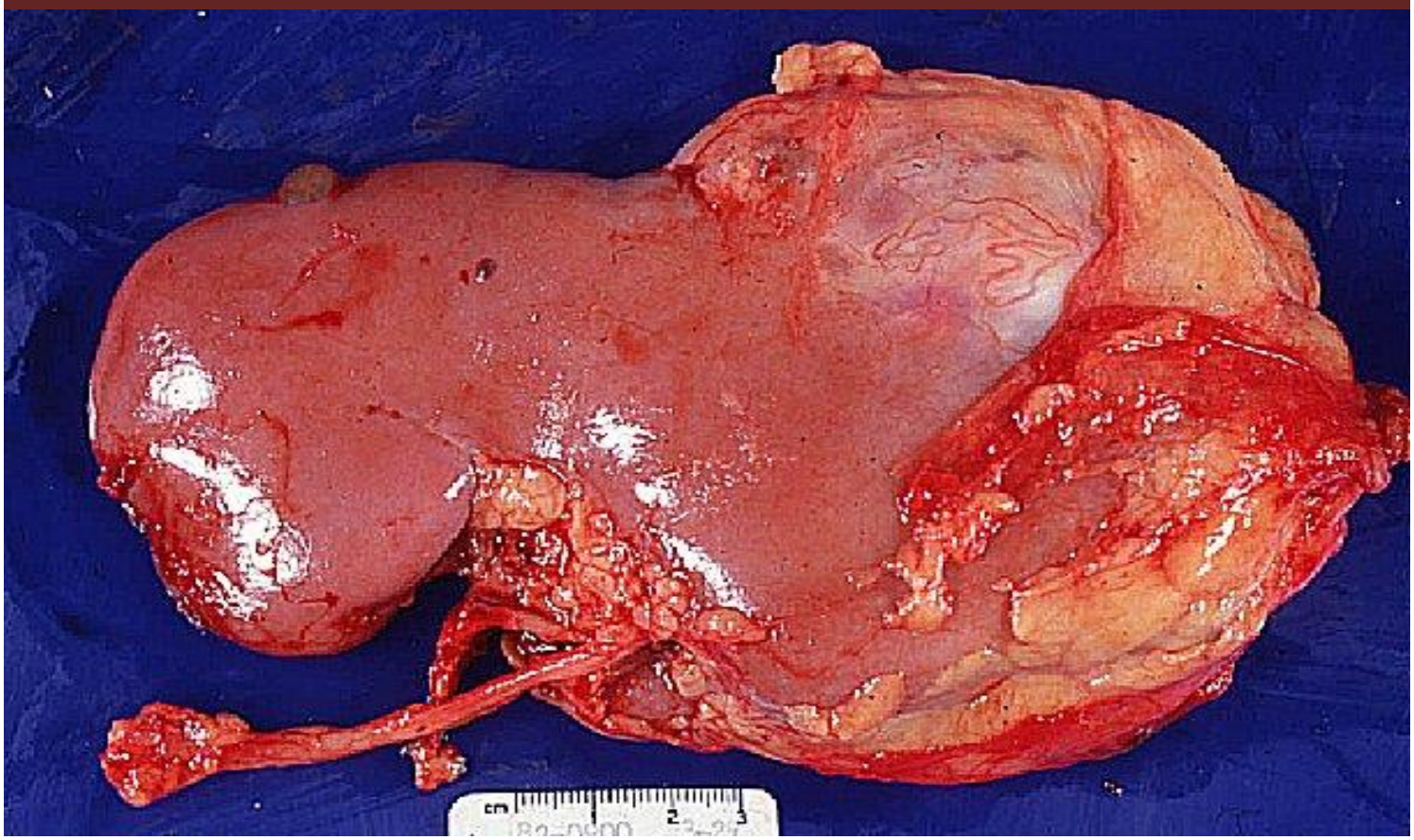


Lecture Six

Tumors of the

Kidney and Urinary Tract

432 ***Pathology*** *Team*

Done By: Fahad *Al-Dhahri*

Reviewed By: Roqaih *Al-Dueb*

Renal Block

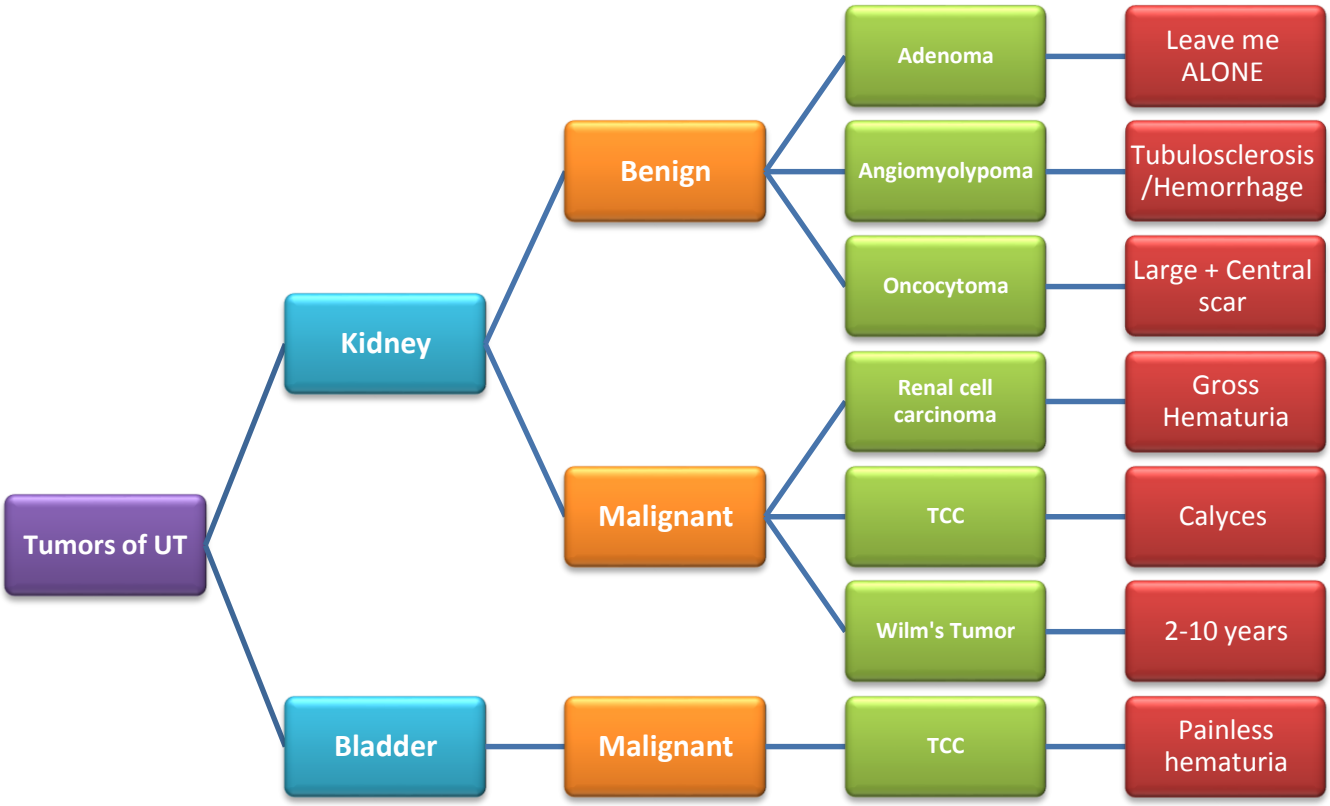
NOTE: female-side notes are written in purple. Red is important. Orange is explanation. Info in the handout not mentioned by Prof. Al-Rikabi are in GREY

Pathology of Kidney & Urinary Bladder Tumors

Lecture Objectives:

- *Not Given*

Mind Map:



Tumors of the Kidney

1- Benign Tumors → Very rare

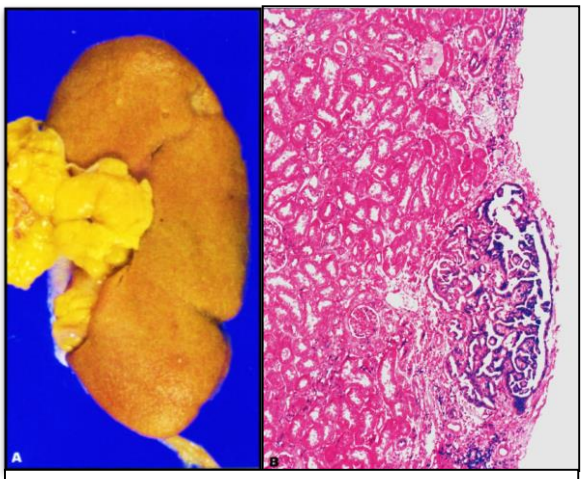
a. Renal Adenoma / Tubuloadenoma

Main characteristic → **small** Pale nodule on the renal cortex

UM[1] →Benign tubular cells that can appear as **Papilloma**.

It is not critical (LEAVE ME ALONE lesion)

Renal adenomas increase in frequency with age, and are asymptomatic, usually found at autopsy.



a. Kidney with ischemic atrophy also bears very small subcapsular **adenomas** near to each pole.

b. Histology of a subcapsular papillary **adenoma** shows tubules arranged in a papillary fashion

b. Angiomyolypoma

Angio = vascular , myo = smooth muscle cells , lypoma= lypomatous lesion.

-It can be large and bilateral → compresses the kidney

-It is very vascular → can cause **hemorrhage**.

-It's a benign tumor that arises from perirenal tissue severe peritoneal hemorrhage (can be mistaken for a malignant tumor).

-It is often associated with **tubulosclerosis** (the patient has to be screened for tubulosclerosis, especially if it's bilateral)

c. Oncocytoma

Similar to tubuloadenoma (but much bigger in size).

UM → benign cells are called **Oncocytes** (reddish granular cells which are **rich in mitochindria**)

Main characteristic → Large **tumor with a central scar** which could be seen in imaging (radio opaque).

Note: It can be mistaken for renal cell carcinoma.

[1] UM : under microsope

2- Malignant Tumors

1) Renal Cell Carcinoma/Allias Gravits Tumor/Clear Cell Carcinoma/Hypernephroma

Most common kidney tumor

General information about the tumor:

-This tumor is very common (5% of malignant tumors).

-It is called (Clear Cell Carcinoma) because the cytoplasm of malignant cells appear clear UM.

-The scientist who discovered this tumor was "Allias Gravits", and this is why the tumor is sometimes referred to as "Gravits Tumor".

- It arise from tubules of the kidney.

- Risk Factors:

Smoking tobacco / inherited or acquired cystic disease / obesity / certain drugs / working on cadmium industry.

Epidemiology:

-It often affects **male** patients who are between 50 and 70 year.

-It occurs in two ways:

1- Inherited → 10% → Absent VHL tumor suppressor gene.

2- Sporadic → 90%

Inherited:

VHL gene problems:

Some patients have a congenital loss or mutation of a VHL (von Hippel-Lindau) gene which is a tumor suppressor gene located on the short arm of chromosome 3. These patients are commonly present with hemangio blastoma (of the cerebellum or retina) and clear cell carcinoma.

Sporadic:

According to Prof.Alrikabi:

"The patient's doesn't have any problems in chromosome3, nor any deletions or problems with VHL"

According to Robbin's:

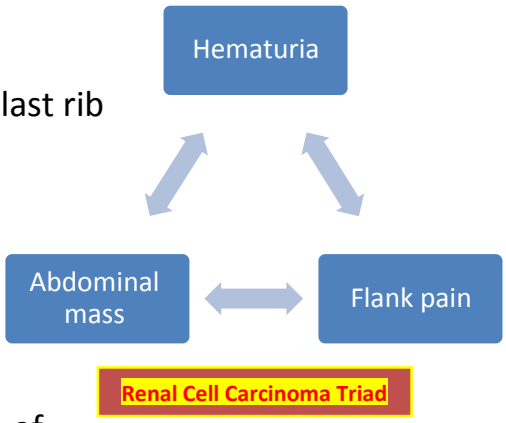
"Homozygous loss of VHL gene seems to be the common underlying molecular abnormality for both familial and sporadic forms"

Presentation:

Renal cell carcinoma patients are usually present with:

Specific

a. **Macroscopic hematuria** → the most common presentation.
b. **Flank pain**, which is a lateral pain between the last rib and the iliac crest.
c. **Abdominal mass**.



Non-Specific

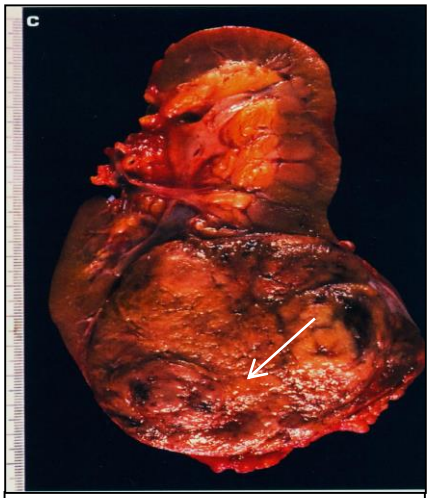
d. **Hyper tension**: This tumor sometimes increases renin secretion.
e. **Weight loss**: Sudden weight loss is generally on of the most common signs of malignancies.
f. **Pyrexia** of unexplained cause.
g. **Polycythemia** : This tumor has a paraneoplastic syndrome of Erythropoietin secretion which will stimulate RBC production(erythropoiesis) .

Metastatic

h. And sometimes –unfortunately- the patient doesn't notice anything until he presents with metastatic symptoms ie:
   i. Severe headache → Metastasis to the brain.
   ii. Pathological fractures → Metastasis to the bones.

GROSS:

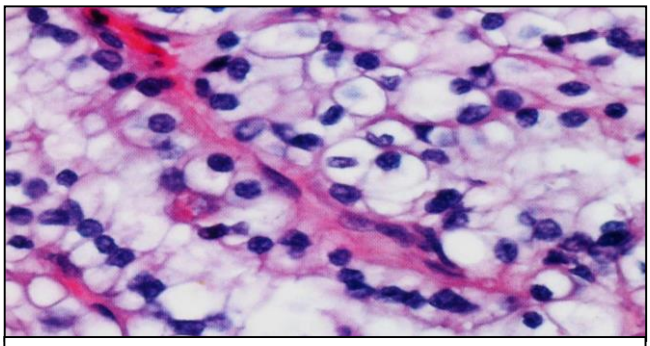
- The tumor is usually **WELL CIRCUMSCRIBED** with very clear margins (which is an unusual appearance of a malignant tumor).
- The cut surface shows a **pale** fatty tumor (it is actually full of lipids and glycogen as described later) with **areas of hemorrhage.**



Cut surface of a Typical renal cell carcinoma affecting the lower pole (arrow), you can notice the well circumscribed rounded and pale tumor with areas of hemorrhage

UM:

- The cells' cytoplasms are **filled with lipids and glycogen**, thus they **appear clear under** the microscope.
- It erodes blood vessels causing hemorrhagic and necrotic areas.



The cells are clear because of lipids and glycogen filling their cytoplasms + Hyperchromatism

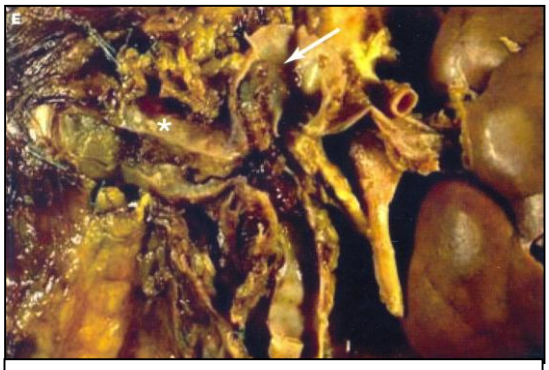
- **Venous Invasion:**

  This tumor likes to invade veins and forms thrombi which can be found even in the right ventricle!

  The route of invasion is as follows:

  (Renal vein → IVC → Right ventricle).

  NOTE: venous invasion is an indication for metastasis and bad prognosis.



Invasion of the renal vein and inferior vena cava (arrow) by **renal cell carcinoma**.

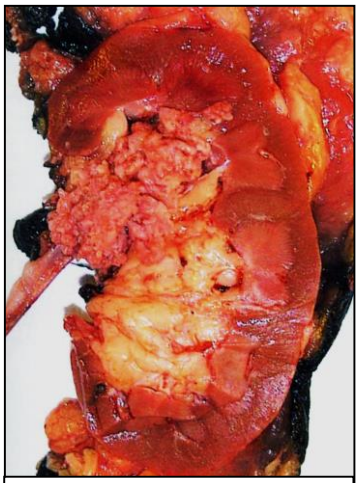
2) Papillary Cell Carcinoma:

- It is caused by a mutation in a gene called **MET**. Or patients have been on long term dialysis
- It has a papillary shaped growth.
- It has a slightly better prognosis than Clear Cell Carcinoma.
- Tumor stage (a measure of invasion and metastasis) is the most important prognostic factor.

3) Chromophobe Renal Cell Carcinoma:

4) Transitional Cell Carcinoma:

- It's a tumor that can appear in both the kidney and the bladder.
- In the kidney the affected region are the **calyces** due to their **transitional** lining.



Papillary urothelial (transitional cell) carcinoma of renal pelvis. Note the exophytic, multifronded nature of the tumor.

5) Nephroblastoma (Willm's Tumor):

- **Common in children between 2-10 years.**
- It rises from the metanephric ridge.
- The main affected cells are **the mesodermal** cells.
- The oncocells are called **(nephrobalstic cells)**
- These Nephroblasts are embryogenic cells that didn't differentiate in the prenatal life → when they become oncogenic they differentiate into different types of tissues which can be noticed UM. Their growth in the same place will result in a large mass.
- They are mainly caused by the absence or mutation of two tumorsupressor genes **WT1**and**WT2** which are present on the short arm of **chromosome 11**

It is the most common primary tumor and abdominal tumor in children.

- Mutation in **WT1** will result in **WAGR syndrome**:
  W: **W**illms tumor.
  A: **A**nyridia → absence of the iris.
  G: **G**enital system abnormality.
  R: motor **R**etardation
- Mutation of WT2 will result in **Beckwith-Wiedmann** syndrome:

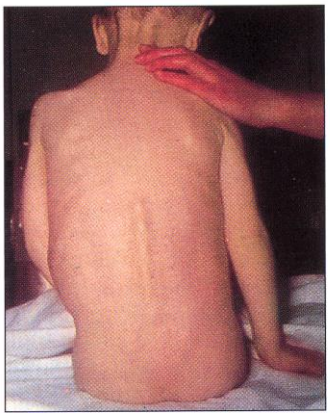
  It's a set of **various anomalies** that present with Wilm's tumor.

  These anomalies are:

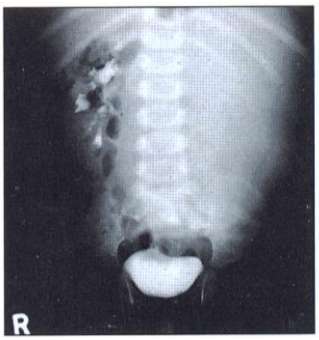
  1. Hemihypertrophy: a gross **asymmetry** due to unilateral muscular hypertrophy.
  2. Macroglossia: Abnormally thick and big tongue.
  3. Organomegaly
  4. They are generally fat.
  5. Neonatal hypoglycemia.

Presentation:

- Most common presentation is with a **big abdominal mass** that could be obviously noticed even by his family. This mass usually appears in th left abdomen and can extend to the middle(Picture)



6.109 Nephroblastoma (Wilms' tumour). This 8-year-old boy had a mass in the left loin which moved on respiration and was ballotable. Its renal nature was confirmed on intravenous urogram (**6.110**) and a nephroblastoma was found at surgery.



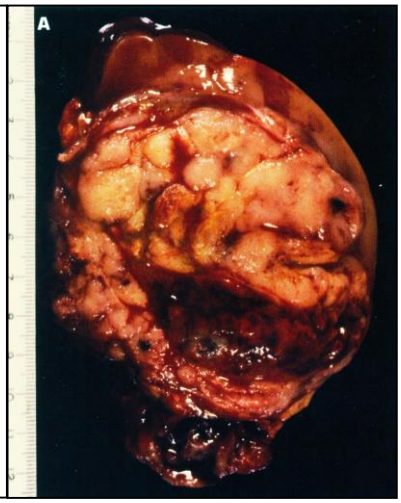
6.110 **Nephroblastoma (Wilms' tumour).** This intravenous urogram shows a vast mass occupying the entire left loin.

- The child usually **fails to thrive** خامل, he is immunosuppressed and his growth is delayed
- He can also be present with HTN(Nephroblastoma is one of the rare causes of hypertension in children).
- Urogram shows the **tumor occupying most of the kidney**, and has damaged the calyces. In some cases you can notice that a small part of the kidney is still functioning.

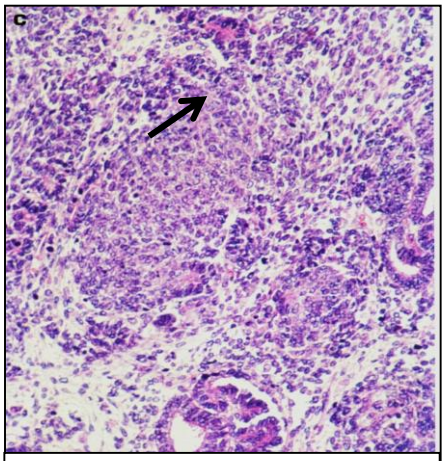
GROSS:

The tumor is firm and pale, with few hemorrhagic and necrotic areas. The kidney is **almost TOTALLY DESTRUCTED**.

Solid, bulging, fleshy tan-white, partially necrotic tumor has replaced much of the kidney and is encompassed by a thin rim of renal tissue.



UM: UM you see very **primitive cells** خلايا بدائية, there are nephroblastic cells, rhabdomyoblasts and mesoblastic cells **forming primitive tissues** (primitive and poorly formed glomeruli, primitive tubules, primitive skeletal muscles…)



Histology shows hypercellular areas comprising undifferentiated blastema, loose stroma with undifferentiated mesglomeruloid body.

(arrow) primitive glomeruli

Summary of the clinical presentation of wilm's tumor:

[Faliure to thrive + abdominal mass + anemia + 2-10 year]

Prognosis:

5% of tumors contain foci of anaplasia.

Anaplasia is an indication of poor prognosis

Tumors of the Urinary Bladder

The most common presentation of bladder tumors is GROSS PAINLESS HEMATURIA.

Thus, when a patient is complaining about passing blood and blood clots in his urine, put in your mind both renal cell carcinoma and bladder tumors.

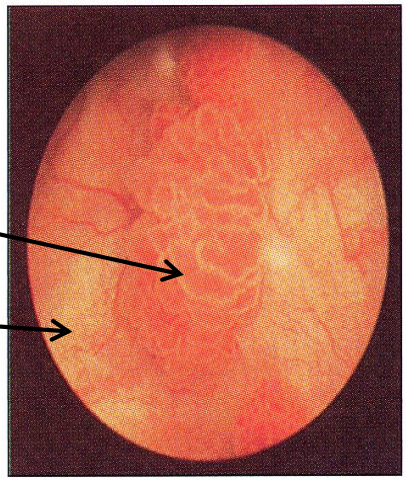
Examination of the bladder if there is a tumor suspicion:

1- CT scan:

CT scan of the abdomen is a usual choice for bladder examination. The tumor will show up as a mass in the bladder. (CT is a good method, especially when you are suspecting both bladder carcinoma and renal cell carcinoma.)

2- Cystoscopy:

This method is done by entering a cystoscope through the penis or the ureter of the patient → Inject a saline → and you examine the bladder with help of a light → take a biopsy

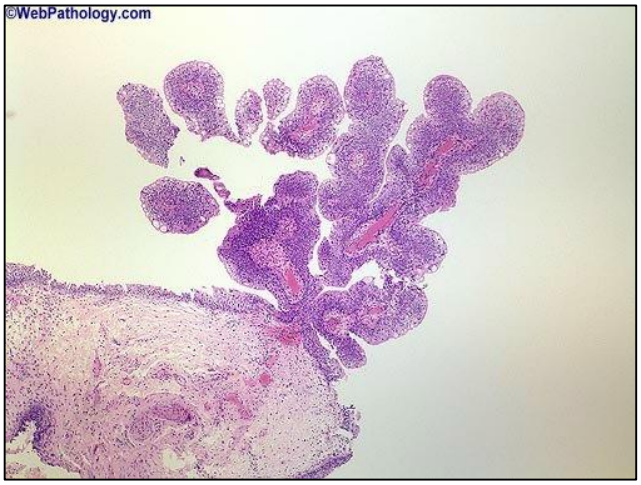


6.26 Cystoscopy revealing a transitional cell carcinoma of the bladder. The patient presented with painless haematuria.

There are different types of urothelial neoplasms:

- Papilloma
- PUNLMP (Papillary urothelial neoplasm of low malignant potential)
- Urothelial carcinoma in situ
- Urothelial carcinoma (low grade and high grade)

1) Papilloma:



- Are rare, benign and usually solitary.
- They measure 0.2- to 1.0-cm frondlike structures having a delicate fibrovascular core covered by multilayered, well-differentiated transitional epithelium.

2)Papillary urothelial neoplasm of low malignant potential (PUNLMP).

- They are well differentiated tumors of low malignant potential (It is benign but have some malignant cells. So I have to keep my eye on the patient.). They are always papillary and are rarely invasive, but they may recur after removal.

Transitional Cell Carcinoma/Squamous Cell Carcinoma Of The Bladder / Urothelial Carcinoma:

General Info:

- It is usually preceded by **Tansitional Cell Carcinoma In Situ**. (up to 75% of **Urothelial carcinoma in situ** cases go on to invasive cancer if untreated.(If the basement membrane raptured it will invade)
- Most of the patients are above 50 year old.
- Its appearance in cystoscopy is **seaweed like**.
- It ranges from well differentiated papillary carcinoma, to poorly differentiated and muscle invasive.
- Main cytogenic molecular findings are deletion of the short or long arm of **chromosome 9**, and **deletions of 17p which involves p53 gene** (an important tumor suppressor gene).

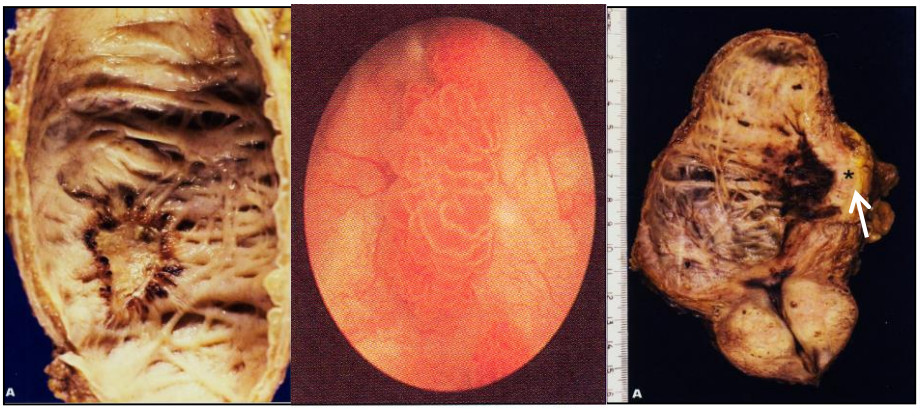
Predisposing Factors:

Cause	Notes
Smoking	Nicotine and its metabolites are carcinogenic for epithelial cells. Increases risk up to five times. It predisposes to both Renal Cell Carcinoma & Transitional Cell Carcinoma.
Analgesics (especially Phenacetin)	Mainly associated with renal pelvis transitional cell carcinoma, but also bladder tumors. Its combination with diuretics will increase the risk.
Occupation (Mainly textile industry workers)	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 (Bilharzias)	Causes chronic inflammation → metaplasia (squamous) of the bladder mucosa →squamous cell carcinoma Schistosomiasis is endemic in certain countries (ex; Egypt) The main cause of infection is swimming in contaminated water.
Chronic infections/inflammation	Some authorities believe that any chronic inflammatory process may predispose to cancer

GROSS:

The lesion could be:

- In situ (most left)
- Papillary (middle)
- Invasive (most right) the tumor is invading the muscular layer (arrow)

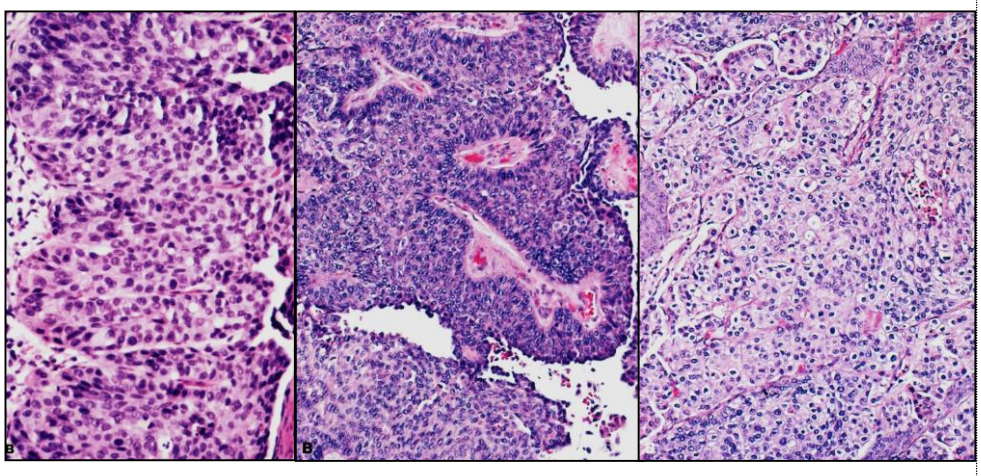


UM:

In histology you could see:

- Carcinoma in situ, where the tumor **didn't invade the basement membrane**

- Moderately differentiated papillary carcinoma.(middle)- Poorly differentiated carcinoma (most left)



GRADING & STAGING OF TCC:

GRADE	DEFINITION
G1	Well differentiated
G2	Moderately differentiated
G3	Poorlydifferentiated/undifferentiated
STAGE	**DEFINTION**
Tis	Carcinom in situ
Ta	Non papillary invasive tumor
T1	Tumor invades suepithelial CT
T2	Tumor invades muscularis propria
T3	Tumor invades beyond muscularis propria
T4	Tumor invades prostate/uterus/abdomin
N0	No lymphnode metastasis
N1	Single lymphnode metastasis
N2	Multiple lymphnode metastasis or ≤5cm
N3	Multiple metastasis ≥5cm

PROGNOSIS:

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

Summary (from Robbins)

Renal cell carcinoma account for 2% to 3% of all cases in adults and are classified into three types:

- **Clear cell carcinomas are the most common and are associated with homozygous loss of the VHL tumor suppressor protein; tumors frequently invade the renal vein.**
- **Papillary renal cell carcinomas frequently are associated with increased expression and activation mutations of the MET oncogene; they tend to be bilateral ant multiple and show variable papilla formation.**
- **Chromophope renal cell carcinomas are less common; tumor cells are not as clear as in the other renal cell carcinomas.**

Questions from Pathology Recall book

1/ In what population is renal cell carcinoma most commonly found?

- Men of 50-70 years of age (men: women = 2:1)

2/ What chromosome is involved in renal cell carcinoma?

- Chromosome 3

3/ Describe the clinical manifestations of renal cell carcinoma?

- Hematuria, palpable mass, flank pain, fever, and secondary polycythemia with erythrocytosis.

4/ What is the method of spread in renal cell carcinoma?

- Hematogenous dissemination by invading renal veins or vena cava.

5/ What is the most common renal malignancy in children?

- Wilms tumor.

6/ What is the most common presentation of Wilms tumor?

- Palpable flank mass causing abdominal distention.

7/ Wilms tumor is associated with deletions of short arm of what chromosome?

- Chromosome 11.

8/ What is the most common presentation of transitional cell carcinoma?

- Painless hematuria.

9/ What toxic exposures are associated with transitional cell carcinoma?

- β – naphthylamine, phenacetin, cigarettes and cyclophosphamide (Dr. Sofia mentioned some of them).

10/ What angiomyolypoma is commonly associated with?

- Tubulosclerosis

Case 1/ A 55- year-old man presents to his primary care physician complaining of gross hematuria and right loin pain. Physical examination reveals a flank mass. The complete blood count reveals a hemoglobin level of 21 g/dL and polycythemia. Ultrasound shows a 6.0-cm mass at the upper pole of the right kidney. What is the most likely diagnosis?

A. Renal cell carcinoma
B. Transitional cell carcinoma
C. Papilloma
D. Angiomyolypoma

Case 2/ Histologic sections from an abdominal mass that was removed from a 13-month-old female reveal undifferentiated mesenchymal cells, immature tubules, and abortive glomerular formation. Which of the following is the most likely diagnosis for this tumor?

A. Dupuytren tumor
B. Ewing tumor
C. Transitional cell carcinoma
D. Wilms tumor

The cases from case files Pathology book

Answers:

- Case 1 / A
- Case 2 / D

اللهم إني استودعتك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي اليه انك على كل شيء قدير

432 Pathology Team

Good Luck ^_^