelial Carcinoma
- C. Obstructive Lesion
  - 1. Sclerosing Retroperitoneal Fibrosis

II. Urinary Bladder
- A. Congenital Anomalies
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- B. Inflammation (Cystitis)
  - 1. Acute Cystitis
  - 2. Chronic Cystitis
  - 3. Main Clinical Manifestations
  - 4. Cystitis - Special Variants
- C. Metaplastic Lesion
  - 1. Cystitis Glandularis And Cystitis Cystica
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- D. Neoplasms
  - 1. Urothelial (Transitional Cell) Tumors
  - 2. Papillary Bladder Tumor
  - 3. Other Types
  - 4. Clinical Manifestations And Course
  - 5. Mesenchymal Tumors
- E. Urinary Bladder: Obstruction
  - 1. Chronic Bladder Obstruction

III. Urethra
- A. Urethritis
- B. Urethral Caruncle
- C. Urethral Carcinoma

IV. Summary

REFERENCES:

Dr. De La Fuente— PPT & Recorded Lecture

I. RENAL VASCULAR DISEASES

Nephrosclerosis	• Benign Nephrosclerosis • Malignant Nephrosclerosis
Renal Artery Stenosis	• Fibromuscular Dysplasia
Thrombotic Microangiopathies	• Typical Hemolytic Uremic Syndrome (HUS) • Atypical Hemolytic Uremic Syndrome (Atypical HUS) • Thrombotic Thrombocytopenic Purpura (TTP)

A. NEPHROSCLEROSIS

- Refers to the renal pathology associated with sclerosis of the renal arterioles and small arteries
- Strongly associated with hypertension which can be both a cause and a consequence of nephrosclerosis

1. BENIGN NEPHROSCLEROSIS

Medial and intimal thickening	Protein extravasation & increased deposition of basement membrane matrix that leads to vascular narrowing
Hyaline deposition	

PATHOGENESIS	
1.	Vascular narrowing
2.	Focal parenchymal ischemia
3.	Patchy ischemic atrophy
4.	Glomerulosclerosis and chronic tubulointerstitial injury
5.	Reduction in the functional renal mass

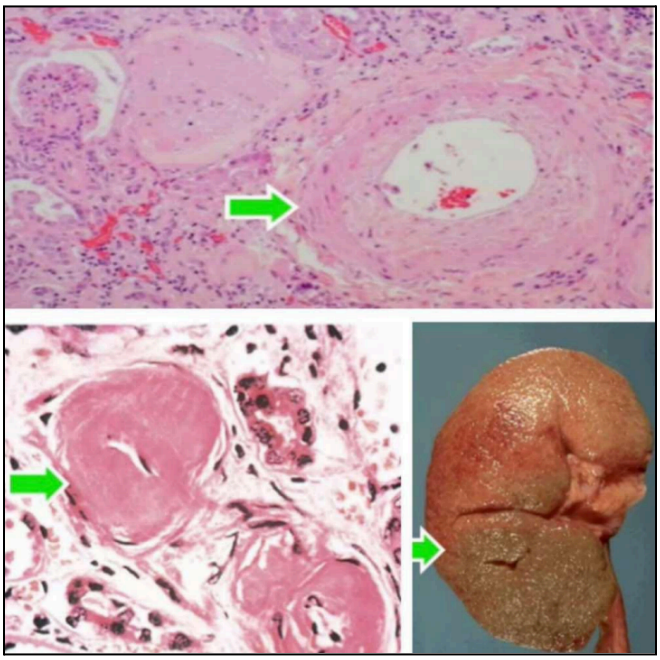


Figure 1. Benign nephrosclerosis exhibiting medial and intimal thickening (top), and vascular narrowing (lower left)

2. MALIGNANT NEPHROSCLEROSIS

- Renal lesions that are associated with malignant hypertension which results to vascular damage and focal death

G	• Characterized by focal small hemorrhages obscuring the corticomedullary junction • "Flea-bitten" kidney
M	Characterized by fibrinoid necrosis and onion skin appearance typical of hyperplastic arteriolosclerosis

PATHOGENESIS	
1.	Vascular damage due to long-standing hypertension, arteritis, coagulopathy (among others)
2.	Increased permeability to fibrinogen & other plasma proteins
3.	Endothelial injury, focal cell death, platelet deposition
4.	Appearance of fibrinoid necrosis in arterioles and small arteries, thrombosis, hyperplastic arteriolosclerosis
5.	Renal ischemia

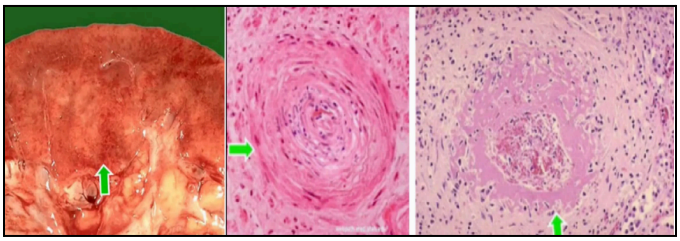


Figure 2. Gross image of a flea-bitten kidney (L); and histologic images depicting onion skin (C), and fibrinoid necrosis (R)

B. RENAL ARTERY STENOSIS

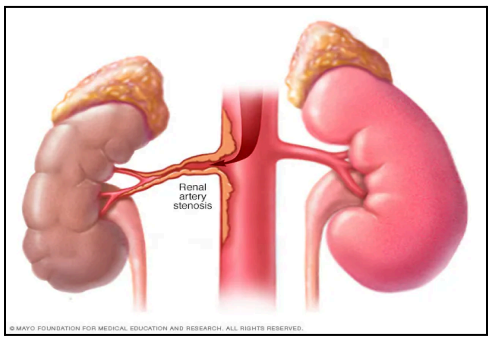


Figure 3. Renal artery stenosis

CAUSES	**Atheromatous plaque** (70%, most common), M>F
	Fibromuscular dysplasia (hyperplasia of the intima, media, or adventitia), F>M
GROSS	• Small or contracted kidneys • Diffuse ischemic atrophy (ischemic kidney)

PATHOGENESIS	
1.	Triggers juxtaglomerular (JG) apparatus to secrete renin (increased production of renin)
2.	Release of Angiotensin II
3.	Vasoconstriction
4.	Hypertension
Note: Whatever the cause, it leads to vasoconstriction and hypertension.	

1. FIBROMUSCULAR DYSPLASIA

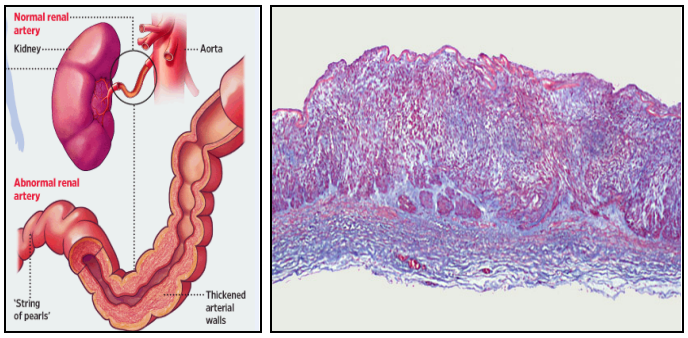


Figure 4. Fibromuscular Dysplasia

- A non-atherosclerotic, non-inflammatory disease of the blood vessels that causes abnormal growth within the wall of an artery
- Has been found in nearly every arterial bed in the body
  - Most common arteries affected: **Renal and carotid arteries**
- Characterized by fibrous thickening of the media
  - Also can be characterized by intimal or adventitial hyperplasia
- More commonly found in women, and appears on the 3rd - 4th decade of life

C. THROMBOTIC MICROANGIOPATHIES

- Group of diseases that are caused by diverse insults that lead to the excessive activation of platelets, which deposit as thrombi in capillaries and arterioles
- Consumption of platelets leads to **thrombocytopenia**
  - Causes microvascular occlusion that leads to ischemia and eventually organ dysfunction
  - Thrombi creates flow abnormalities that destroy the red cells.
- In other words, causing the following:
  - Thrombosis in capillaries and arterioles
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
  - Renal failure in some

1. PATHOGENESIS

- Involves two essential factors:
  - **ENDOTHELIAL INJURY & ACTIVATION**
    - Primary cause in hemolytic uremic syndrome (HUS) and atypical HUS
    - Leads to platelet activation and aggregation
    - Decreases prostacyclin (PGI2) and nitric oxide- will result to vasoconstriction and tissue hypoperfusion
  - **PLATELET ACTIVATION & AGGREGATION**
    - Gives rise to thrombosis and tissue hypoperfusion
    - Inciting event in TTP → vascular obstruction, vasoconstriction → ischemia

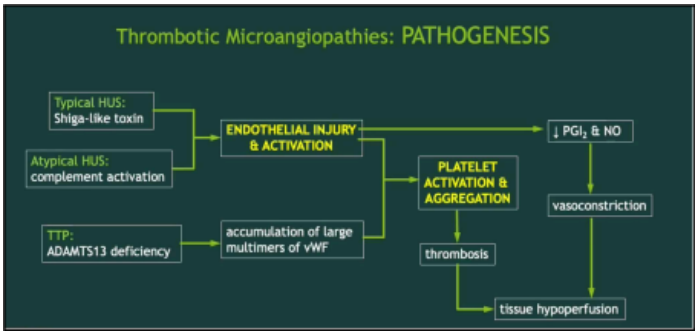


Figure 5. Pathogenesis of thrombotic microangiopathies

1. TYPICAL HEMOLYTIC UREMIC SYNDROME (HUS)

- Epidemic; classic; diarrhea-positive
- Shiga-like toxin
- Also known as epidemic intake of food/water contaminated by bacteria with shiga-like toxin (usually E.coli) → endothelial injury and activation
- Highest risk: Children & Older Adults (Note that it may occur at any age)
- Caused by Shiga-like toxin from E.coli (US) or S.dysentriae (Asia & Africa)
- Prodrome of **watery diarrhea** followed by bleeding (and renal) manifestations including that of hematuria with:
  - Severe oliguria, microangiopathic hemolytic anemia, thrombocytopenia, hematemesis, and melena
- If the renal failure is managed properly with dialysis, most patients recover normal renal function in a matter of weeks; thus it has a good prognosis
- Toxin injures endothelial cells → leukocyte adhesion molecules, endothelin; nitric oxide → platelet activation vasoconstriction

2. ATYPICAL HEMOLYTIC UREMIC SYNDROME (ATYPICAL HUS)

- Non-epidemic; diarrhea-negative
- Complement activation
- Genetic mutations or acquired antibodies that lead to aberrations of the complement regulatory mechanisms → endothelial injury and activation (Endothelial injury due to various causes usually also presents as Atypical HUS)
- Usually seen in children & adults **(No diarrhea)**
- Characterized by a sudden onset of fatigue, drowsiness, and vomiting
- Presence of a **Triad of Microangiopathic Hemolytic Anemia (MAHA), Thrombocytopenia, and Renal Impairment**
  - Seen secondary to certain conditions such as the Antiphospholipid syndrome (APAS), postpartum period, vascular disease, chemotherapy, immunosuppressant therapy and irradiation
- **Poor prognosis** - End Stage Renal Disease (ESRD) occurs in 50% of cases

3. THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- ADAMTS13 Deficiency → Accumulation of large multimers of vWf → Platelet activation & aggregation → Thrombosis → Tissue hypoperfusion (eventually)
- Seen in adults
- **CNS** > Renal Manifestation
- Multiple organs are often involved
- Classic signs: **Fever, thrombocytopenia, MAHA, renal impairment, and neurological abnormalities**
- Plasma exchange provides treatment
- May be autoimmune (autoantibodies), drug-induced or genetic
- **MORPHOLOGY**
    - Thrombi in glomerular capillaries
    - Endothelial swelling
    - Mesangiolysis

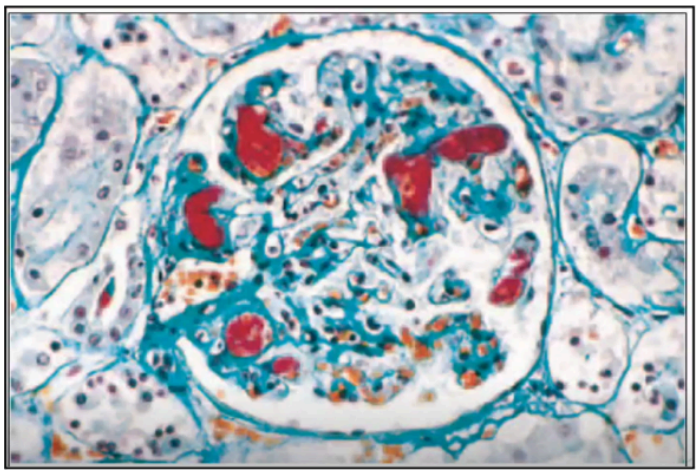


Figure 6. Platelet-fibrin thrombi (in red) in the glomerular capillaries

2. MORPHOLOGY

- The morphologic findings of HUS and TTP are indistinguishable and vary mainly in chronicity rather than cause
- A chronic disease is more common in patients with atypical HUS

ACUTE	CHRONIC
Patchy or diffuse cortical necrosis	Scarred cortex
Subcapsular petechiae	Thickening of the glomerular capillary walls with splitting (“tram-track”)
Thrombus occluding glomerular capillaries, interlobular arteries and arterioles	Arteries and arterioles : “onion-skinning”; fibrinoid necrosiS
Mesangiolysis	Areas of ischemic infarction

PART 1 SUMMARY

- **Nephrosclerosis** is characterized by varying degrees of glomerulosclerosis, interstitial fibrosis and tubular atrophy, arteriosclerosis, and arteriosclerosis.
- **Luminal narrowing of the renal arteries and arterioles** causes patchy ischemic atrophy, glomerulosclerosis and chronic tubulo-interstitial injury.
- **Renal artery stenosis** is caused by atheromatous plaque (more common) and less commonly, fibromuscular dysplasia. The stenosis activates the renin-angiotensin system giving rise to hypertension.
- **Thrombotic microangiopathy** is characterized by thrombosis in capillaries and arterioles, red cell hemolysis (microangiopathic hemolytic anemia). tissue ischemia, organ dysfunction, thrombocytopenia.
- In **typical HUS**, Shiga-like toxin produced most commonly by E. coli strain O157:H7, is responsible for endothelial injury and activation followed by platelet activation and thrombosis.
- In most cases of atypical HUS, aberrant activation of complement due to inherited mutations or acquired autoantibodies is responsible for the endothelial injury.
- In **TTP**, deficiencies of ADAMTS13, a negative regulator of Von Willebrand factor (vWF), permits the formation of abnormally large multimers of vWF that are capable of activating platelets.

II. RENAL CONGENITAL DISEASES

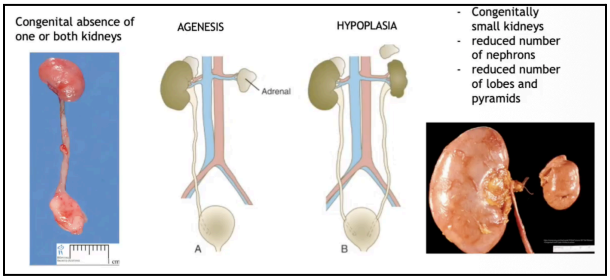


Figure 7. Renal Agenesis and Hypoplasia

A. RENAL AGENESIS

- May be bilateral or unilateral

BILATERAL	UNILATERAL
Not compatible with life	The viable kidney undergoes **hypertrophy** and **glomerular change** → ends in **chronic kidney disease**

B. RENAL HYPOPLASIA

- Failure of the kidneys to develop into the normal size → **congenitally small kidneys**
- The number of lobes, pyramids, and nephrons are decreased
- May be bilateral but is **more often unilateral**

Professor's Notes:

- It is important to differentiate a hypoplastic kidney from a kidney that has grown smaller in size because of scarring due to other diseases.

C. ECTOPIC KIDNEYS

- The normal development of the kidneys involves the movement upward from a much lower location.
  - Their transit can be arrested at any point in between.
- They are usually normal or slightly small in size but otherwise are not remarkable.
- The abnormal position may result in **kinking** or **tortuosity of the ureters → obstruction and predisposition to urinary tract infections**

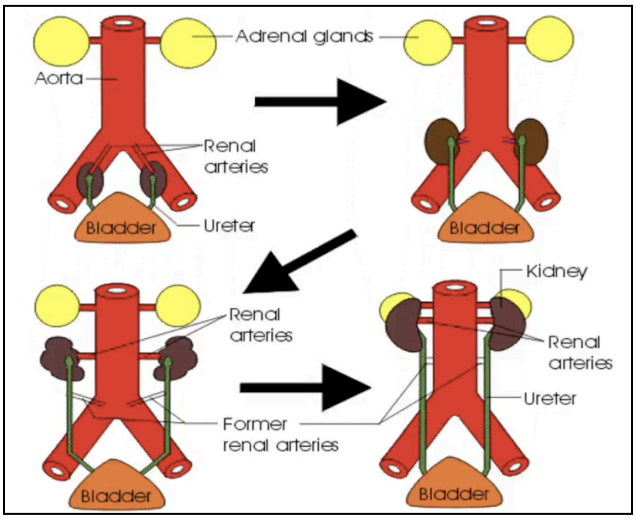


Figure 8. Ectopic Kidneys

D. HORSESHOE KIDNEYS

- An anomaly that is more common than the others
- Involves the **fusion** of the upper poles of the kidney (10%) or lower poles of the kidney (90%)

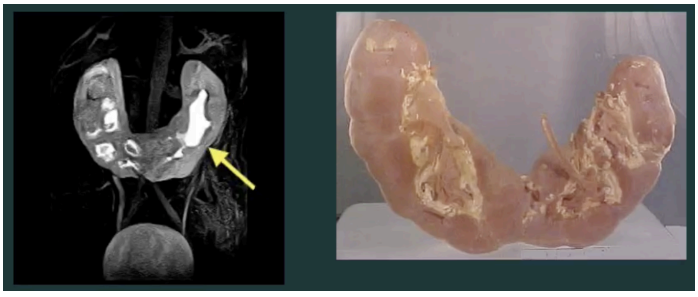


Figure 9. Horseshoe Kidneys

III. RENAL CYSTIC DISEASES

CAUSES	
1	Hereditary or Genetic
2	Developmental but non-hereditary
3	Acquired

CLINICAL SIGNIFICANCE	
1	Commonly occur and present as diagnostic problems
2	Some are major causes of renal failure
3	Confused with malignancy

CYSTIC DISEASES OF THE KIDNEY	
1	Multicystic Renal Dysplasia
2	Autosomal Dominant Polycystic Kidney Disease* (ADPKD)
3	Autosomal Recessive Polycystic Kidney Disease* (ARPKD)
4	Medullary Sponge Kidney
5	Nephronophthisis Medullary Cystic Disease Complex
6	Dialysis-Associated Cystic Disease
7	Simple Cysts

BATCH 2027 TRANS:

- **ADPKD**, **ARPKD**, and the **familial variant of the nephronophthisis** are hereditary or genetic.
  - The rest are developmental or acquired.
- **Medullary Sponge Kidneys** and **Nephronophthisis** are cystic diseases of the renal medulla

PATHOGENESIS OF HEREDITARY CYSTIC DISEASES

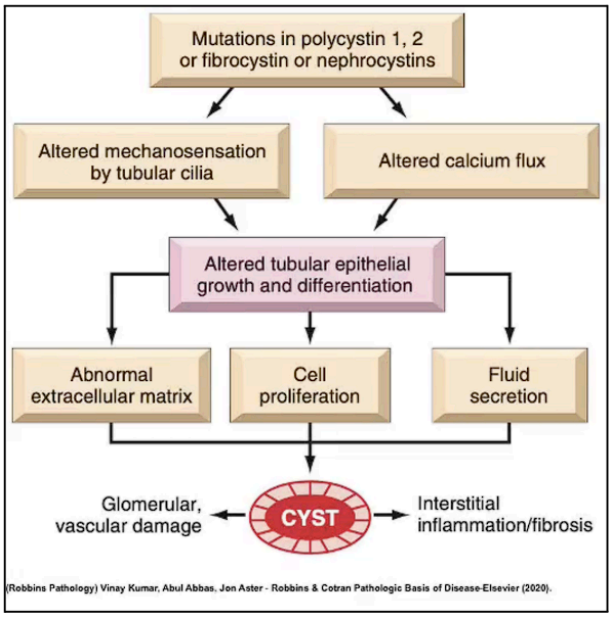


Figure 10. Currently favored Hypothesis on the Pathogenesis of Hereditary Cystic Diseases

- **Mutations in Polycystic 1 and 2** – in **Autosomal Dominant Polycystic Kidney Disease**.
- **Mutations in Fibrocystin** – occur in **Autosomal Recessive Kidney Disease**
- **Mutations in Nephrocystin** – familial variant of the nephronophthisis.

DISORDER	GENE	PROTEIN PRODUCTS AFFECTED
ADPKD	PKD1 PKD2	Polycystin 1 Polycystin 2
ARPKD	PKHD1	Fibrocystin
Nephronophthisis (Familial)	NPHP1 to NPHP11	Nephrocystins

- These mutations cause defects during the epithelial growth and differentiation resulting in the formation of cysts.
- These changes are accompanied by abnormal cell proliferation, abnormal matrix production, and abnormal secretion from the lining epithelial cells.

A. MULTICYSTIC RENAL DYSPLASIA

- A developmental disorder that is due to an abnormality in metanephric differentiation.
- Characterized by the replacement of the renal parenchyma by multiple cysts and nonfunctioning dysplastic tissue.
- Unilateral or bilateral.
- The kidneys are enlarged, irregular, and multicystic.
- In the undifferentiated mesenchyme separating the multiple cysts, **cartilage** and **immature collecting ducts** may be found.
  - **Multiple cysts** are lined by flattened epithelium.
- Normal nephrons are present.

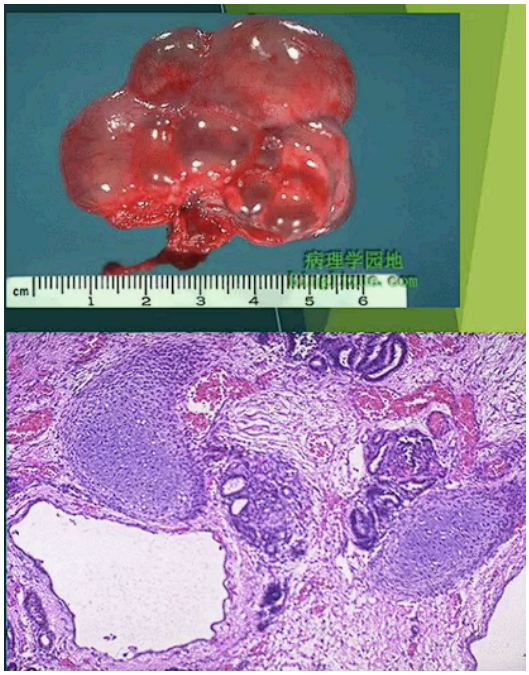


Figure 11. Multicystic Renal Dysplasia

B. AUTOSOMAL DOMINANT POLYCYSTIC (ADPKD)

- Diagnosed during adulthood usually presenting with:
  - Hematuria
  - Proteinuria
  - Progress to chronic kidney disease
- The cysts initially usually involve a minority of the nephrons
  - So renal function is **retained until about the 4th to the 5th decade of life**.

MORPHOLOGY

- Bilateral; adults
- Enlarged kidneys made up of cystic cortical surfaces.
  - Openings that can be observed containing various cysts filling up the entire renal parenchyma.
- Functioning nephrons dispersed between cysts.

MUTATIONS

- **PKD1 (polycystin-1)**
  - More common; Presents with earlier onset of renal failure.
- **PKD2 (polycystin-2)**

PATHOGENESIS

- Polycystin-1 and polycystin-2 regulate intracellular Ca2+ in response to fluid flow
- Disruption in polycystin function → changes in intracellular Ca2+ level → changes in cellular proliferation, basal levels of apoptosis, interactions with the ECM, secretory function of the epithelium
- END RESULT: Increase in number of cells due to abnormal proliferation Increase fluid secretion from lining epithelial cells → progressive cystic enlargement

CYST AND ANOMALIES IN OTHER ORGANS

- Liver, spleen, and pancreas
- Intracranial berry aneurysm
- Mitral valve prolapse

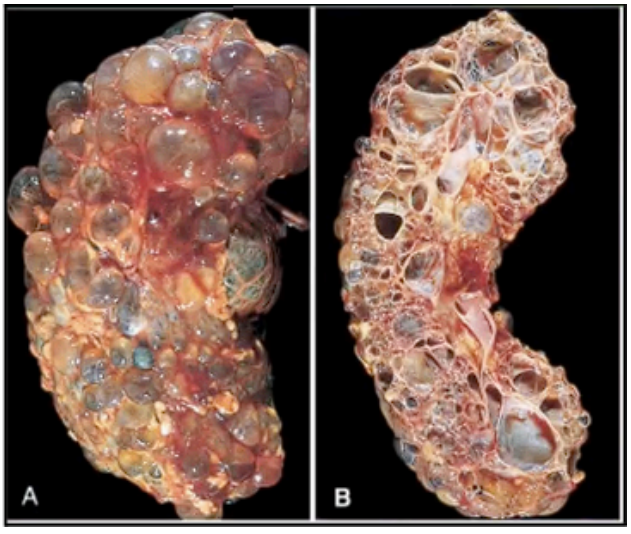


Figure 12. Autosomal Dominant Polycystic Kidney Disease

C. AUTOSOMAL RECESSIVE POLYCYSTIC (ARPKD)

- Diagnosed during Infancy and Childhood
- Mutation in **PKHD1 (fibrocystin)**
- Enlarged kidneys
  - Smooth external appearance
  - Numerous small cysts on cut sections (like a sponge)
- Dilation of collecting tubules
- Associated with **hepatic cysts** and **congenital hepatic fibrosis**

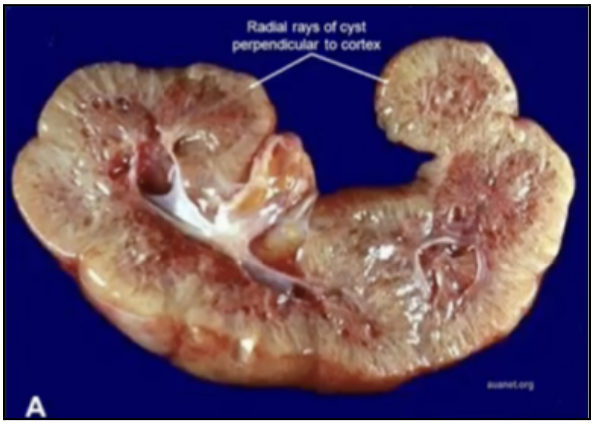


Figure 13. Autosomal Recessive Polycystic Kidney Disease

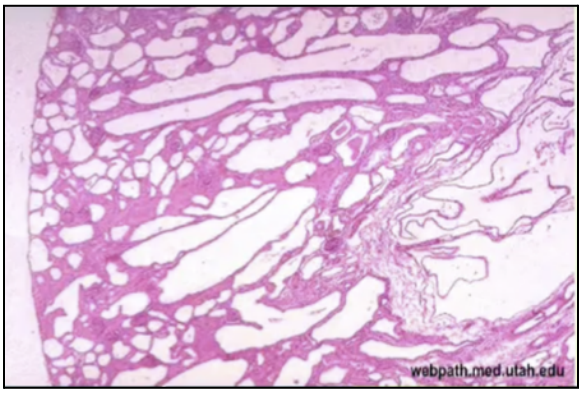


Figure 14. Autosomal Recessive Polycystic Kidney Disease

D. CYSTIC DISEASES OF THE MEDULLA

MEDULLARY SPONGE KIDNEYS

- Multiple cystic dilatation of collecting ducts in the medulla

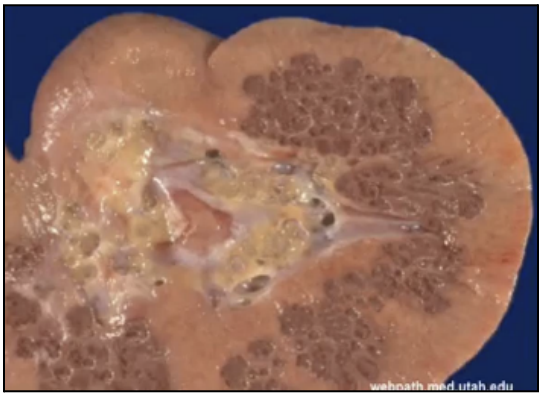


Figure 15. Medullary Sponge Kidneys

BATCH 2027 TRANS:

- Diagnosed in adults, usually discovered as an incidental findings on x-ray or due to complications like calcifications, infections, stones, hematuria.
- Renal function is usually normal
- Cortical surface is smooth

NEPHRONOPHTHISIS

- Cysts in the cortico-medullary junction
  - small, contracted kidneys due to cortical atrophy
  - Cysts are up to 1.0 cm in diameter

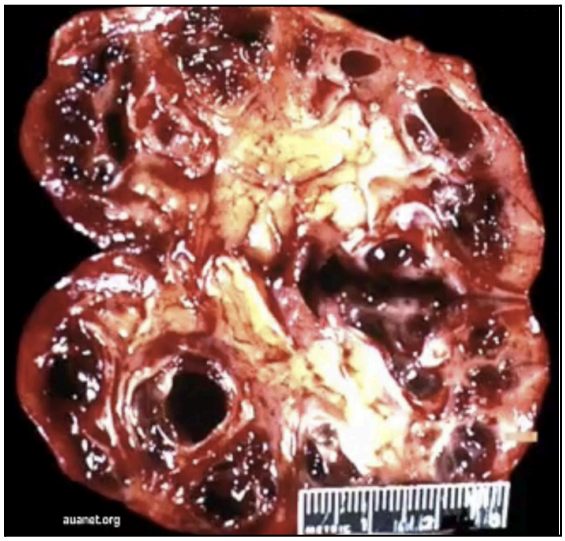


Figure 16. Nephronophthisis

BATCH 2027 TRANS:

- **Juvenile** : NPH1, NPH2, NPH3 📚
- **Adult** : MCKD1, MCKD2 📚

THREE FORMS OF NEPHRONOPHTHISIS	
Sporadic non-familial form	
Familial juvenile nephronophthisis	Most common
Renal-retinal dysplasia	Accompanied by ocular lesions

DIALYSIS-ASSOCIATED CYSTIC DISEASE

- Presents as cysts in the cortical and medullary cysts
  - Form as a result of tubular obstruction by interstitial fibrosis or by oxalate crystals
- 0.5 - 2.0 cm
- Most are asymptomatic
- Hematuria
- Renal Cell Carcinoma
  - most ominous complication

BATCH 2027 TRANS:

- Cysts sometimes bleed and patients will present hematuria
- Renal cell carcinoma
  - Occurring in 7% of dialysed patients observed for 10 years

PART 2 SUMMARY

- **Developmental structural anomalies** involving primarily the kidneys are uncommon except for horseshoe kidney.
- **Hereditary forms of renal cystic disease** involve gene mutations that result in altered tubular epithelial growth and differentiation.
- **ADPKD** is diagnosed in adulthood and is characterized by enlarged kidneys with cystic cortical surface and large cysts within.
- **ARPKD** is diagnosed in childhood and is characterized by enlarged kidneys with smooth cortical surfaces and dilated elongated channels perpendicular to the cortical surface.
- **Medullary sponge kidneys** are characterized by cysts in the collecting ducts in the medulla.
- ***Nephronophthisis*** is characterized by small kidneys and cysts in the corticomedullary junction. The familial variant is autosomal recessive and most common, manifesting during childhood and adolescence.
- **Multicystic renal dysplasia** is an abnormality in metanephric differentiation and is characterized by multiple cysts separated by undifferentiated mesenchyme that contains cartilage and immature collecting ducts.
- **Dialysis-associated cystic disease** forms as a result of tubular obstruction by interstitial fibrosis or oxalate crystals. Renal cell carcinoma may occur as a complication.

IV. OBSTRUCTIVE UROPATHY

- Caused by intrinsic and extrinsic factors

A. CAUSES OF OBSTRUCTION

- Obstructive lesions of the urinary tract **increases susceptibility to infection** and **to stone formation**
- Unrelieved obstruction almost always leads to **permanent renal atrophy** turned **hydronephrosis** or **obstructive uropathy**
- Obstruction along the urinary tract may be due to intrinsic or extrinsic causes
  - They may also be sudden or insidious, partial, or complete, unilateral, or bilateral
- The obstruction may occur at any level of the urinary tract from the **urethra** to the **renal pelvis**
  - When there is an obstruction at any point, there is **dilatation of the segment proximal to it**

1	• Dilatation of renal pelvis and calyces (or **hydronephrosis**) → High pressure causes cortical atrophy
2	• Compression of medullary vasculature → Functional disturbance (impaired concentrating ability)
3	• Interstitial inflammation → Interstitial fibrosis

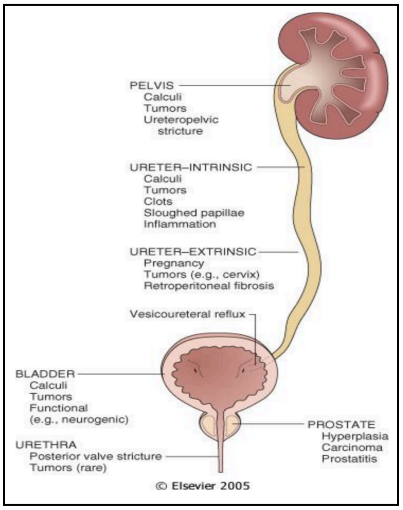


Figure 17. Obstruction causes

B. HYDRONEPHROSIS

- Term used to describe the **dilatation of the renal pelvis and calyces** associated with progressive atrophy of the kidney due to **obstruction of the outflow of urine**
- Notice the **dilated pelvis and calyces**, **thinned out corticomedullary area** (renal parenchyma), which is so severe in the 2nd picture (right)

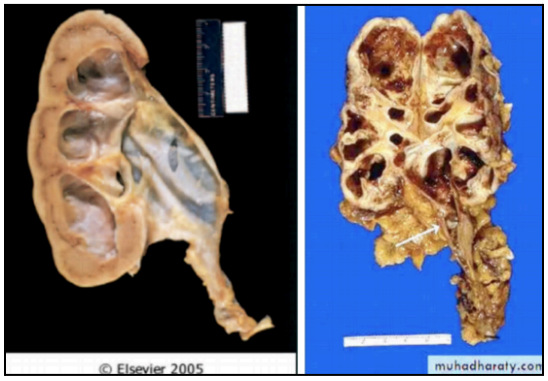


Figure 18. Gross presentation of hydronephrosis

V. UROLITHIASIS

FACTORS THAT INFLUENCE CALCULI FORMATION	
1	Increased concentration of stone constituents (**supersaturation**) → Such that it exceeds their solubility
2	Changes in urinary pH
3	Decreased urine volume
4	Presence of bacteria
5	Deficiency in inhibitors of crystal formation

A. TYPES OF STONES

1. CALCIUM OXALATE STONES (70%)

- With or without hypercalcemia
- Hyperuricosuria (in some cases)
  - Due to uric acid crystals in the collecting duct that cause nucleation of calcium oxalate

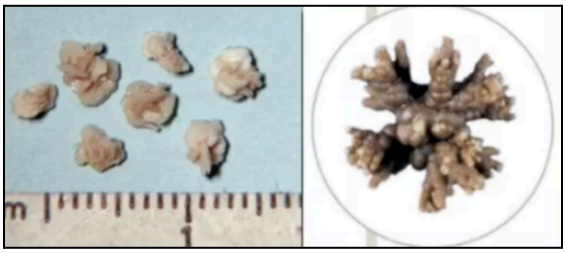


Figure 19. Calcium oxalate stones

- Seen in **hypercalciuria with hypercalcemia (5%)** in hyperparathyroidism and diffused bone diseases, and **hypercalciuria without hypercalcemia (55%)** in absorptive hypercalciuria and renal hypercalciuria
- Associated with **increased uric acid secretion (20%)**
- **Hyperoxaluria (5%)**
- **Hypocitrauria**
- Idiopathic

2. MAGNESIUM AMMONIUM PHOSPHATE STONES (5-10%)

- Also known as **"struvite" stones**
- Formed largely after infections by urea-splitting bacteria (Proteus, Pseudomonas, Klebsiella, Staphylococcus, Mycoplasma)
  - These bacteria convert urea into ammonia
- The resultant alkaline urine causes the precipitation of Magnesium Ammonium Phosphate salts
- These form some of the largest stones as the amount of urea excreted normally is very large
- Staghorn calculi occupying a large portion of the renal pelvis are frequently a consequence of infection

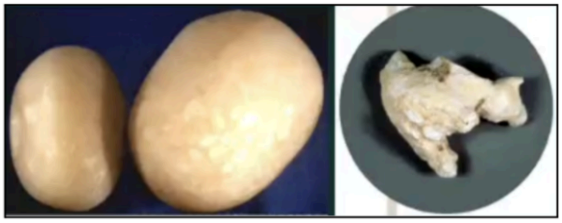


Figure 20. Magnesium Ammonium Phosphate Stones

STAGHORN CALCULI

- Called 'staghorn' because it takes the form of the renal pelvis and calyces resembling a horn of a stag.
- This calculi are made up of **magnesium ammonium phosphate** material.

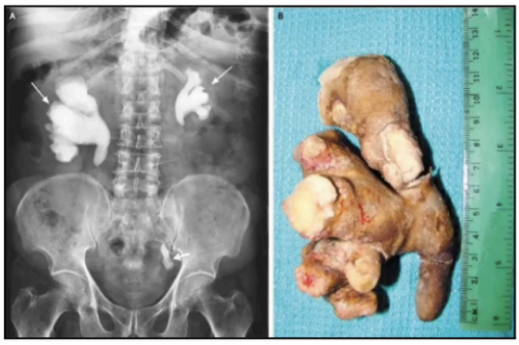


Figure 21. X-ray of Staghorn Calculi

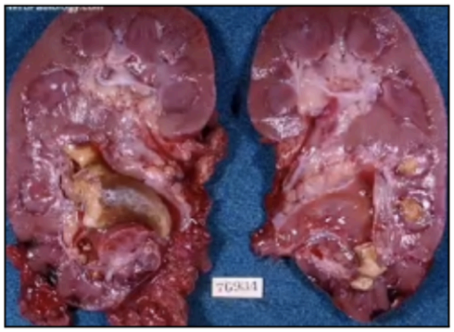


Figure 22. Kidney with a staghorn calculi

3. URIC ACID STONES (5-10%)

- Seen in patients with hyperuricemia (gout) or rapid cell turnover (leukemia)
  - In those undergoing chemotherapy, because the destruction of the WBCs result in the release of purines, which are then converted to uric acid.
- In more than 50% of patients, there is **no hyperuricemia nor hyperuricosuria**
- In these patients, tendency to secrete acidic urine predisposes to formation of **uric acid stones.**
  - These stones are radiolucent

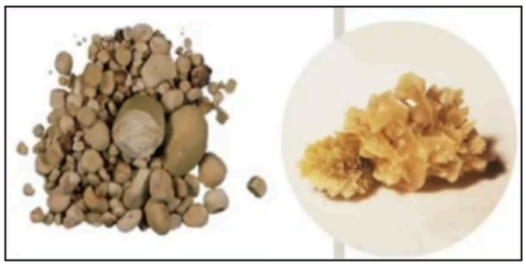


Figure 23. Uric Acid Stones

4. CYSTINE STONES (1-2%)

- Not as frequent
- Occur as a result of genetic defects in the renal absorption of amino acids that includes cysteine

Figure 24. Cystine Stone

PART 3 SUMMARY

- Obstruction in the urinary tract may be due to **tumors, stones, anatomical defects and inflammatory processes.** Pregnancy, tumors and retroperitoneal fibrosis are extrinsic causes of obstruction to the ureter.
- Obstruction causes **dilation of the renal pelvis and calyces** leading to cortical atrophy, compression of the medullary structures leading to impaired concentrating ability of the tubules and interstitial inflammation resulting in **fibrosis**.
- Several factors contribute to the formation of urinary calculi but the common effect is increased urinary concentration of the stones' constituents, such that it exceeds their solubility.
- **Calcium oxalate stones** are the most common uroliths and may or may not be associated with hypercalcemia.
- **Magnesium ammonium phosphate stones** are formed after infections by urea-splitting bacteria. They form the largest stones.
- **Uric acid stones** occur in patients with gout or in conditions with rapid cell turnover, as in leukemia.
- **Cystine stones** are the least common and they occur in association with genetic defects in amino acid absorption.

VI. TUMORS OF THE KIDNEY

A. BENIGN TUMORS

1. RENAL PAPILLARY ADENOMA

- **Most common form of benign, solid, kidney tumor.**
- Typically small or low-grade.
- Their cause is unknown.

2. RENAL FIBROMA

- Benign mesenchymal tumor of the kidney composed of fibroblasts and collagen, typically arising in the renal medulla.

3. ANGIOMYOLIPOMA

- Rare, benign tumors that can be caused by an **inherited genetic mutation.**
- It can occur as an isolated entity but most often they are associated with tuberous sclerosis, which can cause tumors in the:
  - Skin
  - Kidneys
  - Brain
  - Other organ systems
- Most often occur in middle-aged women.

4. RENAL ONCOCYTOMA

- Usually asymptomatic tumor that can grow quite large
- Can develop in any part of the body and is not unique to the kidneys
- Cause is unknown
- Appear in greater frequency in men than in women **(M > W)**

B. MALIGNANT TUMORS

1. RENAL CELL CARCINOMA

- **Most common** malignant tumor in the kidney
- **Adenocarcinoma** of the kidneys
- Used to be called '***hypernephroma***'
- Tumors occur most often in **older** individuals (usually in the 6th or 7th decade of life)
- **2:1 Male preponderance** (M > W)
- **UROTHELIAL CARCINOMA:** 5% to 10% of primary renal tumors originate from the urothelium of the renal pelvis

RISK FACTORS OF RENAL CELL CARCINOMA	
1	**Cigarette Smoking - MOST SIGNIFICANT RISK FACTOR**
2	Obesity
3	Hypertension
4	Unopposed estrogen therapy
5	Exposure to asbestos, petroleum products, and heavy metals

FAMILIAL VARIANTS

- Most renal cancers are **sporadic**
- Familial variants often occur in younger patients

1. Von-Hippel-Lindau Syndrome

- Tumor is seen in one-half to two-thirds of individuals with this syndrome
- Characterized by **cysts and bilateral renal cell carcinoma**
- Mutations in the **VHL gene**

2. Hereditary Leiomyomatosis and Renal Clear Cell Cancer Syndrome

- **Autosomal dominant**
- Characterized by **cutaneous and uterine myomas and aggressive renal papillary carcinoma**
- Mutations in the **FH gene**

3. Hereditary Papillary Carcinoma

- **Autosomal dominant**
- Characterized by **multiple, bilateral renal papillary tumors**
- Mutations in the **MET proto-oncogene**

4. Birt-Hogg-Dube Syndrome

- **Autosomal dominant**
- Characterized by **skin, pulmonary, and renal tumors**
- Mutations in the **BHD gene**

2 MAJOR TYPES

CLEAR CELL CARCINOMA (70-80%)*

- **Most common** among major histologic types of renal cell carcinoma
- 98% are associated with **Von Hippel-Lindau (VHL) syndrome**
- Mutations in **VHL gene**

PAPILLARY CARCINOMA (10-15%)

- Less frequent
- Associated with mutations in **MET proto-oncogenes**

CHROMOPHOBE RENAL CELL CARCINOMA (5%)

- Not discussed

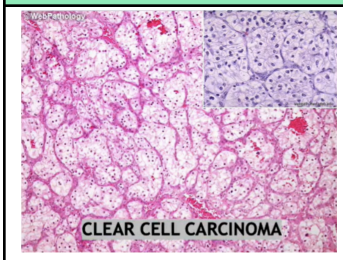
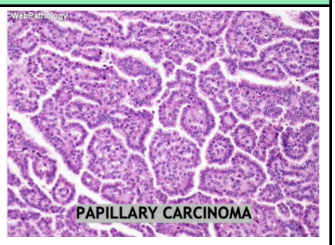
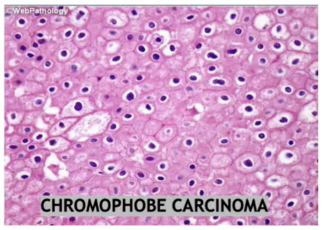
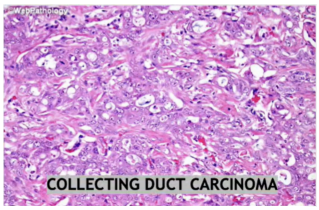
COLLECTING DUCT CARCINOMA (<1%)

- Not discussed

MORPHOLOGY

- Renal cell carcinomas have distinctive appearance
- Often seen in **poles (upper > lower)**
- Solitary, spherical masses with distinct margins
- Cut sections would show bright yellow to gray-white cut surfaces
- Areas of ischemic necrosis, hemorrhagic discoloration, and softening
- Tendency to invade the renal vein
- Papillary Carcinoma:
    - Multifocal
    - Hemorrhagic and cystic

Morphology of Major Types of Renal Cell Carcinoma

Clear Cell Carcinoma (70-80%)*	Papillary Carcinoma (10-15%)
	
• **Most common** • Round, plump cells • Clear cytoplasm • Small central nuclei	• **Papillary fronds lined by tumor cells** • Cross sections of the fronds are observed
Chromophobe Renal Cell Carcinoma (5%)	**Collecting Duct Carcinoma (<1%)**
	
• Characterized by **distinct nuclear halos** • Pink cytoplasm surrounded by prominent cytoplasmic membrane	• Often characterized by **fibrotic strands** separating the tumor islands

CLINICAL FEATURES

- The clinical features of renal carcinoma includes the traditional triad of **costovertebral pain, palpable mass, and hematuria**
    - This triad is seen only in 10% of cases
- Most frequent manifestation is **hematuria**
    - Most reliable clue
- Renal cell carcinoma tends to mimic other cancers because it is associated with paraneoplastic syndromes
- It tends to metastasize widely before giving rise to local signs and symptoms
    - Metastatic sites are most often the **lungs** (>50%) and **bones** (33%)
- The 5-year survival rate is 70% and in the absence of metastasis, the prognosis is good with 95% 5-year survival rate

2. UROTHELIAL CARCINOMA

- Arise from the **lining of the pelvicalyceal system**
- They make up about 7% of primary renal carcinomas
- Risk factors include:

- Tobacco smoking, long term analgesic or phenacetin use, exposure to petrochemicals, thorotrast and even horseshoe kidney
- Almost 2/3 of patients have prior concurrent tumors elsewhere in the urinary tract usually in the bladder
- Histology is similar to urothelial carcinoma of the urinary bladder
- They may have a **papillary configuration** about 70% of these tumors are high grade and prognosis is often poor
- May be multiple (pelvis, ureter, bladder)

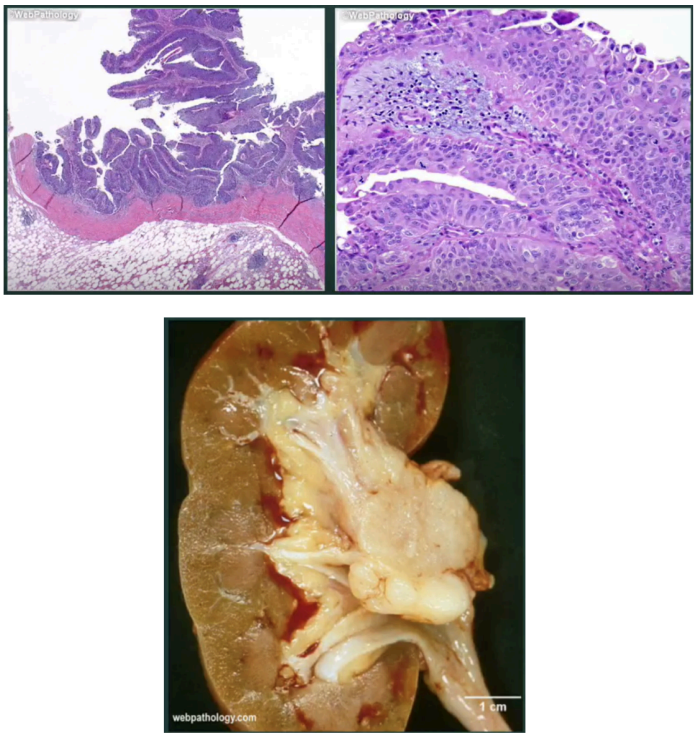


Figure 25. Urothelial Carcinoma, Gross and Histologic Presentation

PART 4 SUMMARY

- The most common benign neoplasm of the kidney is the **renal papillary adenoma**.
- **Smoking** is the most important risk factor for renal cell carcinoma.
- The most common familial variant of RCC is the one associated with **Von-Hippel-Lindau Syndrome,** presenting as clear cell carcinoma. Clear cell carcinoma is also the most common histologic form of RCC.
- RCC often appears as solitary, spherical, well-circumscribed, yellow to gray solid masses, usually in the upper pole. They have a tendency to invade the renal vein.
- The classic triad of **hematuria, costovertebral pain and palpable mass** is only seen in 10% of RCC. The most frequent manifestation is **hematuria**.

- **Urothelial carcinoma** of the kidneys arises from the lining of the pelvis and calyces and therefore are made up of **malignant urothelial cells**. Smoking is also the mst important risk factor. Prognosis for ths cancer is poor.

DISEASES OF LOWER URINARY TRACT

I. URETERS

A. CONGENITAL ANOMALIES

- Main significance: may contribute to **obstruction**

1. DOUBLE URETERS

- Two ureters may **arise from the kidney** and **empty into the bladder** through a **single urethral orifice**
- Most are **unilateral**

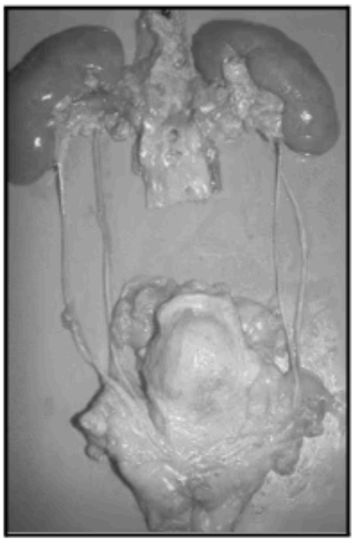


Figure 26. Double ureters on both sides

2. URETEROPELVIC JUNCTION OBSTRUCTION

- **Obstruction and narrowing of the lumen** in this area is caused by:
  - **Abnormal organization** of smooth muscle fibers
  - **Excess collagen** deposition between smooth muscle bundles
- Most common cause of **Hydronephrosis in infants**
- L>R; usually **unilateral**

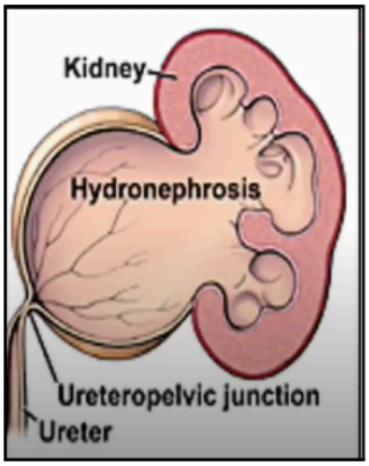


Figure 27. Ureteropelvic junction obstruction

3. DIVERTICULA

- Can be **congenital or acquired**
- Are outpouchings of the ureteral wall → stasis of urine → **infection**

4. VESICOURETERAL REFLUX

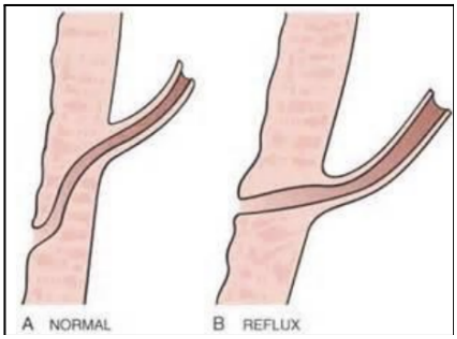


Figure 28. Vesicoureteral Reflux

- **Reflux** of bladder urine into the ureters
- It is one of the important factors that predispose the movement of organisms from the bladder to the kidneys
  - Others include:
    - Urinary obstruction and stasis
    - Intrarenal reflux

CAUSES OF VESICOURETERAL REFLUX	
1	**Congenital absence or shortening** of the intravesical portion of the ureter ● Ureter is not compressed during micturition
2	**Bladder infection** - accentuates reflux
3	**Persistent bladder atony** due to spinal cord injury

B. TUMORS AND TUMOR-LIKE LESION

- Primary tumors of the ureter are rare
- Benign tumors are generally mesenchymal in origin
- Primary malignant tumors of the ureter resemble those arising from the renal pelvis, calyces, and bladder

1. FIBROEPITHELIAL POLYP

- Tumor-like lesions which often occur in **children**
- Composed of loose, vascularized connective tissue overlaid by urothelium

2. LEIOMYOMA

- Benign tumor of the smooth muscle, the ureteral wall

3. UROTHELIAL CARCINOMA

- Majority of primary malignant tumors
- Occur most frequently during **6th and 7th decades of life**
- Cause obstruction of the ureteral lumen
- Occur concurrently with **urothelial carcinomas of the bladder or renal pelvis**

C. OBSTRUCTIVE LESION

- May be due to extrinsic or intrinsic causes
- Involvement of the kidneys is of clinical significance
- Obstruction leads to hydroureter and hydronephrosis
- Unilateral if obstruction is more proximal

INTRINSIC CAUSES	EXTRINSIC CAUSES
● Calculi ● Strictures ● Blood clots ● Neurogenic ● Tumors	● Pregnancy ● Periureteral inflammation ● Endometriosis ● Tumors

1. SCLEROSING RETROPERITONEAL FIBROSIS

- AKA **Ormond's disease**
- Diffuse or localized fibroblastic proliferation associated with chronic inflammation
- Characterized by **fibrotic proliferative inflammatory process t**hat encases the retroperitoneal structures including the ureter and causes **hydronephrosis**
- 📖 Although benign, this lesion can be locally aggressive, with **compression or obstruction** of the ureters and vascular structures, including aorta

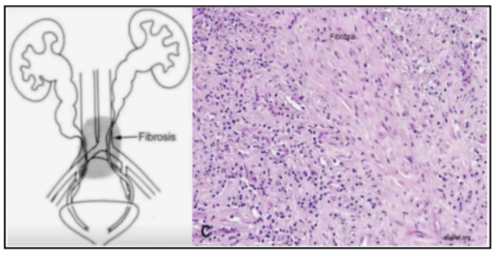


Figure 29. Sclerosing Retroperitoneal Fibrosis

II. URINARY BLADDER

A. CONGENITAL ANOMALIES

1. DIVERTICULA

- Pouchlike evagination of the bladder wall: **<1 cm - 10 cm**
- May be congenital or acquired

Congenital Diverticulum	• Due to abnormal development (focal failure) of bladder musculature • Urinary tract obstruction during fetal development
Acquired Diverticula	• Due to increased pressure in the urinary bladder caused by a distal obstruction to urine outflow • ↑ Intravesical pressure → outpouchings

CLINICAL SIGNIFICANCE OF DIVERTICULA	
1	Can be sites of urinary stasis → **infection**
2	If large enough it may impinge on the ureter → **vesico-ureteral reflux**
3	May give rise to **cancers**

2. EXSTROPHY

- Anterior wall of the abdomen **fails to develop** → bladder communicates directly with the surface of the body or it lies as an open sac
- Mucosa is exposed and can undergo **metaplasia**
- Prone to infections
- Increased risk of developing **adenocarcinoma**

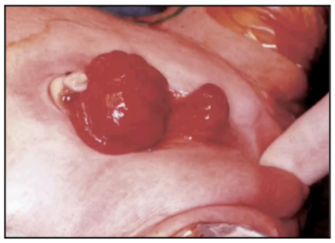


Figure 30. Exstrophy

B. INFLAMMATION (CYSTITIS)

- **Cystitis** is the inflammation of the urinary bladder
- ***E. coli***, ***Proteus***, ***Klebsiella***, and ***Enterobacter*** are the most common bacterial agents
- ***Candida albicans*** and ***Cryptococcus*** infect immunocompromised patients
- For ***E. coli*** infection, the host fecal flora is the most common immediate source for the infecting strain
- Patients with diabetes are more prone to urinary tract infection due to frequent urination and high sugar levels
  - High sugar levels → favorable growth environment to the pathogen

ETIOLOGIC AGENTS	
1	*E. coli*
2	*Proteus, Klebsiella, Enterobacter*
3	*Mycobacterium tuberculosis* (TB)
4	*Candida albicans* (in immunosuppressed)
5	Others: viruses, *Chlamydia, Mycoplasma, Schistosoma*
6	Non-infectious: chemotherapy, radiation therapy, trauma

PREDISPOSING FACTORS	
1	Bladder calculi
2	Obstructions
3	Diabetes mellitus (DM)
4	Instrumentation
5	Immunodeficiency
6	Women – shorter urethra

1. ACUTE CYSTITIS

-

MORPHOLOGY	
G	Hyperemic mucosa (very red); may have exudates
M	Non-specific acute (and chronic) inflammation

TYPES	
1	Hemorrhagic cystitis – after radiation or chemotherapy
2	Suppurative cystitis
3	Ulcerative cystitis

HEMORRHAGIC CYSTITIS

- After radiation treatment or anti-tumor treatment
- May present with gross hematuria and stones scratching on bladder surfaces
- In cystoscopy: the bladder wall is seen as hemorrhagic

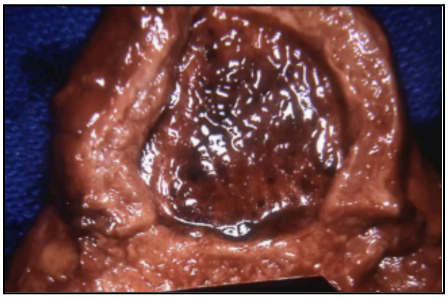


Figure 31. Hemorrhagic cystitis

2. CHRONIC CYSTITIS

MORPHOLOGY	
1	Granular mucosal surface
2	Chronic inflammatory cells
3	Heaping up of the epithelium
4	Fibrous thickening of the muscularis propria → causes the bladder wall to become less elastic

MORPHOLOGIC VARIANTS	
1	**Follicular cystitis** • Lymphoid follicles within the bladder mucosa and wall
2	**Eosinophilic cystitis** • Submucosal eosinophils, fibrosis, occasional giant cells

3. MAIN CLINICAL MANIFESTATIONS

- **Triad:**

1	Frequency
2	Lower abdominal pain
3	Dysuria

- Systemic manifestations such as **fever, chills,** and **body malaise**

4. CYSTITIS - SPECIAL VARIANTS

Interstitial Cystitis (Chronic Pelvic Pain Syndrome)

- Persistent, painful, chronic cystitis associated with inflammation and fibrosis of all layers of the bladder wall
- **Fissures and punctate hemorrhages** (cystoscopy)
- Most frequent among women
- Intermittent, severe, suprapubic pain, urinary frequency, urgency, hematuria, dysuria
  - **Early phase** (non-classic, non-ulcerative) : recent submucosal hemorrhages
  - **Late phase** (classic, ulcerative) : chronic mucosal ulcers (Hunner ulcer)
    - Inflammation and granulation tissue in mucosa, lamina propria and muscularis
    - Mast cells may be prominent

Malacoplakia

- 3 cm - 4 cm, slightly raised, **soft, yellow mucosal plaques**
- Large foamy macrophages with occ. multinucleated giant cells interspersed with lymphocytes
- **Michaelis-Gutmann bodies**
  - Laminated, mineralized concretions (calcium) in macrophages and between cells
- Related to chronic bacterial infection (E.coli, occ. Proteus)

Polypoid Cystitis

- Irritation of the bladder mucosa (catheterization) → marked submucosal edema → urothelium is thrown into broad polypoid projections.
- On gross image, the lesion is broad-based with polypoid fronts
  - This is a reactive lesion in response to inflammatory injury to the bladder urothelium
- Common causes include **indwelling catheters** and **bladder stones**.
- Histologically, the lesion is composed of edematous folds and fronts lined by benign urothelium

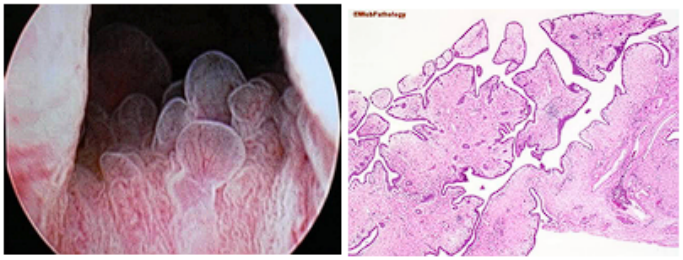


Figure 32. Polypoid Cystitis

C. METAPLASTIC LESION

- Transitional epithelium lining of the bladder may undergo various forms of metaplasia.

1. CYSTITIS GLANDULARIS AND CYSTITIS CYSTICA

- Nests of urothelium or transitional epithelium may go down into the lamina propria (known as **Brunn nests**).
- When the central epithelial cells become cuboidal or columnar, the lesion is called **Cystitis Glandularis**.

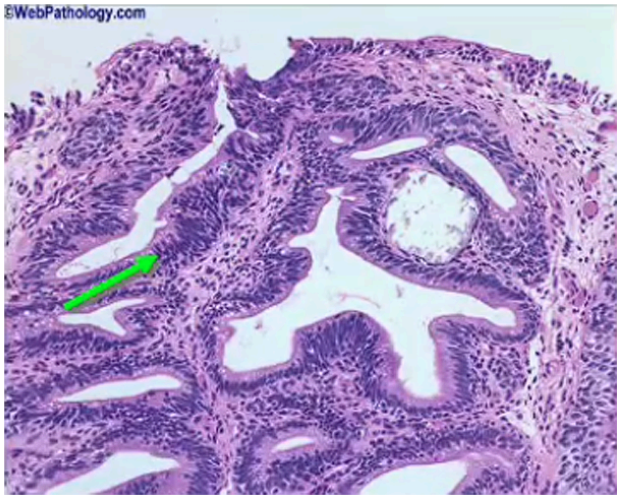


Figure 33. Cystitis Glandularis

- When there are cystic spaces lined by urothelium, the lesion is called **Cystitis Cystica**.

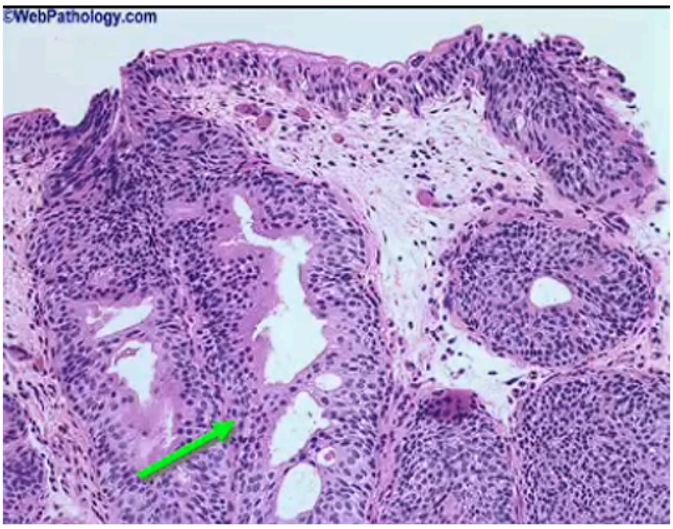


Figure 34. Cystitis Cystica

2. SQUAMOUS METAPLASIA

- As a response to chronic injury, the urothelium is often **replaced by non-keratinizing or keratinizing squamous epithelium**, which is more durable.
- Extensive multifocal keratinizing squamous metaplasia is a precursor to dysplastic lesions and in situ and invasive squamous cell carcinoma.

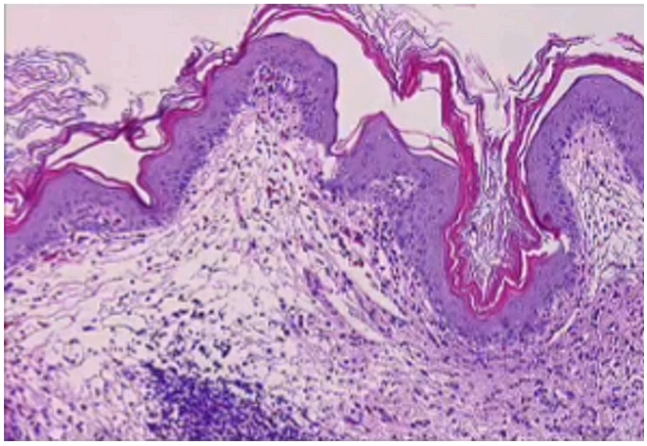


Figure 35. Squamous Metaplasia

3. NEPHROGENIC ADENOMA

- When **shedded renal tubular cells** implant and proliferate at sites of bladder mucosal erosion, the overlying urothelium is focally replaced by cuboidal epithelium, which can assume a **papillary-like growth pattern**. (Gives rise to nephrogenic adenoma).
- Larger lesions may cause signs and symptoms that mimic cancer.
- Tubular proliferation can infiltrate the underlying lamina propria and superficial detrusor muscle, thus histologically appearing like an invasive carcinoma.

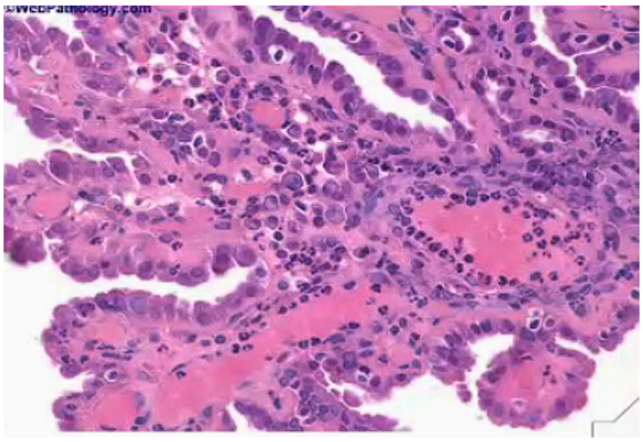


Figure 36. Nephrogenic Adenoma

D. NEOPLASMS

1. UROTHELIAL (TRANSITIONAL CELL) TUMORS

- 90% of bladder tumors
- Range from benign to malignant
- Precursor lesions of invasive urothelial carcinoma
  - Non-invasive papillary tumors
  - Flat non-invasive urothelial carcinoma
    - Also called Carcinoma-in-situ

CAUSATIVE FACTORS

1	**Cigarette smoking**	Most important causative factor
2	**Exposure to arylamines**	• Found in cigarette smoke, permanent hair dyes, and industrial dyes • May also be seen in the leather, rubber, printing, and textile industries
3	***Schistosoma haematobium* infection**	• Incites chronic inflammatory response that can progress to metaplasia and dysplasia. • Squamous cell carcinoma - 70% malignancies that are associated with this parasite
4	**Long-term use of analgesics**	
5	**Heavy, long-term intake of cyclophosphamide**	
6	**Prior radiation exposure of the bladder**	
7	**Genetic alterations**	• Chromosome 9 abnormalities occur in 30-60% of tumors • Chromosome 9 monosomy and chromosome 9 deletions

PATHOGENESIS: GAIN OF FUNCTION ALTERATIONS

- Involve gain-of-function alterations that increase signaling through (growth) factor receptor pathways. (FGFR3, RS)
- Amplifications of FGFR3 tyrosine kinase receptor gene and activating mutation of the genes encoding for RAS and PI 3-kinase
- Often seen in **non-muscle invasive papillary tumors.**
- These tumors frequently recur but progress to muscle invasive tumors in only 20% of cases.

PATHOGENESIS: MUTATION OF TUMOR SUPPRESSOR GENES

- Involve **P53, RB mutations** which are tumor suppressor genes
- Present in **ALL muscle invasive bladder cancer** but occurs
  - Early in the development of carcinoma in situ
  - Later in the progression of papillary cancers.

MORPHOLOGIC PATTERNS

1	**Papilloma**	Non-invasive papillary carcinoma
2	**Invasive papillary carcinoma**	
3	**Flat <u>non-invasive</u> carcinoma (CIS)**	Carcinoma in-situ
4	**Flat invasive carcinoma**	
NOTE: The extent of invasion into the muscularis mucosa is of prognostic significance; almost all invasive urothelial carcinomas are high grade		

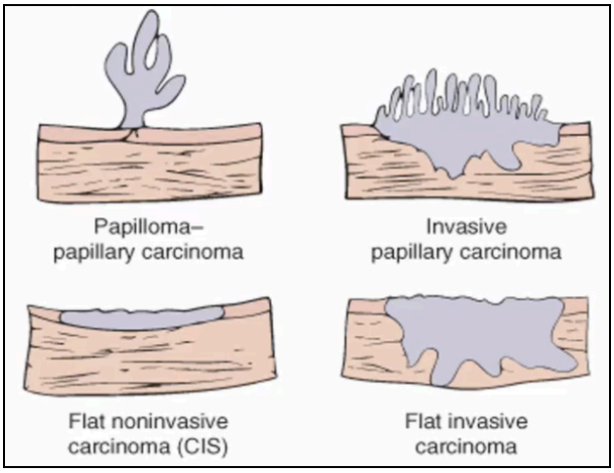


Figure 37. Urothelial tumors morphologic patterns

CARCINOMA IN-SITU

- Cytologically malignant cells within a flat epithelium
- Cells lack cohesiveness
  - Often shed in the urine
- Often multifocal
- If left untreated, 50-70% invade the underlying mucosa

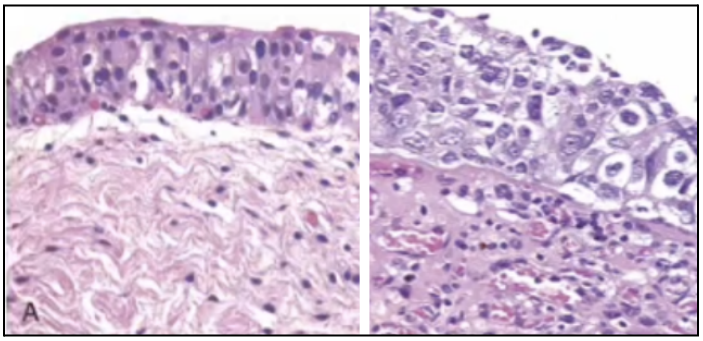


Figure 38. Normal mucosa (right) vs Disorganized array of epithelial cells (left)

CLASSIFICATION (WHO/ISUP)

1	Urothelial Papilloma
2	Papillary Urothelial Neoplasm Of Low Malignant Potential (PUNLMP)
3	**Low-Grade** Papillary Urothelial Carcinoma
4	**High-Grade** Papillary Urothelial Carcinoma

UROTHELIAL PAPILLOMA

- 1% or fewer
- Often seen in **younger patients**
- Small and superficially attached to the mucosa
- Lining is similar to normal urothelium
- **Exophytic** or **Inverted**
  - **Inverted papilloma** - extends to the lamina propria

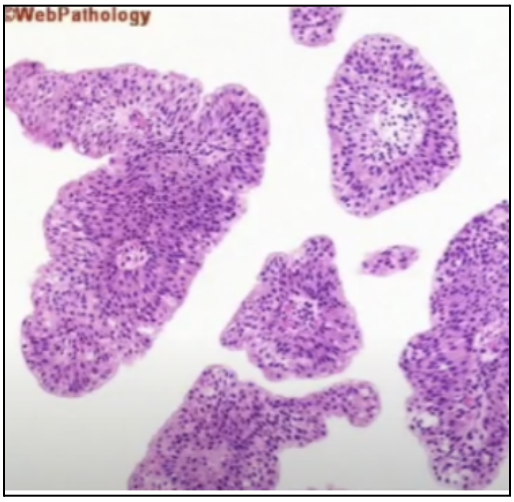


Figure 39. Papilloma

PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL (PUNLMP)

- Histologically similar to the papilloma but with **thicker urothelium**
- Mild, diffused, with nuclear enlargement

- **Larger than papillomas** and may grossly look like low-grade or high-grade lesions
- Still organized and no dysplastic changes

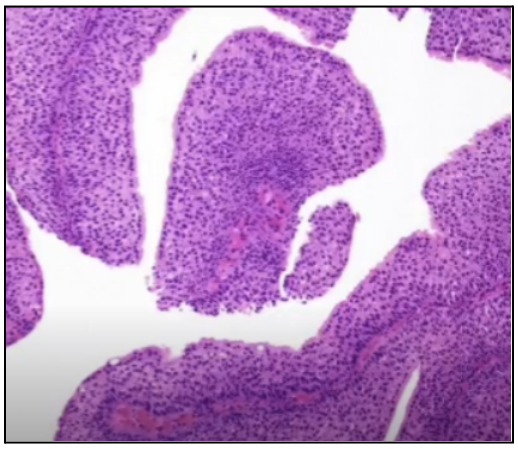


Figure 40. PUNLMP

LOW-GRADE PAPILLARY UROTHELIAL CARCINOMA

- Cells are still **orderly** and **cohesive**
- Mild nuclear atypia
- Infrequent mitosis
  - **Mitotic figures**, if present, are prominent in the **base** but can be present elsewhere

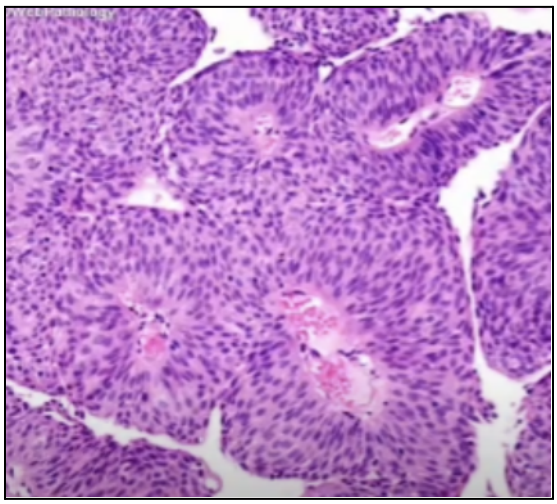


Figure 41. Thickening in low-grade papillary urothelial carcinoma.

HIGH-GRADE PAPILLARY UROTHELIAL CARCINOMA

- Cells are **discohesive** and they have shredded off
- Large, hyperchromatic nuclei
- Several mitotic figures
- **Loss of polarity** - disorganized architecture
- 80% are invasive
- The image below shows marked anisonucleosis, hyperchromasia, pleomorphism, and a lot of mitotic figures

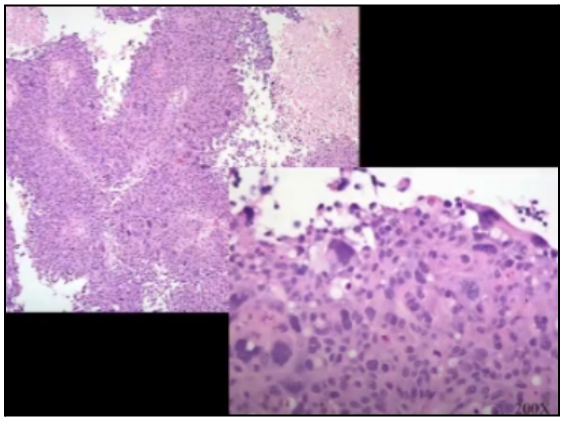


Figure 42. High-Grade Papillary Urothelial Carcinoma

2. PAPILLARY BLADDER TUMOR

- **Aggressive tumors** may extend into the bladder wall, adjacent prostate, seminal vesicles, ureters, and retroperitoneum
  - Others may form fistulous communication with the vagina or rectum
- 40% of deeply invasive tumors metastasize to regional lymph nodes
- Hematogenous spread is to the **liver, lungs, bone marrow**
- The papillary lesion on the left of the image below may or may not be invasive in gross examination

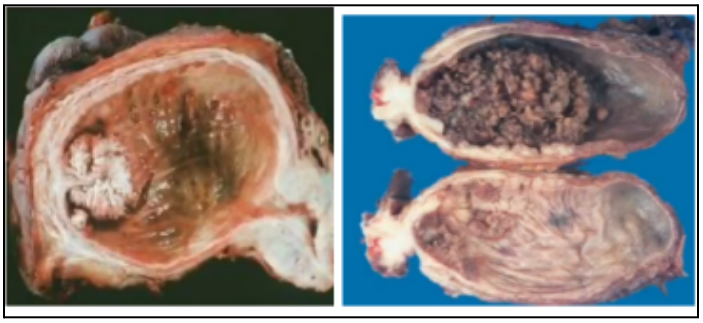


Figure 43. Papillary Lesion (left) and A more diffuse Papillary Lesion (right).

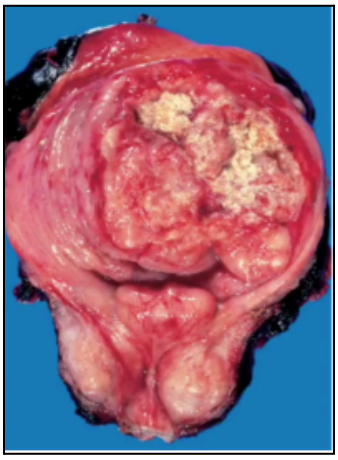


Figure 44. Invasive High Grade Papillary Urothelial Carcinoma. Tumor in the Muscular Wall of the Bladder

3. OTHER TYPES

1	**SQUAMOUS CELL CARCINOMA**	• 3% to 7% • Pure or Mixed (urothelial + squamous cell) • Usually invasive and fungating or ulcerative
2	**ADENOCARCINOMA**	• Rare

4. CLINICAL MANIFESTATIONS AND COURSE

PAINLESS HEMATURIA	• Most common clinical manifestation of bladder tumors, particularly malignancy
TENDENCY TO DEVELOP NEW TUMORS	• 50% of invasive bladder cancers have relatively poor prognosis despite therapy
IMPORTANT PROGNOSTIC FACTORS	• Grade • Stage

PATHOLOGIC STAGING	
Ta	Non-invasive, papillary
T_{IS}	Carcinoma in-situ
T1	Lamina propria invasion
T2	Muscularis propria invasion
T3a	Microscopic extra-vesicle invasion
T3b	Grossly apparent extra-vesicle invasion
T4	Invasion of adjacent structures

5. MESENCHYMAL TUMORS

- May also occur in the urinary bladder

1	**LEIOMYOMA (BBENIGN)**	
2	**SARCOMAS (MMALIGNANT)**	**Embryonal Rhabdomyosarcoma** • More common among infants and children
		Leiomyosarcoma More common among adults

E. URINARY BLADDER OBSTRUCTION

- Often occurs in the bladder neck
- **Clinical Significance:**
  - Morphologic changes in the bladder
  - Deleterious effects on the kidneys

CAUSES OF URINARY BLADDER OBSTRUCTION	
1	Prostatic enlargement (benign or malignant lesions)
2	Cystocele of the bladder
3	Urethral narrowing or stricture
4	Inflammatory fibrosis & contractions in the bladder after cystitis
5	Bladder tumors
6	Calculi or other foreign bodies
7	Neurogenic bladder

1. CHRONIC BLADDER OBSTRUCTION

- Muscle hypertrophy represented by **trabeculations** (green arrow)
- Eventually there can be **diverticula**
- Eventually the bladder wall is **dilated and markedly thinned out**

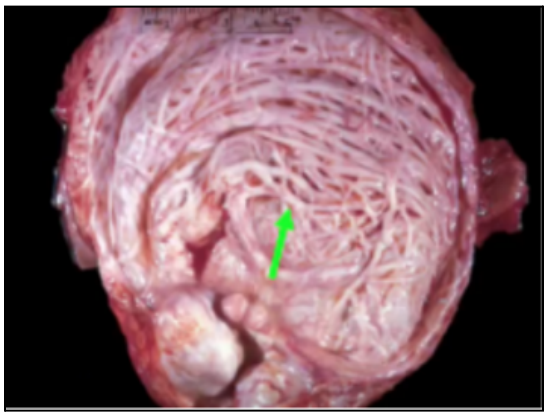


Figure 45. Chronic Bladder Obstruction

III. URETHRA

A. URETHRITIS

- Often infectious in origin
  - Gonococcal
  - Non-gonococcal

B. URETHRAL CARUNCLE

- **Inflammatory lesions** characterized by small, red, painful mass at the **urethral meatus** in females
- **Highly-vascularized** lesion with fibroblastic connective tissue and lymphocytes

C. URETHRAL CARCINOMA

- Urethral carcinoma is **uncommon**
  - **Location and Origin:**
    - **Proximal Urethra:** Urothelial origin
    - **Distal Urethra: Squamous origin**

IV. SUMMARY

- The **congenital lesions of the ureter** are significant because they can predispose to infection and cause obstruction that can compromise the kidney

- In **children**, **congenital UPJ obstruction** is the most common obstructive lesion
- **Bladder diverticula** and **exstrophy** predispose to infection and may increase the risk for cancer
- **Acute or chronic bacterial cystitis** is **common** and results from retrograde spread of colonic bacteria in most cases
- **Cystitis** and its variants commonly present with frequency, lower abdominal pain and dysuria
    - Some forms of cystitis and metaplastic bladder lesions are significant in that they **may clinically and/or histologically mimic bladder cancer**
- **Urothelial tumors of the bladder** range from benign to malignant, may be flat or papillary, non-invasive or invasive
    - Progression to invasive tumors involve **gain-of-function mutations** in growth factor signaling pathways and **inactivation of tumor suppressor genes**
- Other bladder cancers include squamous cell carcinoma, adenocarcinoma and sarcomas
- **Bladder cancers**, regardless of the type, frequently present as **painless hematuria**
- **Obstruction distal to the bladder** causes changes in the bladder that include muscle hypertrophy (**trabeculations**), dilatation and formation of diverticula
- **Urethral caruncle** is a painful vascular mass located in the urethral meatus of females
- **Urethral cancer** is **uncommon**
    - **Proximal cancers** are often **urothelial** in origin
    - **Distal cancers** are often **squamous cell carcinoma**