Lecture (6)

Tumors of the Kidney

Many types of benign and malignant tumors occur in the urinary tract. In general, benign tumors such as small (less than 0.5 cm in diameter) cortical papillary adenomas, which are found in 40% of adults, have no clinical significance.

The most common malignant tumor of the kidney is **renal cell carcinoma**, followed in frequency by **nephroblastoma (Wilms tumor)** and by primary tumors of the calyces and pelvis. Other types of renal cancer are rare and need not be discussed here. *Tumors of the lower urinary tract are about twice as common as renal cell carcinomas.* They are described at the end of this section.

Oncocytoma

Oncocytoma, a benign tumor that arises from the intercalated cells of collecting ducts, represents about 10% of renal tumors. These tumors are associated with genetic changes loss of chromosomes 1, 14, and Y—that distinguish them from other renal neoplasms. Oncocytomas are histologically characterized by a **plethora of mitochondria**, providing the basis for their tan color and their finely granular eosinophilic cytoplasm

that is seen histologically. **A central stellate scar**, which is another feature of oncocytomas, provides a characteristic appearance on imaging studies.

Owing to their large size and clinical and radiologic similarity to some renal cell carcinomas, however, they are removed by nephrectomy, both to prevent such complications as spontaneous hemorrhage and to make a definitive diagnosis.

Renal Cell Carcinoma

Renal cell carcinomas are derived from the renal tubular epithelium and hence they are located predominantly in the cortex. These tumors represent 80% to 85% of all primary malignant tumors of the kidney and 2% to 3% of all cancers in adults. These data translate into about 58,000 cases per year in the United States; 40% of patients die of the disease. Carcinomas of the kidney are most common from the sixth to seventh decades, and men are affected about twice as commonly as women. The risk of developing these tumors is higher in smokers, hypertensive or obese patients, and those who have had occupational exposure to cadmium. The risk of developing renal cell cancer is increased 30-fold in persons who acquire polycystic disease as a complication of chronic dialysis. The role of genetic factors in the causation of these cancers is discussed later on.

Renal cell cancers are classified on the basis of morphology and growth patterns. However, recent advances in the understanding of the genetic basis of renal carcinomas have led to a new classification that takes into account the molecular origins of these tumors. The three most common forms, discussed next, are clear cell carcinoma, papillary renal cell carcinoma, and chromophobe renal carcinoma.

Clear Cell Carcinomas

Clear cell carcinomas are the most common type, accounting for 65% of renal cell cancers. Histologically, they are composed of cells with clear cytoplasm. Although most are sporadic, they also occur in familial forms or in association with von Hippel-Lindau (VHL) disease. It is the study of

VHL disease that has provided molecular insights into the causation of clear cell carcinomas. VHL disease is inherited as an autosomal dominant trait and is characterized by predisposition to a variety of neoplasms, but particularly to hemangioblastomas of the cerebellum and retina. Hundreds of bilateral renal cysts and bilateral, often multiple, clear cell carcinomas develop in 40% to 60% of affected persons. Those with VHL syndrome inherit a germline mutation of the *VHL* gene on chromosomal band 3p25 and lose the second allele by somatic mutation. Thus, the loss of both copies of this tumor suppressor gene is a key step in the development of clear cell carcinoma. The *VHL* gene is also involved in

the majority of sporadic clear cell carcinomas. Cytogenetic abnormalities giving rise to loss of chromosomal segment 3p14 to 3p26 are often seen in sporadic renal cell cancers. This region harbors the *VHL* gene (3p25.3). The second, nondeleted allele is inactivated by a somatic mutation or hypermethylation in 60% of sporadic cases. Thus, homozygous loss of the *VHL* gene seems to be the common underlying molecular abnormality in both sporadic and familial forms of clear cell carcinomas. The VHL protein causes the degradation of hypoxia-induced factors (HIFs), and in the absence of VHL, HIFs are stabilized. HIFs are transcription factors that contribute to carcinogenesis by stimulating the expression of vascular endothelial growth factor (VEGF), an important angiogenic factor, as well as a number of other genes that drive tumor cell growth. An uncommon familial form of clear cell carcinoma unrelated to VHL disease also is associated with cytogenetic abnormalities involving the short arm of chromosome 3 (3p). In addition, recent deep sequencing of clear cell carcinoma genomes has revealed frequent loss-of-function mutations in *SETD2*, *JARID1C*, and *UTX*, all of which encode proteins that regulate histone methylation, suggesting that changes in the "epigenome" have a central role in the genesis of this subtype of renal carcinoma.

Papillary Renal Cell Carcinomas

Papillary renal cell carcinomas account for 10% to 15% of all renal cancers. As the name indicates, they show a papillary growth pattern. These tumors are frequently multifocal and bilateral and appear as early-stage tumors.

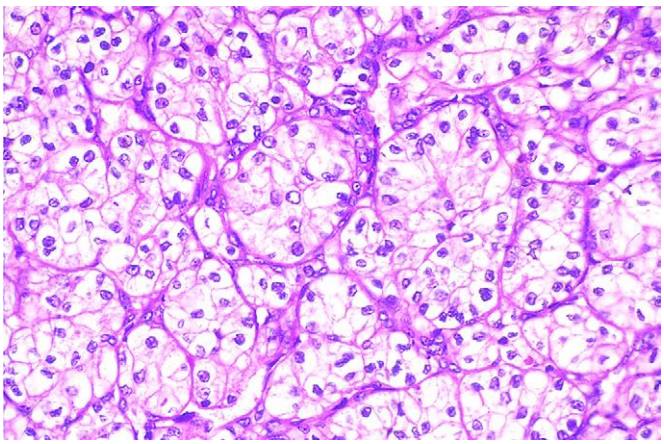
Like clear cell carcinomas, they occur in familial and sporadic forms, but unlike these tumors, papillary renal cancers are not associated with abnormalities of chromosome 3. The culprit in most cases of hereditary papillary renal cell cancers is the *MET* proto-oncogene, located on chromosomal sub-band 7q31. The *MET* gene is a tyrosine kinase receptor for the growth factor called hepatocyte growth factor. The increased dosage of the *MET* gene due to duplications of chromosome 7 seems to spur abnormal growth in the proximal tubular epithelial cell precursors of papillary carcinomas. In familial cases, genetic analysis shows activating mutations of *MET* in the germline, along with increased gene dosage in the cancers. Activating mutations of the *MET* gene also are found in a subset of patients with sporadic forms of papillary renal cell carcinoma.

Chromophobe Renal Carcinomas

Chromophobe renal carcinomas are the least common, representing 5% of all renal cell carcinomas. They arise from intercalated cells of collecting ducts. Their name derives from the observation that the tumor

cells stain more darkly (i.e., they are less clear) than cells in clear cell carcinomas.

These tumors are unique in having multiple losses of entire chromosomes, including chromosomes 1, 2, 6, 10, 13, 17, and 21. Thus, they show extreme hypodiploidy. Because of multiple losses, the "critical hit" has not been determined. In general, chromophobe renal cancers have a good prognosis.



High-power detail of the clear cell pattern of renal cell carcinoma.

***Wilms Tumor* (*nephroblastoma*)**

Although Wilms tumor occurs infrequently in adults, it is the third most common organ cancer in children younger than 10 years of age. These tumors contain a variety of cell and tissue components, all derived from

the mesoderm. Wilms tumor, like retinoblastoma, may arise sporadically or be familial, with the susceptibility to tumorigenesis inherited as an autosomal dominant trait.