Review article

The International Society of Urological Pathology/Vancouver Classification of Renal Neoplasia: New entities of adult renal cell carcinoma

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1. Introduction

During the past decade following the publication of the World Health Organization (WHO) classification of renal tumors in 2004,1 urologists and pathologists have encountered a surge of new entities of renal neoplasms. Scrutiny of subtle histologic features, detailed marker analyses, as well as advances in novel molecular and cytogenetic techniques all facilitate to characterize these entities that were either inadequately defined or categorized as other diseases in the past.

The International Society of Urological Pathology (ISUP) is the international professional organization dedicated to the subspecialty of urological pathology. In 2011, the Society undertook to review all aspects of the pathology of adult renal malignancy through an international consensus conference held in 2012 in Vancouver, Canada.2 The classification working group of the ISUP consensus conference on renal neoplasia was entrusted with the responsibility of reviewing available literature and making recommendations regarding additions, changes, and refinements to the current renal tumor classification system. On the basis of the above inputs, there was a consensus that five entities should be recognized as new distinct epithelial tumors within the classification system.3 There were a number of new concepts and suggested modifications to the existing WHO 2004 categories. The new classification is to be referred to as the ISUP/Vancouver Classification of Renal Neoplasia and is likely to be adopted in the next edition of WHO classifications.

2. Proposed new epithelial neoplasms

This review briefly summarizes the rationale and salient features of the five newly proposed entities.

2.1. Tubulocystic carcinoma

Tubulocystic carcinoma was first described in 1955 by Masson, who designated the lesion “Bellinian epithelioma” because he regarded it as a neoplasm originating in the collecting ducts of Bellini. Later the tumor was designated as “low-grade mucinous tubulocystic renal carcinoma of possible collecting duct origin.”4 With more cases showing similarly clinical and pathological features, the name of the neoplasm was changed to “tubulocystic carcinoma” to denote the specific morphology.5,6

Diagnosis is rendered chiefly on the basis of distinct morphologic characteristics. Grossly, the tumors may have a “bubblewrap”, “Swiss cheese”, or spongy appearance of the cut surface. Microscopically, the tumor is composed of tubules and cystic structures of markedly variable size, separated by delicate septa. Tubules are lined by a single layer of cuboidal epithelial cells with eosinophilic cytoplasm, round nuclei, and characteristically prominent nucleoli (grade 3) in most cases (Fig. 1).

Immunohistochemistry does not play a crucial role in differential diagnosis. Tubulocystic carcinomas express alpha-methylacyl-CoA racemase and CD10. The tumor cells stain positively for cytokeratins CK8, CK18, and CK19 and less frequently for CK7. A proportion of cases stain positively for high-molecular weight keratin (34βE12) and carbonic anhydrase IX.

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There are 3 CME questions based on this article.
Molecular genetics and expression profiling studies demonstrate no overlapping with clear cell, chromophobe, and collecting duct renal cell carcinoma (RCC). A relationship with papillary RCC has been claimed, especially for the frequent gains on chromosome 7 and chromosome 17, and loss of Y chromosome, which are the hallmarks of papillary RCC. Coexisting tubulocystic carcinoma and papillary RCC have been reported, and a tubulocystic pattern is occasionally observed in otherwise typical papillary RCC. Nevertheless, the term tubulocystic carcinoma should be restricted to those tumors that display typical macroscopic and microscopic appearance. The term should not be used in situations where there is a tubulocystic pattern admixed with the usual elements of papillary RCC.

Tubulocystic carcinomas tend to present in low stage and behave indolently. However, sarcomatoid change, as well as local recurrence, distant metastases to lymph nodes, lung, and brain have been reported.

2.2. Acquired cystic disease-associated RCC

Acquired cystic disease (ACD)-associated RCCs are observed exclusively in the background of ACD of the kidney. It has not been reported in noncystic end-stage renal disease (ESRD) and patients without ESRD. It may be detected in patients with clinically renal masses, but more often present as an incidental finding in nephrectomies performed for other nontumorous situations. Grossly, they are usually small and may be found within cysts. Multifocality and bilaterality are not uncommon.

Histologically, ACD-associated RCCs show a spectrum of morphologic features, but the presence of eosinophilic cells with Furman grade 3 nuclei and cribriform, as well as tubulocystic patterns, are consistent findings (Fig. 2). Areas with papillary, alveolar, solid, or diffuse patterns may also be seen. Another peculiar feature of ACD-associated RCC is the presence of intratumoral oxalate crystals in most, but not all, tumors.

The “atypical cysts” in ACD are most likely precursors of ACD-associated RCC. Histologically, the lining epithelium of “atypical cysts” often have eosinophilic cytoplasm and large nuclei similar to that of ACD-associated RCC. Occasionally, there are multilayering of the cystic epithelium with formation of papillary tufts or nodular lesions.

A specific immunohistochemical profile is not required to confirm this diagnosis. ACD-associated RCCs are diffusely immunoreactive for alpha-methylacyl-CoA racemase, CD10, RCC Marker, and glutathione S-transferase-alpha. The tumors usually do not express or only focally express CK7.

ACD-RCC has a relatively good prognosis, because most cases are diagnosed early in patients on long-term follow-up for chronic renal disease. However, sarcomatoid or rhabdoid features have been reported, and a few cases can metastasize.

2.3. Clear cell papillary RCC

Clear cell papillary RCC was first described by Tickoo et al. in their report of a systemic survey of the tumors associated with ESRD. Unlike ACD-associated RCC, clear cell papillary RCCs also arise in the kidneys of noncystic ESRD and the normal kidneys of the general population. Tumors with similar morphology and immunoprofile described under different appellations such as renal angiomyoadenomatous tumor and RCC with diffuse CK7 immunoactivity are now interpreted by consensus as belonging to the morphologic spectrum of clear cell papillary RCC.

The tumors are mostly well circumscribed and enveloped by a thin capsule. Microscopically, the tumor shows a mixed papillary, solid-acinar, tubular, and microcystic pattern. Irrespective of the architecture, the tumors were almost entirely composed of cells with clear cytoplasm (Fig. 3). One characteristic feature is the linear...
arrangement of the nuclei away from the basal aspect, toward the middle or the apex of the cells (reverse polarity). It should be noted that clear cell papillary RCC is a distinct entity from either clear cell RCC and papillary RCC. The tumor is not a hybrid or composite tumor made of clear cell RCC and papillary RCC.

In contrast to other morphologic types of RCC that do not require immunohistochemistry for diagnosis, a proper immunoprofile, namely, the diffuse immunoreactivity for CK7, which is almost always in 100% of the tumor cells, is a prerequisite to establish the diagnosis of clear cell papillary RCC. Tumors morphologically resembling clear cell papillary RCC yet lack typical CK7 immunoreactivity cannot be confidently diagnosed as such. Tumor cells also express carbonic anhydrase IX diffusely in a membranous cup-shaped distribution. Immunostains for alpha-methylacyl-CoA racemase, CD10, and RCC marker are mostly negative.

The small number of published cases with limited follow-up data indicates that these are neoplasms with indolent clinical behavior. Metastases have not been reported to date.

2.4. t(6;11) RCC

The 2004 WHO classification has already included Xp11 translocation carcinoma. While Xp11 translocation RCCs consistently involve the fusion of TFE3, t(6;11) RCCs involve transcription factor EB (TFEB), which is another member of the MiT subfamily of transcription factors. t(6;11) RCCs are characterized by t(6;11)(p21;q12), which results in an Alpha-TFEB gene fusion.7,16

This neoplasm typically demonstrates distinctive biphasic morphology, comprising larger and smaller epithelioid cells, with the latter often clustered around basement membrane material (Fig. 4). The tumors consistently express melanocytic markers such as HMB-45 and Melan-A, but are either negative or only focally positive for epithelial markers such as cytokeratins. The Alpha-TFEB gene fusion results in overexpression of native TFEB. Nuclear labeling for TFEB protein by immunohistochemistry is thus a sensitive and specific assay for diagnosis. Virtually all cases express cathepsin-K, which is also expressed in a subset of Xp11 translocation RCC, but not in other common RCC subtypes.17 The majority of cases express PAX8, supporting renal tubular differentiation.

According to the clinicopathologic, immunohistochemical, and genetic similarities to the Xp11 translocation RCC, there has been a consensus that the t(6;11) RCC should be included with the former under the category of MiT translocation RCC.

Since the available data about this neoplasm have been limited, the clinicopathologic spectrum remains to be elucidated. Some cases metastasized and caused death of the patient.18,19

2.5. Hereditary leiomyomatosis RCC syndrome-associated RCC

Hereditary leiomyomatosis RCC syndrome is autosomal dominant and is associated with germline mutations in the fumarate hydratase gene located at chromosome 1q42. The main features of this syndrome are frequent and multiple cutaneous and uterine leiomyomas, which are difficult to manage and require hysterectomy before the age of 30 years in around half of patients. The RCCs associated with this syndrome affect approximately one third of patients. These syndromic neoplasms are solitary but are highly aggressive, usually presenting in advanced stages and are lethal.20

Hereditary leiomyomatosis RCC-associated RCC (HLRCC) was listed in the 2004 WHO classification under the category of familial RCC.1 The tumor was suggested as a subtype of type 2 papillary RCC at that time. However, the tumor manifests several features distinct from typical papillary RCC, such as prominent eosinophilic nucleoli with a clear halo, mimicking cytomegalovirus inclusions in both the RCC and leiomyomas. Architecturally, HLRCCs frequently have papillary architecture, but other architectures such as cribriform and solid may also be present.21

HLRCCs and leiomyomas in the syndrome demonstrate biallelic inactivation of fumarate hydratase, with germline mutations in one allele and loss of the second allele. Although experience with HLRCC is largely limited to the National Institutes of Health Group, there is a consensus to recognize HLRCC as a distinctive entity. Given the aggressive behavior of the tumor, patients with this syndrome should be followed more closely to eradicate the renal masses even when they are small.

3. Provisional new tumor entities

Aside from the abovementioned new entities, there are three rare RCCs that are considered as emerging or provisional new entities in the ISUP conference. Thyroid-like follicular RCC is characterized by macrofollicular and/or microfollicular architecture associated with dense colloid-like material resembling follicular neoplasm of thyroid (Fig. 5). However, thyroid-like follicular RCCs do not express thyroid markers including thyroid transcription factor-1 and thyroglobulin.22 On the contrary, papillary RCCs or...
other subtypes of RCC occasionally exhibit similar morphology in focal areas also.

Succinate dehydrogenase B (SDHB) deficiency—associated RCC is a renal neoplasm associated with phaeochromocytoma/paraganglioma syndrome type 4.23 Loss of the SDHB protein using immunohistochemistry is reported to be a sensitive and specific marker for these neoplasms. Morphologically, these neoplasms are usually unencapsulated and composed of compact nests of eosinophilic polygonal cells which may have vacuolated cytoplasm or distinctive pale eosinophilic cytoplasmic inclusions corresponding to giant mitochondria upon ultrastructural examination. A recent series showed that all patients undertaking genetic testing harbored germline mutations, mostly in SDHB and rarely in SDHC. The overall incidence of SDHB deficiency-associated RCC in unselected renal tumors was estimated as being from 0.05% to 0.2%.24

Finally, RCCs involving translocation of anaplastic lymphoma kinase (ALK) gene have been reported.11,25 The fusion partners have been reported to be VCL,25 TPM3, or EML4 genes.26 Experience with these emerging entities have been limited. There are still controversies about whether they deserve to be regarded as distinct entities or are variants of existing categories. The biological behavior of these tumors is uncertain given the paucity of reported cases. Further studies are required to clarify the nature of these highly unusual tumors.

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References