Non–Clear Cell Renal Cell Carcinoma, Part 1: Histology

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Abstract: Non–clear cell renal cell carcinomas (RCCs) represent up to 20% of all RCCs. Despite often being clustered as a single entity, these tumors represent a heterogeneous group of diseases with distinct molecular drivers, histologies, and clinical outcomes. Their low incidence and heterogeneity have resulted in a lack of studies that address the optimal strategies for each subtype. This article (the first in a 2-part series) reviews the histology of RCC, whereas the second article reviews current targeted therapies approved for RCC, such as the vascular endothelial growth factor receptor tyrosine kinase inhibitors and the mammalian target of rapamycin inhibitors. Ongoing studies will provide more information regarding the role of these agents in non–clear cell RCC.

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, accounting for approximately 85% of cases.[1,2] The 2004 World Health Organization (WHO) classification identifies various subtypes of RCC, including clear cell (>75%), papillary (~15%), chromophobe (5%), collecting duct (1%), medullary (<1%), post-neuroblastoma (<1%), mucinous tubular and spindle cell (~2%), Xp11.2 translocation (~2%), and unclassified (5%-10%). Additional histologic subtypes not currently included in the 2004 WHO classification include: tubulocystic carcinoma, clear cell tubulopapillary carcinoma (also referred to as clear cell papillary RCC), RCC associated with end-stage renal disease (acquired cystic disease-associated RCC), thyroid-like follicular RCC, succinate–dehydrogenase deficient RCC, and tumors associated with the familial syndrome of hereditary leiomyomatosis and renal cell carcinoma (HLRCC).[1,3] Despite their quite variable pathogenetic mechanisms, histologic appearances, clinical courses, and outcomes, these different RCC subtypes are often collectively identified in current clinical practice as one group, so-called "non–clear cell RCC." This generic grouping springs from low case numbers and the lack of effective treatment options for these histologic variants compared with the more prevalent clear cell subtype.

This article, which is the first in a 2-part series, reviews the histologic, genetic, and clinical differences among non–clear cell RCC subtypes (see the figure and the table). The second article reviews the current approach to the treatment of these tumors.

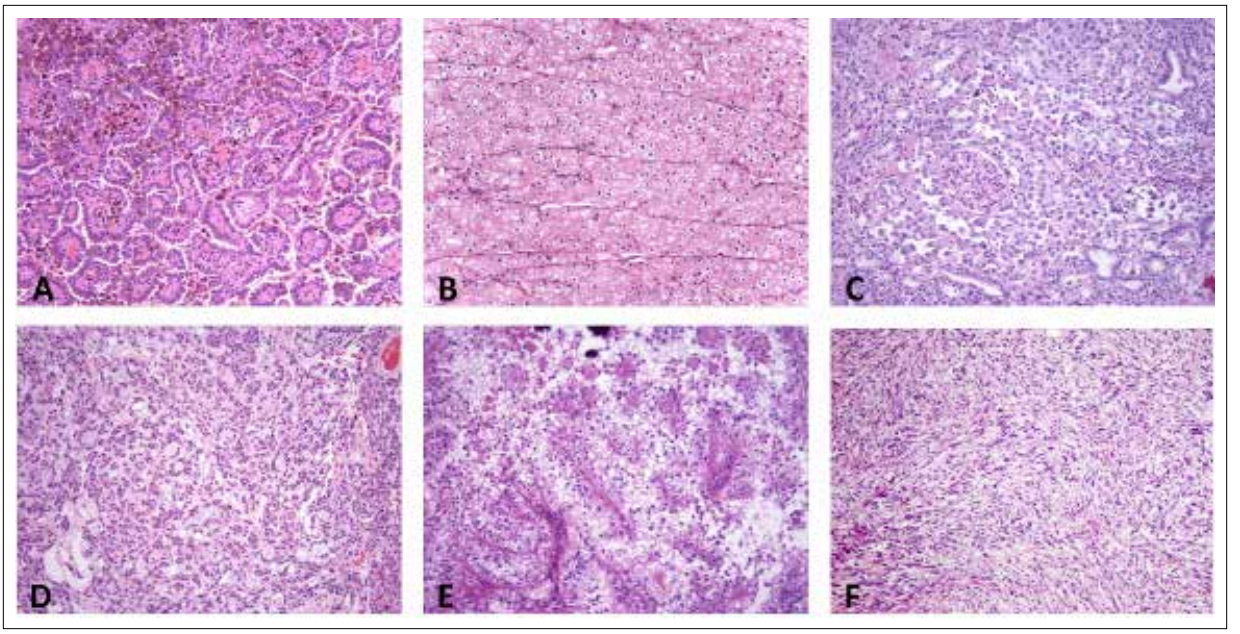

Figure. Classic examples of non–clear cell renal cell carcinoma (RCC). **A,** Papillary RCC. **B,** Chromophobe RCC. **C,** Collecting duct carcinoma. **D,** Mucinous tubular and spindle cell carcinoma. **E,** Xp11.2 (translocation) RCC. **F,** Sarcomatoid differentiation from a clear cell RCC (clear cell component not shown).

Classification

Papillary RCC

Papillary RCC is the second most common subtype of RCC and makes up approximately 10% to 15% of cases.[1,2] Papillary architecture constitutes the great majority of these tumors; however, tubular and solid growth patterns can be seen. The tumor papillae contain a delicate fibrovascular core, which can be accompanied by edema or hyalinized connective tissue.[2]

Papillary carcinomas are often subdivided into 2 subtypes based upon histologic criteria and distinctive gene expression profiles (see below). Type 1 tumors tend to be low-grade and have a better prognosis, whereas type 2 lesions are generally high-grade and impart a poorer prognosis.[4,5] Distinguishing between these 2 so-called histologic types can be difficult because some tumors contain a mixture of both morphologic patterns.

Genetically, both types are characterized by extra copies of chromosomes 7, 12, 16, 17, and 20.[6] When present, these genetic features support the diagnosis of papillary renal carcinoma, even when papillary characteristics are not dominant. Conversely, neoplasms lacking these genetic features should not be designated as papillary renal carcinoma even when papillary architecture is prominent because the latter morphology can be present in other subtypes, such as Xp11.2 RCCs and clear cell tubulopapillary carcinomas.[1,2]

Mucinous tubular and spindle cell carcinomas (MTSCCs) also can be confused with papillary RCC, especially when the latter has a prominent tubular architecture. In classic cases, MTSCC has several distinctive features: a prominent tubular architecture, a component of low-grade spindle cell formation, and a myxoid matrix.[1] These features can also be present in a small subset of papillary RCC.

In difficult cases, distinguishing papillary RCC from other, less common, subtypes such as MTSCC can be accomplished with ancillary studies, including immunohistochemistry and fluorescence in situ hybridization. MTSCC is associated with chromosomal loss, whereas chromosomal gains are seen in papillary RCC.[6,7] It is important to distinguish between the low-grade spindle cell component in MTSCC and the high-grade sarcomatoid differentiation (described later) that can be seen in any subtype of RCC. Sarcomatoid features can be present in MTSCC as well.[1,8]

Despite what is known morphologically and genetically, the oncogenetic events and critical pathways that drive papillary RCC largely remain unknown. Recent work assessed somatic alterations in papillary RCC and revealed that *MET, SLC5A3, NF2, PNKD, CPQ, LRP2, CHD3, SLC9A3R1, SETD2,* and *CRTC1* were significantly mutated in these tumors.[9] Amplification and activating mutations of *MET*, which is located on chromosome 7, have been described in familial and some sporadic cases of papillary type 1 RCC.[9-11] c-MET is triggered by its ligand hepatocyte growth factor/scattered factor (HGF/SF).[12] The signaling pathways mediated through HGF/SF and c-MET promote angiogenesis, tumor invasion, and metastasis across a wide

Table. Overview of the Incidence, Histologic Features, Genetics, Prognosis, and Proposed Rational Treatments for the Non–Clear Cell Renal Cell Carcinoma Subtypes

Subtype	Incidence	Histology	Genetics	Prognosis	Rational Treatment[a]
Papillary	10%-15% RCC	- Papillary architecture is frequent - Type 1: small cells with scanty cytoplasm and low nuclear grade - Type 2: high nuclear grade with eosinophilic cytoplasm	- No loss of 3p - Extra copies of 7, 12, 16, 17, 20 - Trisomies 7, 12, 16, 17, 20 - Loss of Y - MET mutation (especially type 1) - MET upregulation and copy number changes	- Aggressiveness relates to grade, stage, and presence of sarcomatoid features - Type 2 usually has high grade and poorer outcome	- VEGF/R targeted agents - mTOR inhibitors - Activity reported with MET inhibitors - Clinical trials
Chromophobe	~5% RCC	- Solid, sometimes tubular/acinar - Long linear parallel vessels - Cells with eosinophilic cytoplasm and well-defined cell borders	- Loss of chromosomes 1, 2, 6, 10, 13, 17, and 21	- Tends to present at a low stage - Lower risk of metastases and death than papillary or clear cell RCC - High-grade and high-stage tumors can be aggressive	- VEGF/R targeted agents - mTOR inhibitors - Clinical trials
Collecting duct carcinoma	<1% RCC	- Angulated glands infiltrate renal parenchyma and desmoplastic stroma - High nuclear grade - High proportion of sarcomatoid features	- Poorly understood	- Advanced disease in most cases - Poor outcome	- Gemcitabine and platinum-based therapy - VEGF/R inhibitors - Clinical trials
Xp11.2 translocation carcinoma	1%-3% RCC	- Nested to papillary architecture with clear cells and/or granular to eosinophilic cytoplasm - Diagnosis confirmed with strong and diffuse nuclear immunoreactivity for TFE3 protein or a translocation of the TFE3 gene by FISH	- Chromosome translocation involving Xp11.2 resulting in gene fusions of the TFE3 gene	- Aggressive behavior described in adults - More indolent in children	- Paucity of data - VEGF/R inhibitors - Clinical trials
RCC with sarcomatoid differentiation	~5% RCC (varies with histologic subtype)	- Can occur with any type of RCC - Spindle-like cells, high cellularity, cellular atypia, increased mitotic activity, and necrosis	- Complex karyotypes with chromosomal changes that reflect the underlying subtype	- Aggressive variant, especially if ≥20%-30% of the tumor demonstrates sarcomatoid differentiation	- Gemcitabine and doxorubicin - VEGF/R inhibitors - mTOR inhibitors - Clinical trial: eg, gemcitabine plus sunitinib

FISH, fluorescence in situ hybridization; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; TFE3, transcription factor E3; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

[a] Clinical trials should be considered for first-line therapy in all non–clear cell patients given the absence of standard treatments.

variety of human carcinomas.[13] However, MET pathway alterations are not completely limited to papillary RCC, and also can be found in a subset of clear cell RCC.[14]

The renal tumors seen in HLRCC have papillary architecture and eosinophilic cytoplasm that are both morphologically similar to that seen in so-called "type 2"

papillary RCC but have more distinct red nucleoli and perinucleolar halos.[2,15,16] The HLRCC familial syndrome is an autosomal dominant condition associated with a germline fumarate hydratase *(FH)* gene mutation.[15,16] FH is a tricarboxylic acid (Krebs) cycle enzyme that plays a role in aerobic cellular metabolism.[15,16] Inactivation of FH results in the generation of a pseudohypoxic state, similar to that induced by mutations or inactivation of the VHL pathway.

Chromophobe RCC

Chromophobe histology accounts for approximately 5% of RCCs.[1,2] In general, the growth pattern is solid, but tubular architecture can be present. Occasionally, focal calcifications and broad fibrotic septa are present. The latter often contain long linear vessels, which contrast with the thin, delicate wrapping vessels of clear cell RCC. Hale's colloidal iron stain is typically positive in chromophobe RCC and may be helpful in diagnosing this histologic subtype.[2] Overexpression of KIT has been observed more frequently in chromophobe and renal oncocytomas than in other subtypes.[17] However, this overexpression has not been associated with *KIT* gene mutations,[17] and could be due to gene amplification (the presence of multiple copies of the wild-type *KIT* gene).[18]

Genetically, chromophobe RCC is characterized by extensive chromosomal loss[19]; most frequently in chromosomes 1, 2, 6, 10, 13, and 17. Recently, *TP53*, *PTEN*, *FAAH2, PDHB, PDXDC1,* and *ZNF765* were found to be significantly mutated in chromophobe RCC specimens.[9] The Cancer Genome Atlas (TCGA) analysis of somatic genomic alterations in chromophobe RCC revealed promoter rearrangement in telomerase reverse transcriptase (TERT), which translated to elevated TERT expression in these tumors.[19] In addition, it seems that mitochondrial DNA alterations are more common in chromophobe RCC than in clear cell RCC, where there generally is lower expression of genes involved in mitochondrial activity.[19,20]

Most chromophobe RCCs are sporadic. However, renal tumors with similar morphology but distinct genetic features can be associated with Birt-Hogg-Dubé (BHD) syndrome.[21] The *BHD* gene is located on chromosome 17p11 and encodes a potential tumor suppressor protein called folliculin.[21,22] The syndrome is an autosomal dominant disorder that induces fibrofolliculomas, renal epithelial tumors (eg, chromophobe RCC, oncocytomas, and clear cell RCC), and pulmonary cysts that can result in spontaneous pneumothorax. The renal tumors in this syndrome are frequently bilateral and multifocal. Chromophobe RCCs typically have a lower risk of disease progression and death compared with papillary or clear cell RCCs, although these better outcomes are likely in part due to the fact that patients generally present at an earlier stage.[23-25] High-grade and more advanced stage chromophobe tumors portend a worse prognosis.

In addition to morphologic differences, distinct gene expression profiles observed in non–clear cell RCC further support the concept of tumor subtype heterogeneity. Durinck and colleagues recently reported on their gene expression analysis in non–clear cell RCC, which revealed that papillary RCCs have a higher mutational burden than chromophobe RCC or oncocytomas.[9] They found a possible 5-gene set—*ASB1, GLYAT, PDZK1P1, PLCG2,* and *SDCBP2*—that might be able to stratify papillary RCC, chromophobe RCC, and renal oncocytomas. Prospective validation is required.

Collecting Duct Carcinoma

Previously known as Bellini duct carcinoma, collecting duct carcinoma (CDC) is a rare variant, accounting for less than 1% of RCCs.[1,2] Criteria for diagnosing CDCs are not well established. Nevertheless, the diagnosis requires a primary location in the medulla and exclusion of other RCC subtypes. The growth pattern is frequently tubular or tubulopapillary, in which irregular, angulated glands infiltrate the renal parenchyma and are associated with a desmoplastic stroma.[1,2] The tumor cells generally display high-grade nuclear features. Molecular events that contribute to the development of CDC are poorly understood, but chromosomal loss has been observed.[26] Histologically, CDC can be difficult to distinguish from urothelial carcinomas, thus Becker and colleagues undertook an analysis of the genetic differences between the two.[27] Using comparative genomic hybridization, they observed differences in the chromosomal alteration patterns between the 2 types of cancer. CDCs tended to have more chromosomal losses than gains, and no amplifications were seen. The most common CDC alterations were DNA losses at 8p, 16p, 1p, and 9p, as well as gains at 13q. This subtype is generally clinically aggressive and tends to present with more advanced stage, with resultant poor prognosis.

Renal Medullary Carcinoma

Medullary carcinoma is another aggressive subtype of RCC that has morphologic features similar to those of CDC, but typically occurs in younger patients and is associated with sickle cell trait.[2,28] Loss of INI1 (SMARCB1) and presence of OCT3/4 on immunohistochemistry may help distinguish renal medullary carcinoma from CDC.[29-32] INI1-negative tumors with morphologic features similar to those of CDC and medullary carcinomas, but in the absence of sickle cell trait, should be referred to as "unclassified RCC with medullary features."[33]

Renal Carcinoma Associated With Xp11.2 Translocation

Xp11.2 RCC is a rare but also likely underdiagnosed subtype of RCC. It was first recognized in children and is

described in the 2004 WHO classification. These tumors are part of the family of microphthalmia transcription factor (MITF)-associated tumors and are characterized by chromosome translocations involving Xp11.2, which results in a gene rearrangement involving the *TFE3* gene.[1,2] A genome-wide analysis using RNA and exome sequencing identified 3 novel MITF/TFE partners involved in RNA splicing, expanding the spectrum of translocations associated with this disease.[34] The study also revealed mutations in chromatin remodeling genes. In general, Xp11.2 RCCs typically have heterogeneous morphologic features, including a nested to papillary architecture, clear to granular/eosinophilic cytology, and voluminous cytoplasm.[1,35] Although there can be issues with sensitivity, nuclear immunoreactivity for the transcription factor E3 (TFE3) protein is relatively specific for Xp11.2 translocation RCC.[35,36] Of note, TFE3 can be positive in alveolar soft part sarcoma, which shares the same translocation. In the absence of a conventional karyotype and a reliable TFE3 antibody, fluorescence in situ hybridization can be performed in formalin-fixed, paraffin-embedded tissue to confirm the diagnosis.[36] Elevations in baculoviral IAP repeat-containing protein 7 (BIRC7) expression were observed in the majority of Xp11.2 RCC in 1 cohort, which may be useful in the diagnosis of all MITF family members.[9]

Xp11.2 RCC seems to be more indolent in children and adolescents, even when diagnosed at an advanced stage.[37,38] In contrast, this subtype tends to be more clinically aggressive in adults (with a greater proportion of middle-aged females being affected), and generally presents at an advanced stage (III or IV) with a tendency toward lymph node metastases.[39,40]

Sarcomatoid Component

Sarcomatoid differentiation in RCC is not a distinct histologic subtype, but rather a pathologic feature that can be observed in any RCC subtype. The histologic characteristics are similar to many other high-grade sarcomas, and include spindle-like cells, high cellularity, cellular atypia, increased mitotic activity, and necrosis.[41] The presence of paired box gene 8 (PAX8) in the spindle cell component can help confirm the diagnosis of a poorly differentiated RCC.[42] A sarcoma involving or adjacent to the kidney also should be excluded in the absence of an underlying well-differentiated RCC. The presence of sarcomatoid features in RCC portends an aggressive clinical course and is an independent predictor of poor survival.[41] Although the frequency varies by stage, most series report a 5% incidence of sarcomatoid features in RCC.[41,43] Patients whose primary tumor has no more than 25% to 30% of sarcomatoid features may have a better prognosis than those whose primary tumor has a higher percentage.[44,45] Higher percentages also may predict a greater chance of systemic disease.[44,45] RNA sequencing of adjacent clear cell and sarcomatoid components has revealed increases in proliferation pathways and aurora kinase–dependent activation of the mTOR pathway in the sarcomatiod tissue.[46] The latter finding may have therapeutic implications, given the approved mTOR inhibitors for RCC.

Conclusion

In summary, this article reviews the various distinct subtypes of non–clear cell RCC, including: papillary RCC, chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, and renal carcinoma associated with the Xp11.2 translocation, and describes the classification of sarcomatoid differentiation in RCC. In the second part of this 2-part series, we will focus on the treatment of the different subtypes.

Disclosures

Drs Valenca and Hirsch have declared no financial conflicts of interest. Dr Choueiri has served on the advisory boards of Novartis, Pfizer, GlaxoSmithKline, Merck, Bristol-Myers Squibb, and Bayer. Dr Harshman has served on the advisory boards of Genentech, Bristol-Myers Squibb, Aveo, and Pfizer, and receives research funding or support from Pfizer and Medivation.

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