Lecture 7- Renal and Lower Urinary tract tumors

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Please note that I added some information to make sense of what's written in the slides.

In this lecture, we'll discuss two main cancer categories, a) Those affecting the kidneys (Renal carcinomas) b) Those affecting the lower Urinary tract (mostly the Urinary bladder).

Please note that all the neoplasms discussed in this lecture are malignant (Cancers), benign neoplasms do exist of course but are not discussed in the slides.

A) Renal tumors. ===> We will discuss Renal Cell Carcinoma (associated with the elderly) and Wilms tumor (associated with children)

I) Renal Cell Carcinoma (RCC): As the name implies, it's a carcinoma thus has an epithelial origin. This helps you remember that the cell of origin is the renal tubular epithelial cells **in the cortex.**

Epidemiology: Affects the elderly (6^{th}-7^{th} decades).

Also, it's more common in males than females (M:F ratio is 2:1, how to remember that? Link it with the risk factors discussed below).

RCC is the most common malignant tumor of the kidneys.

Risk factors: a) Occupational exposure to Cadmium in the workplace (Examples include Soldering(,(لحام Nickel-cadmium batteries, and dealing with Cadmium containing paints.)

b) Smoking cigarettes.

NOTE: Men are more likely to work in Soldering and thus get exposed to Cadmium containing substances. Also, prevalence of smoking is generally higher in men than women). I use this to remember that the prevalence of RCC is greater in Men than women.

c) Hypertension and obesity.

d) A patient who has end-stage renal failure would undergo chronic dialysis sessions. This chronic dialysis exposes the patient to an acquired cause of renal cystic disease called Acquired cystic kidney disease. Patients with this disease have much greater risk of developing renal cell carcinoma (This was discussed in the renal cystic disease lecture, I guess.)

RCC is divided genetically and molecularly into three subtypes:

A) **Clear cell carcinoma:** As the name implies, it microscopically appears to have cells with clear cytoplasm. It's the most common RCC subtype accounting for 70-80 % percent of RCC cases.

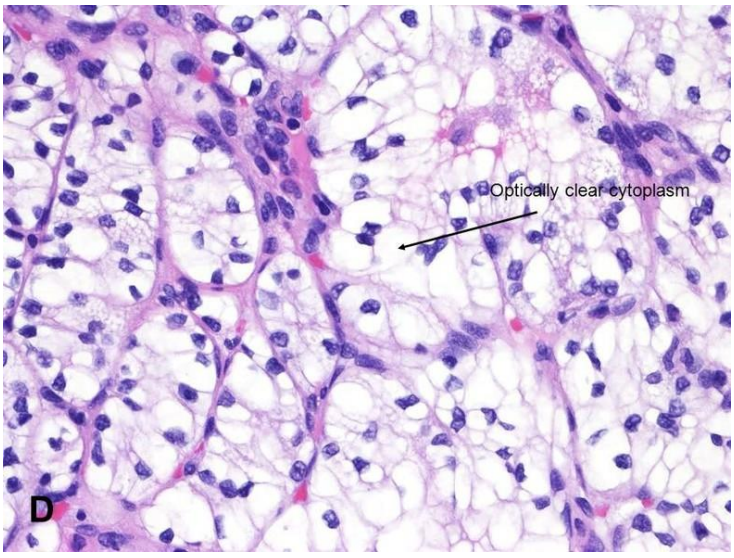
Like most other cancers, clear cell renal carcinoma could occur either sporadically or could be inherited. (Most cases occur sporadically in fact)

Without digging into a lot of details, the most important genetic mutation associated with clear cell carcinoma is the mutation in the tumor suppressor gene called VHL (Von-Hippel Lindau) gene.

I) Familial cases occur in the settings of VHL disease (we discussed it briefly during the Neuroscience lectures, within the familial tumor syndromes lecture. We said that patients born with a mutation in VHL genes inherited in an autosomal dominant fashion usually have hemangioblastomas of the cerebellum and the retina. **We also said that those patients have an increased risk of renal cell carcinoma**, now you know why! VHL is a tumor suppressor gene on 3p chromosome and its loss results in an oncogenic cascade of events that I'd rather not discuss so you don't get lost with the details).

Ii) Sporadic cases: Acquired mutations in one VHL gene followed by a "second hit" or hypermethylation of the other (normal/healthy) VHL gene accounts for 60% of cases of sporadic clear cell renal carcinoma.

Bottom line: Although other mutations do exist, just keep this association in mind (VHL with Clear cell renal carcinoma).



B) Papillary renal cell carcinoma:

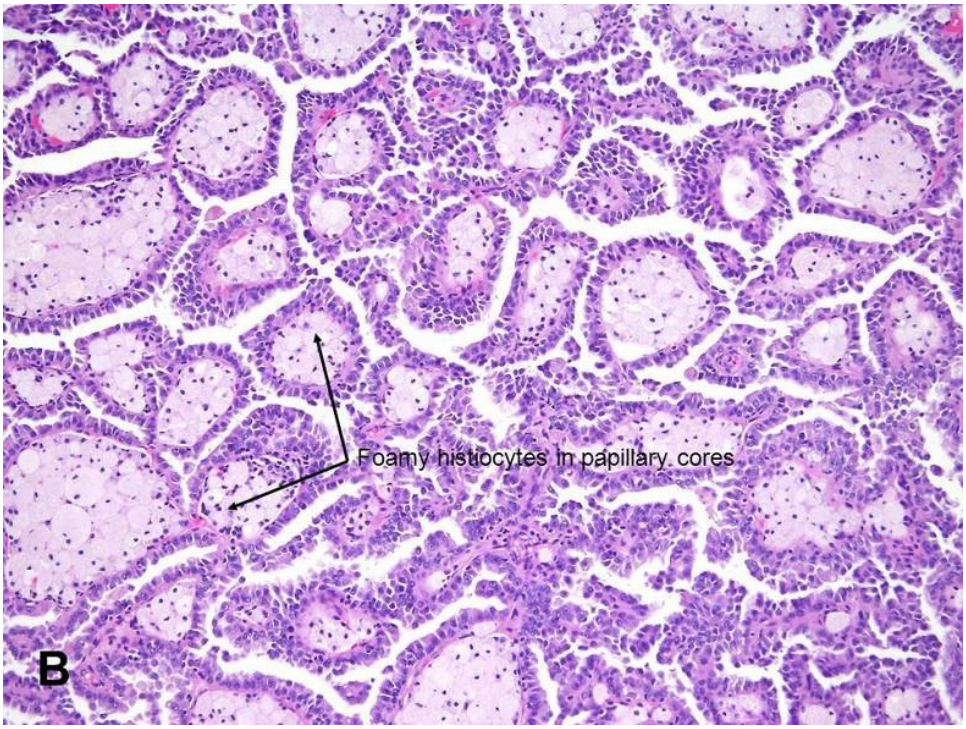
As the name implies, cells grow in an outer projecting fashion; papilla.

Those account for 10 –15% of RCC cases (comes 2nd after clear renal cell carcinoma).

They occur **bilaterally** in both kidneys and are usually **multifocal**.

Similarly to clear cell carcinoma, papillary renal cell carcinoma can occur both sporadically and as a part of a familial syndrome. However, **papillary renal cell carcinoma mutation occurs in the MET proto-oncogene on chromosome 7q**, while **clear cell carcinoma mutation occurs in the VHL tumor suppressor gene of chromosome 3p)**

This MET over activation results in uncontrolled growth of epithelial cells at the level of the proximal tubular epithelial cells accounting for the papillary overgrowth.



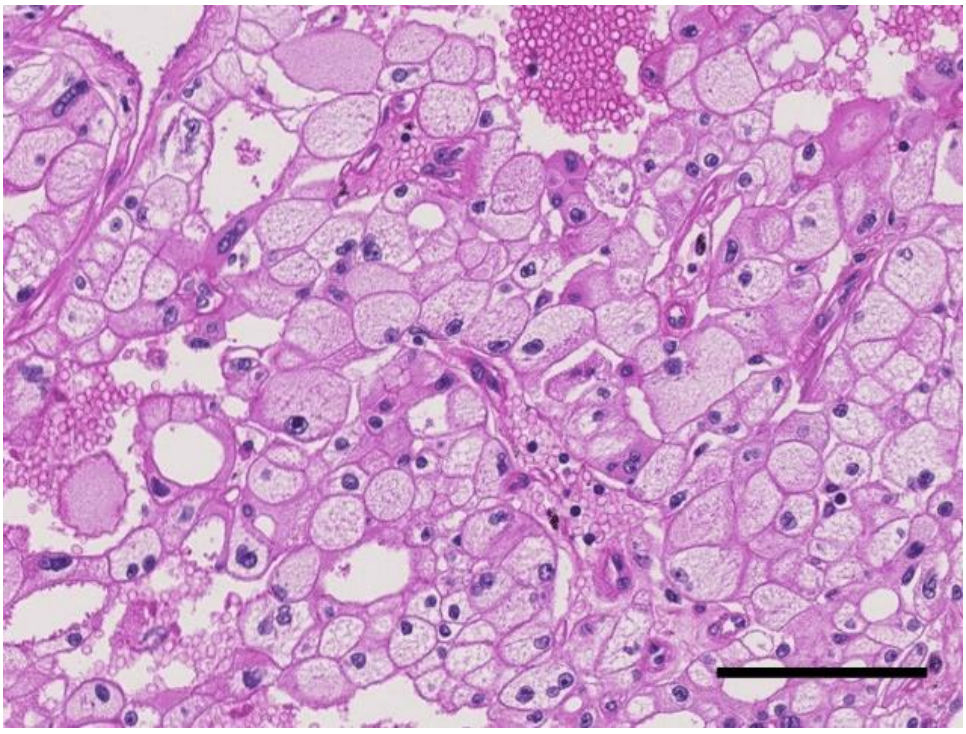
C) Chromophobe Renal Carcinoma: As the name implies, the cytoplasm of such cells looks "less clear" than the clear cell carcinoma subtype.

Cell of origin: Intercalated cells of the collecting ducts.

-**They are the least common subtype of RCC** (Remember clear cell carcinoma> Papillary renal cell carcinoma> Chromophobe renal carcinoma).

What's so special about their etiology? The underlying cause is not an aberration within the chromosomal structure as seen with the two previous entities, the abnormality is a COMPLETE LOSS of whole chromosomes, resulting in hypodiploidy (that is having chromosomal number fewer than the diploid number of chromosomes). And since multiple chromosomes can actually be lost including chromosomes 1,2,6,10,13, 17, 21, this results in what's called EXTREME hypodiploidy, owing to the fact of the loss of MULTIPLE chromosomes).

-It has a very good Prognosis.



Clinical presentation of Renal Cell Carcinoma:

A) A classical triad of painless hematuria, palpable abdominal mass, and flank pain is typical for RCC. However, the most important of this triad is the painless hematuria which occurs in 50% of RCC patients.

B) Paraneoplastic syndromes:

I) Release of Erythropoietin accounts for the occurrence of Polycythemia (in 5-10 % of patients)

Ii) Release of Parathyroid hormone releasing protein accounts for hypercalcemia.

Iii) Release of ACTH accounts for Cushing's Syndrome.

IV) Release of Renin accounts for Hypertension (through RAAS system, revise CVS).

V) Feminization/ Masculinization.

C) Fever is also seen.

Unfortunately, RCC can metastasize, commonly to the lungs and bones.

-One important clinical correlate includes the fact that RCC could lead to compression of the renal vein. Why is that important? If the left renal vein is occluded by RCC in the left kidney, this leads to back flow of blood through the left testicular vein to the left testis resulting in a Varicocele (دوالي الخصية). This only applies to the left renal vein because the left testicular vein drains into it. Whereas the right testicular vein drains directly into the IVC and not into the right renal vein, so even if it is occluded it won't lead to the occurrence of a varicocele (This is quick revision, as we took this earlier in the GI system).

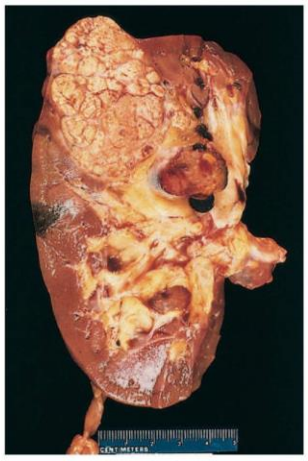
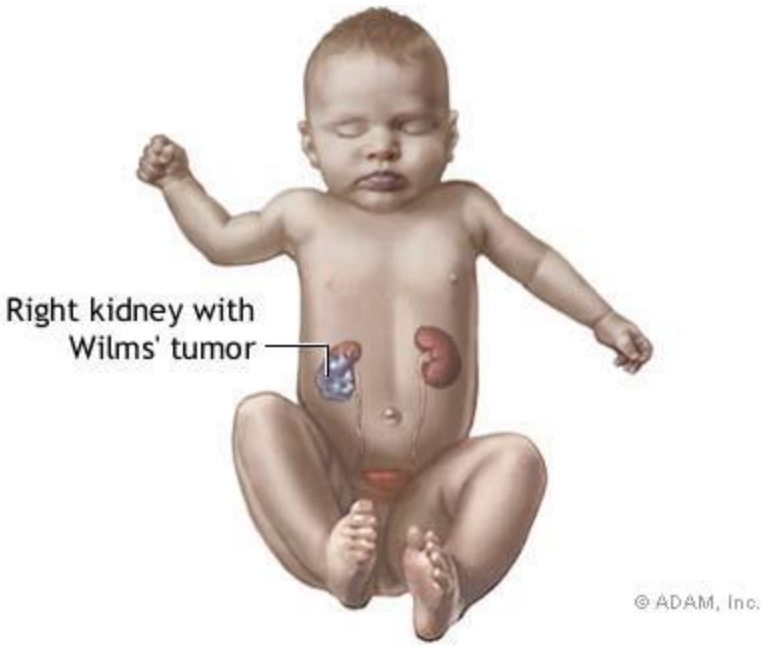


Fig. 14.24 Renal cell carcinoma: Representative cross-section showing yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated, thrombosed renal vein.

2) Wilms tumor: If you see a *CHILD* with a renal mass, consider Wilms tumor in your differential dx.

- **It's the third most common solid cancer in *children* younger than ten-year-old.**
- **Again, it could be sporadic or familial (if familial; syndromes implicated are inherited in Autosomal dominant fashion)**
- **What's special about this tumor is that it contains *multiple different cell types* and tissue components (like primitive glomeruli, renal tubules and stromal cells), all of which are mesoderm derived.**
- **The mutations involved are in WT-1 and WT-2 genes (WT: Wilsons Tumor)**
- **Treatment options include surgery and chemotherapy.**



This photo is just to make sure that you truly appreciate the association between Wilms tumor and CHILDREN.

Now, we will briefly discuss tumors that occur in the lower urinary tract, which are most associated with the urinary bladder. (they are twice as common as renal cell carcinomas)(The slides VERY briefly discuss this topic, so I will not dig deep into it).

Bladder cancer is of three subtypes:

A) Urothelial carcinomas (aka Transitional cell carcinomas) ==> Most common subtype accounting for about 90% of bladder cancer cases.

B) Squamous cell carcinoma==> 3-7% of cases

C) Adenocarcinomas ==> Those are rare.

A) Urothelial carcinomas (Transitional cell carcinoma)

First, the urinary bladder (and the ureter) is lined with urothelium, which is a special type of transitional epithelium. Remember that the transitional epithelium has a functional significance for the urinary bladder (When the urinary bladder is relaxed, it would be made up of multiple layers of stratified epithelial cells with dome-shaped superficial cells, then when the bladder starts filling with urine, a TRANSITION occurs in the epithelium where the superficial dome-shaped cells acquire a more flattened shape allowing the epithelium to appear "flatter". Why is that important? This helps the urinary bladder fill with urine without destruction to the epithelium as a result of urinary filling; allows for distention of the urinary bladder).

- **What is the most important prognostic factor in urothelial neoplasms? The grade and staging at the initial time of diagnosis. Thus urothelial neoplasms are divided into three subtypes according to certain morphological and cytological features determining their grade into : a) Benign papilloma. B) Papillary urothelial neoplasms of low grade(low grade are rarely invasive). C) Papillary urothelial carcinoma of high grade.**
- **Please note that RECURRENCE IS COMMON AFTER REMOVAL (important).**

B) Squamous cell carcinoma: 3-7% of cases (about 5%)

==> This occurs more commonly in regions where Schistosoma haematobium infection is endemic(التي تسبب بلهارزيا و هو المرض الذي مات بسببه عبدالحليم حافظ رحمه الله) ==> This is common in Egypt (دائما اربط ببالك صورة شخص بسبح بالترعة و صار معه بلهارزيا) Chronic inflammation associated with Schistosomiasis builds the background for squamous metaplasia, then dysplasia occurs, then squamous cells carcinoma occurs.

-Associated with long-standing cases of renal stones as well.

Some notes for bladder cancers:

A) The most common presentation is painless hematuria.

B) It's more common in males than females (3:1) and more common in elderly (50-70 years).

C) If the cancer is low-grade and shallow (no/little invasion), then prognosis is good. However, if the cancer is high grade and deep (invasive) then prognosis is bad.

Predisposing factors for bladder cancers include:

A) Most important risk factor is SMOKING, which also contains Beta-naphthylamine which is by itself carcinogenic (Naphthylamine is also found in paints).

B) Schistosomiasis ==> increases the risk of Squamous cells carcinoma.

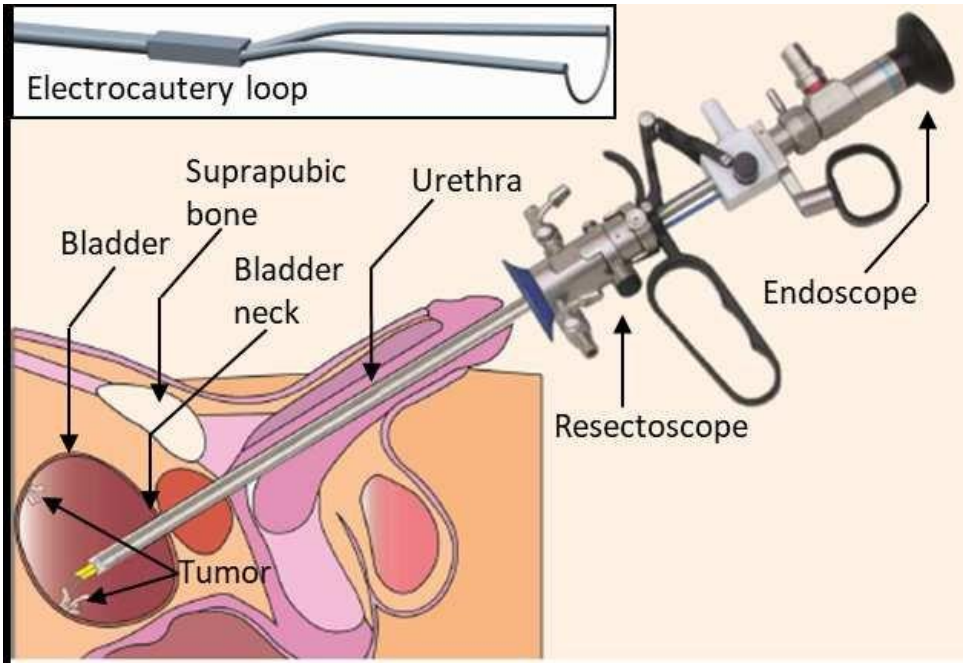
C) Chronic cystitis.

D) Drugs like cyclophosphamide (which is a chemotherapeutic drug used to treat cancers!)

E) NOT FAMILIAL

Treatment of bladder cancers

A) Transurethral resection. This is done by inserting a cystoscope through the urethra into the urinary bladder. This can have both diagnostic and therapeutic values. How? A sample from the bladder could be taken for histological examination(thus diagnostic), and the tumor itself could be removed using this device (thus therapeutic)



B) Another option is to inject the patient with BCG within the urinary bladder. As you know, BCG is capable of eliciting a granulomatous reaction, which is also capable of eliciting a local anti tumor immune response.

==> Please note that we previously stated that RECURRENCE IS COMMON, so the patient needs constant follow up with cystoscopy and urine cytologic studies for the rest of his/her life.

C) If the bladder cancer case is unfortunately advanced, then chemotherapy and removal of the urinary bladder (radical cystectomy) could be options.