Pathology of Renal Cell Carcinoma

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Ming Zhou and Huiying He

Arising from the renal tubular epithelial cells, renal cell carcinoma (RCC) accounts for more than 90% of primary kidney tumors in adults. It encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as distinct prognosis and therapeutic responses. It is therefore of paramount importance to accurately classify renal tumors. In this chapter, we review the pathological and molecular characteristics of major histological subtypes of RCC that are recognized by the 2004 World Health Organization (WHO) classification of renal tumors [1]. We also discuss several newly described subtypes of RCC and RCC associated with inherited cancer syndromes. The prognostic significance of various histological parameters will also be highlighted [2–4].

Pathological Classification of RCC

In addition to rendering an accurate diagnosis, pathological classification of RCC also provides relevant prognostic information and guidance to therapy. The current classification of renal tumors was introduced by WHO in 2004 (Table 2.1) [1]. It is based primarily on morphology but has also incorporated characteristic genetic and molecular features of renal tumors. These ten tumors represent the most common RCC subtypes encountered clinically. However, many other less common subtypes of RCC have been described with distinct clinical, pathological, and genetic features, and it is likely that additional ones will be identified in the future. As the molecular mechanisms of renal tumors have been increasingly elucidated, molecular classification will eventually replace morphological classification [2–4].

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Pathologic and Molecular Characteristics of RCC Histologic Subtypes

Renal Cell Carcinoma, Clear Cell (CCRCC) Type

Clinical Features

CCRCC type is the most common histological subtype and accounts for 60–70% of all RCCs. Although it may occur in all age groups, it most commonly affects patients in their sixth to seventh decades of life and the majority are males with a ratio of approximately 2:1 [5]. Most CCRCC arises sporadically, with only 2–4% of the cases presenting as part of an inherited cancer syndrome, including von Hippel–Lindau (VHL) syndrome, Birt–Hogg–Dube (BHD) syndrome,

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Table 2.1 2004 World Health Organization classification of renal cell carcinoma

Renal cell carcinoma
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

and constitutional chromosomal 3 translocation syndrome [6, 7]. As a general rule, familial CCRCC presents at a younger age and is much more likely to be multifocal and bilateral.

Pathology

Grossly, CCRCC usually presents as a unilateral and unicentric, round and well-demarcated mass with a fibrous capsule. The cut surface often has characteristic golden yellow color with variable degree of hemorrhage, necrosis, cystic degeneration, and calcification (Fig. 2.1a). Bilaterality and/or multicentricity occur in <5% of sporadic CCRCC cases but are more common in inherited cancer syndromes.

Microscopically the tumor cells are arranged in compact nests, sheets, alveolar, or acinar structures separated by thin-walled blood vessels. Tumor cells have clear cytoplasm (Fig. 2.1b) due to loss of cytoplasmic lipid and glycogen during tissue processing and slide preparation. In high-grade and poorly differentiated tumors, cells lose their cytoplasmic clearing and acquire granular eosinophilic cytoplasm (Fig. 2.1c).

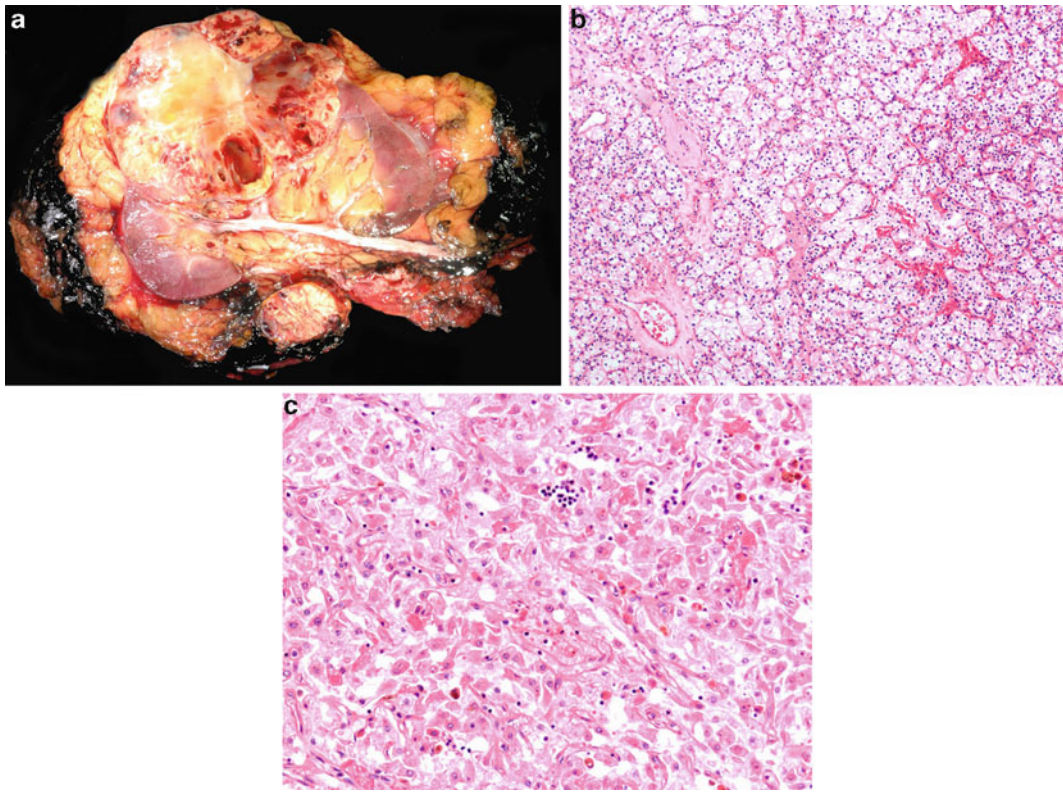

Fig. 2.1 (**a**) Large clear cell renal cell carcinoma with characteristic *bright golden yellow color* extends into perinephric and sinus fat. Adrenal metastasis is also seen on the *bottom of the image* (**a**). Clear cell RCC is composed of compact nests of tumor cells with clear cytoplasm separated by delicate arborizing vasculature (**b**). High-grade clear cell RCC can show eosinophilic and granular cytoplasm (**c**)

Molecular Genetics

Seventy to ninety percent of CCRCCs harbor chromosome 3p alterations which comprise deletion, mutation, or methylation of several important genes, including *von Hippel–Lindau* (*VHL*) gene on chromosome 3p25-26, *RASSF1A* on 3p21 and *FHIT* on 3p14.2. Duplication of 5q22 is the second most common cytogenetic finding and may be associated with better prognosis. Other cytogenetic alterations involve loss of chromosomes 6q, 8p12, 9p21, 9q22, 10q, 17p, and 14q [3, 8, 9].

Somatic mutations in *VHL* gene have been found in 18–82% of sporadic CCRCC cases. Loss of heterozygosity at the *VHL* locus has been reported in up to 98% of cases [10–12]. Hypermethylation of the *VHL* gene promoter resulting in gene inactivation has been detected in 5–20% of patients without gene alteration. The vast majority of CCRCC showing somatic *VHL* mutations also exhibit allelic loss or LOH at the *VHL* locus, consistent with Knudson's two-hit model of tumorigenesis.

VHL protein plays a critical role in the cellular response to hypoxia (Fig. 2.2). Hypoxia-inducible factor (HIF) is a transcriptional factor whose cellular level is regulated by VHL. Under normoxic condition, HIF is hydroxylated, and the wild-type VHL protein binds and targets this form of HIF for degradation in proteosomes. Consequently, HIF levels are kept low within normal cells under normoxic conditions through the action of functional VHL. Under hypoxic condition, however, HIF is not hydroxylated and cannot be recognized by VHL, and therefore begins to accumulate. This in turn activates many downstream hypoxia-driven genes, including genes that promote angiogenesis [vascular endothelial growth

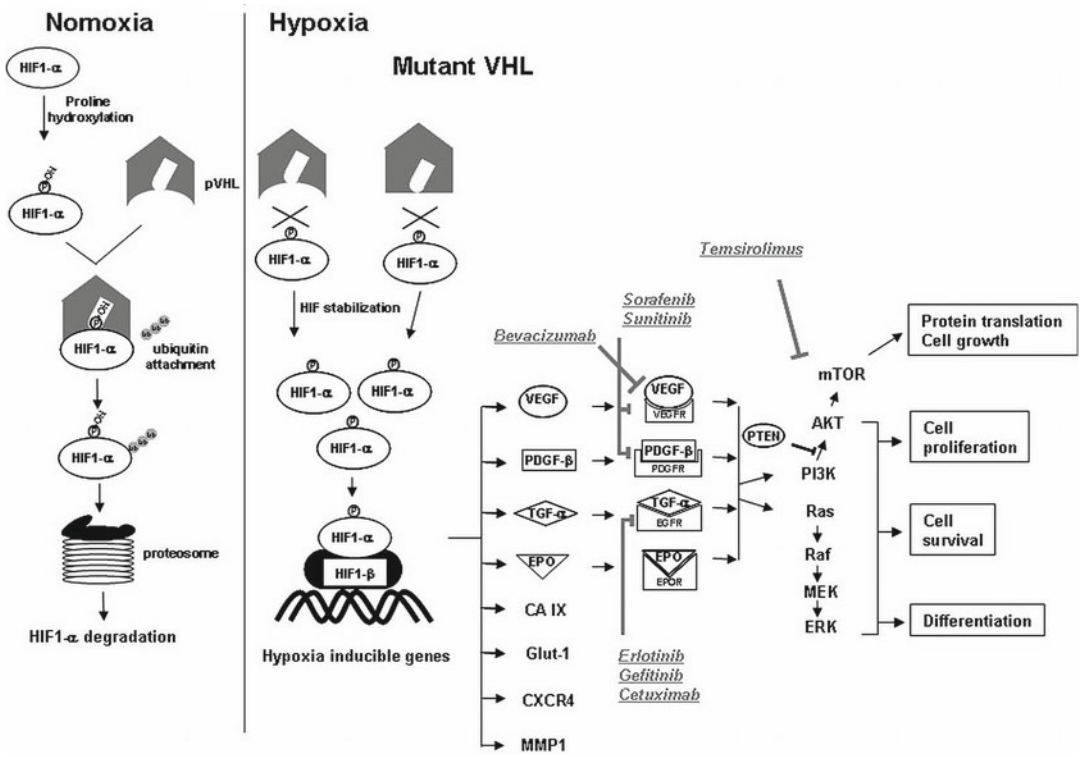

Fig. 2.2 Molecular pathways involving the *VHL* gene. Under normoxic condition, VHL directs HIF for proteolytic degradation. Under hypoxic condition or when VHL gene expression is inactivated by mutation or promoter hypermethylation, HIF accumulates and activates multiple target genes and signal transduction pathways to control cell proliferation, survival, growth, and differentiation. Several small molecule inhibitors can block various critical steps in these pathways and are currently used to treat advanced stage disease

factor (*VEGF*) and platelet-derived growth factor β (*PDGF-β*)], cell growth or survival [transforming growth factor α (*TGF-α*)], anaerobic metabolism (*Glut-1*), acid base balance (*CA IX*), and red cell production (*erythropoietin*). Along the way numerous intracellular signal transduction pathways are activated, including PI3 kinase-Akt-mTOR pathway and Ras-raf-erk-mek pathway, which are involved in various cellular processes, including cell proliferation, survival, and differentiation [12, 13]. These signal transduction pathways serve a beneficial role by stimulating angiogenesis and compensatory metabolic changes in normal cells coping with hypoxia. When *VHL* gene is inactivated by mutation or promoter hypermethylation, no functional VHL is produced. The end result is activation of the aforementioned cellular processes which are no longer controlled by normal physiological mechanisms and therefore contribute to the tumorigenesis and many of the clinical manifestations of CCRCC. Recent clinical trials have targeted the critical components of these pathways in patients with advanced stage CCRCC, including VEGF using neutralizing antibody bevacizumab; VEGFR and PDGFR using small molecule inhibitors of tyrosine kinase, such as sorafenib and sunitinib; EGFR using erlotinib, and mTOR using temsirolimus [14, 15] (Fig. 2.2).

Renal Cell Carcinoma, Papillary Type (Papillary RCC)

Clinical Features

Papillary RCC (PRCC) is the second most common type of RCC and accounts for 10–15% of RCCs. The gender and age distribution are similar to those of CCRCC. However, PRCC has a better prognosis with a 5-year survival approaching 90% [5]. The vast majority of tumors occur sporadically, but some develop in members of families with hereditary PRCC (HPRCC) [16] or rarely in hereditary leiomyomatosis and renal cell cancer (HLRCC) [17].

Pathology

Grossly, PRCC typically presents as a well-circumscribed mass enclosed within a pseudocapsule. Some tumors appear entirely necrotic and friable (Fig. 2.3a). PRCC is more likely to be bilateral and multifocal than the other types of RCC.

Microscopically, PRCC is composed of varying proportions of papillae, tubulopapillae, and tubules. Occasionally it has tightly packed tubules or papillae and imparts a solid appearance. The papillae characteristically contain delicate fibrovascular cores infiltrated by foamy histiocytes (Fig. 2.3b). Necrosis, hemorrhage, acute and chronic inflammation, hemosiderin deposition, and psammoma bodies are common.

Two subtypes of PRCC are recognized based on the histology [18]. Accounting for about two-thirds of PRCC, type I tumor contains papillae that are delicate and short, lined with single layer of tumor cells with scant cytoplasm and low-grade nuclei (Fig. 2.3b). In contrast, papillae in type II PRCC are large and lined with cells having abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli (Fig. 2.3c). Patients with type I PRCC have a better prognosis than those with type II tumor.

Molecular Genetics

Trisomy or tetrasomy 7, trisomy 17, and loss of Y chromosome (in men) are the most common cytogenetic changes in PRCC [19]. Types I and II PRCC have distinct genetic features, for example, gain of 7p and 17p is more common in type I tumors [20]. Deletion of 9p is present in approximately 20% of PRCC and loss of heterozygosity at 9p13, limited to type II tumors in recent studies, has been linked to shorter survival [21].

Renal Cell Carcinoma, Chromophobe Type (Chromophobe RCC)

Clinical Features

Chromophobe RCC (ChRCC) accounts for approximately 5% of RCCs and is believed to arise from the intercalated cells of the collecting ducts [22]. ChRCC can occur in patients of wide age range. Males and females are affected almost equally. The prognosis is significantly better than that of CCRCC, with disease recurrence in <5%

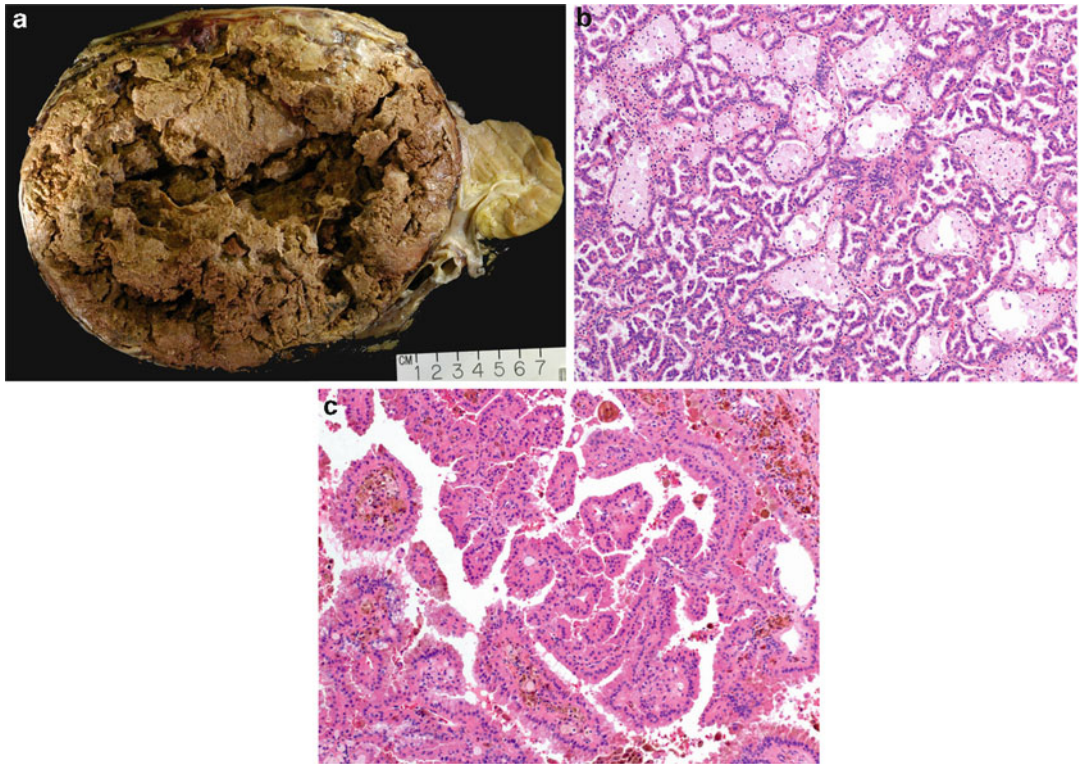

Fig. 2.3 Papillary renal cell carcinoma has a thick tumor capsule and extensive necrosis (**a**). Type I tumors are composed of papillae covered by a single layer of tumor cells with scant cytoplasm and low-grade nuclei. The fibrovascular cores are expanded with foamy histiocytes (**b**). Type II tumor cells have abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli (**c**)

of patients [5]. Most cases arise sporadically, while some familial cases are associated with BHD syndrome [23, 24].

Pathology

ChRCC is typically a solitary, well-circumscribed and nonencapsulated mass with homogenous light brown solid cut surface (Fig. 2.4a). Hemorrhage and/or necrosis are uncommon. A central stellate scar can be seen in large tumors.

Microscopically, the tumor cells are usually arranged in solid sheets with some cases demonstrating areas of tubulocystic architecture. The classic ChRCC tumor consists of large and polygonal cells with finely reticulated cytoplasm due to numerous cytoplasmic microvesicles, and prominent "plant cell like" cell membrane. The nuclei are typically irregular, hyperchromatic and wrinkled with perinuclear haloes (Fig. 2.4b). Not infrequently the tumor consists predominantly of cells with intensely eosinophilic cytoplasm, termed eosinophilic variant [25]. However, there is no substantial difference in the clinical characteristics between the two variants.

Molecular Genetics

ChRCC harbors extensive chromosomal loss, most commonly involving chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 [26]. Occasionally, ChRCC occurs in BHD syndrome, characterized by mutations in Birt–Hogg–Dube gene (*BHD*) on 17p11.2, which encodes the protein folliculin [27]. However, *BHD* mutations are rarely found in sporadic ChRCC. It has been proposed that ChRCC may evolve from oncocytoma after acquiring additional cytogenetic abnormality [28].

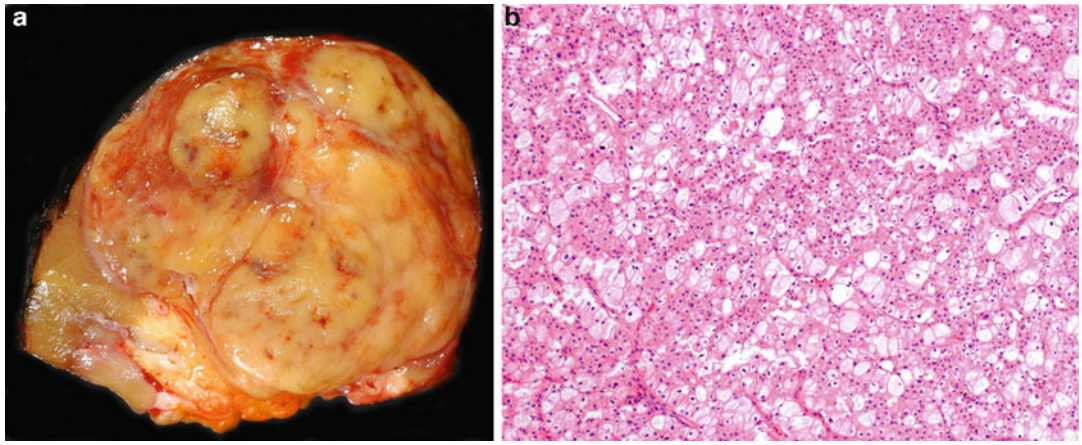

Fig. 2.4 Chromophobe renal cell carcinoma forms a circumscribed, nonencapsulated mass with a homogenous *light brown* cut surface (**a**). The large and polygonal tumor cells have finely reticulated cytoplasm, prominent cell border, and irregular nuclei with perinuclear clearing (**b**)

Other Uncommon Subtypes of Renal Cell Carcinoma

Other subtypes of RCC are uncommon and collectively account for <5% of RCC cases in the kidney. However, they have clinical, pathological, and genetic characteristics distinct from the more common types discussed previously. The clinical, pathological, and genetic features of these uncommon RCC subtypes are summarized in Table 2.2 (Figs. 2.5–2.9).

Renal Cell Carcinoma, Unclassified Type

RCC, unclassified type, is a term for the designation of RCC that does not fit into any of the accepted categories. It is important to understand that this is a diagnostic category rather than a true biological entity. These tumors represent a heterogeneous group of malignancies with poorly defined clinical, morphological, or genetic features and therefore cannot be classified using the current criteria. Most unclassified tumors are poorly differentiated and are associated with a poor prognosis. As our understanding of RCC improves, this category is destined to diminish and perhaps eventually disappear. There are several other entities that were identified very recently and were not included in the 2004 WHO classification. Several of these entities are reviewed in Table 2.3 (Fig. 2.10).

Renal Cell Carcinomas in Inherited Cancer Syndromes

Less than 5% of RCC occur in the setting of inherited cancer syndromes, including von Hippel–Lindau disease (VHLD), HPRCC, hereditary leiomyomatosis and renal cell cancer (HLRCC), and BHD syndrome [6]. Each inherited cancer syndrome predisposes patients to distinct subtypes of RCC which often occur at a young age and have a higher incidence of bilaterality and multifocality [56].

von Hippel–Lindau Disease

VHLD is an autosomal-dominant hereditary condition with stigmata including CCRCCs, central nervous system hemangioblastomas, pheochromocytomas, pancreatic cysts and endolymphatic sac tumors of the inner ear [13]. It is caused by germline mutations in *VHL* gene. VHLD patients are born with a germline defect in one of the alleles. Inactivation of the second allele results in

Table 2.2 Clinical, pathological, and genetic features of uncommon RCC subtypes included in the 2004 WHO classification of RCC

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Multilocular cystic RCC (Fig. 2.5)	Variant of CCRCC (5% of CCRCC) Mean age 51 years (range 20–76) Male:female = 2–3:1	Well-circumscribed, entirely cystic mass; no grossly visible nodules expanding the septa; necrosis is absent	Variably sized cysts lined with one or several layers of flat or plump clear cells; no expansile cellular nodules; low grade nuclei (Fuhrman nuclear grade 1 or 2)	3p deletion as observed in CCRCC	Favorable No local or distant metastasis after complete surgical removal	[29, 30]
Carcinoma of the collecting ducts of Bellini (Fig. 2.6)	<1% of all renal tumors; arising in the collecting ducts of Bellini Often seen in 4th to 7th decade with mean age 55 years Male:female = 2:1	Poorly circumscribed; usually centrally located; cut surface usually gray, white and firm	High-grade tumor cells form complex tubulocystic structures; prominent desmoplastic stroma	Variable results LOH on chromosomes 1q, 6p, 8p,9p, 13q, 19q32 and 21q; *c-erB2* amplification associated with unfavorable outcome	Poor; 1/3 presenting with metastasis 2/3 patients dead of disease within 2 years of diagnosis	[31–34]
Medullary carcinoma (Fig. 2.7)	Exceedingly rare; almost exclusively in patients with sickle cell hemoglobinopathies or traits; majority are African-Americans Mean age 19 years (5–69) Male:female = 2:1	More common in right kidney; poorly circumscribed, centrally located; tan to gray, with varying degrees of hemorrhage and necrosis	High-grade tumor cells with reticular, microcystic or solid pattern Desmoplastic stroma; may have abundant neutrophils	Not well defined	Highly aggressive 95% presenting with metastasis; often dead of disease within 6 months of diagnosis	[35, 36]
Xp11.2 translocation carcinoma (Fig. 2.8)	Predominantly affecting children and young adults; accounts for 40% of RCCs in this age group; occurs post-chemotherapy in some cases male = female also affects adult patients with a striking female predominance	Usually circumscribed; may resemble PRCC	Most distinctive features: papillary structures lined with clear cells (Fig. 2.8a) Confirmatory test: positive nuclear immunostain for TFE3 protein (Fig. 2.8b)	Chromosomal translocation involving *TFE3* gene on Xp11.2 resulting in overexpression of the TFE3 protein; has several Translocation partner genes	Present at advanced stage, but with indolent clinical course in children; Adult patients may pursue more aggressive course	[37–43]
Mucinous tubular spindle cell carcinoma (Fig. 2.9)	Mean age 53 years (range 13–82) Affects predominantly female patients (male:female = 1:4) incidental finding in most cases	Sharply circumscribed; gray–white with myxoid appearance; many have minimal hemorrhage and/or necrosis	Elongated compressed tubules and bland spindle cells embedded in a lightly basophilic myxoid stroma Low-grade nuclei	Not well defined Losses involving chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22 reported; 3p alterations and gain of chromosome 7, and 17 not present	Favorable; majority of patients remain disease free after surgical resection	[44–47]
Post-neuroblastoma renal cell carcinoma	In long-term survivors of neuroblastoma; male = female neuroblastoma diagnosis in the first 2 years of life; mean age of RCC diagnosis 13.5 years (range 2–35)	Same as CCRCC	Limited data; many tumors are typical CCRCC; some tumors have cells with abundant granular cytoplasm and arranged in solid, nests or in papillae	Not well defined Loss of multiple chromosomal loci observed	Similar to other common RCC subtypes	[48, 49]

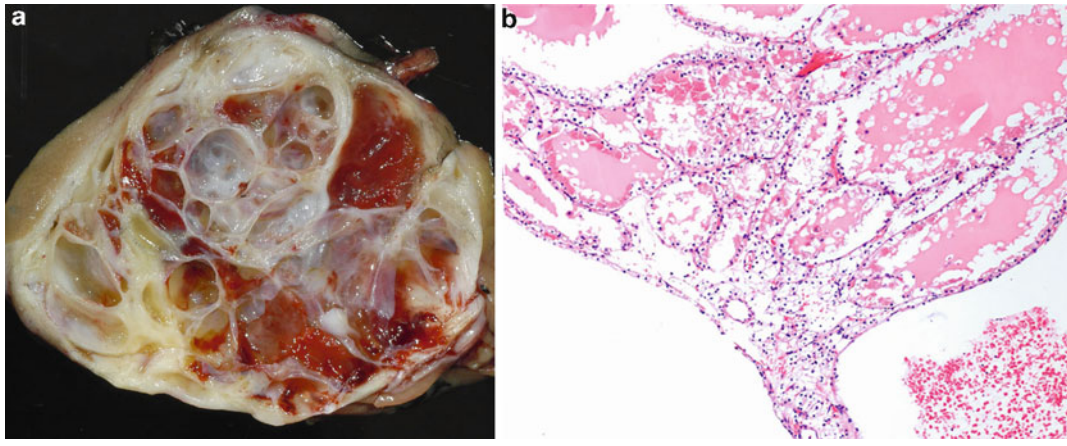

Fig. 2.5 Multilocular cystic renal cell carcinoma is a well-circumscribed entirely cystic mass (**a**). The cystic septa are delicate without solid tumor nodules. The cysts are lined with one or several layers of tumor cells with clear cytoplasm and uniformly small, dense and low grade nuclei (**b**)

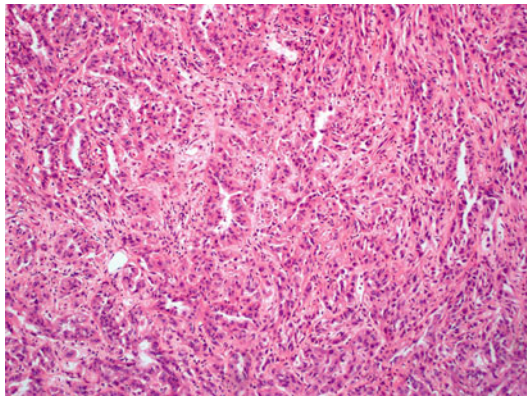

Fig. 2.6 Collecting duct carcinoma consists of high-grade tumor cells forming complex tubules or tubulopapillary structures embedded in a remarkably desmoplastic stroma

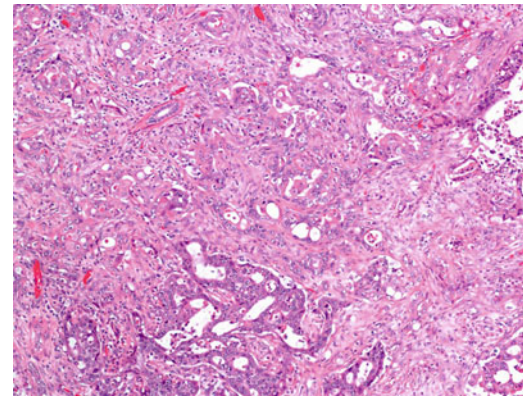

Fig. 2.7 Renal medullary carcinoma comprises high-grade tumor cells arranged in irregular nests with microcystic formation. The stroma is desmoplastic

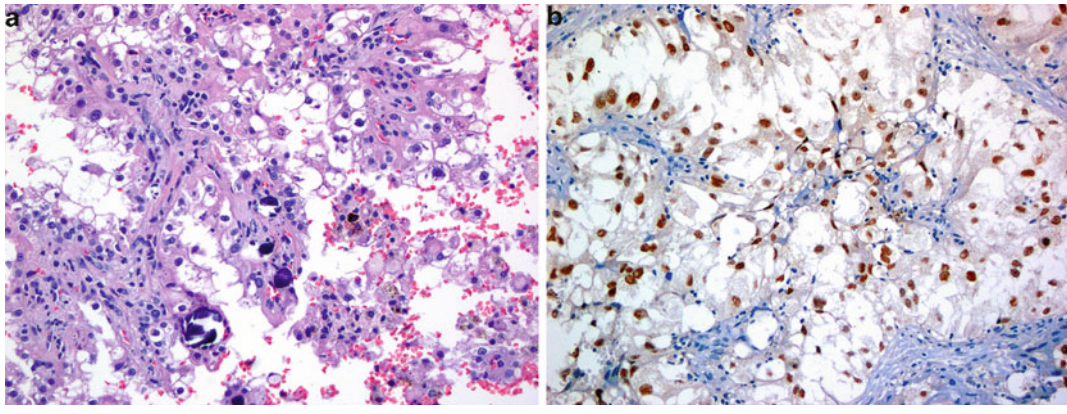

Fig. 2.8 ASPL-TFE3 renal cell carcinoma with *t*(X;17)(p11.2;q25) chromosomal translocation shows nests or pseudopapillary structures lined by cells with abundant clear, sometimes eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Psammomatous calcification is also present (**a**). The tumor cells are positive for nuclear TFE3 protein by immunostaining (**b**)

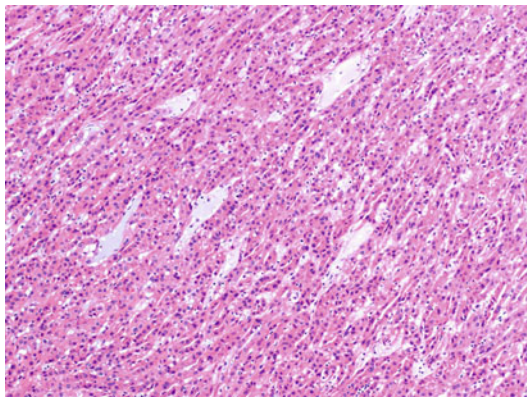

Fig. 2.9 Mucinous tubular and spindle cell carcinoma is composed of elongated cords and collapsed tubules with slit-like spaces embedded in a lightly basophilic myxoid background. The tumor cells have low-grade nuclear features

uncontrolled cell growth and tumor formation. Renal lesions in VHLD are always CCRCC and tend to be bilateral and multifocal. Dozens or even hundreds of microscopic tumor foci can be identified in resected kidney specimens. VHLD-related RCC develops early with a mean age of onset of 37 years as compared to 61 years for sporadic CCRCC. Although metastasis typically only occurs when tumors are greater than 3 cm, RCC is nevertheless the leading cause of death in this syndrome. However, VHLD patients with renal involvement have better 10-year survival than their sporadic counterparts [6].

Hereditary Papillary Renal Cell Carcinoma

HPRCC is an inherited renal cancer characterized by a predisposition to develop multiple bilateral papillary renal tumors of type I histology. To date, kidney is the only organ to be affected in these patients [16]. HPRCC is associated with a germline mutation in the tyrosine kinase domain of the *c-met* proto-oncogene on chromosome 7q31. *c-met* gene encodes a cell surface receptor protein for hepatocyte growth factor (HGF) and has tyrosine kinase activity [57]. Gain-of-function mutations result in activated cellular processes that contribute to carcinogenesis, including angiogenesis, cell motility, proliferation, and morphogenic differentiation. The tyrosine kinase domain of MET is a promising therapeutic target [58].

Hereditary Leiomyomatosis and Renal Cell Cancer

HLRCC is an autosomal-dominant disease and predisposes patients to cutaneous leiomyomas, uterine leiomyomas in women, and PRCC of type II histology. The renal tumors are often solitary, unilateral, and more likely to be aggressive and lethal. Only 20–35% of patients develop RCC. Germline mutations are identified in the fumarate hydratase (*FH*) gene on chromosome 1 (1q42.3–43) [59], which is an essential regulator of the Krebs cycle. Inactivation of *FH* impairs the Krebs cycle, thereby activating anaerobic metabolism and upregulation of HIF and hypoxia-inducible genes.

Birt–Hogg–Dube Syndrome

RCC is also part of the BHD syndrome, an autosomal-dominant disorder characterized by benign skin tumors (fibrofolliculomas, trichodiscomas of hair follicles, and skin tag), renal epithelial neoplasms, lung cysts, and spontaneous pneumothorax [24]. Renal neoplasms are often multifocal and bilateral, the most common being hybrid oncocytic tumors (50%) with features of both ChRCC and oncocytoma [60]. Renal tumors can also include ChRCC (33%), oncocytomas (5%), and occasionally CCRCC or PRCC. *BHD*, the gene implicated in the syndrome, is a potential tumor suppressor gene on 17p11.2 and encodes the protein folliculin.

Common Benign Renal Tumors

Papillary Adenoma

By WHO definition, papillary adenoma constitutes epithelial neoplasms with papillary and/or tubular architecture, <5 mm in size and low-grade nuclei.

Table 2.3 Uncommon subtypes of renal cell carcinoma not included in 2004 WHO classification [4]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Tubulocystic carcinoma	Occurs in 5th and 6th decades (range 30–94 years); male: female = 7:1	Usually solitary; circumscribed and unencapsulated; spongy cut surface resembling "bubble wrap"	Circumscribed collection of tubules and cysts of varied sizes; separated by fibrous stroma; no desmoplastic reaction; the lining cells usually exhibit high-grade nuclei and eosinophilic cytoplasm	Gain in chromosome 7 and 17 in some cases; may be related to PRCC	Not fully established; majority cases are have indolent clinical course; recurrence or metastasis in a few cases	[50–52]
Clear cell tubulopapillary carcinoma	Mean age 60 years; male = female	Small tumor with mean size of 2.4 cm; the majority are cystic and have prominent fibrous capsule and stroma	Branching tubules, acini and/or clear cell ribbons with low-grade nuclei; positive for CK7 and negative for CD10	Limited data; do not exhibit the genetic changes characteristic of CCRCC and PRCC	Low-grade and low-stage tumor; mostly biological indolent tumors	[53]
Thyroid-like follicular carcinoma	Very rare; mean age 45 years	Wide size range; tan colored	Prominent pseudocapsule; micro- and macrofollicles lined with low-grade cells; colloid-like material present in >50% of follicles; negative for TTF-1 and thyroglobulin	Limited data	Not well defined; available cases are free of disease after surgical resection	[54]
Acquired cystic kidney disease (ACKD)-associated RCC (Fig. 2.10)	2–7% incidence in ACKD patients; occur in relatively young patients; male predominance	Frequently multicentric and bilateral; generally well circumscribed	About 40% are classic CCRCC, PRCC or ChRCC; various architectures; 80% of tumor cells show abundant intratumoral calcium oxalate crystals	Limited data; gains in chromosomes 1, 2, 6, and 10	Less aggressive than sporadic RCC	[55]

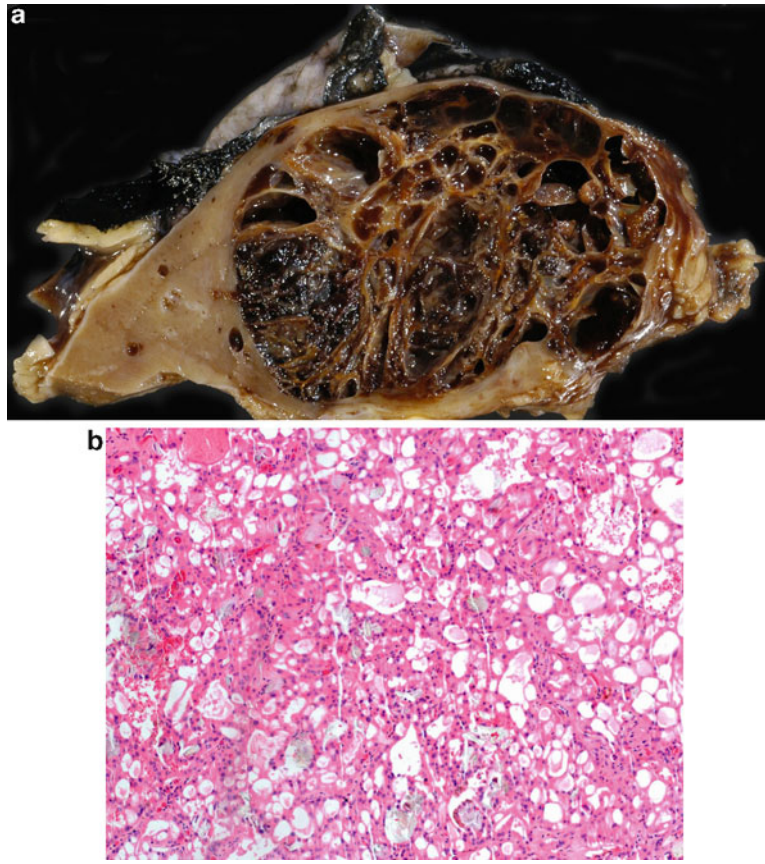

Fig. 2.10 Acquired cystic disease-associated renal cell carcinoma forms a well-circumscribed mass with cysts and solid nodules (**a**). The non-neoplastic kidney is atrophic with several cysts. The tumor exhibits tubulocystic architectures and contains calcium oxalate crystals (**b**)

Clinical Features

Adenoma is the most common renal cell neoplasm, frequently presenting as incidental findings after nephrectomy or at autopsy. In one autopsy study, papillary adenomas were found in up to 40% of patients older than 70 years of age. Its incidence increases with age and also in patients on long-term dialysis.

Pathology

Papillary adenomas appear as small (<5 mm), well circumscribed, yellow or white nodules in the renal cortex. They have papillary, tubular, or tubulopapillary architecture, similar to PRCC [61]. The tumor cells have uniform small nuclei and inconspicuous nucleoli equivalent to Fuhrman grade 1 or 2 nuclei (Fig. 2.11).

Molecular Genetics

Papillary adenomas share many genetic alterations with PRCC; both have combined gains of chromosomes 7 and 17 and loss of the Y chromosome in men. PRCCs acquire additional genetic alterations, including trisomy 12, 16, or 20. The cytogenetic findings support the hypothesis that papillary adenoma is a precursor of PRCC [62].

Renal Oncocytoma

Clinical Features

Renal oncocytoma accounts for 5% of surgically resected nonurothelial renal neoplasms. Patients vary greatly in age with a peak incidence in the seventh decade of life. The male-to-female ratio

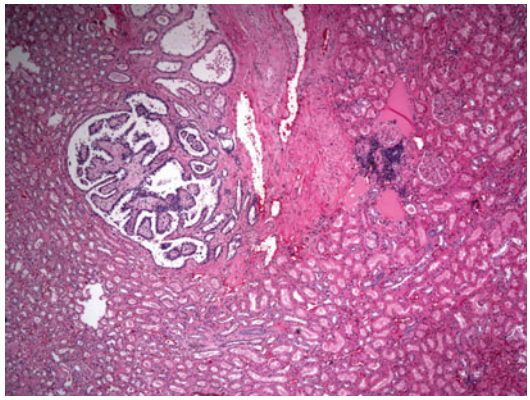

Fig. 2.11 Papillary adenoma comprises collection of papillae that are lined with cells with uniform small nuclei and inconspicuous nucleoli. The tumor size is less than 5 mm

is 1.7:1. Most cases are sporadic, although familial cases have been reported in association with BHD syndrome and familial renal oncocytoma syndrome.

Pathology

Oncocytoma is typically solitary, well circumscribed and has varying degrees of encapsulation (Fig. 2.12a). The cut surface exhibits a characteristic homogeneous mahogany-brown color. A central stellate scar can be seen in one-third of the cases, more commonly in larger tumors. More than 10% of cases have multifocal or bilateral lesions.

Microscopically, oncocytoma is characterized by bright eosinophilic cells, termed oncocytes, arranged in nested, acinar or microcystic pattern associated with a loose hypocellular and hyalinized stroma (Fig. 2.12b). Extension of oncocytoma into the perinephric fat, or rarely into vascular space, can be found sometimes and does not adversely affect the benign prognosis of the lesion.

Molecular Genetics

Most oncocytomas are composed of a mixed population of cells with normal and abnormal karyotypes [63]. Combined loss of chromosomes 1 and X/Y is the most frequent chromosome abnormality. Translocations involving chromosome 11, with a breakpoint at 11q12-13, have also been reported. Other rare chromosome rearrangements have been reported, such as t(1;12)(p36;q13), loss of chromosome 14 and gain of chromosome 12 [64]. Oncocytoma can be a manifestation of BHD syndrome.

Whether oncocytoma and ChRCC are related is still controversial. They not only have overlapping morphological features but also share some cytogenetic changes, such as the loss of heterozygosity at chromosome 1 [65]. However, monosomy of chromosomes 2, 10, 13, 17, and 21 occurred exclusively in ChRCC [66].

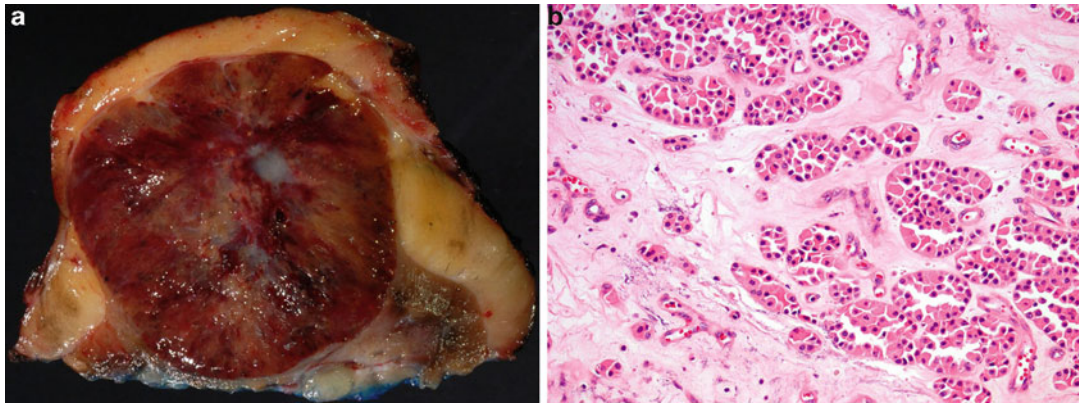

Fig. 2.12 Renal oncocytoma forms a solitary, well-circumscribed, nonencapsulated mass with homogeneous *dark-brown* cut surface (**a**). It consists of bright eosinophilic cells nested in a loose stroma. The tumor cells are uniform, round to polygonal with granular eosinophilic cytoplasm and regular round nuclei (**b**)

Pathological Prognosis Parameters for Renal Cell Carcinoma

Fuhrman Nuclear Grading

Currently, the four-tiered Fuhrman grading scheme, first described in 1982, remains the most commonly used grading system for RCC [67]. Fuhrman grade, based on the nuclear size and shape, chromatin and nucleolar prominence, is categorized into G1–4 (Table 2.4) (Fig. 2.13). Most studies have confirmed that Fuhrman nuclear grade is an independent prognostic predictor for CCRCC [68]. Simplified two-tiered (G1–2 vs. G3–4) or three-tiered (G1–2 vs. G3 vs. G4) Fuhrman systems have been proposed to improve interobserver agreement and still preserve its prognostic significance [69]. Grade 1 and grade 2 may be grouped together as low grade since the two are not prognostically different in multivariate analysis. However, studies have shown that grade 3 and grade 4 tumors should not be grouped together as grade 3 tumors have better 5-year cancer-specific survival than grade 4 tumors (45–65% in grade 3 cancers vs. 25–40% in grade 4 cancers). A recent study showed that the three-tiered Fuhrman grading system is an appropriate option for the prognostication of CCRCC in both univariate analysis and multivariate model setting [70]. The use of a simplified Fuhrman nuclear grading system in clinical practice requires further clarification and preferably a consensus between pathologists and urologists.

The prognostic value of Fuhrman grading for nonclear cell RCC, however, remains controversial. For PRCC, it is significantly associated with survival in univariate analysis but this significance is lost in multivariate models. One recent study demonstrated that only nucleolar prominence is significantly associated with survival in both univariate and multivariate analyses [71]. Another study showed that Fuhrman grade, not the nucleolar grade, is an independent prognostic factor and should be used as the standard grading system for PRCC [72]. Only a few studies addressed the prognostic significance of Fuhrman grading system for ChRCC using univariate analysis. A recent study found that Fuhrman grading does not correlate with survival, therefore is not appropriate for ChRCC [73]. A new grading system was recently proposed for ChRCC based on the assessment of geographic nuclear crowding and anaplasia. This grading scheme was shown to be an independent predictor of clinical outcomes for ChRCC [74].

Sarcomatoid and Rhabdoid Differentiation

Sarcomatoid differentiation is present in about 5% of RCCs and can be observed in any RCC subtype [75]. Therefore, sarcomatoid RCC is not considered a distinct subtype of RCC by 2004 WHO classification; rather, it is thought to represent a high-grade and poorly differentiated component.

RCC with sarcomatoid differentiation typically has other adverse pathological features, including large tumor size, extension into perinephric fat and vessels, and presence of hemorrhage and necrosis. It is also significantly associated with an increased likelihood of distant metastasis and cancer-specific death. It is an adverse independent prognostic indicator in both univariate and multivariate analyses [76]. Any

Table 2.4 Fuhrman nuclear grading system [67]

Grade	Nuclear size	Nuclear shape	Chromatin	Nucleoli
1	<10 μm	Round	Dense	Inconspicuous
2	15 μm	Round	Finely granular	Small, not visible at 10× magnification
3	20 μm	Round/oval	Coarsely granular	Prominent, visible at 10× magnification
4	>20 μm	Pleomorphic, multilobated	Open, hyperchromatic	Macronucleoli

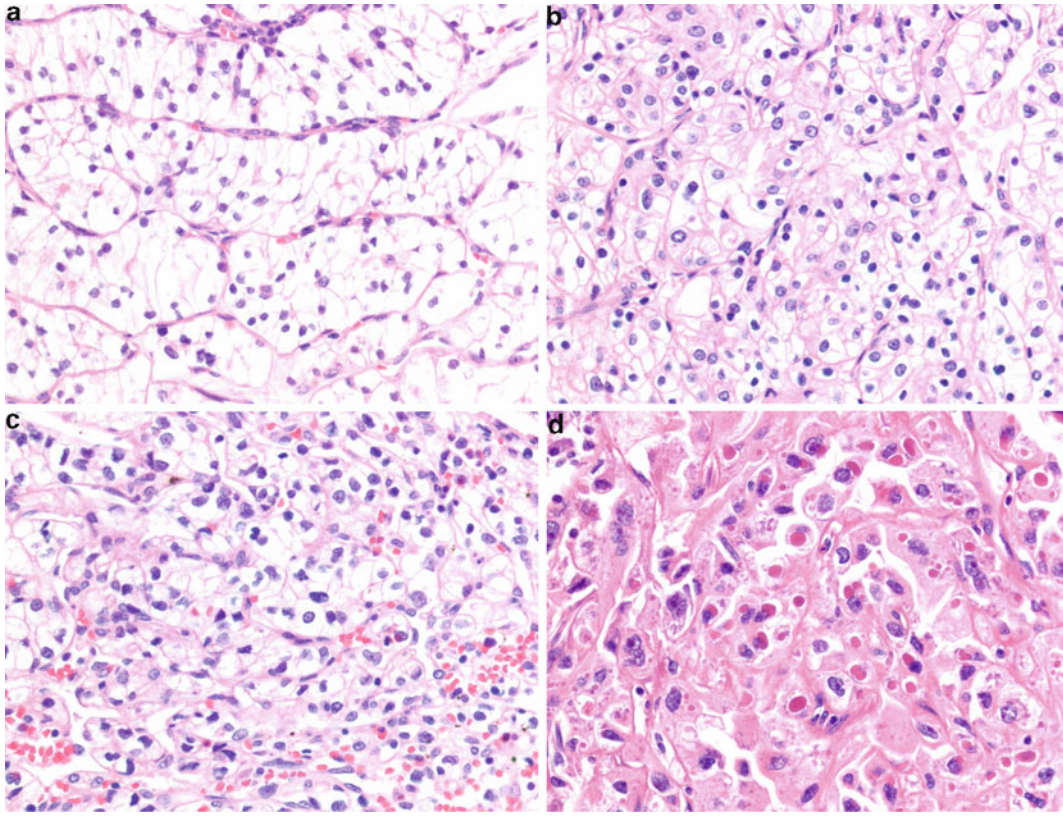

Fig. 2.13 Fuhrman grading system is based on the nuclear size, irregularity of the nuclear membrane and nucleolar prominence. Grade I RCC has uniformly small and dense nuclei (**a**). Grade 2 nuclei have smooth open chromatin but inconspicuous nucleoli (**b**). In grade 3 RCC, nuclei have open chromatin and prominent nucleoli visible at low magnification (**c**). Grade 4 nuclei are markedly pleomorphic, hyperchromatic with single or multiple macronucleoli (**d**)

RCC with sarcomatoid differentiation is assigned a Fuhrman grade 4.

Sarcomatoid components usually appear as bulging, lobulated areas with white to gray, firm and fibrous cut surface within a tumor (Fig. 2.14). Histologically, the sarcomatoid component ranges from malignant spindle cells to those resembling leiomyosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and other sarcomas. The coexisting RCC component, including clear cell, papillary, chromophobe RCC and sometimes collecting duct RCC, can often to be identified and is used to subtype the RCC with sarcomatoid differentiation. However, such subtyping may not be possible if the sarcomatoid component overruns RCC epithelial components, a rare occurrence.

Rhabdoid differentiation can be identified in approximately 5% of RCCs with tumor cells having large eccentric nuclei, macronucleoli and prominent acidophilic globular cytoplasm (Fig. 2.15). The presence of rhabdoid component is also associated with high grade and high stage with frequent extrarenal extension. The rhabdoid foci may account for 5–90% of the tumor area. It is a marker of high risk for metastasis and poor prognosis even when the rhabdoid component is limited [77].

Tumor Necrosis

For CCRCC, tumor necrosis, identified either macroscopically or microscopically, is an adverse

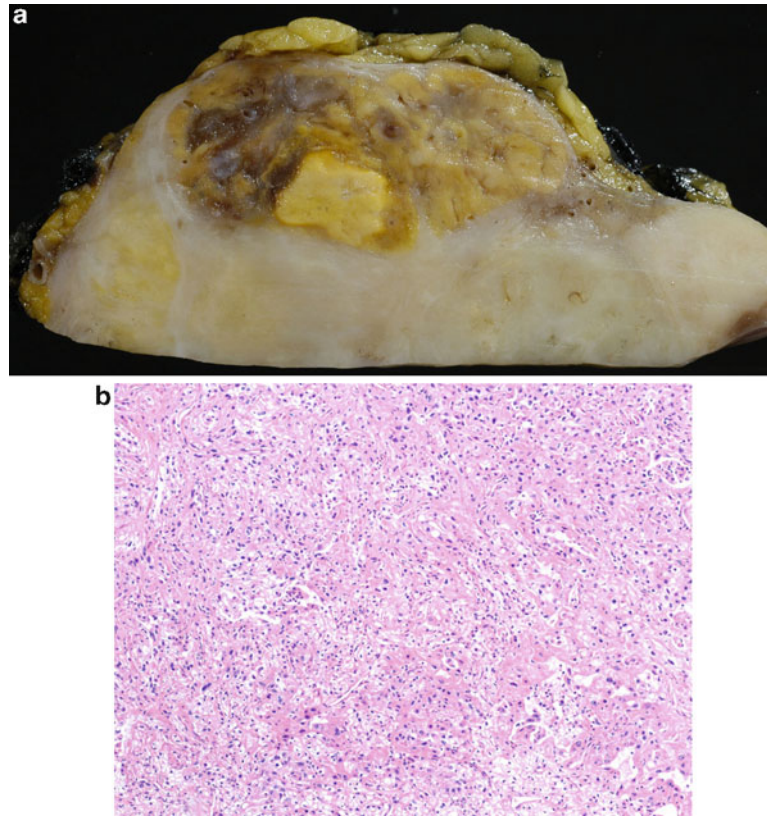

Fig. 2.14 Renal cell carcinoma with sarcomatoid differentiation. The *upper portion* of this renal tumor is *golden yellow*, characteristic of clear cell RCC. The *lower portion* has a fleshy appearance, suggestive of sarcomatoid differentiation (**a**). Microscopically the sarcomatoid component shows the malignant spindle cells (**b**)

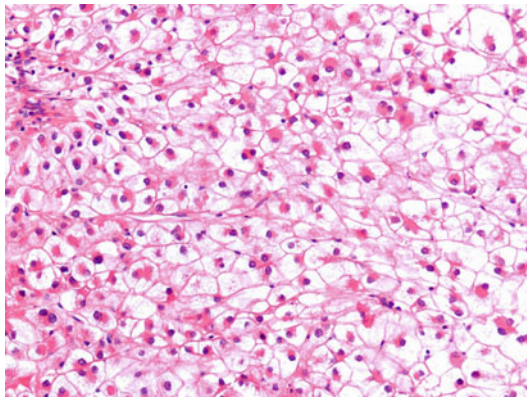

Fig. 2.15 Renal cell carcinoma with so-called "rhabdoid" morphology contains large eccentric nuclei, macronucleoli and prominent acidophilic globular cytoplasm

pathological factor and is associated with worse clinical outcomes in both uni- and multivariate analyses. Studies from Mayo Clinic clearly showed that histological necrosis is associated with twice the cancer-specific death rate compared to those without necrosis [5]. The presence and extent of histological necrosis in CCRCC are independent predictors of survival in localized but not metastatic cases, although one recent study showed limited prognostic value [78]. Two outcome prediction models, SSIGN from Mayo Clinic, and the postoperative outcome nomogram from MSKCC, both incorporate tumor necrosis in their models [79, 80]. A few recent studies also reported that the proportional extent of necrosis

correlated with a worse cancer-specific death [81, 82]. The data on the prognostic role of tumor necrosis in nonclear cell RCC is limited.

Microvascular Invasion

Microvascular invasion (MVI), defined as neoplastic cells invading the vessel wall or neoplastic emboli in the intratumoral vessel detected microscopically, is present in 13.6–44.6% of RCC. It is more common in RCC of high stage and grade, and large size. An important prognostic factor in various malignancies including liver, testis, bladder and upper tract urothelial carcinoma, its prognostic role in RCC is controversial. Several studies have demonstrated that MVI may have an independent predictive role for either disease recurrence or cancer-specific mortality after adjusting for other clinical and pathologic covariates [83, 84]. Further studies are needed to better define its prognostic significance.

Summary

RCC encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as distinct prognosis and therapeutic responses. The current classification is based primarily on morphology but genetic features of renal tumors have been increasingly incorporated into the classification scheme. Many histological parameters obtained from routine pathological examination of renal tumor provide invaluable prognostic values. The clinical, pathological, and genetic features in combination will eventually enable urologists to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized management and treatment options.

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