UGS PATHOLOGY

MID | LECTURE 6

URINARY SYSTEM TUMORS

Done by:

Laith Alhuniti

Mahmoud Aljunaidi

Renal Tumors

- Benign neoplasms, which are all adenomas, such as small cortical papillary adenomas (<0.5 cm in diameter), are found in up to 40% of adults in autopsies. They are usually small and have no clinical manifestations; thereby they may go unnoticed and only to be seen postmortem.
- The most common malignant neoplasm of the kidney is **renal cell carcinoma (RCC)**, particularly in adulthood (middle age or older).
- **Nephroblastoma (Wilms tumor)** is the second most common type of tumor and occurs mostly in children and the younger ages.

✓ Any tumor arising in the kidneys should be addressed and is considered significant whether benign or malignant.

Oncocytoma

- A **benign neoplasm** that arises from the intercalated cells of collecting ducts.
- It presents as a cortical mass, that can mimic malignant neoplasms.
- It represents about 10% of renal neoplasms.
- It is associated with loss of **chromosomes 1 and Y**, which is characteristic.
- Oncocytomas are characterized by a **plethora (large number) of mitochondria**, causing a tan color and finely granular eosinophilic, bright pink, cytoplasm seen histologically.
- A **central stellate (star) scar** is a characteristic feature of oncocytomas seen on imaging studies.

Renal Cell Carcinoma (RCC)

- It is derived from the renal tubular epithelium.
- It is located predominantly in the **cortex**.
- It represents 80–85% of all primary **malignant** neoplasms of the kidney and 2–3% of all cancers in adults.
- Most common in the 6th–7th decades of life.
- Male to female ratio (M:F) = 2:1 (males are more affected)

❖ **Risk Factors of RCC:**

1. Smoking.
2. Hypertension.
3. Obesity.
4. Occupational exposure to cadmium, a heavy metal.
5. Acquired polycystic renal disease, like kidney stones (30× increase in risk).
6. Genetic factors.

❖ Classification of RCC:

The three most common forms/ subtypes are:

1. Clear cell carcinoma
2. Papillary renal cell carcinoma
3. Chromophobe renal carcinoma

➢ Classification is dependent on the histological appearance of the neoplastic cells; however, each subtype has its own genetic mutation that is characteristic.

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1) Clear Cell Carcinoma

- It is the **most common type**.
- Accounts for 65% of renal cell cancers.
- Mostly sporadic, but also occurs in familial forms or in association with **von Hippel–Lindau (VHL) disease;** inherited forms are associated with VHL disease.
- Histologically composed of large cells with **clear cytoplasm**; thereby "clear" cells.

Von Hippel–Lindau (VHL) Disease

- Inherited as an **autosomal dominant trait.**
- Characterized by:
    1. Predisposition to a variety of neoplasms, particularly hemangioblastomas of the cerebellum and retina.
    2. Bilateral renal cysts and bilateral multiple clear cell carcinomas (in 40–60% of affected individuals).

❖ Genetics of VHL

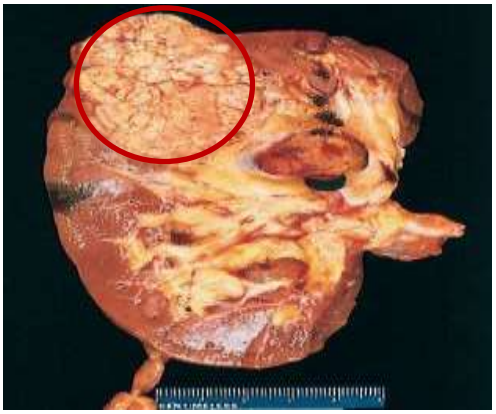
- Individuals with VHL disease inherit a germline mutation of the VHL gene on **chromosomal band 3p25**, an inevitable event, and lose the second allele by somatic mutation, creating a condition of homozygosity of the gene mutation and is presented in younger age.
- The VHL gene is also involved in the majority of sporadic clear cell carcinomas, but development and presentation take time, because it requires the 2 alleles to be mutated and inactive.
- **Loss of a segment on chromosome 3p that harbors the VHL gene is often seen in sporadic renal cell cancers.**
- The second, non-deleted allele is inactivated by somatic mutation or hypermethylation in 60% of sporadic cases.

❖ Pathogenesis of VHL:

- The VHL protein causes degradation of **hypoxia-inducible factors (HIFs)**.
- HIFs are transcription factors that contribute to carcinogenesis by stimulating the expression of **vascular endothelial growth factor (VEGF)** and other genes that drive tumor cell growth.
- If the VHL gene fails to degrade hypoxia-inducible factor (HIF), HIF accumulates within the cell and **triggers nuclear signaling pathways**. This activation is linked to key growth factors involved in carcinogenesis, particularly VEGF. As a result, continuous signals promoting cell proliferation are generated. This explains how mutation of the VHL gene contributes to the development of cancer.

➢ An uncommon familial form of clear cell carcinoma, unrelated to VHL disease, is associated with cytogenetic abnormalities involving the **short arm of chromosome 3 (3p).**

❖ Morphology:



- Usually solitary and large.
- Spherical and may arise anywhere in the cortex.
- Well demarcated, but with tumor progression, the clear boundary may be lost as the tumor begins to invade surrounding tissues, and this invasion can occur in multiple directions as the tumor advances.
- Tumor growth can extend into several structures, including:

1. The cortical tissue.
2. The renal capsule, which becomes stretched due to tumor expansion.
3. The perinephric fat.
4. The adrenal gland.

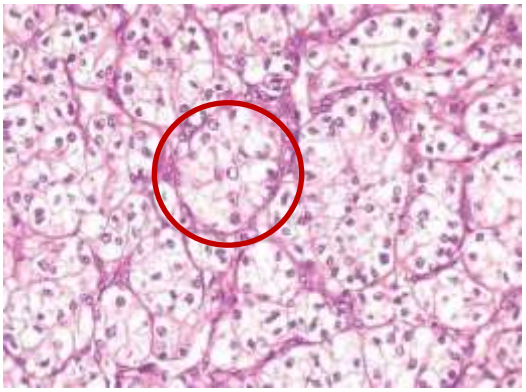
- Cut surface: yellow to orange to gray-white, with prominent areas of cystic softening or hemorrhage, and with higher grades necrosis can be seen.

❖ Tumor Behavior

- Initially well-defined margins, but local invasion occurs with tumor progression.
- The tumor invades the renal vein and grows as a solid column within the vessel.
- It may extend in a serpentine fashion into the **inferior vena cava (IVC)** and even into the right side of the heart.
- Direct invasion into perinephric fat and adrenal gland may occur.
- The tumor can invade the draining veins, particularly the IVC, and form intraluminal tumor columns (tumor thrombi) that partially or completely obstruct

blood flow. This can lead to significant clinical manifestations related to venous obstruction.

❖ Histology:



- The tumor cells are relatively large due to their abundant cytoplasm.
- The cytoplasm appears empty on microscopy, not because it is truly empty, but because it contains glycogen and lipids that are dissolved during tissue processing, giving the cells a "clear" appearance.
- **And depending on lipid and glycogen content, cells may appear vacuolated or solid.**
- Classic clear cells are **lipid-laden** and demarcated by cell membranes.
- Nuclei are usually small and round, and their appearance is very important in tumor grading.
  - ✓ Tumor grading is crucial because it reflects the patient's prognosis.
  - ✓ One of the key parameters used in grading is the appearance of the nuclei, particularly the **degree of pleomorphism, hyperchromasia, and the presence and size of nucleoli.**
- Tumor cells may also be **granular**, resembling tubular epithelium of the collecting ducts with small, round, regular nuclei and pink cytoplasm. And these granular cells are sometimes mixed with clear cells.
- **Highly anaplastic tumors show:**
  - ✓ Numerous mitotic figures.
  - ✓ Enlarged, hyperchromatic, pleomorphic nuclei.
- Stroma is usually scant but **highly vascularized**, since it's an aggressive tumor.
- The tumor is arranged in nests or islands separated by delicate fibrous septa. When clear cells predominate, the tumor is classified as clear cell carcinoma, although mixed patterns with other tumor cell types can also be seen.

❖ Summary Morphology

- Solitary, large tumors when symptomatic.
- Spherical masses measuring 3–15 cm in diameter.
- Arise anywhere in the cortex.
- Cut surface: yellow/orange/gray-white with cystic and hemorrhagic areas.
- Margins initially well defined.

❖ Extension

- Tumor **invades** renal vein and may extend to inferior vena cava and heart.
- Some tumors are highly anaplastic.
- Higher-grade tumors show marked cellular atypia, with bizarre and pleomorphic cells. In some cases, the tumor undergoes **sarcomatoid differentiation**, which represents a high-grade pattern associated with very aggressive behavior.
- These tumors may exhibit features resembling various sarcomas, such as fibrosarcoma, leiomyosarcoma, and rhabdomyosarcoma, with highly atypical, pleomorphic cells.

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2) Papillary Renal Cell Carcinoma

- Accounts for 10–15% of renal cancers.
- Defined by **papillary growth pattern**; finger-like projections composed of tumor cells arranged over a central fibrovascular core.
- Frequently multifocal and bilateral, involving both kidneys.
- Often presents as early-stage tumors or low-grade tumors.
- Occurs in familial and sporadic forms.
- Arises from **proximal tubular epithelial cells**.

❖ Genetics

- **Not** associated with chromosome 3 abnormalities, unlike clear cell carcinoma.
- Characterized by mutation of the **MET proto-oncogene on chromosome 7q.**
- **MET encodes a tyrosine kinase receptor for hepatocyte growth factor**. A mutation in this gene leads to continuous signaling for cell division, promoting oncogenesis and tumor development. So, hepatocyte growth factor plays a role in tumor metastasis and invasion.

❖ Morphology

- Shows various degrees papillary structures with fibrovascular cores.
- Often bilateral and multiple.
- May show necrosis, hemorrhage, and cystic degeneration.
- **Less orange-yellow due to lower lipid content.**
- Cells may have clear or more commonly pink cytoplasm.

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3) Chromophobe Renal Carcinoma

- **Least common type** (5% of RCCs).
- Arises from **intercalated cells of collecting ducts**, same as oncocytoma.
- Cells stain darker (i.e, they are less clear) than those in clear cell carcinoma.

- Characterized by **loss of multiple entire chromosomes** → extreme hypoploidy (reduced chromosome number). So, this tumor is characterized by not having a specific gene mutation.

❖ Morphology

- Grossly **tan-brown** tumor.
- Cells usually have clear, flocculent cytoplasm with prominent distinct cell membranes.
- Nuclei are surrounded by halos of clear cytoplasm (perinuclear halos).
- Ultrastructurally show numerous **macrovesicles**.

❖ Prognosis

- Chromophobe renal cancers have a favorable prognosis, better than other subtypes.

❖ Clinical Features of RCC in general:

- A patient in the appropriate age group may present with a characteristic triad of symptoms, raising suspicion for this cancer and prompting further evaluation, such as radiological imaging.
- Most common presentation: **hematuria (blood in urine)** (>50%).
  - ✓ Painless hematuria is a key feature, leading to discoloration of the urine that the patient may notice.
- Macroscopic hematuria (visible) is intermittent, fleeting, and occurs on top of persistent microscopic hematuria.
- Less commonly: flank pain and palpable mass mainly in the posterior aspect.

❖ Paraneoplastic Effects (extrarenal effects):

- Fever
- Polycythemia (increased red blood cells) due to excess **erythropoietin (EPO)** production. It occurs in 5–10% of patients.
- Paraneoplastic syndrome due to tumor production of other hormone-like substances resulting in:
  - Hypercalcemia (parathyroid)
  - Hypertension (aldosterone)
  - Cushing syndrome (cortisol)
  - Feminization or masculinization (corticosteroids or androgens)

❖ Urinary Bladder Tumors

- Bladder cancer accounts for approximately 5% of cancers.
- The bladder is lined by urothelium, which is also found throughout much of the urinary system and part of the urethra. Therefore, tumors that develop in the bladder can also arise in other areas lined by the same epithelium.

❖ Types

1. Urothelial carcinoma, also called transitional cell carcinoma. (Vast majority)
2. Squamous cell carcinoma, caused by metaplasia due to chronic irritants. (3–7%)
3. Adenocarcinoma (rare)

- Male predominance (M > F)
- 80% of patients are aged 50–80 years.

❖ Risk Factors

1. Cigarette smoking.
2. Occupational carcinogens: therefore, it is important to take a detailed occupational and environmental history, as exposure to certain carcinogens may help explain the development of cancer.
3. Cyclophosphamide therapy or radiation.
4. **Family history of bladder cancer.**
5. Squamous cell carcinoma linked to **Schistosoma haematobium** infection (endemic areas).
6. **Acquired** genetic mutations.

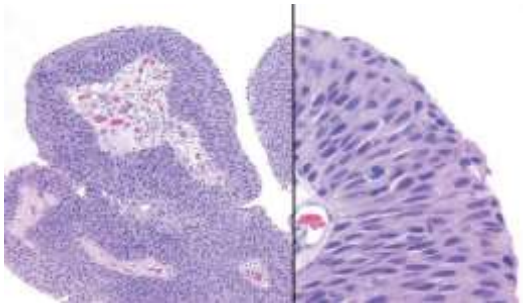
❖ Precursor Lesions of invasive urothelial carcinoma:

- A key aspect of urothelial carcinoma is the presence of precursor lesions, which can be identified before the development of invasive carcinoma. Recognizing these early changes is important, as it allows for close monitoring and appropriate follow-up of the patient.
- **Two main types:**

1. Noninvasive papillary tumor (most common)
2. Carcinoma in situ (CIS)

❖ Grading of Noninvasive Papillary urothelial Tumors

- Most important prognostic factor is **grade**.
- The grade is based on architectural (degree of the dysplasia of the epithelium) and cytologic (dysplastic features of the nuclei) features.



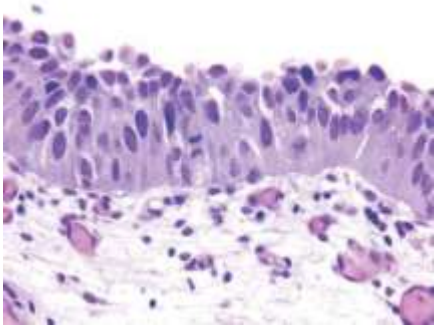
- From the figure you can see Noninvasive low-grade papillary urothelial carcinoma. Higher magnification (right) shows slightly irregular nuclei with scattered mitotic figures.
- The core of the papillae is composed of **vascularized fibrous tissue** (the red structures in the light region). The overlying epithelium shows features of nuclear dysplasia, with tumor cells exhibiting mitotic activity. The extent of these changes varies depending on the tumor grade.

❖ Classification according to grading:

1. Papilloma, benign lesion characterized by a papillary architecture lined by normal epithelium.
2. Papillary urothelial neoplasm of low malignant potential (**PUNLMP**), some nuclear changes may be present, which may indicate potential progression toward a more advanced tumor.
3. Low-grade papillary urothelial carcinoma
4. High-grade papillary urothelial carcinoma
   - ✓ (3+4) are invasive subtypes that are classified based on the depth of invasion, including involvement of the subepithelial tissue or extension into the muscular wall.

❖ Carcinoma in Situ (CIS)

- Defined as malignant appearing cells within flat urothelium.
- Carcinoma in situ (CIS) is characterized by the absence of invasion, no increase in epithelial thickness, and no papillary architecture. Despite these features, it is clinically important because it has a **high potential to progress to invasive carcinoma.**
- **Often multifocal.**
- May involve bladder, ureters, and urethra.
- Without treatment, 50–75% progress to invasive cancer.
- From the figure on the right, you can see carcinoma in situ (CIS) with enlarged **hyperchromatic nuclei and a mitotic figure**.
- This represents urothelial (transitional) epithelium in which **nuclear atypia involves the full thickness of the epithelial layer**, with features such as pleomorphism and hyperchromasia, and these define carcinoma in situ (CIS).
- Normally, the superficial urothelial cells (umbrella cells) are larger, with abundant cytoplasm and clear maturation. In CIS, this **normal maturation is lost**, highlighting the abnormal state.



- It is termed “in situ” because the **basement membrane remains intact**, appearing as a thin, continuous line with no evidence of invasion into the underlying tissue.

❖ Invasive Urothelial Carcinoma

- May arise from high-grade papillary urothelial tumors (often high grade) or CIS.
- Can invade:
  - Lamina propria (superficial layer)
  - Muscle layer (deep invasion)
- Most important prognostic factor: **stage (extent of invasion and spread at the time of initial diagnosis)**
- **Almost all infiltrating urothelial carcinomas are high grade.**

❖ Clinical Features of Bladder Cancer

- Painless hematuria: This represents an early yet serious manifestation, as the urothelium can undergo bleeding or necrosis. Therefore, it is essential to proceed with further investigations to evaluate for an underlying tumor.

❖ Risk of Recurrence Depends On:

1. Tumor size
2. Stage
3. Grade
4. Multifocality (multiple tumors)
5. Mitotic index (cell division rate)
6. Associated dysplasia
7. Presence of CIS in surrounding mucosa.

➢ Urothelial carcinomas have a strong tendency to recur and are quite common. Patients often require long-term follow-up due to repeated recurrences. Additionally, increased exposure to risk factors further raises the likelihood of developing and recurring disease.

Quiz on this lecture: [Link]

Anything wrong? [Feedback Form]