Differential Diagnosis of Renal Tumors With Clear Cytoplasm

Clinical Relevance of Renal Tumor Subclassification in the Era of Targeted Therapies and Personalized Medicine

Rajen Goyal, MD; Elizabeth Gersbach, MD; Ximing J. Yang, MD, PhD; Stephen M. Rohan, MD

● ***Context.***—**The World Health Organization classification of renal tumors synthesizes morphologic, immunohistochemical, and molecular findings to define more than 40 tumor types. Of these, clear cell (conventional) renal cell carcinoma is the most common malignant tumor in adults and—with the exception of some rare tumors—the most deadly. The diagnosis of clear cell renal cell carcinoma on morphologic grounds alone is generally straightforward, but challenging cases are not infrequent. A misdiagnosis of clear cell renal cell carcinoma has clinical consequences, particularly in the current era of targeted therapies.**

Objective.—**To highlight morphologic mimics of clear cell renal cell carcinoma and provide strategies to help differentiate clear cell renal cell carcinoma from other renal tumors and lesions. The role of the pathologist in guiding treatment for renal malignancies will be emphasized to stress the importance of proper tumor classification in patient management.**

Data Sources.—**Published literature and personal experience.**

Conclusions.—**In challenging cases, submission of additional tissue is often an inexpensive and effective way to facilitate a correct diagnosis. If immunohistochemical stains are to be used, it is best to use a panel of markers, as no one marker is specific for a given renal tumor subtype. Selection of limited markers, based on a specific differential diagnosis, can be as useful as a large panel in reaching a definitive diagnosis. For renal tumors, both the presence and absence of immunoreactivity and the pattern of labeling (membranous, cytoplasmic, diffuse, focal) are important when interpreting the results of immunohistochemical stains.**

(*Arch Pathol Lab Med.* 2013;137:467–480; doi: 10.5858/arpa.2012-0085-RA)

The first case of a primary malignant tumor of the kidney was reported in the medical literature more than 175 years ago.[1] Ever since this initial case report, physicians and scientists interested in renal tumors have recognized, to varying extents, that there are different types of renal malignancies. Numerous classification schemes have come and gone over the years and the modern classification of renal neoplasms represents our current understanding of these tumors, based on existing morphologic, clinical, immunohistochemical, and molecular findings. At the morphologic level there can be significant overlap between renal tumor subtypes, and many different tumors in the kidney can exhibit clear cytoplasmic changes. Of the currently recognized renal tumors, 3 types—clear cell renal cell carcinoma (CCRCC), papillary renal cell carcinoma (PRCC), and chromophobe renal cell carcinoma (ChRCC)—account for approximately 90% to 95% of all malignant kidney tumors in adults.[2,3] Clear cell renal cell carcinoma is the most common malignant tumor of renal epithelial origin and—with the exception of some rare tumors—the most deadly. Recognition of CCRCC and differentiation from its morphologic mimics is important not only for prognostication but also for treatment-related reasons as discussed in this review.

The treatment paradigm for renal tumors in general and renal cell carcinomas (RCCs) specifically are changing, and these changes are in part driven by tumor classification. Pathologists will play a major role in these new treatment models, which include minimally invasive, ablative techniques and medical therapies targeted at cellular pathways that are active in specific tumor types. Traditionally, RCC has been considered a surgical disease. With the widespread use of modern imaging techniques in the last several decades, there has been a significant increase in the number of incidentally discovered small renal tumors, many of which are indolent.[4,5] Currently, there are no reliable noninvasive methods to preoperatively distinguish an indolent tumor from a potentially aggressive carcinoma; this is especially true when these lesions present incidentally

Accepted for publication April 13, 2012.

From the Department of Pathology, Northwestern Memorial Hospital, Northwestern University, Feinberg School of Medicine, Chicago, Illinois.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Stephen M. Rohan, MD, Department of Pathology, Northwestern Memorial Hospital, Northwestern University, Feinberg School of Medicine, Feinberg 7-332, 251 E Huron St, Chicago, IL 60611 (e-mail: s-rohan@northwestern.edu).

as small localized tumors. In some cases, surgery with its associated complications and negative impact on long-term renal function may be more harmful than simple observation—also known as active surveillance—when dealing with small renal tumors even when these lesions are potentially malignant.[6,7] Currently, observation of a solid renal mass is generally a viable option for elderly patients or patients with comorbidities that make them poor surgical candidates.[8] Given the aging population and the prevalence of chronic renal disease in the United States, it is likely that in the near future simple observation of small renal tumors, with or without concomitant percutaneous biopsy to establish a pathologic diagnosis, will become more common.[9] In observation protocols using biopsies, the histopathologic diagnosis may lead to ablative therapies for aggressive tumor types, such as CCRCC, with alternate diagnoses being triaged to active surveillance.

While small, potentially indolent tumors represent a significant management dilemma today, at the other end of the spectrum, approximately 20% of patients with RCC will present with metastatic disease and another 10%—even if treated by nephrectomy—will develop metastases at some point during their disease course.[10] Of the patients presenting with or ultimately developing metastases, most will have a diagnosis of CCRCC.[11] Traditional chemotherapy and radiation therapy are largely ineffective in the treatment of RCC of all subtypes.[10,12] As a result, numerous drugs have been developed for the treatment of metastatic RCC that target molecular pathways known to be altered in these tumors.[13] The cloning and identification of the von Hippel-Lindau tumor suppressor gene (*VHL*) located on the short arm of chromosome 3 at locus 3p25.3 and the recognition that *VHL* silencing also occurs in most sporadic CCRCCs, planted the seeds for the modern classification system and the development of novel targeted therapies.[14–16] Because inactivation of *VHL* does not occur in non–clear cell RCCs, most of the clinical trials evaluating the efficacy of drugs targeting molecules overexpressed as a result of *VHL* inactivation have been limited to CCRCC.[11,17] Thus, prospective randomized controlled trial data demonstrating the efficacy of many targeted therapies in metastatic non–clear cell RCC are lacking.[17] Currently, efforts are underway to identify molecular pathways and drugs that are effective in treating metastatic non–clear cell RCC subtypes.[17] Therefore, the challenges for pathologists in the era of modern therapies for renal tumors are 2-fold: arriving at a diagnosis based on a small amount of tissue in the case of active surveillance protocols and correctly subclassifying high-grade or poorly differentiated tumors to guide neoadjuvant or adjuvant molecular-based therapies.

Clear Cell (Conventional) Renal Cell Carcinoma

Clear cell renal cell carcinoma is the most common malignant tumor of renal epithelial origin, accounting for approximately 70% of renal tumors in adults.[3,18–20] Sporadic cases of CCRCC typically arise in patients older than 40 years, and men are affected more frequently than women. Approximately one-third of patients diagnosed with CCRCC will develop metastases during the course of their illness.[10,12] Most metastases from CCRCC develop within 3 years of initial presentation, but so-called late metastases occurring 10 years or more after diagnosis are a well-documented phenomenon.[21] The most common sites of metastases from CCRCC are lung, liver, and bone, but virtually any site in the body can be affected.

Grossly, CCRCC is classically described as a solid, lobulated, well-circumscribed, golden-yellow mass. However, the gross appearance can be variable, with areas of necrosis and dark red discoloration reflecting hemorrhage; prominent cystic changes are also frequent findings. In a minority of cases CCRCC will have a white sclerotic appearance, with or without grossly evident calcifications or even ossification. Additionally, CCRCC can have a significant component that grossly appears fleshy and tan, reflecting microscopic sarcomatoid differentiation. Sampling of all areas of tumor that appear grossly distinct often aids greatly in arriving at the correct diagnosis. Recent studies have emphasized the importance of evaluating the renal sinus for proper staging and, thus, careful gross and microscopic examination of this area should be performed in all nephrectomy cases.[22]

Microscopically, CCRCC has highly variable architectural patterns and nuclear/cytoplasmic features. One possible point of confusion when examining cases of CCRCC under the microscope is that there may be very little, if any, clear cells. In fact, in high-grade tumors, the cytoplasm of CCRCC often has a more eosinophilic or granular quality. Conversely, many renal tumors that are not CCRCCs can exhibit clear cytoplasmic changes. Thus, many experts have noted that the most reliable diagnostic feature of CCRCC is its vascular pattern rather than the quality or characteristics of the cytoplasm.[2,3,20] The distinctive blood vessels seen in CCRCC are of small caliber and completely invest clusters of tumor cells, imparting what is often referred to as an alveolar pattern to the tumor (Figure 1, A). This vascular pattern is usually present, albeit sometimes focally, regardless of tumor grade and cytoplasmic features (Figure 1, B). In approximately 5% of cases, a sarcomatoid or spindle cell pattern can be seen and, when prominent, can make diagnosis of the underlying CCRCC difficult.[23] In such situations—which have a tendency to occur in large tumors—submission of additional sections is often useful. The recognition that CCRCC may have very few, if any, cells with clear cytoplasm and that sarcomatoid differentiation may be seen in CCRCC, as well as any other RCC subtype, has led to the elimination of "sarcomatoid RCC" and "granular cell RCC" as specific subtypes of renal malignancies.[2]

Notwithstanding the microscopic features seen in difficult cases mentioned above, the diagnosis of CCRCC is straightforward on hematoxylin-eosin (H&E)–stained sections alone in most cases. Most of the CCRCCs encountered in clinical practice do have the optically clear cytoplasm for which these tumors are named. This finding of cytoplasmic clarity is actually an artifact of routine tissue processing, as the glycogen and lipid present in the cytoplasm is lost during this process. Owing to the rich vascularity of CCRCC, many cases exhibit areas of hemorrhage, which frequently occur within the center of a cluster or nest of cells, forming what has been variably referred to as "blood lakes" or "bloody glands" (Figure 1, C). Other architectural patterns seen include microcystic, macrocystic, and pseudopapillary. The finding of a pseudopapillary pattern is often seen in the context of high-grade tumors that have begun to outgrow their blood supply, resulting in cell dropout and necrosis (Figure 1, D). The tumor cells in CCRCC are usually cuboidal with a centrally or basally located nucleus. Many cases of CCRCC—even those without frank sarcomatoid

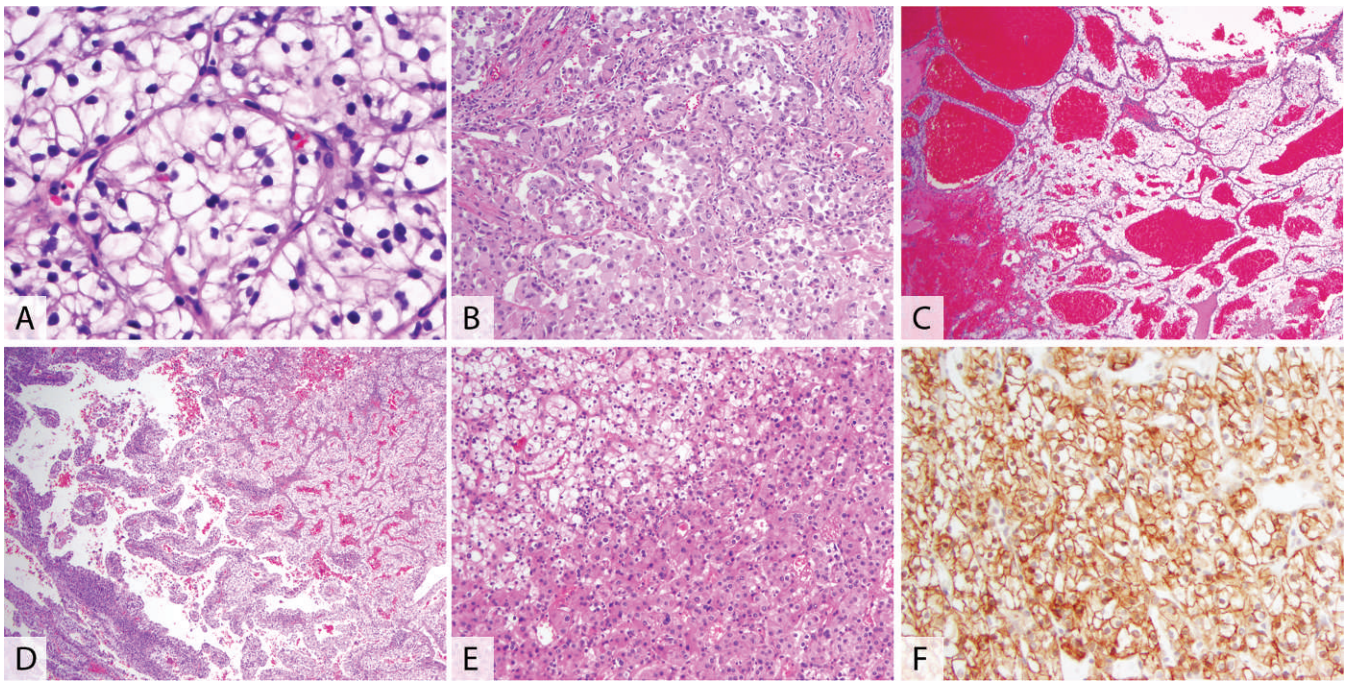


Figure 1. *The spectrum of microscopic findings seen in clear cell renal cell carcinoma. A, Typical appearance with characteristic delicate blood vessels, nested growth, and optically clear cytoplasm. B, High-grade cases often lack clear cytoplasm but the characteristic vasculature is maintained. C, A classic finding is intratumoral hemorrhage resulting in a "bloody glands" appearance. D, In some cases a pseudopapillary growth pattern can be seen, as shown in the left half of the picture. E, Many cases show a mixture of cells with clear cytoplasm (upper left) and cells with more eosinophilic, granular cytoplasm (lower right). F, Carbonic anhydrase IX (CA9) usually shows diffuse membranous positivity (hematoxylin-eosin, original magnifications ×200 [A], ×100 [B, and E and ×40 [C and D]; ×100 [F].*

differentiation—are heterogeneous microscopically with a mixture of growth patterns, cytoplasmic features, and nuclear grades seen in a single tumor (Figure 1, E). The recommended grading system is that of Fuhrman et al,[24] which is based on nuclear size, nucleolar prominence, and nuclear membrane irregularities.

At the molecular level, the genetic hallmark of CCRCC is biallelic inactivation of the *VHL* tumor suppressor gene.[14] To some extent the central role of *VHL* inactivation in CCRCC pathogenesis has been challenged in recent years.[25,26] Several studies[25,27,28] have documented the potential role of other tumor suppressor genes located on the short arm of chromosome 3, namely, *FHIT*, *PBRM1*, and *RASSF1A*, in CCRCC pathogenesis. Irrespective of which of these tumor suppressor genes are genetic "drivers" of CCRCC pathogenesis, all of them would require 2 genetic hits to have a central role in tumor development. Thus, at the molecular level, genetic alterations involving the p arm of both copies of chromosome 3 in the region of the abovementioned tumor suppressor genes should be present in CCRCC, although which specific gene(s) in this chromosomal region is(are) most important in CCRCC pathogenesis is a matter of active investigation. For the purposes of this review, we will focus on the role of *VHL* in CCRCC pathogenesis, since the involvement of this gene has the greatest amount of supporting evidence currently.

In sporadic CCRCC, genetic lesions involving *VHL* vary and include complete or partial loss of chromosome 3, somatic mutations, and *VHL* promoter hypermethylation, which result in loss of function of the *VHL* gene product pVHL.[29,30] When not mutated or otherwise lost, pVHL regulates cell signaling under normal oxygen tension by targeting Hypoxia inducible factor-1a (HIF-1α) for ubiquitin-mediated proteasomal degradation.[31] HIF-1α is a transcription factor that regulates expression of numerous downstream target genes including vascular endothelial growth factor (*VEGF*), platelet-derived growth factor β (*PDGFB*), transforming growth factor α (*TGFA*), glucose transporter 1 *SLC2A1* (GLUT1), and carbonic anhydrase IX (*CA9*), all of which are important in angiogenesis and for maintaining cellular homeostasis under hypoxic conditions.[32] When pVHL function is lost, the result is accumulation of HIF-1α and increased transcription of downstream HIF-regulated genes.[33–36] The mammalian target of rapamycin (mTOR) pathway also appears to regulate HIF-1α expression.[37,38] The knowledge of the importance and interdependence of the VHL/HIF and mTOR pathways in CCRCC tumorigenesis served as the basis for the development of several targeted therapies currently in use. Phase III prospective randomized controlled trial evidence has shown that the use of mTOR inhibitors (temsirolimus, everolimus) and drugs aimed at VEGF and other downstream targets of VHL/HIF (sorafenib, sunitinib) are effective in treating metastatic CCRCC.[10]

There is no single marker that is specific for CCRCC and therefore it is generally recommended that a panel of markers be used if immunohistochemistry is necessary in a given case.[39] The exact panel one should use varies with the differential diagnosis, and the immunohistochemical markers commonly used for the lesions discussed in this review are summarized in the table below. It is important to note that evaluation of both the presence and/or absence of immunoreactivity, as well as the pattern of staining (membranous, cytoplasmic, nuclear, diffuse, focal), are critical when interpreting immunostain results in renal neoplasms.

Summary of Immunohistochemical Markers in Tumors With Clear Cytoplasm								
	Clear Cell RCC	Papillary RCC	Chromophobe RCC	Clear Cell Papillary RCC	*TFE/MiTF* Translocation Carcinoma	Epithelioid Angiomyolipoma	Oncocytoma	Adrenal Cortical Tumors
CA9	+	−/+[a]	−[a]	+	−/+[a]	−[a]	−	−[a]
AMACR	−[b]	+	−	−	+	−	−	−
CD117	−	−	+	−	−	−	+	−
CD10	+	+	−/+	−/+	−/+	−	−/+	−
PAX8	+	+	+	+	+	−	−	−
CK7	−[b]	−/+	+	+	−	−	−[b]	−
34βE12	−	−	−	−/+	+	−	−	−
TFE3	−	−	−	−	−/+	−/+	−	−
TFEB	−	−	−	−	−/+	−	−	−
EMA	+	+	+	+	−[b]	−	+	−
HMB-45	ND	ND	ND	ND	−/+	+	ND	−
Melan-A	−[b]	ND	ND	ND	+	+	ND	+
SMA	−	−	−	−/+[c]	−	+	+	−
Cathepsin K	−	−	−	ND	+	+	−	−
Synaptophysin	−	−	−	−	−	−	−	+
Inhibin	−[b]	−	−	−	−	−	−	+

Abbreviations: AMACR, α-methylacyl-coenzyme A racemase; CA9, carbonic anhydrase IX; CK7, cytokeratin 7; EMA, epithelial membrane antigen; ND, no published data; RCC, renal cell carcinoma; SMA, smooth muscle action; definition; +, positive labeling; −, negative labeling; −/+, variable labeling.

[a] Any tumor exhibiting necrosis can show membranous positivity in perinecrotic tissue.
[b] Negative in our experience but controversial, as cases with patchy and/or diffuse staining have been reported.
[c] Intratumoral stroma can be positive.

Of the stains we often use in difficult cases, the one we most frequently rely upon to support a diagnosis of CCRCC is CA9, a membrane-bound protein that functions in intracellular and extracellular pH regulation and whose expression is driven by hypoxia. In the case of CCRCC, CA9 expression is due to increased HIF-driven transcription that is secondary to loss of pVHL function.[33] The pattern of CA9 staining in CCRCC is membranous and typically diffuse (Figure 1, F). This expression in CCRCC is usually maintained even in cases with sarcomatoid differentiation.[40] However, it is essential to interpret staining in the context of morphology. One major pitfall of CA9 immunohistochemistry is that any tissue or tumor that is hypoxic or necrotic can exhibit membranous labeling.[41] This physiologic expression of CA9 is usually not diffuse in hypoxic tissue and when microscopic necrosis is evident, membranous expression of CA9 is usually only present in tissue immediately surrounding the areas of necrosis.[42] Problems with the use of CA9 immunohistochemistry in the subtyping of renal cell carcinoma typically arise in the 2 scenarios in which these stains are most needed—situations with limited tissue, such as needle core biopsies, and in large high-grade tumors, which frequently exhibit necrosis. In these situations, the use of a panel of immunohistochemical markers is essential and frequently will help resolve these problems, as highlighted in a recent study of needle core biopsies of renal tumors.[39]

Papillary Renal Cell Carcinoma

Papillary renal cell carcinoma is the second most common malignant renal tumor in adults, accounting for approximately 10% to 15% of malignant renal epithelial neoplasms.[2] Papillary architectural patterns in renal cancers have been appreciated by pathologists since the 1800s.[1] However, it was not until the 1970s, when the first case series of these tumors was reported in the literature, that momentum began to build to recognize PRCC as a distinct entity.[43] PRCC is less aggressive than CCRCC with metastases reported in 5% to 12% of patients.[19,44] In recent years, PRCC has been divided into 2 subtypes on the basis of cytoplasmic features, nuclear features, and the presence or absence of nuclear pseudostratification.[45] A 2005 study[46] suggested that PRCC can be further subdivided into 4 different morphologic categories, which correspond to 2 different molecular groups, based on gene expression profiling data. However, the clinical significance of subtyping of PRCC has been challenged recently.[47] Regardless of these controversies and unresolved issues, 2 types of PRCC are currently recognized in the World Health Organization (WHO) classification, with type 2 tumors described as behaving more aggressively and characterized by eosinophilic cytoplasm, high nuclear grade, and nuclear pseudostratification.[2,45,48] While clear cell cytoplasmic changes can be seen in both type 1 and type 2 PRCC, in this review we will focus primarily on type 1 PRCC—especially with regard to morphologic details—as it is this subtype that is more likely to exhibit clear cytoplasmic changes in our experience.

Papillary renal cell carcinoma is the most common bilateral and multifocal renal cell carcinoma variant. These tumors are typically well circumscribed and often have a well-formed fibrous pseudocapsule. The gross color of PRCC ranges from a dull-yellow to red-brown, depending on the amount of foamy macrophages or the presence of hemorrhage, respectively. Cystic change and necrosis are also common findings. In fewer than 5% of cases sarcomatoid differentiation is present, which usually manifests grossly as a tan, fleshy quality to the tumor.[23] Again, in tumors that are heterogenous grossly, the importance of adequate tissue sampling to aid in arriving at the correct microscopic diagnosis cannot be overemphasized.

At the microscopic level, type 1 PRCC can exhibit a wide range of architectural patterns. While a papillary pattern predominates in many cases and is usually present at least focally in most cases, other architectural patterns include tubular, solid, micropapillary, and glomeruloid. The papillae in type 1 PRCC are characterized by a central fibrovascular core that often contains a variable number of foamy

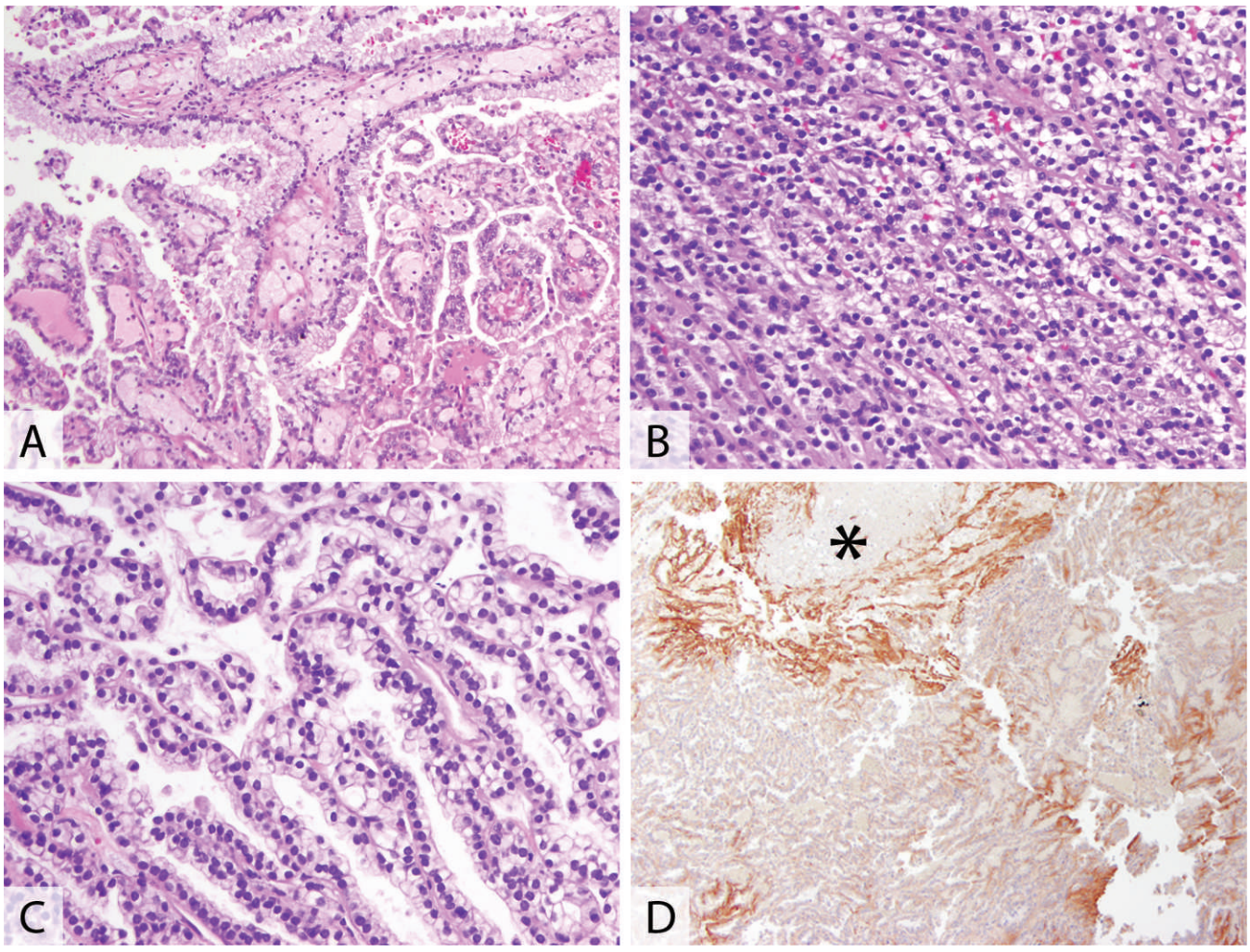


Figure 2. *Clear cytoplasm is almost always seen at least focally in type 1 papillary renal cell carcinoma, leading to possible diagnostic dilemmas or to misinterpretations as a "mixed" tumor. A, A classic example with abundant foamy macrophages within the fibrovascular cores. Note the "pale" or clear quality of the cytoplasm of the neoplastic cells. B, Solid growth and cytoplasmic clearing can also be seen; note the absence of the characteristic blood vessels usually seen in clear cell renal cell carcinoma. C, In some cases with clear cytoplasmic features and papillary growth, foamy macrophages are absent. D, Immunohistochemistry for carbonic anhydrase IX (CA9) is usually perinecrotic (asterisk [*] indicates necrosis) or patchy (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B and C]; original magnification ×40 [D]).*

macrophages. On occasion, there is a paucity of foamy macrophages within the papillae and instead, the papillary cores are dilated by edema fluid forming large cystic structures that superficially resemble chorionic villi or thyroid follicles. Other common findings include numerous hemosiderin-laden macrophages, hemosiderin deposition within tumor cells, and psammoma bodies. The cells of type 1 PRCC are generally cuboidal, with round to oval nuclei, often with nuclear membrane irregularities, and small, inconspicuous nucleoli. The cytoplasmic features of type 1 PRCC are variably described in literature as either amphophilic, "scant," or "pale."[45,48] These latter 2 adjectives have likely been chosen very carefully in the literature to avoid using the term *clear* to describe the cytoplasm. However, in reality the cytoplasm of the neoplastic cells in PRCC is often at least focally clear (Figure 2, A through C). The finding of clear cytoplasm in an otherwise typical PRCC is well recognized and was noted in the first reported series of PRCC, in several large series of PRCC, and in major surgical pathology textbooks.[3,19,20,43,49] Some observers have astutely pointed out that even in PRCC cases with clear cytoplasm, the quality of the cytoplasm differs from that seen in CCRCC in that it typically has a reticular or granular quality, but this distinction is subtle.[50] In exceptional cases, cytoplasmic clarity predominates throughout the tumor and, in conjunction with either solid growth or a relative paucity of papillae, can lead to diagnostic confusion.

We have seen many cases of type 1 PRCC with clear cytoplasmic features that have been mistaken for CCRCC and/or "mixed tumors"/unclassified renal cell carcinoma (discussed below). Morphologically, cases of PRCC with clear cytoplasmic features should lack the characteristic vascular pattern seen in CCRCC and the distinctive immunoprofile of CCRCC. It is worth emphasizing again that cytoplasmic clarity in PRCC is not uncommon and that "clear cell cytoplasmic *features*" does not equate to "clear cell carcinoma *differentiation*" in these cases. The former term simply refers to a morphologic finding (ie, cytoplasmic clarity), and the latter term implies a combination of morphologic findings and the concomitant molecular changes associated with CCRCC. Recent studies of "renal cell carcinomas with papillary architecture and clear cell

components" and "renal cell carcinoma with mixed features of papillary and clear cell cytomorphology" have shown that PRCC with clear cytoplasmic features can usually be accurately classified by using routine immunohistochemistry, which correlates well with the typical molecular features of PRCC.[51,52]

At the molecular level, sporadic PRCC is characterized by gains of chromosomes 7 and 17 and losses of chromosome Y, findings that distinguish PRCC from other renal carcinoma subtypes.[53,54] While the recurrent gains of chromosomes 7 and 17 have been useful in defining PRCC as an entity, such large genetic changes are relatively nonspecific for providing clues to tumor pathogenesis that might be useful in developing targeted therapies. Relative to CCRCC, much less is known about the details of specific pathway activation in PRCC. Loss of heterozygosity involving the short arm of chromosome 3 has been documented in PRCC, as have occasional *VHL* mutations, but the biallelic inactivation of *VHL*, which would be required for a pathogenic effect, has not been demonstrated.[55–58] Additionally, markers of HIF pathway activation are typically negative in PRCC, suggesting that the cellular mechanisms underlying this tumor type are different from those seen in CCRCC.[59] These genetic differences likely underlie the decreased response to sunitinib and other targeted therapies seen in cases of metastatic PRCC.[11,44] There was hope that the study of cases of inherited type 1 PRCC, which are due to activating germline mutations of the c-*MET* oncogene, might provide insight into the inner workings of sporadic PRCC. Unfortunately, these activating mutations are uncommon outside of the syndromic setting, being present in approximately 10% of sporadic type 1 PRCCs.[60] Nonetheless, efforts are currently underway to develop therapies that target the c-*MET*/hepatocyte growth factor pathway, which may have a role in treating PRCC and other malignancies in the future.[61]

The most useful positive immunohistochemical stain in supporting a diagnosis of PRCC is α-methylacyl-coenzyme A racemase (AMACR), a protein involved in the metabolism of branched chain fatty acids. Its utility as an immunohistochemical marker was initially recognized in the evaluation of prostate cancer in which AMACR is strongly expressed.[62] Subsequently, AMACR was also noted to diffusely label PRCC in a granular cytoplasmic fashion.[63] It is now recognized that AMACR can show positivity in tumors from many different organs and in several different types of renal tumors, including most MiTF/TFE family translocation carcinomas, tubulocystic carcinomas, some collecting duct carcinomas, most mucinous tubular and spindle cell carcinomas, most acquired cystic disease–associated renal cell carcinomas, and some high-grade urothelial carcinomas of the renal pelvis.[50,64–68] Despite this immunohistochemical promiscuity, AMACR is useful in a panel of markers if the differential diagnosis is PRCC versus CCRCC. AMACR staining is often negative in CCRCC but it can be focally or, rarely, diffusely positive in CCRCC.[39,63,69] For this particular differential diagnosis, a panel including AMACR, CA9, and cytokeratin 7 (CK7) is quite useful. While CK7 staining has been described in CCRCC, this is an uncommon finding; staining is usually patchy and centered around cystic areas within a tumor.[70–72] In contrast, most type 1 PRCCs will be diffusely positive for CK7.[72] The pattern of CA9 expression in PRCC, which is patchy and often perinecrotic when present, is usually easily distinguished from the diffuse membranous pattern seen in CCRCC[39,42,73,74] (Figure 2, D).

Chromophobe Renal Cell Carcinoma

Of the 3 most common variants of renal cell carcinoma, the chromophobe variant is the most recently recognized, having initially been described by Thoenes et al[75] in the 1980s. There are 2 well-described variants of ChRCC—the classic type and the eosinophilic type. Of these 2 types of ChRCC, usually the classic type arises as a diagnostic possibility when dealing with a renal tumor with cytoplasmic clarity. In fact, the morphologic overlap of ChRCC and CCRCC was a point emphasized in many of the early descriptions of this tumor type.[76,77] In general, it is believed that ChRCC has a better prognosis than CCRCC.[78,79] The data regarding a difference in prognosis between PRCC and ChRCC are less clear, with some studies suggesting ChRCC is more indolent than PRCC and others showing no difference in metastases or survival between these 2 tumor types.[19,80,81] Two recent large series[78,79] report that the percentage of patients with ChRCC presenting with or ultimately developing metastases is 6% to 12%.

Grossly, ChRCCs are typically light brown, well circumscribed, and unencapsulated. Generally, tumors that are brown grossly tend to have more eosinophilic cytoplasmic features microscopically. On occasion, these tumors can have a central stellate scar mimicking the classic gross appearance of an oncocytoma. Sarcomatoid differentiation, which can be appreciated grossly as tan, soft, fleshy areas, was once thought to be more common in ChRCC than CCRCC and PRCC. However, the 2 largest reported series of ChRCC have documented different rates of sarcomatoid differentiation in these tumors, calling into question this commonly held belief.[78,79] The mean size of ChRCC at the time of surgery is 6.5 to 8.0 cm. Multifocal ChRCC is seen in fewer than 10% of patients and bilaterally, in fewer than 5% of cases.[78,79]

Chromophobe renal cell carcinoma in its classic form often has an abundance of clear cells and in such cases the differential diagnosis includes CCRCC (Figure 3, A and B). Since the eosinophilic variant of chromophobe carcinoma is typically not in the microscopic differential diagnosis of a CCRCC, it will not be discussed in any detail here. Three cell types have been described in classic cases of ChRCC: polygonal cells with pale, reticulated cytoplasm and distinct cell borders; smaller cells with eosinophilic cytoplasm; and large cells with abundant foamy cytoplasm, which are often described as "hydropic" in appearance. These 3 cell types can be present in a given tumor in varying proportions, and it is often cases that show a predominance of cells with pale cytoplasm that cause a diagnostic dilemma. However, several features, including distinct or "accentuated" cell borders, perinuclear cytoplasmic clearing or "halos," and hyperchromatic wrinkled or "raisinoid" nuclei, are useful morphologic features that favor a diagnosis of ChRCC.[82] The perinuclear cytoplasmic clearing seen in ChRCC is due to the presence of numerous 160 to 300-nm cytoplasmic vesicles that displace the remaining organelles to the periphery of the cell.[75,82] The typical growth pattern of sheets of cells separated by incomplete vascular septae in ChRCCs can be a useful finding in distinguishing these tumors from CCRCCs, which classically have thin blood vessels that completely envelope nests of tumor cells. Other architectural patterns seen in ChRCC include nested, alveolar, solid, tubular, cystic, and tubulocystic patterns. Exceptional cases can exhibit a papillary architectural pattern but this finding is uncommon.[79]

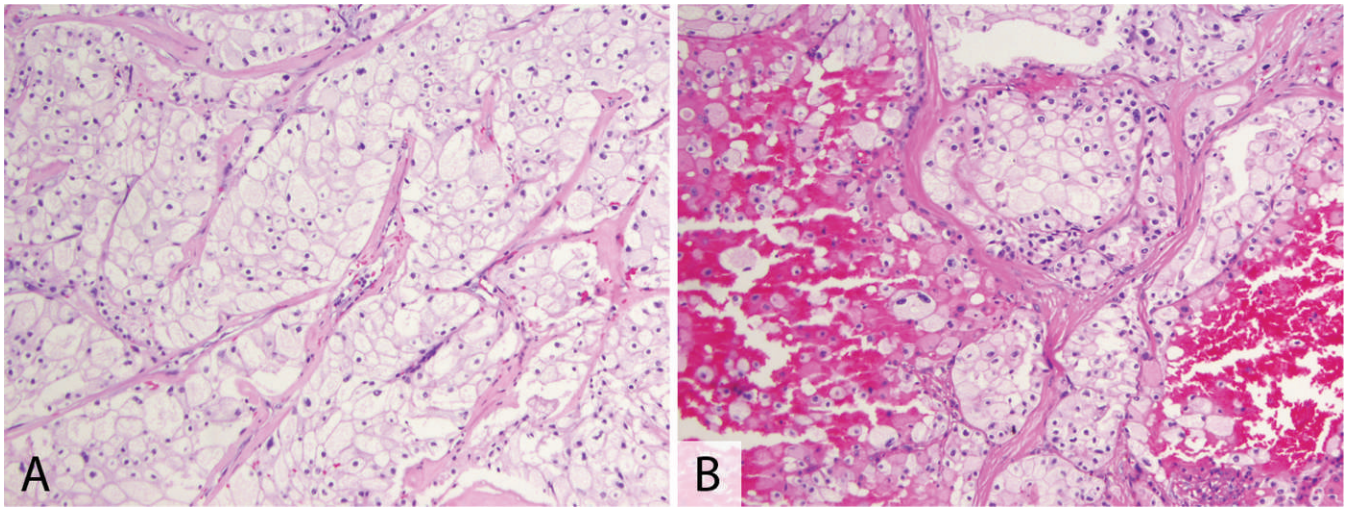


Figure 3. *Chromophobe renal cell carcinoma can have a predominance of clear cells. A, Note the incomplete vascular septae and prominent cell borders. B, On occasion, cases can exhibit diffuse hemorrhage, mimicking the "bloody glands" appearance associated with clear cell renal cell carcinoma (hematoxylin-eosin, original magnifications ×100 [A and B]).*

The molecular hallmark of ChRCC is loss of multiple chromosomes including chromosome 1, 2, 6, 10, 13, 17, 21, and Y.[83,84] While this general aneuploidy has been useful in classifying these tumors to date, similar to PRCC, there has been relatively little progress made in identifying potential targets for molecular therapies in ChRCC. The Birt-Hogg-Dubé (BHD) syndrome, a rare inherited genodermatosis that predisposes affected individuals to development of hamartomas of the skin, pulmonary cysts, and renal tumors, seems like an ideal model system to study ChRCC tumorigenesis.[85] Unlike VHL syndrome, in which patients develop CCRCC specifically, patients with BHD more commonly develop multiple, bilateral oncocytic renal tumors, many of which are ChRCCs.[86] The BHD syndrome–associated gene (*FLCN*) is located on chromosome 17 at locus 17p11.2 and functions as a tumor suppressor gene.[85] The protein product of *FLCN*, known as folliculin, has been shown in cell culture and coimmunoprecipitation studies to interact with the mTOR pathway.[87] To date, however, studies in which *FLCN* mutational analysis was performed on renal tumors believed to be sporadic have failed to demonstrate any such alterations or, when mutations have been identified, they have ultimately been shown to be germline mutations.[88–91] Studies evaluating ChRCC for *VHL* inactivation and 3p losses have shown that these tumors lack these changes and the subsequent activation of the HIF pathway as seen in CCRCC.[58] Thus, the molecular rationale for treating these tumors with currently available targeted therapies is lacking, possibly explaining the decreased response rates seen in ChRCC relative to CCRCC when such therapies are used.[11,92]

In cases for which the differential diagnosis is ChRCC versus CCRCC, molecular studies, such as fluorescence in situ hybridization or electron microscopy, can be helpful. However, these techniques are not readily available to most practicing pathologists. Hale colloidal iron is a histochemical stain that labels acid mucopolysaccharides present in the cytoplasmic microvesicles of ChRCC. This stain will impart a reticular cytoplasmic staining pattern in most cells when applied to a classic ChRCC. In contrast, CCRCC will have a negative staining profile or exhibit only focal staining. Unfortunately, it is technically very difficult to perform this staining procedure and, thus, it is not of great utility for most practicing pathologists. Fortunately, there are several immunohistochemical stains that are useful in distinguishing ChRCC from CCRCC. An immunohistochemical panel that includes CA9, CD117 (c-kit), and CK7 is often very useful. Of these, CD117 and CK7 are frequently coexpressed in a membranous fashion in ChRCC, while they show negativity in most CCRCC. The staining profile with carbonic anhydrase IX is negative in most ChRCCs and when positive, it is usually patchy and seen in association with necrosis.[42]

Clear Cell Papillary Renal Cell Carcinoma

In the years since the publication of the 2004 WHO classification of renal tumors, several novel renal tumor types have been described. One such tumor, clear cell papillary renal cell carcinoma (CpRCC), was initially characterized in the setting of end-stage renal disease.[65] Subsequent studies described cases outside the setting of impaired renal function and have confirmed the unique morphologic, immunohistochemical, and molecular features of CpRCC.[71,93,94] These tumors appear to be fairly uncommon in adults, with one large academic institution reporting that approximately 1% of its renal cell carcinoma cases during a 10-year period (n = 632) fit the morphologic criteria of CpRCC.[95] Interestingly, these tumors appear to be more common in patients younger than 40 years.[96] All cases of CpRCC reported in the literature have been organ confined and most have been low grade.[71,93,95,97–99] No metastases from CpRCC have been reported to date, suggesting that these tumors may be less aggressive than CCRCC, PRCC, and ChRCC.

Grossly, CpRCC are generally small tumors that appear encapsulated. They often exhibit cystic change to varying extents. On occasion, these tumors can appear quite sclerotic. The gross color varies from case to case but is often described as white, red, or yellow. In the setting of acquired cystic disease of the kidney, these tumors can be multifocal. Cases of bilateral CpRCC have also been described. Morphologically, the most distinctive feature of CpRCC is the positioning of the nuclei away from the

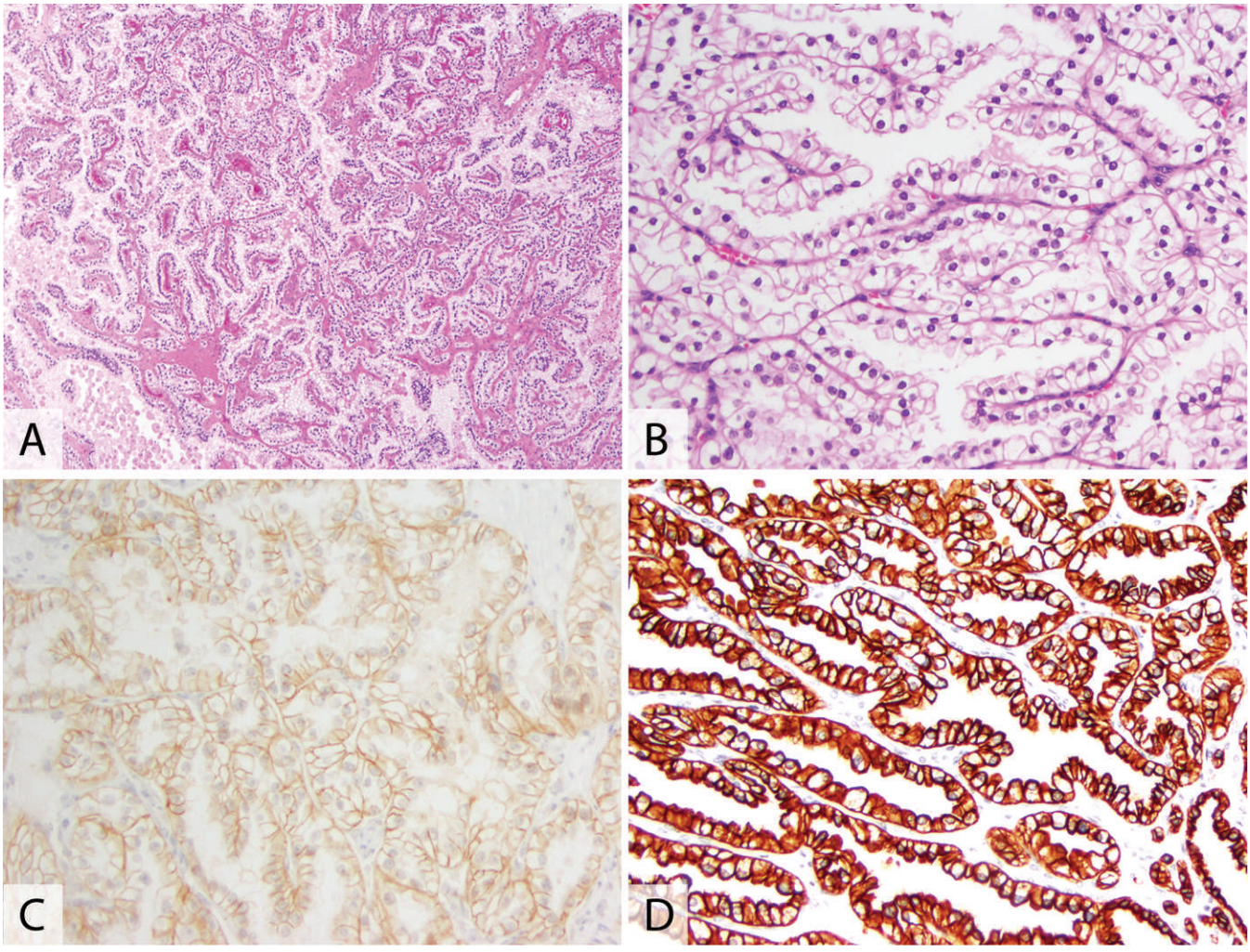


Figure 4. *Clear cell papillary renal cell carcinoma is not currently recognized in the World Health Organization classification of renal tumors but has very distinct morphologic and immunohistochemical findings. A, In exceptional cases a papillary architecture predominates. The characteristic arrangement of the nuclei away from the basement membrane and supporting vasculature is the key diagnostic feature. B, Many cases exhibit a predominantly tubular growth, but the typical positioning of the nuclei in such cases is maintained. C, Carbonic anhydrase IX (CA9) is usually diffusely positive, with low-level expression and a basolateral labeling pattern ("cup shaped" staining) being characteristic of these tumors. D, Unlike clear cell renal cell carcinoma, these tumors label diffusely and strongly for cytokeratin 7 (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B and C; (×200 [D]).*

basement membrane/supporting vasculature (Figure 4, A and B). This imparts an appearance reminiscent of secretory endometrium, papillary cystadenoma of the epididymis, and/or fetal adenocarcinoma of the lung. This finding is consistently present within these tumors, regardless of the architectural growth pattern, which can be quite variable.[71,93] Despite its name, clear cell papillary renal cell carcinoma can be relatively devoid of papillary architecture, and several studies have documented a tubular growth pattern as a frequent occurrence in these tumors, leading some to use the alternative nomenclature *clear cell tubulopapillary renal cell carcinoma*.[71,93] Other growth patterns that have been described include cystic, alveolar/nested, and retiform.[71] The tumor cells are characterized by a moderate to abundant amount of optically clear cytoplasm, with the distinctive nuclear positioning described above being the most characteristic feature. The Fuhrman nuclear grade is usually low. These tumors frequently have a fibrous capsule of variable thickness and often have hyalinized or sclerotic stroma either focally or diffusely. Cases of CpRCC with smooth muscle metaplasia within intratumoral stroma have been described and have engendered some debate regarding distinction from the renal angiomyoadenomatous tumors originally described by Michal et al.[100] Whether these 2 entities are related, or perhaps even variants of the same tumor, is a matter of ongoing discussion.[71,101]

The increasing recognition and acceptance of CpRCC as a unique entity is largely based on this tumor's distinct or, perhaps more accurately, lack of distinct molecular features. Like many in the pathology community, we initially believed CpRCC to simply be an unusual morphologic manifestation of CCRCC. However, numerous studies[71,93,102] have now shown that sporadic CpRCCs lack *VHL* mutations, 3p25 deletions, hypermethylation of the *VHL* promoter, and other recurrent copy number changes, which are characteristic of typical CCRCC. Of the cases reported to date, only 1 *VHL* mutation occurring in a CpRCC arising in a patient with known VHL disease, and 1 case of loss of heterozygosity of the *VHL* locus have been

described.[93,97] Additionally, most CpRCCs lack the characteristic gains of chromosomes 7 and 17 typically seen in PRCC.[71,93,102] Recent data in support of CpRCC as a unique tumor type came in the form of a gene expression profile meta-analysis of CCRCC reported by Brannon et al.[103] These investigators used bioinformatic tools to examine several publicly available CCRCC gene expression profile databases and were able to identify 3 distinct molecular subgroups within cases that had been morphologically classified as CCRCC. One of these groups—described as cluster 3 in the study—corresponded to a *VHL* wild-type pattern of gene expression and, from the images provided in the article,[103] morphologically appears to represent CpRCC. This study highlights the fact that many CpRCCs were likely diagnosed as CCRCC in the past, while also emphasizing that these 2 tumor types are distinct at the molecular level.

In most cases the morphologic features of CpRCC are unique enough to allow for distinction from CCRCC, based on H&E-stained slides. In some cases, immunohistochemical stains can be helpful, as CpRCC and CCRCC have different immunoprofiles. Both CpRCC and CCRCC typically express CA9, but the former usually exhibits weak expression, which is localized to the basal and lateral aspects of the tumor cells, so-called cup-shaped expression[71] (Figure 4, C). CD10 and 34BE12 show variable expression in these 2 tumor types, with the former more frequently positively expressed in CpRCC. Cytokeratin 7 appears to be the most reliable marker for differentiating these 2 entities, as it is nearly always diffusely, strongly positive in CpRCC while only infrequently positive in CCRCC[70,72] (Figure 4, D). In general, when CK7 labeling is present in a CCRCC, it is focal or, at most, patchy and centered around cystic spaces.[71] Expression of AMACR is usually negative in both of these tumor types; thus, it is not of any use in this differential, but it can be useful in cases of CpRCC if the alternate consideration is PRCC. The typical immunoprofile of CpRCC carcinoma can be summarized as CA9+, CK7+, AMACR–, CD10$^{+/-}$, and 34BE12+/–.[71,93]

MiTF/TFE Family Translocation–Associated Carcinoma

Renal cell carcinomas arising in pediatric patients with translocations involving the X chromosome were initially described in scattered case reports in the mid 1980s and early 1990s.[104,105] However, it was not until Argani and colleagues[106] undertook a systematic study of unclassified renal cell carcinoma cases and renal cell carcinoma cases occurring in young patients, that the concept of renal tumors with recurrent translocations as a distinct subset of RCC began to crystallize.[106] In the past 10 years, numerous studies[67,106,107] have validated the fact that renal cell carcinomas with translocations involving the *TFE3* gene located at the Xp11.2 locus or the *TFEB* gene located at the 6p21 locus are a unique—albeit relatively rare—group of renal malignancies. Initially described in children and young adults, a recent series documented the occurrence of these tumors in adults, with the oldest patient being 78 years old.[108] Recently, the umbrella term "MiTF/TFE family translocation–associated carcinoma" has been proposed for tumors that have translocations involving *TFE3* or *TFEB*.[109] *TFE3* and *TFEB* are transcription factors that belong to the same family of transcription factors that includes *MiTF*. Tumors with t(6;11)(p12;q12) will have a resulting fusion of *TFEB* and the *Alpha* gene, ultimately resulting in nuclear expression of *TFEB*, which can be detected immunohistochemically.[110,111] Similarly, tumors bearing a translocation involving *TFE3* and one of its many translocation partner genes—which include *ASPL*, *PRCC*, *PSF*, *NoNo*, *CTLC*, and several unknown genes—will overexpress nuclear TFE3 at the protein level.[108,112] These immunohistochemical findings are important given the occurrence of these tumors in the adult population, as they morphologically overlap with CCRCC and PRCC. In general, translocation-associated carcinomas tend to have clear cytoplasmic features and they can exhibit a nested or alveolar growth pattern (Figure 5, A and B). It has been reported that the morphology of a MiTF/TFE translocation–associated carcinoma will vary in accordance with the specific translocation present, but there is a definite variability in morphologic features from case to case. In particular, tumors with t(X;17) resulting in an *ASPL-TFE3* fusion have been reported to commonly have abundant clear cytoplasm, while tumors with t(X;1) resulting in a *PRCC-TFE3* fusion have a tendency to display a nested growth pattern.[113] TFE3 and TFEB immunohistochemical stains are reported to be sensitive and specific for a diagnosis of translocation-associated carcinoma as long as the labeling is strong, diffuse, and nuclear[108] (Figure 5, C). These immunostains are particularly useful if the differential diagnosis includes CCRCC. It should be mentioned that several studies have documented TFE3 labeling in a subset of tumors in the perivascular epithelioid cell neoplasm (PEComa) family and in alveolar soft part sarcoma. In addition to TFE3 and TFEB immunostains, which are not widely available, several other markers can be useful in distinguishing these tumors from CCRCC. Recently, cathepsin K, a protein whose expression is mediated by MiTF, has been shown to be sensitive and specific for differentiating translocation-associated carcinomas from CCRCC.[114] Additionally, translocation-associated carcinomas are frequently negative or at most demonstrate patchy positivity for cytokeratin and epithelial membrane antigen (EMA), a finding that would be unusual in CCRCC (Figure 5, D). Both translocation-associated renal cell carcinomas and CCRCCs can express CD10 and CA9, although labeling with CA9 is usually focal and patchy in the former.[115] Finally, molecular studies demonstrating rearrangement of *TFE3* or *TFEB* by fluorescence in situ hybridization or the presence of translocation-associated gene fusion products by polymerase chain reaction techniques can be helpful in this differential diagnosis.

The optimal therapy for MiTF/TFE family translocation–associated carcinomas, which can be aggressive neoplasms, has not yet been defined. We are not aware of any systematic study of available targeted therapies for these tumors. MiTF/TFE family translocation–associated carcinomas were recently shown to lack expression of HIF-1α protein, suggesting that the VHL/HIF pathway is not activated in these tumors and thus, there does not appear to be a rational basis for using therapies aimed at downstream targets of HIF.[115]

From rare cases reported in the literature, these tumors do not appear to respond to immunotherapy, but robust data on this topic are lacking.[115] One possible target for future therapies in these tumors is c-*MET*. Tumors bearing *TFE3* gene fusions have been shown to overexpress c-*MET* at the mRNA and protein levels.[116,117] Furthermore, in vitro studies of cell lines with a *TFE3* gene fusion have shown growth inhibition upon exposure to MET inhibitors.[117]

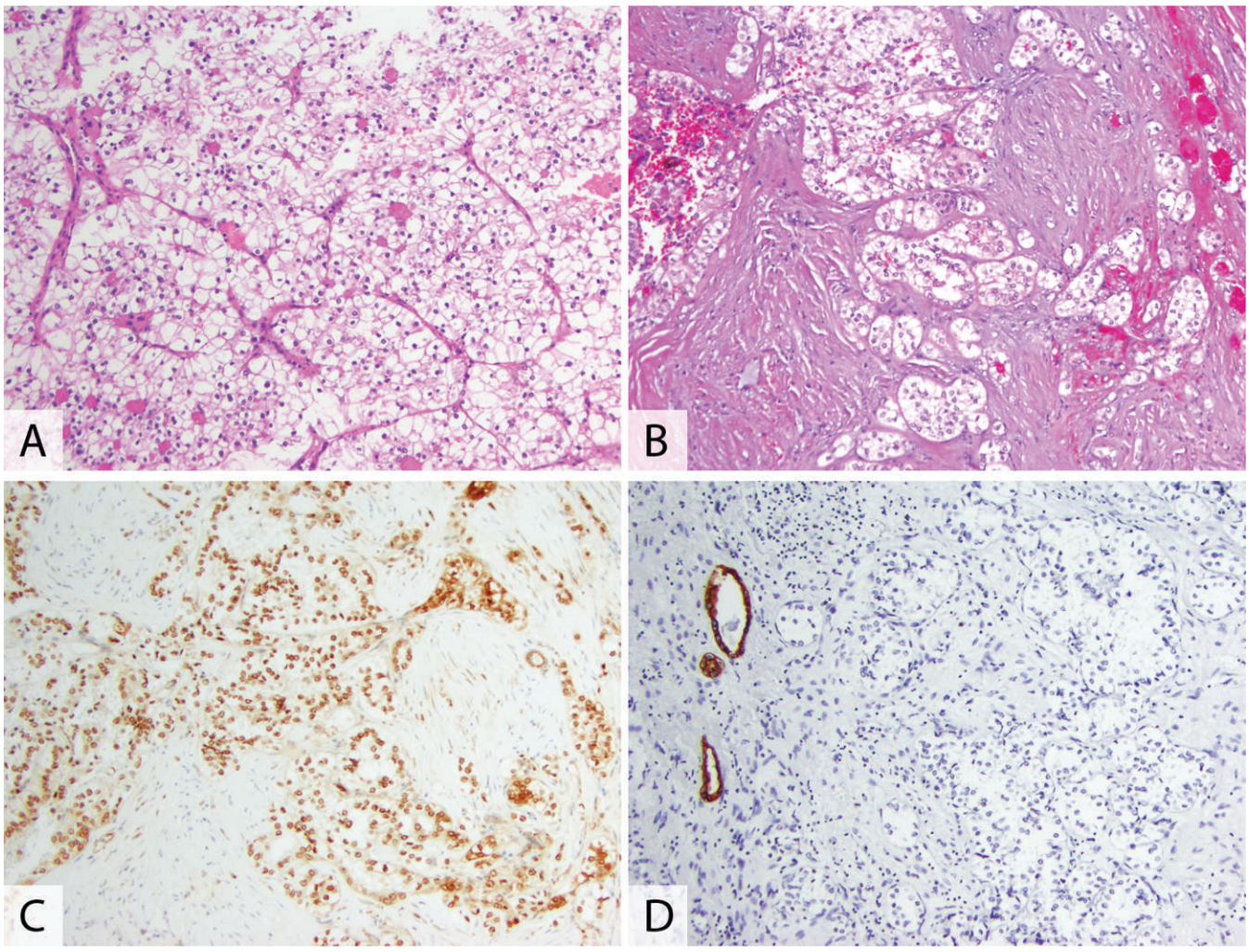
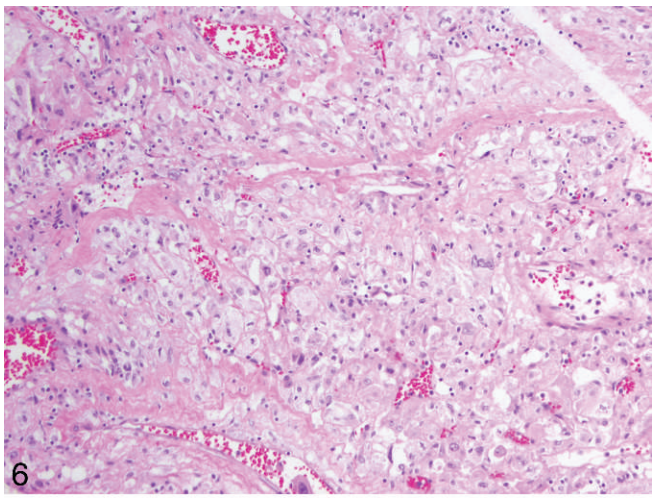


Figure 5. *An example of a* TFE3*-associated translocation carcinoma with clear cell features. A, Low-power examination reveals morphologic overlap with clear cell renal cell carcinoma in this case. B, In some areas a nested growth pattern and hemorrhage are present. C, Diffuse strong nuclear labeling for TFE3 is characteristic of these tumors. D, Negative or patchy labeling for epithelial membrane antigen (EMA)—which would be unusual in other types of renal cell carcinoma—is often a helpful finding (hematoxylin-eosin, original magnifications ×100 [A and B]; original magnifications ×100 [C and D]).*

Epithelioid Angiomyolipoma

Angiomyolipomas (AMLs) belong to the broader group of neoplasms known as perivascular epithelioid cell tumors or PEComas. Most AMLs are sporadic but these tumors also occur in the setting of tuberous sclerosis. Genetically, both syndrome-related and sporadic AMLs are characterized by alterations of the *TSC1* and/or *TSC2* genes, the only difference being that these alterations are germline in the former and somatic in the latter.[2] In the classic triphasic form, AMLs do not enter into the differential diagnosis of a renal tumor with clear cytoplasmic features. However, an uncommon variant of AML—known as epithelioid AML or alternatively, pure epithelioid PEComa—often demonstrates a nested growth pattern and variably clear cytoplasm (Figure 6). Angiomyolipomas account for approximately 1% of surgically removed renal tumors. Pure epithelioid AMLs are exceedingly rare, accounting for only a small fraction of all AMLs, based on recent large series.[2,118,119] In most cases, epithelioid features in an AML will coexist with areas of classic triphasic AML. In cases lacking any typical features of an AML, thoroughly examining a tumor for the classic vasculature of a CCRCC is probably the most reliable H&E finding that can differentiate these tumors. In cases in which immunohistochemistry is required, a panel that includes cytokeratin and EMA (positive profile in most CCRCC), in conjunction with HMB-45, cathepsin K, Melan-A, and smooth muscle actin (positive profile in epithelioid AML), is generally helpful.

The behavior of epithelioid AML is a matter of ongoing debate, with some studies documenting high rates of metastases and others suggesting that these tumors infrequently behave aggressively.[118–120] Given the rarity of this diagnosis, the treatment modalities for metastatic epithelioid AML are understandably poorly defined. However, the knowledge of the role of *TSC1* and/or *TSC2* silencing and downstream activation of the mTOR pathway in these tumors has led to the empiric use of mTOR inhibitors in treating metastatic cases, with some reported dramatic responses.[121]



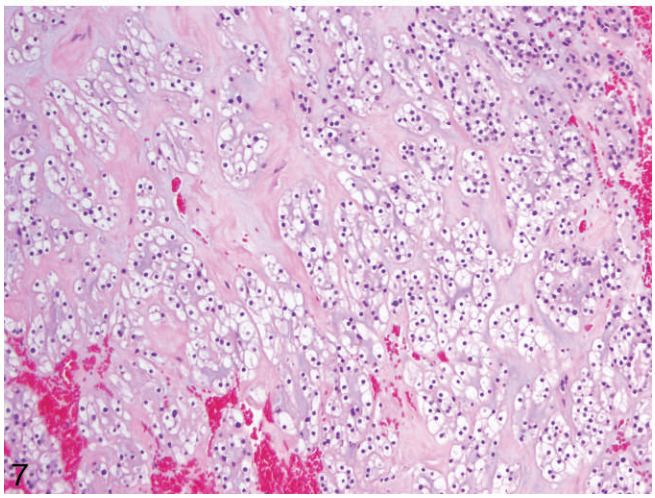


Figure 6. *In some cases of epithelioid angiomyolipoma there is a superficial resemblance to clear cell renal cell carcinoma. The vasculature in epithelioid angiomyolipoma is typically characterized by thick-walled hyalinized vessels (hematoxylin-eosin, original magnification ×200).*

Figure 7. *Rarely, in renal oncocytomas one may see cytoplasmic clearing as shown in this case. This is usually a focal finding that is present in areas of stromal hyalinization (hematoxylin-eosin, original magnification ×100).*

Unclassified Renal Cell Carcinoma

Unclassified RCC, in our opinion, is an underutilized diagnosis. The WHO defines unclassified RCC as a tumor with "...apparent composites of recognized types, sarcomatoid morphology without recognizable epithelial elements, mucin production, mixtures of epithelial and stromal elements, and unrecognizable cell types."[2] In large series this category accounts for approximately 6% of all RCCs.[19] It is important to emphasize that unclassified RCC is not a specific entity but rather a collection of tumors with highly variable morphologic features that defy current classification but that with future research may be defined with more specific criteria. The unclassified category of tumors includes both highly aggressive tumors and others that appear to be indolent.[3,122,123] There is considerable controversy, even among expert genitourinary pathologists, regarding the appropriate use of the term *unclassified renal cell carcinoma*. Specifically, some genitourinary pathologists do not consider tumors that are "apparent composites of recognized types" as unclassified but rather simply mixed tumors in which different subtypes of RCC coexist. Herein we describe our approach, which strictly follows the WHO definition, when working up tumors that we consider unclassified.

When we are confronted with a difficult, potentially unclassified carcinoma with clear cytoplasmic features, we always use immunohistochemical stains. The carcinomas we have ultimately diagnosed as unclassified lack the immunoprofiles of specific subtypes outlined in this review but do express markers suggestive of renal tubular origin, such as PAX8. Generally, unclassified cases we have seen in consultation are more of the "unrecognized cell type" variety and are PAX8 positive. At the Memorial Sloan-Kettering Cancer Center, 20% of cases diagnosed as unclassified renal cell carcinoma have clear cell features.[3] Unclassified cases we have seen with clear cytoplasmic cytoplasmic change have lacked the characteristic immunophenotype and the specific vascular pattern of CCRCC, suggesting that the "clear cell *features*" seen in these cases are not indicative of "clear cell renal cell carcinoma *differentiation*." In unclassified cases with clear cytoplasmic features, we always have a discussion with the treating physicians to emphasize that therapies directed at CCRCC may not be appropriate or effective in such cases. In our experience, tumors that are "apparent composites of recognized types," which by WHO criteria are unclassified, are uncommon. In cases that truly consist of a mixture of recognized subtypes that includes a *bona fide* CCRCC component, based on morphologic, immunohistochemical, and molecular findings, a diagnosis in which the percentage of each subtype present is documented would be appropriate, and such cases may benefit from CCRCC-directed targeted therapies.

In the era of targeted therapies the unclassified category is important for several reasons. First, in the setting of clinical trials, rendering a diagnosis of unclassified RCC when appropriate, rather than forcing a tumor into a specific category, maintains the integrity of the trial. If the input into a trial that has specific tumor-type criteria for enrollment is heterogeneous, the conclusions and results of the entire trial can be affected, which harms all current and future patients with kidney cancer. Secondly, it prevents patients with kidney cancer who have tumors with ambiguous morphologic features from undergoing expensive targeted therapies that can have serious side effects and which may not be effective forms of therapy for that particular patient and tumor. Finally, the unclassified category is fertile ground for future research, as this group of tumors likely includes novel tumor types that may hold important keys for understanding, diagnosing, and treating kidney cancer.

Oncocytoma

Renal oncocytoma is almost never considered in the differential diagnosis of a renal tumor with clear cytoplasm. However, focal clear cell change in an oncocytoma is a recognized phenomenon (Figure 7).[3] A recent abstract by Brunelli et al[124] highlighted the finding of clear cells within the fibrous areas of renal oncocytoma and showed that these clear cells retain strong expression of CK7. The clear cells in oncocytoma express CK7 and CD117, which facilitates distinction from CCRCC. Theoretically, clear cell change in an oncocytoma could be a problem when only a small amount of tissue is available for diagnosis—such as in a needle core biopsy—and serves to emphasize that in

situations where only a small amount of tissue is available, the consistent use of a panel of immunohistochemical markers is prudent.

Adrenal Cortical Tumors and Tissue

The morphologic similarities between adrenal cortical tissue/tumors and CCRCC are well documented and are the historical basis for older terminology for CCRCC, such as *hypernephroma*.[1] The difficulty of this particular differential diagnosis is compounded by the close anatomic relationship between the adrenal glands and the kidneys and by the fact that on occasion one can observe intrarenal adrenal tissue.[125] Cases in which the adrenal glands are fused to the external surface of the kidney (so-called renal-adrenal fusion) have also been documented and can simulate a renal mass clinically and radiographically.[125] At the morphologic/H&E level, the characteristic cytoplasmic features of adrenal cortical cells—namely, the vacuolated, bubbly nature of the cytoplasm—is probably the most helpful finding. In cases of renal-adrenal fusion, examining the tissue for the typical morphologic features of adrenal medullary cells can also be helpful. In difficult cases, immunohistochemical stains such as inhibin and synaptophysin, which show positivity in adrenal cortical tissue and adrenal cortical tumors, can be used. Immunohistochemical stains that would label CCRCC and not adrenal cortical tissue/tumors include CA9, EMA, and CD10.[126]

References

1. Delahunt B, Eble JN. History of the development of the classification of renal cell neoplasia. *Clin Lab Med*. 2005;25(2):231–246.
2. Eble JN, Togashi K, Pisani P. Renal Cell Carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004:9–87.
3. Reuter VE, Tickoo, SK. Adult renal tumors. In: Mills SE, Carter D, Greenson JK, Reuter VE, Stoler MH, eds. *Sternberg's Diagnostic Surgical Pathology*. Vol 2. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:1758–1798.
4. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol*. 2003;170(6, pt 1):2217–2220.
5. Thompson RH, Kurta JM, Kaag M, et al. Tumor size is associated with malignant potential in renal cell carcinoma cases. *J Urol*. 2009;181(5):2033–2036.
6. Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer*. 2010;116(13):3119–3126.
7. Sun M, Trinh QD, Bianchi M, et al. A non-cancer-related survival benefit is associated with partial nephrectomy. *Eur Urol*. 2012;61(4):725–731.
8. Chawla SN, Crispen PL, Hanlon AL, Greenberg RE, Chen DY, Uzzo RG. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. *J Urol*. 2006;175(2):425–431.
9. Sun M, Abdollah F, Bianchi M, et al. Treatment management of small renal masses in the 21st century: a paradigm shift [published online ahead of print February 10, 2012]. *Ann Surg Oncol*. doi:10.1245/s10434-012-2247-0.
10. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. 2009;373(9669):1119–1132.
11. Molina AM, Feldman DR, Ginsberg MS, et al. Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma. *Invest New Drugs*. 2012;30(1):335–340.
12. Drucker BJ. Renal cell carcinoma: current status and future prospects. *Cancer Treat Rev*. 2005;31(7):536–545.
13. Santos N, Wenger JB, Havre P, et al. Combination therapy for renal cell cancer: what are possible options? *Oncology*. 2011;81(3–4):220–229.
14. Foster K, Prowse A, van den Berg A, et al. Somatic mutations of the von Hippel-Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma. *Hum Mol Genet*. 1994;3(12):2169–2173.
15. Seizinger BR, Rouleau GA, Ozelius LJ, et al. Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma. *Nature*. 1988;332(6161):268–269.
16. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260(5112):1317–1320.
17. Bitting RL, Madden J, Armstrong AJ. Therapy for non-clear cell histologies in renal cancer. *Curr Clin Pharmacol*. 2011;6(3):169–180.
18. Storkel S, Eble JN, Adlakha K, et al. Classification of renal cell carcinoma: Workgroup No. 1, Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). *Cancer*. 1997;80(5):987–989.
19. Amin MB, Tamboli P, Javidan J, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. *Am J Surg Pathol*. 2002;26(3):281–291.
20. MacLennan GT, Cheng, L. Neoplasms of the kidney. In: Bostwik DG, Cheng L, eds. *Urologic Surgical Pathology*. 2nd ed. London, United Kingdom: Mosby Elsevier; 2008;77–171.
21. Kim SP, Weight CJ, Leibovich BC, et al. Outcomes and clinicopathologic variables associated with late recurrence after nephrectomy for localized renal cell carcinoma. *Urology*. 2011;78(5):1101–1106.
22. Bonsib SM. T2 clear cell renal cell carcinoma is a rare entity: a study of 120 clear cell renal cell carcinomas [discussion in *J Urol*. 2005;174(4, pt 1):1202]. *J Urol*. 2005;174(4, pt 1):1199–1202.
23. de Peralta-Venturina M, Moch H, Amin M, et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. *Am J Surg Pathol*. 2001;25(3):275–284.
24. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol*. 1982;6(7):655–663.
25. Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature*. 2011;469(7331):539–542.
26. Huebner K. Tumor suppressors on 3p: a neoclassic quartet. *Proc Natl Acad Sci U S A*. 2001;98(26):14763–14765.
27. Dreijerink K, Braga E, Kuzmin I, et al. The candidate tumor suppressor gene, RASSF1A, from human chromosome 3p21.3 is involved in kidney tumorigenesis. *Proc Natl Acad Sci U S A*. 2001;98(13):7504–7509.
28. Sukosd F, Kuroda N, Beothe T, Kaur AP, Kovacs G. Deletion of chromosome 3p14.2-p25 involving the VHL and FHIT genes in conventional renal cell carcinoma. *Cancer Res*. 2003;63(2):455–457.
29. Nickerson ML, Jaeger E, Shi Y, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res*. 2008;14(15):4726–4734.
30. Kovacs G, Erlandsson R, Boldog F, et al. Consistent chromosome 3p deletion and loss of heterozygosity in renal cell carcinoma. *Proc Natl Acad Sci U S A*. 1988;85(5):1571–1575.
31. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*. 1999;399(6733):271–275.
32. Maxwell PH, Pugh CW, Ratcliffe PJ. The pVHL-hIF-1 system: a key mediator of oxygen homeostasis. *Adv Exp Med Biol*. 2001;502:365–376.
33. Grabmaier K, AdW, MC, Verhaegh GW, Schalken JA, Oosterwijk E. Strict regulation of CAIX(G250/MN) by HIF-1alpha in clear cell renal cell carcinoma. *Oncogene*. 2004;23(33):5624–5631.
34. Wiesener MS, Munchenhagen PM, Berger I, et al. Constitutive activation of hypoxia-inducible genes related to overexpression of hypoxia-inducible factor-1alpha in clear cell renal carcinomas. *Cancer Res*. 2001;61(13):5215–5222.
35. Krieg M, Haas R, Brauch H, Acker T, Flamme I, Plate KH. Up-regulation of hypoxia-inducible factors HIF-1alpha and HIF-2alpha under normoxic conditions in renal carcinoma cells by von Hippel-Lindau tumor suppressor gene loss of function. *Oncogene*. 2000;19(48):5435–5443.
36. Gunaratnam L, Morley M, Franovic A, et al. Hypoxia inducible factor activates the transforming growth factor-alpha/epidermal growth factor receptor growth stimulatory pathway in VHL(-/-) renal cell carcinoma cells. *J Biol Chem*. 2003;278(45):44966–44974.
37. Hudson CC, Liu M, Chiang GG, et al. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. *Mol Cell Biol*. 2002;22(20):7004–7014.
38. Thomas GV, Tran C, Mellinghoff IK, et al. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat Med*. 2006;12(1):122–127.
39. Al-Ahmadie HA, Alden D, Fine SW, et al. Role of immunohistochemistry in the evaluation of needle core biopsies in adult renal cortical tumors: an ex vivo study. *Am J Surg Pathol*. 2011;35(7):949–961.
40. Tickoo SK, Alden D, Olgac S, et al. Immunohistochemical expression of hypoxia inducible factor-1alpha and its downstream molecules in sarcomatoid renal cell carcinoma. *J Urol*. 2007;177(4):1258–1263.
41. Wykoff CC, Beasley NJ, Watson PH, et al. Hypoxia-inducible expression of tumor-associated carbonic anhydrases. *Cancer Res*. 2000;60(24):7075–7083.
42. Goyal R, Zhu, B, Parimi, V, et al. Immunohistochemical (IHC) expression of carbonic anhydrase IX (CA9) in papillary (PRCC) and chromophobe (CHRCC) renal cell carcinoma is associated with necrosis. *Mod Pathol*. 2011;24(1S):194A.
43. Mancilla-Jimenez R, Stanley RJ, Blath RA. Papillary renal cell carcinoma: a clinical, radiologic, and pathologic study of 34 cases. *Cancer*. 1976;38(6):2469–2480.
44. Ronnen EA, Kondagunta GV, Ishill N, et al. Treatment outcome for metastatic papillary renal cell carcinoma patients. *Cancer*. 2006;107(11):2617–2621.
45. Delahunt B, Eble JN, McCredie MR, Bethwaite PB, Stewart JH, Bilous AM. Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. *Hum Pathol*. 2001;32(6):590–595.
46. Yang XJ, Tan MH, Kim HL, et al. A molecular classification of papillary renal cell carcinoma. *Cancer Res*. 2005;65(13):5628–5637.
47. Sukov WR, Lohse CM, Leibovich BC, Thompson RH, Cheville JC. Clinical and pathological features associated with prognosis in patients with papillary renal cell carcinoma. *J Urol*. 2012;187(1):54–59.

48. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Mod Pathol*. 1997;10(6):537–544.

49. Amin MB, Corless CL, Renshaw AA, Tickoo SK, Kubus J, Schultz DS. Papillary (chromophil) renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 62 cases. *Am J Surg Pathol*. 1997;21(6):621–635.

50. Tickoo SK, Reuter VE. Differential diagnosis of renal tumors with papillary architecture. *Adv Anat Pathol*. 2011;18(2):120–132.

51. Gobbo S, Eble JN, Maclennan GT, et al. Renal cell carcinomas with papillary architecture and clear cell components: the utility of immunohistochemical and cytogenetical analyses in differential diagnosis. *Am J Surg Pathol*. 2008;32(12):1780–1786.

52. Mai KT, Faraji H, Desantis D, Robertson SJ, Belanger EC, Levac J. Renal cell carcinoma with mixed features of papillary and clear cell cytomorphology: a fluorescent in situ hybridization study. *Virchows Arch*. 2010;456(1):77–84.

53. Klatte T, Pantuck AJ, Said JW, et al. Cytogenetic and molecular tumor profiling for type 1 and type 2 papillary renal cell carcinoma. *Clin Cancer Res*. 2009;15(4):1162–1169.

54. Lager DJ, Huston BJ, Timmerman TG, Bonsib SM. Papillary renal tumors: morphologic, cytochemical, and genotypic features. *Cancer*. 1995;76(4):669–673.

55. van Houwelingen KP, van Dijk BA, Hulsbergen-van de Kaa CA, et al. Prevalence of von Hippel-Lindau gene mutations in sporadic renal cell carcinoma: results from The Netherlands cohort study. *BMC Cancer*. 2005;5:57.

56. Sanders ME, Mick R, Tomaszewski JE, Barr FG. Unique patterns of allelic imbalance distinguish type 1 from type 2 sporadic papillary renal cell carcinoma. *Am J Pathol*. 2002;161(3):997–1005.

57. Velickovic M, Delahunt B, Storkel S, Grebem SK. VHL. and FHIT locus loss of heterozygosity is common in all renal cancer morphotypes but differs in pattern and prognostic significance. *Cancer Res*. 2001;61(12):4815–4819.

58. Kondo K, Yao M, Yoshida M, et al. Comprehensive mutational analysis of the VHL gene in sporadic renal cell carcinoma: relationship to clinicopathological parameters. *Genes Chromosomes Cancer*. 2002;34(1):58–68.

59. Rohan SM, Al-Ahmadie, HA, Fine, SW, et al Hypoxia inducible factor (HIF) pathway in papillary renal cell carcinoma: a tissue microarray based study. *Mod Pathol*. 2008;21(1S):178A.

60. Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. *Oncogene*. 1999;18(14):2343–2350.

61. Heng DY, Choueiri TK. Non-clear cell renal cancer: features and medical management. *J Natl Compr Canc Netw*. 2009;7(6):659–665.

62. Rubin MA, Zhou M, Dhanasekaran SM, et al. Alpha-methylacyl coenzyme A racemase as a tissue biomarker for prostate cancer. *JAMA*. 2002; 287(13):1662–1670.

63. Tretiakova MS, Sahoo S, Takahashi M, et al. Expression of alpha-methylacyl-CoA racemase in papillary renal cell carcinoma. *Am J Surg Pathol*. 2004;28(1):69–76.

64. Yang XJ, Zhou M, Hes O, et al. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. *Am J Surg Pathol*. 2008;32(2): 177–187.

65. Tickoo SK, dePeralta-Venturina MN, Harik LR, et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. *Am J Surg Pathol*. 2006;30(2):141–153.

66. Langner C, Rupar G, Leibl S, et al. Alpha-methylacyl-CoA racemase (AMACR/P504S) protein expression in urothelial carcinoma of the upper urinary tract correlates with tumour progression. *Virchows Arch*. 2006;448(3):325–330.

67. Camparo P, Vasiliu V, Molinie V, et al. Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. *Am J Surg Pathol*. 2008;32(5):656–670.

68. Paner GP, Srigley JR, Radhakrishnan A, et al. Immunohistochemical analysis of mucinous tubular and spindle cell carcinoma and papillary renal cell carcinoma of the kidney: significant immunophenotypic overlap warrants diagnostic caution. *Am J Surg Pathol*. 2006;30(1):13–19.

69. Molinie V, Balaton A, Rotman S, et al. Alpha-methyl CoA racemase expression in renal cell carcinomas. *Hum Pathol*. 2006;37(6):698–703.

70. Mai KT, Kohler DM, Belanger EC, Robertson SJ, Wang D. Sporadic clear cell renal cell carcinoma with diffuse cytokeratin 7 immunoreactivity. *Pathology*. 2008;40(5):481–486.

71. Rohan SM, Xiao Y, Liang Y, et al. Clear-cell papillary renal cell carcinoma: molecular and immunohistochemical analysis with emphasis on the von Hippel-Lindau gene and hypoxia-inducible factor pathway-related proteins. *Mod Pathol*. 2011;24(9):1207–1220.

72. Skinnider BF, Folpe AL, Hennigar RA, et al. Distribution of cytokeratins and vimentin in adult renal neoplasms and normal renal tissue: potential utility of a cytokeratin antibody panel in the differential diagnosis of renal tumors. *Am J Surg Pathol*. 2005;29(6):747–754.

73. Al-Ahmadie HA, Alden D, Qin LX, et al. Carbonic anhydrase IX expression in clear cell renal cell carcinoma: an immunohistochemical study comparing 2 antibodies. *Am J Surg Pathol*. 2008;32(3):377–382.

74. Donato DP, Johnson MT, Yang XJ, Zynger DL. Expression of carbonic anhydrase IX in genitourinary and adrenal tumours. *Histopathology*. 2011;59(6): 1229–1239.

75. Thoenes W, Storkel S, Rumpelt HJ. Human chromophobe cell renal carcinoma. *Virchows Arch B Cell Pathol Incl Mol Pathol*. 1985;48(3):207–217.

76. Bonsib SM, Lager DJ. Chromophobe cell carcinoma: analysis of five cases. *Am J Surg Pathol*. 1990;14(3):260–267.

77. Thoenes W, Storkel S, Rumpelt HJ, Moll R, Baum HP, Werner S. Chromophobe cell renal carcinoma and its variants—a report on 32 cases. *J Pathol*. 1988;155(4):277–287.

78. Amin MB, Paner GP, Alvarado-Cabrero I, et al. Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. *Am J Surg Pathol*. 2008;32(12): 1822–1834.

79. Przybycin CG, Cronin AM, Darvishian F, et al. Chromophobe renal cell carcinoma: a clinicopathologic study of 203 tumors in 200 patients with primary resection at a single institution. *Am J Surg Pathol*. 2011;35(7):962–970.

80. Leibovich BC, Lohse CM, Crispen PL, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. *J Urol*. 2010;183(4):1309–1315.

81. Beck SD, Patel MI, Snyder ME, et al. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Ann Surg Oncol*. 2004;11(1):71–77.

82. Abrahams NA, MacLennan GT, Khoury JD, et al. Chromophobe renal cell carcinoma: a comparative study of histological, immunohistochemical and ultrastructural features using high throughput tissue microarray. *Histopathology*. 2004;45(6):593–602.

83. Bugert P, Gaul C, Weber K, et al. Specific genetic changes of diagnostic importance in chromophobe renal cell carcinomas. *Lab Invest*. 1997;76(2):203–208.

84. Kovacs A, Kovacs G. Low chromosome number in chromophobe renal cell carcinomas. *Genes Chromosomes Cancer*. 1992;4(3):267–268.

85. Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. *J Med Genet*. 2008;45(6):321–331.

86. Pavlovich CP, Walther MM, Eyler RA, et al. Renal tumors in the Birt-Hogg-Dube syndrome. *Am J Surg Pathol*. 2002;26(12):1542–1552.

87. Baba M, Hong SB, Sharma N, et al. Folliculin encoded by the BHD gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling. *Proc Natl Acad Sci U S A*. 2006;103(42):15552–15557.

88. Gad S, Lefevre SH, Khoo SK, et al. Mutations in BHD and TP53 genes, but not in HNF1beta gene, in a large series of sporadic chromophobe renal cell carcinoma. *Br J Cancer*. 2007;96(2):336–340.

89. Murakami T, Sano F, Huang Y, et al. Identification and characterization of Birt-Hogg-Dube associated renal carcinoma. *J Pathol*. 2007;211(5):524–531.

90. Woodward ER, Ricketts C, Killick P, et al. Familial non-VHL clear cell (conventional) renal cell carcinoma: clinical features, segregation analysis, and mutation analysis of FLCN. *Clin Cancer Res*. 2008;14(18):5925–5930.

91. Nagy A, Zoubakov D, Stupar Z, Kovacs G. Lack of mutation of the folliculin gene in sporadic chromophobe renal cell carcinoma and renal oncocytoma. *Int J Cancer*. 2004;109(3):472–475.

92. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol*. 2008;26(1):127–131.

93. Aydin H, Chen L, Cheng L, et al. Clear cell tubulopapillary renal cell carcinoma: a study of 36 distinctive low-grade epithelial tumors of the kidney. *Am J Surg Pathol*. 2010;34(11):1608–1621.

94. Gobbo S, Eble JN, Grignon DJ, et al. Clear cell papillary renal cell carcinoma: a distinct histopathologic and molecular genetic entity. *Am J Surg Pathol*. 2008;32(8):1239–1245.

95. Duan L, Youseff RF, Margulis V, et al. Clear cell papillary renal cell carcinoma: clinicopathologic, immunohistochemical, and molecular analysis. *Mod Pathol*. 2011;24(suppl):189A.

96. Lopez JI, Moreno V, Garcia H, et al. Renal cell carcinoma in young adults: a study of 130 cases and a review of previous series. *Urol Int*. 2010;84(3):292–300.

97. Sailey CJ, Dvorakova M, Papadimitriou JC, Borin JF, Ali T, Parwani AV. Molecular, immunohistochemical, and ultrastructural characterization of clear cell papillary renal cell carcinoma. *Mod Pathol*. 2010;23(1S):216A.

98. Herrera LP, Hes O, Hirsch M, et al. Clear cell papillary renal cell carcinoma (Cp-RCC) not associated with end stage renal disease: clinicopathiologic analysis of 50 tumors confirming a novel subtype of renal cell carcinoma (rcc) occuring in a sporadic setting. *Mod Pathol*. 2011;2011;24:197A.

99. Song L, Lal P, Tomaszewski JE, Bing Z. Immunohistochemical study of clear cell papillary renal cell carcinoma. *Mod Pathol*. 2011;24(1S):208A.

100. Michal M, Hes O, Nemcova J, et al. Renal angiomyoadenomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity. *Virchows Arch*. 2009;454(1):89–99.

101. Behdad A, Monzon FA, Hes O, et al. Relationship between sporadic clear cell-papillary renal cell carcinoma (CP-RCC) and renal angiomyoadenomatous tumor (RAT) of the kidney: analysis by virtual-karyotyping, fluorescent in situ analysis and immunohistochemistry (IHC). *Mod Pathol*. 2011;24(1S):179A.

102. Adam J, Couturier J, Molinie V, Vieillefond A, Sibony M. Clear-cell papillary renal cell carcinoma: 24 cases of a distinct low-grade renal tumour and a comparative genomic hybridization array study of seven cases. *Histopathology*. 2011;58(7):1064–1071.

103. Brannon AR, Haake SM, Hacker KE, et al. Meta-analysis of clear cell renal cell carcinoma gene expression defines a variant subgroup and identifies gender influences on tumor biology. *Eur Urol*. 2012;61(2):258–268.

104. Tomlinson GE, Nisen PD, Timmons CF, Schneider NR. Cytogenetics of a renal cell carcinoma in a 17-month-old child: evidence for Xp11.2 as a recurring breakpoint. *Cancer Genet Cytogenet*. 1991;57(1):11–17.

105. de Jong B, Molenaar IM, Leeuw JA, Idenberg VJ, Oosterhuis JW. Cytogenetics of a renal adenocarcinoma in a 2-year-old child. *Cancer Genet Cytogenet*. 1986;21(2):165–169.

106. Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. *Am J Pathol*. 2001;159(1):179–192.

107. Argani P, Hawkins A, Griffin CA, et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. *Am J Pathol*. 2001;158(6):2089–2096.

108. Argani P, Olgac S, Tickoo SK, et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. *Am J Surg Pathol*. 2007;31(8):1149–1160.

109. Argani P, Ladanyi M. Translocation carcinomas of the kidney. *Clin Lab Med*. 2005;25(2):363–378.

110. Davis IJ, Hsi BL, Arroyo JD, et al. Cloning of an alpha-TFEB fusion in renal tumors harboring the t(6;11)(p21;q13) chromosome translocation. *Proc Natl Acad Sci U S A*. 2003;100(10):6051–6056.

111. Argani P, Lae M, Hutchinson B, et al. Renal carcinomas with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. *Am J Surg Pathol*. 2005;29(2):230–240.

112. Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE, Ladanyi M. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. *Am J Surg Pathol*. 2003;27(6):750–761.

113. Ross H, Argani P. Xp11 translocation renal cell carcinoma. *Pathology*. 2010;42(4):369–373.

114. Martignoni G, Pea M, Gobbo S, et al. Cathepsin-K immunoreactivity distinguishes MiTF/TFE family renal translocation carcinomas from other renal carcinomas. *Mod Pathol*. 2009;22(8):1016–1022.

115. Argani P, Hicks J, De Marzo AM, et al. Xp11 translocation renal cell carcinoma (RCC): extended immunohistochemical profile emphasizing novel RCC markers. *Am J Surg Pathol*. 2010;34(9):1295–1303.

116. Argani P, Tsuda M, Chen M-S, Edgar M, Ladanyi M. Overexpression of the MET receptor tyrosine kinase in tumors with TFE3 gene fusions. *Mod Pathol*. 2006;19(S1):297A.

117. Tsuda M, Davis IJ, Argani P, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. *Cancer Res*. 2007;67(3):919–929.

118. Nese N, Martignoni G, Fletcher CD, et al. Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: a clinicopathologic study of 41 cases—detailed assessment of morphology and risk stratification. *Am J Surg Pathol*. 2011;35(2):161–176.

119. Aydin H, Magi-Galluzzi C, Lane BR, et al. Renal angiomyolipoma: clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association. *Am J Surg Pathol*. 2009;33(2):289–297.

120. He W, Cheville JC, Sadow PM, et al. Pathologic characteristics and clinical outcome of renal epithelioid angiomyolipoma: a multi-unstitutional experience based on primary tumor resections. *Mod Pathol*. 2011;24(S1):196A.

121. Wolff N, Kabbani W, Bradley T, Raj G, Watumull L, Brugarolas J. Sirolimus and temsirolimus for epithelioid angiomyolipoma. *J Clin Oncol*. 2010;28(5):e65–e68.

122. Reuter VE. The pathology of renal epithelial neoplasms. *Semin Oncol*. 2006;33(5):534–543.

123. Murphy D, Grignon DJ, Perlman EJ. In: *Tumors of the Kidney, Bladder, and Urinary Structures*. Washington, DC: American Registry of Pathology; 2004;149–152. *Atlas of Tumor Pathology*. 4th series, fascicle 1.

124. Brunelli M, Gobbo S, Segala D, et al. Clear or basophilic type 1 papillary renal cell carcinoma-like cells occuring in the central fibrous scar of renal oncocytoma represent a potential diagnostic pitfall. *Mod Pathol*. 2010;23(1S):182A.

125. Ye H, Yoon GS, Epstein JI. Intrarenal ectopic adrenal tissue and renal-adrenal fusion: a report of nine cases. *Mod Pathol*. 2009;22(2):175–181.

126. Sangoi AR, Fujiwara M, West RB, et al. Immunohistochemical distinction of primary adrenal cortical lesions from metastatic clear cell renal cell carcinoma: a study of 248 cases. *Am J Surg Pathol*. 2011;35(5):678–686.