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Solid Tumour Section

Review

Kidney: Renal cell carcinoma

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Classification

Note

Renal cell cancer (RCC) constitutes a group of epithelial tumors that are highly heterogeneous with respect to morphology and clinical behaviour.

Classification

The major morphological classifications (WHO/ AFIP; modified Mainz classification, and the Heidelberg classification) discriminate eight sub-types of renal cell tumors related to the basic cell types of the nephron from which they are derived, and in line with the genetic facts as presently understood:

1) metanephric adenoma and metanephric adenofibroma,
2) papillary adenoma,
3) renal oncocytoma, all three benign parenchymal neoplasms

Malignant parenchymal neoplasms are:

4) common or conventional (clear cell) renal carcinoma,
5) papillary (formerly chromophilic or tubulopapillary) renal carcinoma,
6) chromophobe renal carcinoma,
7) collecting duct carcinoma, and
8) renal cell carcinoma, unclassified.

Clinics and pathology

Note

Although common RCC and papillary RCC both are derived from the same part of the renal tubule and have a similar antigenic phenotype, they differ in genetic changes. This might be explained by the fact that common RCC arises from mature renal tubular cells, whereas papillary tumors are from embryonal origin.

Embryonic origin

In former times it was believed that certain clear cell epithelial renal tumors are derived from ectopic adreno-cortical elements as expressed by Virchow and advocated by Grawitz. This has led to the term "hypernephroma" or Grawitz tumor. Nowadays, there is evidence that the usual (nonembryonic) RCC in all its variants derives, in principle, from the mature uriniferous tubule (nephron). This evidence is corroborated by animal experiments and observation of pre-stages and early stages of epithelial renal tumors in human kidneys.

Etiology

A specific factor in the etiology of RCC is not known at the moment, although a number of dietary, environmental factors, hormonal, celllular and genetic factors associated with increased risk. RCC consists of number histologically defined entities which may occur either non-hereditary or hereditary, e.g. the influence of genetic factors in VHL disease, in hereditary papillary RCC and familial RCC.

Epidemiology

RCC is the most common malignant tumor arising in the kidney and accounts for 2% of all new cancers diagnosed, representing 85% all primary renal neoplasms in adults. RCC affects males twice as often as females and shows a peak in the sixth decade. Although rarely, RCC can occur in children and adolescents. There is no clear geographical or ethnic preference. An increased incidence of RCC has been associated with end-stage renal disease and with acquired cystic kidney disease. RCCs are often large at detection and frequently already have metastasized.

Pathology

The present classification is primarily based on cytologic appearance and the cell type of origin in combination with growth pattern and genetic alterations.

Common (or non papillary or clear cell) RCC is the most common form of RCC, comprising 70-75% of cases.They show a male preponderance of 2:1. The tumor mass of common RCC is multi-colored, with a predominantly yellow cur surface with white or gray foci. The tumor shows a solid growth pattern, but in some cases cystic appearance is seen. The cytoplasm is clear, due to an intensive intracytoplasmatic accumulation of glycogen and lipids. Usually, the nuclei are condensed and hyperchromatic. Electronmicroscopical features resembling the proximale tubule can be found i.e. brush border formation and basal infoldings. Tumor cells express antigens of the proximal tubule.

Papillary (or chromophilic) cell tumors (thought to arise from the proximal tubule) comprise 10-15% of RCC cases. Papillary RCC can be devided in adenomas and carcinomas. The adenomas tend to beige- to white colored small tumor masses whereas the carcinomas show an extensive greasy-brown colored central necrosis resulting from consecutive hemorrhages. The tumor cells exhibit centrally located small nuclei and the cytoplasm is contains few organelles only, especially endoplasm-matic reticulum. As a rule the tumor cells are arranged in a (tubulo) papillary architecture.

For both common and papillary RCC, hereditary as well as sporadic cases of papillary RCC have been found. Hereditary RCC is characterized by the appearance of multiple and bilateral tumors and an early age of onset.

The chromophobic type (2-5%) resembles the intercalated cells type B from the cortical collecting duct. The antigen profiles of the chromophobic tumor exhibit collecting duct phenotypic features. No male preponderance is found. Chromophobic RCC consists of one or more solid tumor nodules with a slightly lobulated surface and the cut surface appears orange. The tumor cells are polygonal with a transparent, not clear, but reticulated cytoplasm. Nuclei are moderate with clear nucleoli. Ultrastructurally, the cytoplasm is crowded with glycogen deposits and numerous, sometimes invaginated, vesicles. Chromophobic RCC is diagnosed by a positive Hale's acid iron colloid stain and is positive for carbonic anhydrase C, but does not express band-3 protein.

Renal oncocytoma (thought to arise from the distal nephron) comprises 5% of RCC and shows a 2.5:1 male to female ratio. Renal oncocytomas are solitary, well circumscribed, slightly lobulated solid tumors with a tan-brown cut surface and in larger tumors a central scar. The tumor cells show abundant granular eosinophilic cytoplasm and arranged in solid nests.The nuclei are generally round. Ultrastructurally, the cytoplasm is packed with numerous mitochondria. Renal oncocytomas find their origin in the intercalated cells type A of the cortical collecting tubule, which is substantiated by the shared expression of carbonic anhydrase C and band-3 protein.

Collecting duct (duct Bellini) RCC comprises 1% and is closely related to the princi-pal cells of the medullary collecting duct. These tumors are usually localized in the renal medulla and white colored. The growth pattern is mainly tubular. The tumor cells have a basophilic cytoplasm due to pronounced formation of endoplasmatic reticulum and glycogen deposits. Nuclei are anaplastic.

Variants can be assigned to all these basic types which are characterized by augmentation of mitochondria leading to a stronger eosinophilia or granularity, respectively, of the cytoplasm. Spindle-shaped/pleomorphic variants as a result of sarco-matoid transformation can also be deduced from all the basic types.

The differential diagnosis between renal cell adenomas and carcinomas has been a matter of controversy for long time. Although initially Bells' rule generally was followed (3 cm: carcinoma), this appeared unreliable and is still a matter of debate.

Treatment

The standard treatment for RCC is surgery by radical or partial nephrectomy. At present there is no effective therapy for metastatic RCC and patients with irresectable disease have a poor prognosis.

Evolution

About 50% of patients with localized disease progress with distant metastasis.

Prognosis

The anatomic extent of the disease represented by stage of disease is the single most important indicator of prognosis in RCC.

Cytogenetics

Note

Cytogenetically, no differences are observed between hereditary tumors (usually presenting as multiple/bilateral tumors at an early age of onset) and sporadic papillary tumors.

Increasing evidence exists on the presence of clonal, mostly numerical, chromosomal changes in apparantly normal kidney tissue from patients with a normal constitutional karyotype like trisomy 7, 5, 8, 10, 18 and loss of the Y chromosome. These changes are not an in vitro artefact and are independent of the length of cell culture. The presence of clonal and non clonal aberrations in apparantly normal kidney tissue merely indicates a chromosome instability pattern or

mosaicism, and this condition should not be considered as strictly neoplastic.

Cytogenetics Morphological

The most frequently encountered RCC subtype is **common or conventional type renal cell cancer** characterized by loss of (part of) the short arm of chromosome 3 due to (a) deletion(s) or unbalanced translocation(s). Regions frequently lost are are 3p12-14, 3p21 and 3p25. Loss of at least two of these regions is necessary for kidney cells to develop into common type renal cell carcinoma, and loss of 3p21 is obligatory. Therefore, if a tumor shows only one deletion at 3p, either 3p14 or 3p25, it should be designated common type renal cell adenomas.

Other aberrations frequently found incommon RCC are (partial) trisomy of chromosome 5, especially the 5q22-qter segment. Trisomy 12, and 20, and loss of chromosomes 8, 9, 13q, 14q, and structural abnormalities of the long arm of chromosomes 6 and 10 are also found and correlated with progression.

Most **papillary renal adenomas and carcinomas** are characterized by a unique combination of autosomal trisomies with trisomy 17. Papillary adenomas specifically show a -Y,+7,+17 chromoso-mal pattern as well as trisomy 3 or gain of the long arm of chromosome 3, probably reflecting malignant transformation. Trisomy of chromo-somes 12, 16, 20 as well as loss of the extra copy of chromosome 17 or loss of 17p are associated with progression from the adenoma into the carcinoma stage, i.e. papillary renal cell carcinomas. The high incidence of loss of the Y chromosome combined with the strong male preponderance suggests that loss of specific sequences harboured on the Y chromosome probably is important for developing this subtype.

A small subset of **papillary RCC** is characterized by X; autosome translocations. The t(X;1)(p11.2;q21), resulting in a fusion of the trans-cription factor TFE3 on the X chromosome, with a novel gene, designated PRCC, on chromosome 1, appears to be a specific primary anomaly characterizing a distinct subgroup of papillary RCC with common RCC like features as clear cytoplasma. These tumors occur preferentially in young (male) adults and children.

Metanephric adenoma or adenofibroma shows gain of chromosomes 7 and 17 with Y chromosome loss suggesting a relationship with papillary renal cell adenomas and carcinomas.

In **renal oncocytoma** several genetic subsets can be distinghuished: one with mixed populations of normal and abnormal karyotypes without any cytogenetic similarity (yet), a group defined by (variant) translocations involving 11q13, and one with specifically defined numerical anomalies, in particular loss of chromosomes 1, and Y/X.

The finding of mitochondrial DNA changes and the loss of Y/X in both **renal oncocytoma** and **chromophobe carcinoma** might indicate progression from renal oncocytoma to chromo-phobe renal cell carcinomas through additional chromosome losses, also explaining the occasion-ally malignant behavior of renal oncocytomas.

Chromophobe renal carcinomas show multiple losses of entire chromosomes, i.e. loss of chromo-somes 1, 2, 6, 10, 13, 17, 21, and the Y or X chromosome, leading to a low chromosome number.

Collecting duct carcinomas do not show consistent chromosomal abnormalities as yet: probably involvement of the short arm of chromosome 8 related to poor prognosis and loss of the long arm of chromosome 13 as well as loss of part of the long arm of chromosome 1q32.

Losses of chromosome1 material seem to be a hallmark for all distal nephron tumors.

Sarcomatoid transformation in RCC represents the highest form of dedifferentiation and can in principle be derived from all the basic cell types. Cytogenetic data on sarcomatoid RCC is scarce: some show structural abnormalities of chromoso-mes 1, 5, 16, and 19 and losses of 3p, 4(q), 6q, 8p, 9, 13, 14, 17p, and gain of 5, 12, and 20 as well as TP53 mutations.

Genes involved and proteins

Note

The most frequent occurring RCC is common RCC characterized by loss of (part) of the short arm of chromosome 3 due to a deletion or unbalanced translocation and restricted to this type. Until today no tumor suppressor gene responsible for, or at least contributing to, cRCC has been identified -except for VHL-, in the different regions, although many candidate genes have been suggested such as FHIT(fragile histidine triad); TTRC1 (two-three-renal-cancer-1); DUTT1 (deleted in U-twenty twenty); locus NCR-1 (nonpapillary renal cell carcinoma 1) and RASSF1A (RAS association family 1).

In papillary RCC, the TP53 gene most likely does not play an important role, since no mutations of TP53 have been observed in this subtype. Microsatellite analysis revealed allelic duplications a.o. at 20q11.2 and 20q13.2 suggesting new tumor genes in papillary renal carcinoma. The MET proto oncogene, assigned to 7q31 and encoding the hepatocyte growth factor receptor/scatter factor implicated in the proliferation and invasiveness, has been found mutated in germline and somatic mutations in papillary renal tumors. Loss of heterozygosity on chromosomes 8p or 9p provide prognostic significance in patients with locally advanced cRCC. PTEN/MMAC1 (chromosome 10) inactivation may play a role in the progression of cRCC.

To be noted

Animal model Eker rats with a germline inacti-vation of the TSC-2 tumor suppressor gene develop RCC. Using this model, it was found that overexpression of transforming growth factor a is an early event in the development of RCC as it is seen in dysplasia and adenomas.

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