Renal Neoplasia: WHO 2003.

The Increasing Influence of Molecular Pathology

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Introduction

In recent years there have been considerable advances in our understanding of the pathogenesis of renal neoplasia and this has been underscored by the increasing complexity of the various classification systems that have been proposed. Prior to 1986 it was generally considered that renal epithelial tumours could be divided into benign and malignant forms with a tumour diameter of >3cm being the most important diagnostic criterion for malignancy. Malignant tumours were classified as renal adenocarcinoma or renal cell carcinoma (RCC) and while reports did recognise that some morphotypes were associated with a more favourable prognosis, this was not generally accepted in most classifications.[1] This simplistic approach is well illustrated by the first edition of the WHO classification published in 1981, which represents the first international consensus classification of renal neoplasia.[2]

The Mainz classification of 1986 provided a major step forward in the realisation that, rather than being a single tumour entity, RCC is a group of tumours with each subtype having unique morphologic and genotypic features.[3] While the Mainz Classification did promote recognition of a variety of subtypes of RCC, the various categories defined in it were hampered by a confused and complex terminology.

The diagnostic categories of the Mainz classification were redefined at two consensus conferences held in 1996 and 1997.[4,5] The result of these conferences was the establishment of the Heidelberg/Rochester classification of renal parenchymal tumours which has gained widespread support and has provided a sound basis for further investigation, resulting in the description of additional categories of renal cell neoplasia. A feature of the Heidelberg/ Rochester classification was the recommendation that if a malignant tumour could not readily be assigned to one of the four diagnostic categories, then it should be reported as renal cell carcinoma, unclassified and it was anticipated that approximately 5% of tumours would be so designated. This recommendation has had the benefit of identifying clearly defined groups of apparently novel tumours for further detailed study. This has also ensured that studies on established subtypes of renal cell neoplasia are not confounded by the inclusion of atypical forms or hitherto unrecognised diagnostic categories.

In the six years since the publication of the consensus classifications a variety of additional subtypes of renal neoplasia have been described and it became clear that there was a need to modify the existing classification in order to accommodate these newly recognised entities. In 2002 the WHO established a working group to make recommendations regarding the establishment of a comprehensive classification for renal neoplasia. The working party met in Lyon in December 2002 and the resultant classification (Appendix) is due for publication in 2003. WHO 2003 represents an extensive revision of the classification of renal neoplasia and include several new tumour entities described since the Heidelberg/Rochester consensus conferences.

Clear cell renal cell carcinoma

Clear cell RCC remains the most frequently encountered form of renal parenchymal tumour comprising 60-70% of malignant tumours in adults. Diagnosis of the tumour relies on the detection of a characteristic vascular network even in the absence of clear cells. In most cases small groups of cells with clear cytoplasm are found even in tumours composed predominantly

of cells with eosinophilic cytoplasm.

Prognostic assessment for clear cell RCC relies primarily on evaluation of clinical stage although histologic grade and a variety of other parameters have been shown to be of clinical utility.[6]

The Robson staging system classifies all localised tumours as stage 1 while in the UICC/TNM system tumour size is taken into account.[7] The current trend towards partial nephrectomy for the management of localised clear cell RCC has led to detailed assessment of the prognostic significance of tumour size. In the 1997 UICC/AJCC staging system, pT1 and pT2 tumours were separated according to size (≤, > 7cm), although the sensitivity of this as a predictor of cases suitable for partial nephrectomy has been questioned. In response to these criticisms a subdivision has been added to the 2002 revision of the classification with pT1a ≤ 4.0cm, pT1b > 4.0cm).[8] Clinical studies have confirmed that any of the size cutpoints defined in the various editions of the TNM classification are significantly associated with survival. The predictive value of those data in individual cases is however, limited as size is a constant variable and in sufficiently large series any cutpoint will correlate with survival.[9]

Fuhrman grading of RCC remains the most widely utilised grading classification and although this has recently been validated in large series of clear cell and papillary RCC,[10] a number of difficulties remain. In particular the relationship between nuclear size, nuclear shape and nucleolar prominence is unknown, and while all of these features are included in the Fuhrman grading system, in practice pathologists assign grade on nucleolar prominence alone. The other point of difficulty relates to whether or not tumour grading should be based on the average, dominant or highest degree of nuclear pleomorphism. In the case of the latter option, the minimal area of tumour exhibiting the highest nuclear grade that is acceptable for assessment purposes has yet to be defined.

Sarcomatoid change is associated with a poor clinical outcome, and more recently a similarly poor prognosis has been described for tumours showing "rhabdoid" morphology. Rhabdoid differentiation is seen in about 3% of clear cell tumours and usually presents at high clinical stage with a median survival of 8 months.[11,12]

Clear cell RCC is frequently associated with mutation of the *VHL* gene at 3p25-26, gene

rearrangement or promoter region hypermethylation.[13] Additional regions on 3p are associated with clear cell carcinogenesis and LOH studies have shown mutations at 3p14 and 3p21-22 to be early events in neoplastic tranformation.[14,15] Recent studies have shown that while a variety of chromosomal abnormalities are associated with advanced tumours, LOH at 9p13, 14q and 10q (PTEN/*MMAC1*) are associated with poor prognosis,[16-18] while gains of 5q correlate with a more favourable outcome.[19]

Multilocular cystic renal cell carcinoma

The true nature of multilocular cystic RCC and its relationship to clear cell RCC remains to be elucidated. Unlike clear cell carcinoma, multilocular cystic RCC appears to have a benign course as, in the more than 50 cases that have been reported in the literature to date, no instance of metastatic disease has been described. These tumours usually exhibit a low nuclear grade and are composed of cystic structures with fibrous tissue septae lined by a single layer of epithelial cells with clear cytoplasm.[20] Clear cells are also present individually in microscopic nests within the septal wall, however, if epithelial nests are visible microscopically then the tumour should be diagnosed as a clear cell carcinoma.

Studies on G250 expression suggest that multilocular cystic RCC is a true neoplasm. G250 antigen is detectable by immunohistochemistry in virtually all clear cell RCC and recently quantitative measurement of gene expression shows G250 expression in 95% clear cell RCC, 77% multilocular cystic RCC, 43% chromophobe renal carcinoma with no expression in oncocytoma, cystic nephroma or normal renal epithelium.[21]

Papillary renal cell carcinoma

Papillary RCC constitute approximately 10% of RCC in large surgical series. The tumour typically consists of epithelial covered papillae with a central fibrovascular core, although they may consist solely of a compact tubular architecture or sheets of short papillae resembling glomeruli. Two varieties of the tumour are recognised. Type 1 tumours have papillae covered by small cells with scanty cytoplasm arranged in a single layer on the papillary basement membrane. Type 2 tumours exhibit pseudostratification of epithelial cells which are usually of higher nuclear grade and have voluminous eosinophilic cytoplasm. Type 1 tumours often contain aggregates of foamy macrophages and scattered psammoma bodies. These tumours are

usually multifocal and are frequently associated with sclerosis of adjacent non-neoplastic renal tissue.[22]

Papillary RCCs co-express vimentin and epithelial markers and are also often positive for CD-10 (93%) RCC antibody (93%) and S-100 protein (55%). Cytokeratin 7 and MUC1 immunohistochemical expression is more frequently seen in type 1 than type 2 papillary RCC. Type 1 and 2 tumours differ in genotype and clinical outcome. Type 1 tumours show gains of chromosomes 7p and 17p, and differing patterns of allelic imbalance at 17q and 9p have been noted between the two tumour types.[23] Type 1 tumours are usually of lower nuclear grade and clinical stage than type 2 tumours, while longer post-treatment survival for patients with type 1 tumours has been shown on multivariate analysis.[24]

Chromophobe renal cell carcinoma

Prior to 1986 chromophobe RCCs were included in series of clear cell RCC and at that time contributed to the favourable outcome reported for tumours supposedly of low histologic grade. The publication of detailed descriptions of similar tumours in nitrosamine-induced animal models led to the realisation that this was a novel class of RCC which was later shown to be of low malignant potential.

As is the case for carcinogen-induced chromophobe RCC in rodents, human chromophobe RCCs exhibit a wide histologic spectrum ranging from typical balloon cells with abundant granular pale cytoplasm, to tumours composed of smaller cells with deeply eosinophilic cytoplasm, resembling those commonly associated with oncocytoma.[25]

In some cases and particularly in larger tumours, it may be difficult to differentiate between the eosinophilic variant of chromophobe RCC and oncocytoma, and it has been suggested that a hybrid form of the tumour exists. In support of this is the observation that chromophobe RCC and oncocytoma may co-exist in kidneys with so-called oncocytomatosis where several to occasionally hundreds of tumours are present in the same kidney.[26] Ten percent of chromophobe RCC consist predominantly of eosinophilic cells and in such cases features in favour of carcinoma over oncocytoma are; 1) cellular dyscohesion in paraffin embedded sections, 2) wrinkling of the nuclear margin with an inconspicuous nucleolus, 3) perinuclear cytoplasmic clearing (perinuclear halo), 4) hyalinisation of the walls of larger vessels, 5)

diffuse Hale's colloidal iron staining, 6) the presence of classical "balloon" chromophobe cells elsewhere in the tumour (sample widely) and 7) the presence of amorphous calcific deposits but not psammoma bodies within the tumour interstitium.

Chromophobe RCC typically has loss of heterozygosity involving numerous chromosome and chromosome regions with 1, 2, 6, 10, 13, 17 and 21 monosomy and loss of X or Y being most frequently reported.[27]

Oncocytomas are characterised by a variety of LOH in chromosome 1, 6p, 14, and/or 21 in some tumours, while 5:11 translocation has also been reported. Recent studies have shown that loss of two or more of chromosomes 1, 2, 6, 10 and 17 as detected by FISH differentiates classic/eosinophilic chromophobe RCC from oncocytoma with a sensitivity of 90% and a specificity of 100%.[28]

Currently immunohistochemistry is of limited value in differentiating chromophobe RCC from oncocytoma. CD-10 expression is positive in approximately 10% of oncocytoma, 28% of classic chromophobe RCC and 100% of eosinophilic chromophobe RCC. Both types of chromophobe RCC show diffuse positivity for CK7 in >80% of tumours and while 100% of oncocytoma show CK7 positivity, expression is confined to single cells or small groups of cells.[29] Recent reports suggest that CD74 expression may distinguish chromophobe RCC from oncocytoma, with positive staining being reported in 4 of 6 carcinomas, compared to negative staining in all of 8 oncocytomas studies.[30]

Several studies have confirmed the favourable prognosis of chromophobe RCC with metastatic spread being seen in <10% of tumours regardless of the size of the primary malignancy.[31] Early indications were, however, that chromophobe RCC was associated with a higher rate of sarcomatoid progression than other RCC morphotypes[32] and recent studies have confirmed these early observations with tumours showing sarcomatoid morphology in >1 high power field in approximately 10% of cases.[33]

Carcinoma of the collecting ducts of Bellini

These rare tumours are characterised by pleomorphic cells arranged in irregular tubules within a desmoplastic stroma. These tumours originate in the renal medulla however often the site of origin is unclear due to the advanced stage of the tumour at presentation. Immunoexpression of *Ulex europeaus* agglutinin lectin is an important diagnostic features.

The nature of so-called low grade collecting duct carcinoma[34] is unresolved and its relationship to true collecting duct carcinoma remains in question. Unlike true collecting duct tumours, low grade carcinomas have been found confined to the renal cortex. Their designation as low grade carcinoma is also debated as they do have a metastatic potential and in the main they exhibit Fuhrman grade 2 and 3 morphology.

Renal medullary carcinoma

In the WHO 2003 classification of renal neoplasia, renal medullary carcinoma is recognised as distinctive entity separate from collecting duct carcinoma. These tumours originate in the renal medulla and are almost always confined to those with sickle cell trait. Intrarenal infiltration and satellitosis is common and in the many cases intravascular invasion by tumour is found.[35] The majority of tumours consist of nests of highly pleomorphic cells although focally then may show a papillary or cystic architecture. The tumour cell cytoplasm frequently contains eosinophilic hyaline gloubles.[36] Immunohistochemical studies are limited due to the rarity of these tumours and positivity for EMA, cytokeratin AE1/AE2 and CEA has been reported.

Renal carcinoma associated with Xp11.2 translocation/*TFE3* gene fusion

Sporadic reports dating back to 1986 have indicated that a population of apparent clear cell RCC is associated with translocation involving Xp11.2, known as the *TFE3* transcription factor gene. In the majority of cases these tumours are found in children and young adults and have, in previous reports, been recognised as "clear cell papillary RCC with voluminous cytoplasm". Early reports were confined to individual cases however review of published cases with additional cases proven by cytogenetics or detection of fusion transcripts by RT-PCR, showed these tumours to have a similar morphology.

The initial series investigated those tumours showing *ASPL-TFE3* gene fusion and it was

recognised that these fusion transcripts were similar to those seen in alveolar soft part sarcoma although, unlike sarcomas, the translocation was balanced [t (X;17) (p11.2;q25)].[37] In this series the patient ranged in age from 2 to 17 years and the tumours were mostly of high clinical stage at presentation.

Histologically the tumours form sheets, acini, trabeculae or papillary structures with the tumour cells having prominent cell borders and a predominantly clear cytoplasm rich in glycogen. Nuclei are small and while a prominent eosinophilic nucleolus is usually present, mitotic figures are rare. Psammoma bodies are present in all tumours and in places these appear to arise in eosinophilic proteinaceous hyaline aggregates present within tumour cell cytoplasm. Ultrastructure examination shows features of an epithelial tumour. The immunohistochemical expression of these tumours differs from that of clear cell RCC in that vimentin and cytokeratin/EMA expression is either absent or focal. These tumours show diffuse staining for CD-10 and RCC, while desmin and HMB-45 are negative.

A systematic review of published case reports and detailed study of cases identified from several tumour registries led to the description of tumours showing similar features to *ASPL-TFE3* tumour however these were characterised by translocation of *TFE3* and the *PRCC* gene at 1q 21.2.[38]

As for *ASPL-TFE3* tumours, *PRCC-TFE3* carcinoma are more common in younger patients with a mean age of 21.3 years at diagnosis being reported. The gross morphology is non-specific although the tumours usually have a pronounced pseudocapsule that is often calcified. Histologically the tumours show features similar to those with *ASPL-TFE3* translocation consisting of large cells with clear cytoplasm. An alveolar architecture is most frequently present although acinar, tubular and papillary areas may also be seen. Psammoma bodies and aggregates of foam cells are occasionally present and mitotic figures are rare. The immunohistochemical profile is similar to *ASPL-TFE3* tumours while ultrastructurally these tumours closely resemble clear cell RCC.

The prognosis of Xp11 translocation tumours is difficult to assess due to the small numbers of reported cases. Data to date suggest that *ASPL-TFE3* tumours are associated with a more favourable prognosis than clear cell RCC despite an apparent higher stage of presentation for most tumours.[37,38,40]

Two other translocation tumours involving Xp11.2 have been reported. In these tumours *TFE3* was found to fuse with splicing factor genes *PSF* (1p34) or *NonO* (Xq12).[39] The morphologic features of tumours showing these genetic rearrangements have yet to be fully characterised.

Post-neuroblastoma renal cell carcinoma

This is a rare entity based on four cases published in 1999.[41] All tumours occurred in females less than 14 years of age who had been treated for neuroblastoma 3.1 to 11.5 years previously. The renal tumours were unilateral in three cases and bilateral/multifocal in one case. Review of the literature revealed a further 14 cases (3 female, 2 male, aged 3 to 22 years and treated for neuroblastoma 2 to 21 years earlier). Histologically the tumours have a mixed solid/ papillary architecture being predominantly composed of cells with bulky eosinophilic and granular cytoplasm. The degree of nuclear pleomorphism varies as does the mitotic rate. The tumours show patchy positivity for vimentin and epithelial membrane antigen while cytokeratin 7 and S-100 protein are negative. These tumours may be the result of adjuvant therapy however as not all patients with neuroblastoma were treated initially, it has been speculated that the subsequent RCC is the result of genetic predisposition.

Mucinous, tubular and spindle cell carcinoma

In 2001 a series of four cases of low-grade myxoid renal epithelial tumour was reported. These tumours showed a characteristic biphasic morphology of sheets of spindle cells, and epithelial cells arranged in tubules, set within a mucinous stroma.[42] Since this time two further series of a total of 16 cases have been published, leading to the classification of these tumours as a novel form of renal neoplasia.[43,44]

Mucinous, tubular and spindle cell carcinomas most commonly occur in adult females with age at diagnosis ranging from 22 to 79 years. In all but three cases tumours were confined to the kidney at the time of nephrectomy, being well circumscribed without an investing pseudocapsule. Histologically the tumours consist of cuboidal to elongate cells showing a tubular growth pattern. These areas blend into foci showing a solid growth pattern and here the epithelial cells have a more spindled appearance. There is prominent extracellular mucin, which is alcian blue positive, and aggregates of foamy mucin-filled macrophages may be present.

There is some variation in the reported immunohistochemical expression of these tumours. In all cases the tumours show strong expression for CK AE1/AE3 and EMA while most tumours are positive for vimentin. Immunohistochemical stains for SMA, desmin, S-100 protein, and HMB-45 are negative. Markers of proximal nephron epithelium (villin, CD-10 and RCC) are usually negative and *Ulex europeaus* expression is variable, leading to debate as to whether or not these tumours are of distal nephron origin.

Studies on the genetics of mucinous, tubular and spindle cell carcinoma are limited although in one series constant losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15 and 22 were reported.[44]

Prognostic studies are limited to three reported case series and despite evidence of extrarenal extension in two cases and multiple recurrence in a third case, no tumour related deaths have been reported in follow-up intervals ranging up to 23 years.

Papillary adenoma

The category of a benign papillary neoplasm of the renal parenchyma proposed in the Heidelberg/Rochester classifications has been retained in the WHO 2003 classification. In the WHO 1998 classification no size limitation was included in the definition of the tumour, however in the latest edition a size of <5mm is specified. Papillary adenoma may show type 1 or type 2 morphology and unlike papillary carcinomas are well circumscribed with absent or thin investing pseudocapsule.

Papillary adenomas may be difficult to distinguish from metanephric adenomas. Immunohistochemistry does provide some assistance as S-100 protein expression is positive in up to 100% of metanephric adenomas while epithelial membrane antigen and vimentin staining is usually negative.[45] Unlike metanephric adenoma, papillary adenoma is associated with trisomy 7 and 17 and loss of Y chromosome. These genetic changes have been considered to be early events in the development of papillary neoplasia with further gains, specifically of chromosomes 12, 16 and 20, being associated with malignant tranformation.[46] Recent studies using fluorescence in-situ hybridisation have shown additions of chromosome 12 (40%), 16 (50%) and 20 (50%) in well characterised papillary adenomas, while 90% showed loss of chromosome Y. These results suggest that widespread loss of heterozygosity is an early event in papillary neoplasia and that this is not related to malignant

transformation .[47]

Oncocytoma

Oncocytomas comprise approximately 5% of renal parenchymal tumours, excluding renal adenoma and are usually asymptomatic, being most commonly found in males. The tumours typically have a tan/yellow surface upon sectioning and larger tumours often have a characteristic central stellate scar.

Oncocytomas exhibit variable architectural patterns, forming sheets, acini, tubules and nests of epithelial cells within an oedematous or hyalinised stroma. Two cell types are usually encountered; a larger cell with voluminous eosinophilic cytoplasm and the smaller so-called oncoblast with less conspicuous paler cytoplasm. These tumours show evidence of low level cell cycle activity having low Ki-67 indices and rare mitoses. Oncocytoma are not graded because of their benign nature and individual cells and cell nests may exhibit quite marked nuclear enlargement and irregularity.

Despite the benign course of oncocytoma, microscopic infiltration of perirenal fat is frequently seen and vascular invasion has also been reported.[48] Extensive infiltration by tumour should raise the possibility that the tumour is an eosinophilic variant of chromophobe carcinoma and appropriate ancillary studies are indicated (see chromophobe RCC). It should be noted that Hale's colloidal iron may show rare positivity in an otherwise typical oncocytoma, however unlike chromophobe carcinoma, staining is focal rather than diffuse.

While oncocytoma lacks the typical anastomosing vascular architecture of clear cell carcinoma, occasional cells with clear cytoplasm may be seen. These cells do not have the appearance of glycogen/lipid rich clear cell RCC but are rather the product of focal degeneration with associated cytoplasmic oedema. A diffuse papillary architecture is not a feature of oncocytoma although it is now accepted that small papillary excrescences, usually situated within dilated cystic structures, may be present and should not lead to the reclassification of a tumour as papillary renal cell carcinoma.[49]

APPENDIX

WHO: 2003. TUMOURS OF THE KIDNEY

1.1 Renal Cell Neoplasia

1.1.1 Familial renal cancer

- von Hippel-Lindau
- Hereditary papillary renal carcinoma
- Hereditary leiomyoma - renal cell carcinoma
- Birt-Hogg-Dube syndrome

1.1.2 Clear cell renal cell carcinoma

1.1.3 Multilocular cystic renal cell carcinoma

1.1.4 Papillary renal cell carcinoma

- Type 1
- Type 2

1.1.5 Chromophobe renal cell carcinoma

1.1.6 Carcinoma of collecting ducts of Bellini

1.1.7 Renal medullary carcinoma

1.1.8 Renal carcinoma associated with Xp11.2 translocation/*TFE* gene fusion

1.1.9 Renal cell carcinoma associated with neuroblastoma

1.1.10 Mucinous, tubular and spindle cell carcinoma

1.1.11 Renal cell carcinoma, unclassified

1.1.12 Papillary adenoma

1.1.13 Oncocytoma

1.2 Metanephric Neoplasia

1.2.1 Metanephric adenoma

1.2.2 Metanephric adenofibroma

1.2.3 Metanephric stromal tumour

1.3 Nephroblastic neoplasms

1.3.1 Nephroblastoma

1.3.2 Nephrogenic nests and nephroblastomatosis

1.3.3 Cystic partially differentiated nephroblastoma

1.4 Mesenchymal neoplasms

1.4.1 Clear cell sarcoma

1.4.2 Rhabdoid tumour

1.4.3 Ossifying renal tumour of infancy

1.4.4 Leiomyosarcoma

1.4.5 Angiosarcoma

1.4.6 Malignant fibrous histiocytoma

1.4.7 Osteosarcoma

1.4.8 Angiomyolipoma

1.4.9 Epithelioid angiomyolipoma

1.4.10 Leiomyoma

1.4.11 Lymphangioma

1.4.12 Juxtaglomerular cell tumour

1.4.13 Renomedullary interstitial cell tumour

1.4.14 Schwannoma

1.4.15 Solitary fibrous tumour

1.5 Mixed mesenchymal and epithelial neoplasms

1.5.1 Cystic nephroma

1.5.2 Mixed epithelial and stromal tumour

1.5.3 Synovial sarcoma

1.6 Neuroendocrine neoplasms

1.6.1 Carcinoid

1.6.2 Neuroendocrine carcinoma

1.6.3 Primitive neuroectodermal tumour (Ewing's)

1.6.4 Neuroblastoma

1.6.5 Paraganglioma/phaeochromocytoma

1.7 Haematopoietic and lymphoid neoplasms

1.7.1 Lymphoma

1.7.2 Plasmacytoma

1.8 Metastatic neoplasms

1.9 Germ cell tumours

1.9.1 Choriocarcinoma

1.9.2 Teratoma

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