Review

Contemporary approach to diagnosis and classification of renal cell carcinoma with mixed histologic features

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Abstract

Renal cell carcinoma (RCC) is an important contributor to cancer-specific mortality worldwide. Targeted agents that inhibit key subtype-specific signaling pathways have improved survival times and have recently become part of the standard of care for this disease. Accurately diagnosing and classifying RCC on the basis of tumor histology is thus critical. RCC has been traditionally divided into clear-cell and non-clear-cell categories, with papillary RCC forming the most common subtype of non-clear-cell RCC. Renal neoplasms with overlapping histologies, such as tumors with mixed clear-cell and papillary features and hybrid renal oncocytic tumors, are increasingly seen in contemporary practice and present a diagnostic challenge with important therapeutic implications. In this review, we discuss the histologic, immunohistochemical, cytogenetic, and clinicopathologic aspects of these differential diagnoses and illustrate how the classification of RCC has evolved to integrate both the tumor's microscopic appearance and its molecular fingerprint.

Key words Renal cell carcinoma, clear-cell renal carcinoma, papillary renal carcinoma, hybrid oncocytic tumors, immunohistochemistry, fluorescence *in situ* hybridization

Renal cell carcinoma (RCC) accounts for over 115,000 deaths worldwide[1]. It is resistant to both traditional chemotherapy and radiation therapy, with relatively few patients benefitting from immunological regimens. Over the past decade, the major clinical breakthrough in this area has been the unraveling of signaling pathways that drive RCC growth[2]—up-regulation of the hypoxia-inducible factor (HIF1α and HIF2α) and mammalian target of rapamycin (mTOR) pathways—and the successful abrogation of these pathways with targeted therapies[3,4]. Because most clinical studies have been conducted using patients with the clear-cell subtype of RCC, their findings may not be applicable for the non–clear-cell RCC subtypes, which differ molecularly as well as histologically[5]. Hence, accurate diagnosis and

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subclassification of RCC is important not only for prognostication but also for prediction of therapeutic response.

Diagnosis and Classification of RCC

The clear-cell cytological features of RCC on hematoxylin and eosin (HE) preparations have long been recognized. Early pathologists proposed that RCC originated from adrenal rests and referred to renal epithelial tumors as "hypernephromas" because of their histologic similarity to adrenal cortical cells. The renal tubular derivation of clear-cell RCC was postulated in the early 1960s based on ultrastructural studies showing similarities between RCC and the proximal renal tubular epithelium[6]. By the 1980s, additional types of RCC—e.g., papillary and chromophobe subtypes—were recognized[7], forming the basis for the 1986 Mainz classification system wherein renal epithelial tumors were grouped as clear cell, chromophil, chromophobe, collecting duct RCC, or benign oncocytomas. RCC classification was solidly based on light microscopic features and was dichotomized as tumors possessing either a tinctorially clear or a non-clear "granular" cytoplasm on HE-stained preparations. During the

following decade, the common RCC types were characterized at the cytogenetic level. This was formalized with the Heidelberg classification of 1997, which served as the basis for the most recent iteration of the World Health Organization classification of RCC in 2004[8] (Table 1). More recently, expression profiling has shown a strong correlation between gene expression pattern and RCC histologic type[9] and has reinforced the notion that RCC subtypes are biologically distinct entities.

Diagnosis and subclassification of RCC continue to be based primarily on histopathology. These processes are generally straightforward given the typical architectural and cytological features of clear-cell RCC (a solid or nested pattern with clear-cell cytoplasm), which differs from papillary RCC (overt papillae with non-clear, eosinophilic or basophilic cytoplasm) (Figures 1A–D). The current state of knowledge permits classification of 90%–95% of RCC; the remaining 5%–10%, however, cannot be properly classified and are thus designated as "RCC, unclassified." A salient diagnostic challenge is evaluating RCC that shows mixed, overlapping histologic features. We will discuss the scenario of tumors with a papillary architecture and clear-cell cytoplasmic features (Figures 1E, F) as well as renal oncocytic tumors with hybrid features. Other combinations are also encountered in practice, such as tumors with a solid architecture and non-clear cytoplasm. Multiple patterns may coexist, particularly in high-grade renal carcinomas, rendering diagnosis challenging without supportive ancillary studies or a more classic concomitant low-grade pattern.

Diagnosis of RCC on needle core biopsies

In recent years, imaging-guided needle core biopsy has increasingly been used to pathologically diagnose renal masses for treatment planning purposes. The use of newer imaging modalities and refined needle biopsy techniques has made renal biopsy a safe and reliable procedure with a low complication rate. At M. D.

Anderson Cancer Center, most patients undergoing biopsy for a renal mass usually fall into one of the following categories: (i) patients being followed for a non-renal primary tumor who develop a renal mass that is detected by imaging; (ii) patients being considered for enrollment in neoadjuvant therapy clinical trials for clear-cell RCC; (iii) patients with metastasis and an unresectable renal mass; and (iv) patients undergoing treatment of a renal mass using ablative techniques. Of course, for clinical decision making, pathologic diagnosis is weighed differently in each of those categories. For most needle core biopsies of kidney masses, we receive two or three needle cores, all of which are embedded in one cassette. For these cases, we cut two sections for HE staining (levels 1 and 8), saving the 6 intervening levels as unstained sections on charged slides for possible immunohistochemical stains. Immunohistochemical stains are frequently needed to classify the type of RCC. Limitations of biopsy cores include the minute amount of viable tumor present in some cores and inadequate sampling, especially when dealing with larger tumors that may harbor neoplastic cells with different morphologic features. Needle cores may not always sample the higher grade tumor or foci of sarcomatoid dedifferentiation, which may change the patient's subsequent management.

RCC with Mixed Clear-cell and Papillary Features

RCC with a papillary architecture and clear-cell cytoplasm may be divided into two groups: (1) tumors in which this admixture is intrinsic to the tumor type and (2) tumors in which this admixture represents variant morphology and may be a focal finding (Figure 2A and Table 2). The latter group poses a challenge in contemporary practice. Indeed, pathologists may be unable to review the entire tumor but are now expected

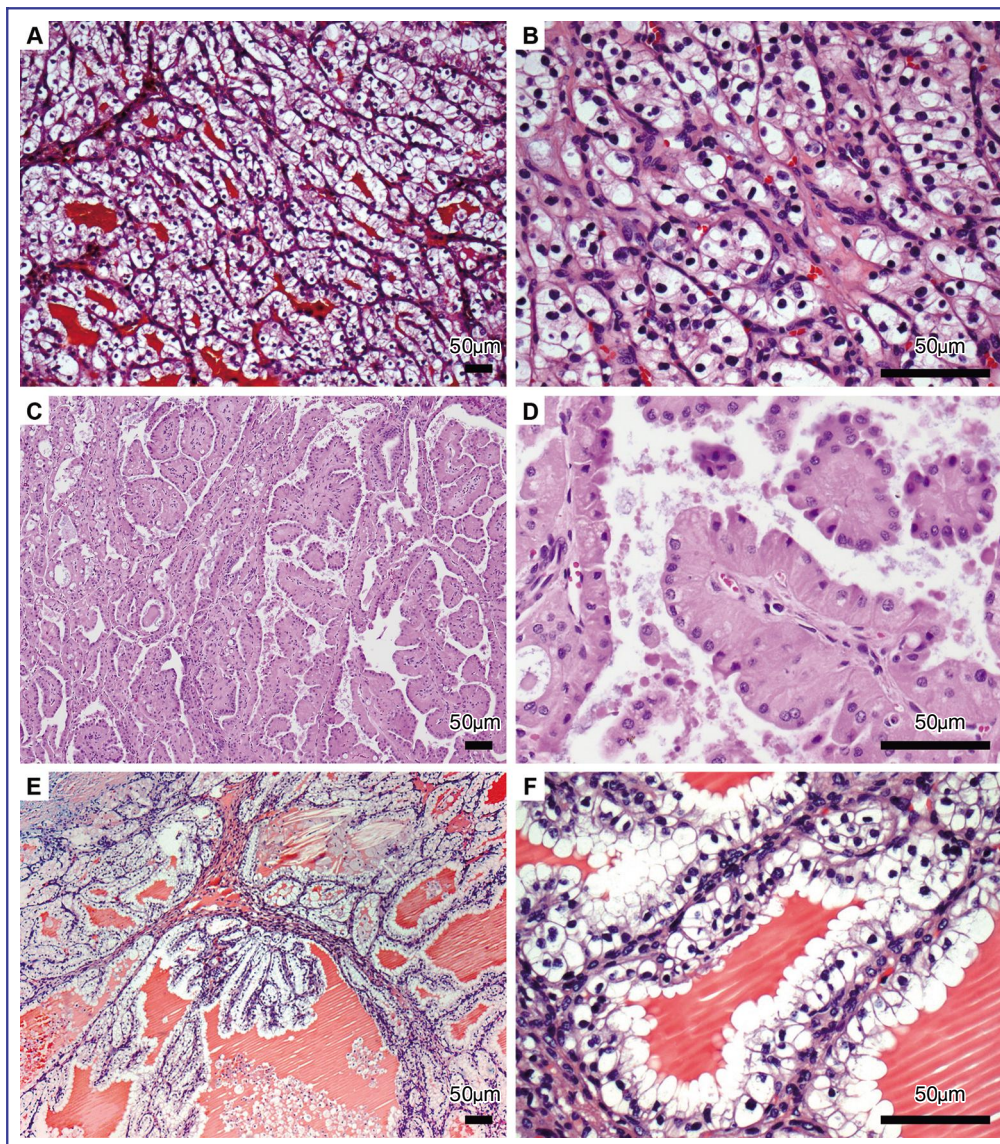| Table 1. World Health Organization classification and incidence rates of renal cell carcinoma (RCC) subtypes	
RCC subtype	Incidence (%)
Clear-cell	75
Papillary	10
Chromophobe	5
Collecting duct of Bellini	1
Medullary	<1
Post-neuroblastoma	<1
Xp11 translocation	<1
Mucinous tubular and spindle cell	<1
Multilocular cystic	<1
Unclassified	5–10

Figure 1. Architectural and cytological patterns of different subtypes of renal cell carcinoma (RCC). HE stained sections show architectural and cytological characteristics of clear-cell RCC (A, B), papillary RCC (C, D), and RCC shows an admixture of papillary architecture and clear-cell cytology (E, F).

to render a diagnosis based on scant renal biopsy tissue in which focal histologic changes may predominate. Thus, with the advent of subtype-specific targeted therapy as well as an evolving biopsy strategy, pathologic diagnosis is now both more important for patient care and more challenging because of the small amount of material evaluated.

Clear-cell RCC

Clear-cell RCC is the most common subtype, typically occurring in the sixth and seventh decades of life. Generally, these tumors show solid, alveolar, and papillary architecture with a plexiform vascular pattern and clear cytoplasm. The clear cytoplasm on HE-stained preparations is due to the accumulation of cytoplasmic lipid and glycogen within tumor cells. Clear-cell RCC is the most aggressive of the common subtypes, with prognosis related primarily to the pathologic stage but also to the nuclear tumor grade[10].

Clear-cell RCC demonstrates characteristic DNA copy number alterations across the genome, the most significant of which is the loss of chromosome 3p (Figure 2B). The loss of 3p is important because the 3p25.3 region houses the von Hippel-Lindau (VHL) gene, which also can be altered in RCC by promoter methylation or mutation. VHL normally suppresses the HIF1α and HIF2α transcription factors, and aberrant or deleted VHL leads to HIF hyperactivation[11]. HIF-regulated genes include vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and glucose transporter 1 (GLUT1) [12]. The importance of VEGF
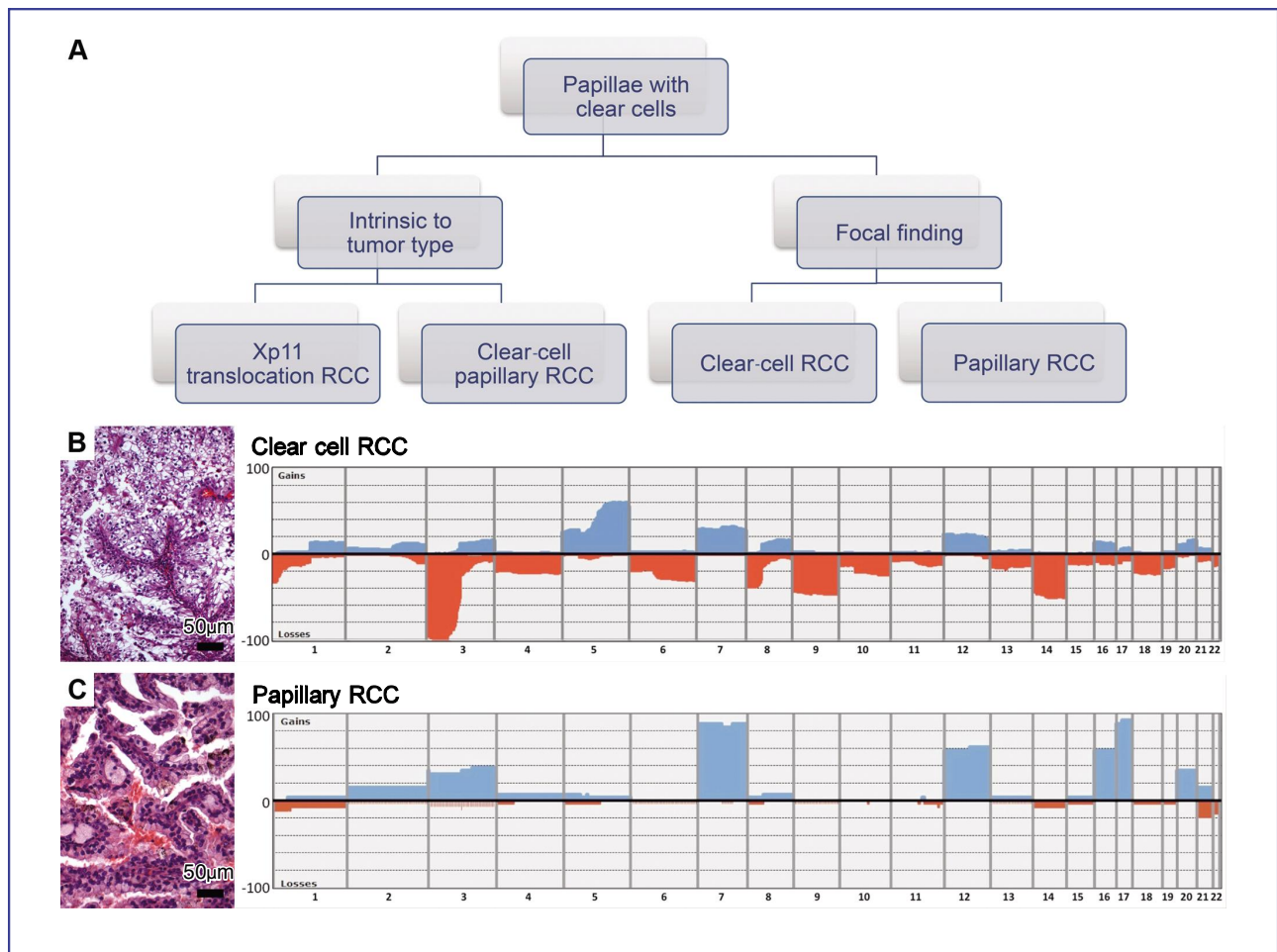
Figure 2. **Diagnostic approach for RCC with papillary and clear cell features.** Differential diagnosis of RCC with clear-cell cytology and papillary architecture (A). Histopathology (HE) and DNA copy number alterations for clear-cell RCC (B) and papillary RCC (C) with gain and loss of genomic DNA indicated in blue and red, respectively. All scale bars are 50 μm. (This figure was cited from reference [5] and modified with permission.)

overexpression is manifested by the high degree of vascularity seen in clear-cell RCC. Furthermore, VEGF overexpression has resulted in clear-cell RCC being a sensitive tumor to VEGF ligand and receptor inhibiting therapies. There are now five VEGF-pathway inhibiting agents approved for use in advanced RCC by the US Food and Drug Administration: sunitinib[13], sorafenib[14,15], pazopanib[16], bevacizumab[14], and axitinib[17].

Papillary RCC

Papillary RCC is the second-most common RCC subtype. Well-developed fibrovascular cores expanded by foa my macrophages, psammomatous microcalcifi- cations, and eosinophilic or basophilic cytoplasm is usual, although clear-cell cytoplasm may be encountered focally. Papillary RCC also shows characteristic DNA copy number aberrations that differ from those in

clear-cell RCC (Figure 2C). Papillary RCC show polysomies of chromosomes 7 and 17 without losses of 3p or *VHL* alterations. These tumors show a distinct immunoprofile and behave less aggressively than clear-cell RCC[18]. Prognosis is related primarily to stage, with nuclear grading less established for this subtype[19]. Targeted therapies using anti-angiogenic agents have been disappointing. Agents directed specifically at the papillary molecular phenotype are in early-phase clinical trials and include MET (hepatocyte growth factor receptor) inhibitors and dual vascular endothelial growth factor/epidermal growth factor receptor (VEGF/EGFR) blockers[20].

Among RCCs that intrinsically possess a papillary architecture and clear cytoplasm, two major subtypes enter the differential diagnosis: clear-cell papillary RCC and Xp11 translocation RCC.

Table 2. Morphology, immunohistochemistry, and cytogenetics of RCC with mixed clear cell and papillary features

RCC subtype	Histologic features	Immunoprofile +	Immunoprofile −	Cytogenetics
Clear-cell	Solid, nested, or tubular architecture; thin-walled plexiform vasculature; optically clear cytoplasm	EMA, VIM, RCC, CD10, CAIX	CK7, AMACR, TFE3	3p12− , 3p21− , 3p25− , 5q22+
Papillary	Papillary, tubular, or solid architecture; frequent hemorrhage and necrosis; foamy macrophages and psammomatous microcalcifications	EMA, VIM, RCC, CK7, CD10, AMACR	TFE3	+7; +17; −Y
Xp11 translocation	Papillary and solid architecture with psammomatous microcalcifications; optically clear cytoplasm with eosinophilic inclusions	TFE3, CD10, AMACR	EMA, CK7	t(X;17)(p11.2;q25) t(X;1)(p11.2;q21)
Clear-cell papillary[a]	Cystic tumor with tubulopapillary architecture; clear cytoplasm and apically located, low grade nuclei	CK7, EMA	AMACR, CD10, TFE3	No recurrent gains or losses

[a]Not included in the 2004 World Health Organization classification of RCC.

Clear-cell papillary RCC

Clear-cell papillary RCC was first described as occurring in the background of end-stage kidney disease [21]. Subsequent reports, however, established that similar tumors could be seen in a non–end-stage kidney disease setting[22]. Patients with clear-cell papillary RCC are mostly in their fifth or sixth decades, and their cancers show a tubulopapillary architecture with clear cytoplasm and tumor nuclei that are positioned toward the apical cell membrane (Figures 3A–C). These tumors have generally been of low nuclear grade, less than 5 cm in diameter, and confined to the kidney[21-23]. Immunohistochemical features are distinctive and helpful in differential diagnosis (Figure 3D, Table 2). No recurrent DNA copy number aberrations have been identified. In particular, the copy number changes characteristic of clear-cell RCC and papillary RCC have not been seen[23-25]. A significant attribute of this tumor is its indolent clinical course, with no tumor recurrences or metastases reported to date[22-24]. Patients with clear-cell papillary RCC may prove to be appropriate candidates for active surveillance protocols, given their small tumor size and the emerging trend towards biopsy-based diagnosis of RCC.

Xp11 translocation RCC

Xp11 translocation RCC is the second subtype in which tumor cells largely possess a papillary architecture and clear cytoplasm (Figure 3E). These RCC are much more common among younger patients. In fact, they constitute the majority of pediatric RCC, but given the relative rarity of pediatric RCC, the absolute number of Xp11 translocation RCC is much greater in adults. Among adults, these cancers are more prevalent in younger adults (20–45 years) than in the typical age group of patients with RCC (>60 years) [26-29]. These tumors frequently show concentric, laminated—so-called "psammomatous"—microcalcifications, and their nuclear grade is typically high (Figure 3F). Xp11 translocation RCC are clinically aggressive, with the majority presenting with metastatic disease. The defining genetic abnormality underlying these cancers is a balanced translocation between the short arm of the X chromosome and another partner chromosome, resulting in a fusion transcript between the transcription factor binding to IGHM enhancer 3 (*TFE3*) gene at the Xp11 locus[30] and a variety of partner genes, including alveolar soft part sarcoma locus (*ASPL*), papillary renal cell carcinoma translocation associated (*PRCC*), and PTB-associated splicing factor (*PSF*)[31]. The outcome of this fusion event is that the *TFE3* gene is overexpressed and can be detected by nuclear immunolabeling with antibodies directed against the TFE3 protein (Figure 3G)[32]. Early reports suggested a high degree of specificity and sensitivity to TFE using immunohisto-chemistry[33], although the clinical experience has varied between institutions and methodologies[34]. Ancillary studies, including additional immunohistochemical and molecular studies, are required for more confident diagnosis. Of the confirmatory molecular assays, a break-apart TFE3 fluorescence *in situ* hybridization probe is the most practical (Figure 3H) because tumor cells

can be visualized and no foreknowledge of the fusion partner is required, as with reverse transcription–PCR approach[34]. To date, the only risk factor that has been identified for Xp11 translocation RCC is prior chemotherapy that is postulated to cause DNA breaks, thereby predisposing patients to translocation events[29]. Effective therapies for translocation RCC have, as yet, not been identified, although there is some evidence for the efficacy of anti-angiogenic drugs[35-38].

Renal Oncocytic Tumors with Hybrid Features

There has been considerable interest recently in the pathology of renal oncocytic tumors that show overlapping histologic features between renal oncocytoma and chromophobe RCC[39]. Renal oncocytoma is a benign tumor, whereas chromophobe RCC may infrequently
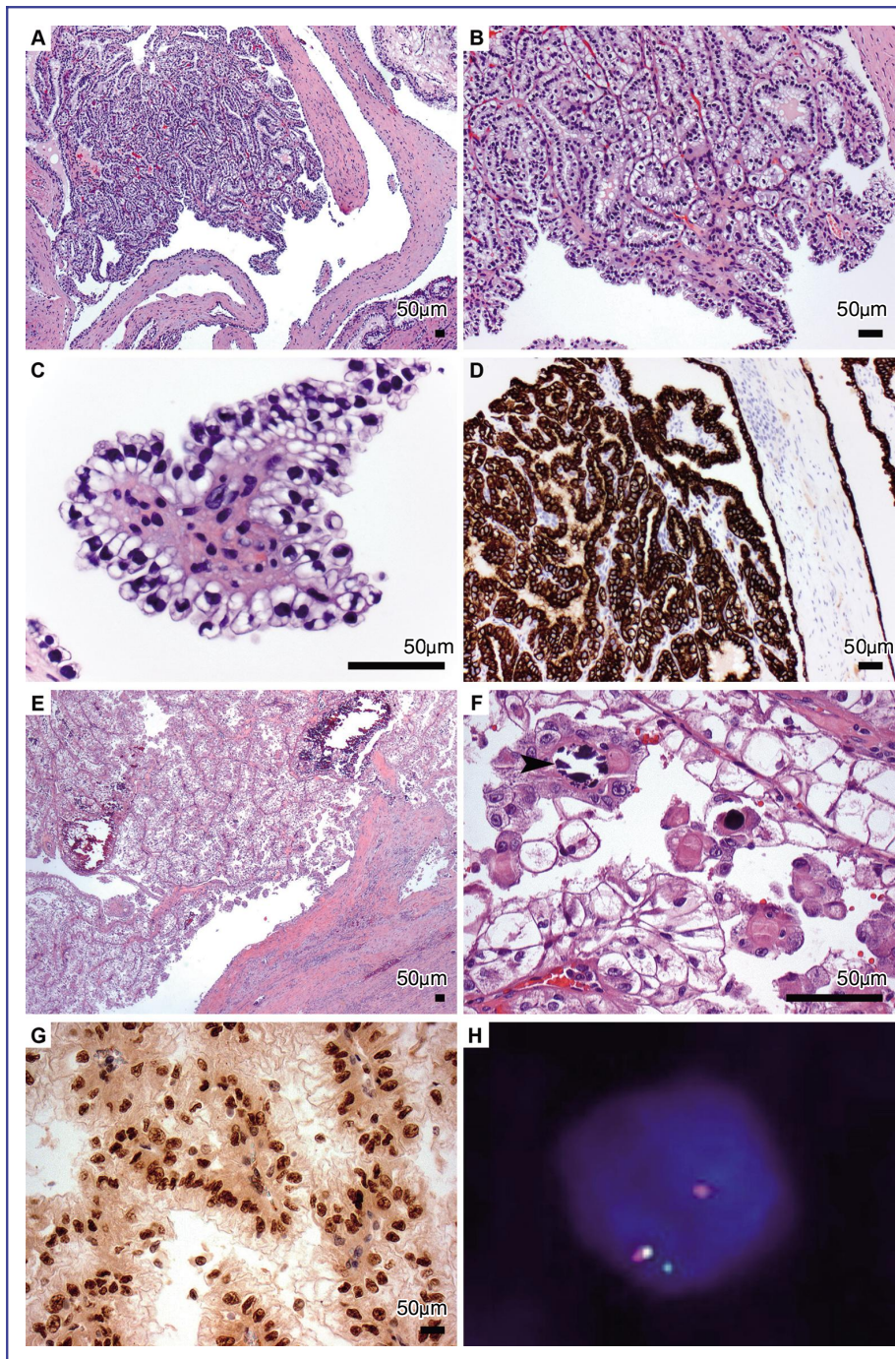

Figure 3. RCC that show intrinsic papillary architecture and clear-cell cytology. HE-stained sections illustrate clear-cell papillary RCC with a partially cystic papillary lesion and fibrotic stroma (A), characteristic branching acini with short papillae (B), low-grade, apically positioned nuclei (C), and strong immunohistochemical positivity for cytokeratin 7 (D). E, Xp11 translocation RCC with tubulopapillary architecture (HE). F, high-grade nuclei and psammomatous calcifica-tions (arrowhead) are typical (HE). G, nuclear immunohistochemical positivity for TFE3 indicates tumor cells that overexpress the TFE3 transcription factor, which results from a translocation involving the TFE3 locus on the X chromosome. H, a break-apart fluorescence *in situ* hybridization assay is shown, with the split red and green signals demonstrating the Xp11 translocation event involving one allele and the fused red-yellow signal indicating the absence of a translocation in the other allele (Courtesy of Dr. M. Stanton).

behave aggressively, undergoing sarcomatoid transformation and showing metastatic spread. Tumors with a composite oncocytoma or chromophobe RCC histology were originally identified in patients with the Birt-Hogg Dubé syndrome, an autosomal dominant genodermatosis characterized by mutations in the folliculin (*FLCN*) gene at chromosome 17p11.2. Affected patients develop fibrofolliculomas of the skin and have an increased incidence of lung cysts, spontaneous pneumothorax, and renal tumors [40,41]. The pathology of these renal tumors often poses a diagnostic conundrum for the pathologist. However, recognition of hybrid renal oncocytic tumors is important because the renal pathology may be the first or only manifestation of Birt-Hogg Dubé syndrome, which may require subsequent genetic investigation and counseling.

Hybrid renal oncocytic tumors were also described in the setting of kidneys containing multiple small oncocytic nodules (termed "renal oncocytosis"). The pathologic features of renal oncocytoma, chromophobe RCC, and hybrid renal oncocytic tumor are illustrated in Figures 4A–G. The tumors in the initial series reported by Tickoo *et al.*[39] showed areas resembling chromophobe RCC admixed with more typical areas demonstrating renal oncocytoma-like histology. Tumors may show a gradual transition between the different morphologies, with areas
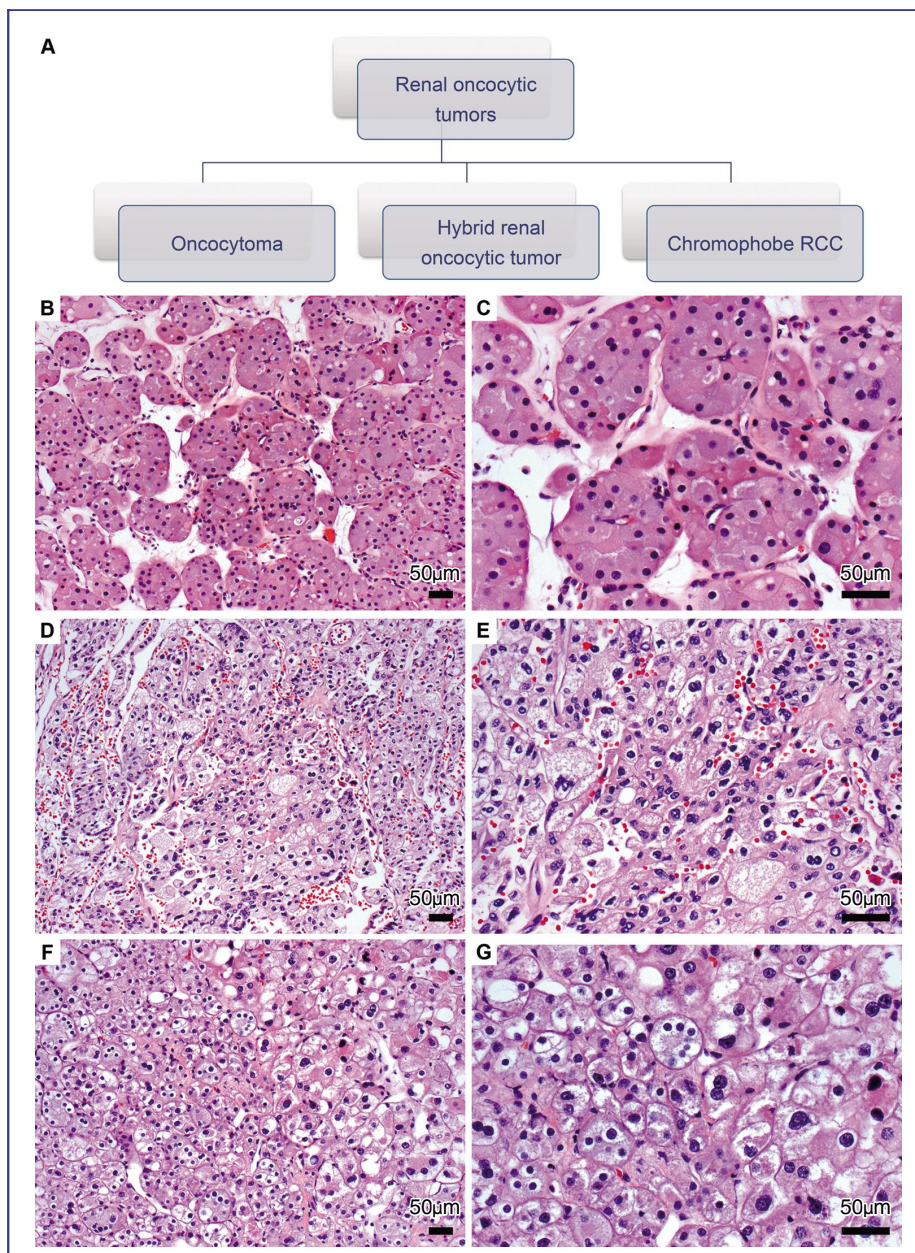

Figure 4. **Diagnostic approach for renal oncocytic tumors with hybrid features.** A, differential diagnosis of renal oncocytic tumors. HE stained sections show oncocytoma with islands of tumor within loose stroma (B) and eosinophilic cytoplasm with bland, uniform nuclear features (C). Chromophobe RCC with sheet-like growth pattern (D) and nuclear wrinkling, perinuclear clearing and binucleation (E). Hybrid renal oncocytic tumor (F, G) shows composite features of oncocytoma and chromophobe carcinoma, with one population of cells showing nuclear irregularities and the other population showing uniform, bland nuclei.

displaying the subtle nuclear changes reminiscent of chromophobe RCC, such as hyperchromasia, wrinkling, and perinuclear clearing, amidst an otherwise typical renal oncocytoma-like morphology.

Hybrid renal oncocytic tumors are diagnosed largely based on morphology, though they are immunopositive for CK7 to a greater extent than renal oncocytomas (which are usually negative or only focally positive). Hybrid tumors are negative for AMACR and CD10. E-cadherin and CD117 may be positive, and MIB-1 proliferation rates are usually low [42]. The prognosis is excellent with one group reporting a 100% 3-year survival rate for their 16 studied hybrid tumors [43]. Data regarding long-term survival is limited, however, and additional series with longer follow-up will be required to determine the natural history and true biologic potential of these neoplasms [44].

It should be noted that hybrid renal oncocytic tumors may also occur in a sporadic setting. In such cases, there is typically no associated renal oncocytosis noted. Sporadic hybrid oncocytic tumors have been shown to contain multiple numerical chromosomal aberrations including monosomies and polysomies of 1, 2, 6, 9, 10, 13, 17, 21, and 22 without any reported mutations in the *VHL*, *c-kit*, platelet-derived growth factor receptor alpha (*PDGFRA*), and *FLCN* genes [42,45]. Much like hybrid oncocytic tumors arising in the setting of Birt-Hogg Dubé syndrome, tumors arising in a sporadic setting also follow an indolent clinical course [42].

Conclusions

In summary, the medical community's understanding of RCC has evolved over many decades to the current classification, which recognizes RCC subtypes as genetically distinct with disparate behaviors and responses to therapy. The overlapping histologic features seen in contemporary practice require use of ancillary immunologic and molecular tests to arrive at an accurate diagnosis that, in turn, has a major prognostic and therapeutic impact.

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