Chapter 2
Pathology of Renal Tumors

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Introduction

In this chapter we provide a brief overview of renal cortical neoplasms, including benign and malignant tumors. In the last several years, the International Society of Urological Pathology (ISUP) and the World Health Organization (WHO) have standardized the nomenclature and categorization of renal tumors (Table 2.1). In addition, the original classification of renal tumors has been revised to add several newly recognized morphologically and immunophenotypically distinct entities. Standardized reporting of histologic findings is performed according to the College of American Pathologists (CAP) Cancer Protocol Templates [1]. Renal cell carcinoma (RCC) is staged using the 8th edition of the American Joint Committee on Cancer Staging Manual [2].

Malignant Renal Tumors

Clear Cell (Conventional) Renal Cell Carcinoma

Clear cell RCC is the most common malignant renal tumor, accounting for approximately 70% of all renal cancers [3–5]. Although most of these tumors occur sporadically, some cases are hereditary [6]. The majority of clear cell RCCs are

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Table 2.1 World Health Organization (WHO) 2016 classification of kidney tumors

Renal cell tumors
Previously established tumors
Clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
Mucinous tubular and spindle cell carcinoma
Unclassified renal cell carcinoma
Papillary adenoma
Oncocytoma
Newly accepted tumors
Multilocular cystic renal neoplasm of low malignant potential
Hybrid oncocytic/chromophobe tumor
MiT family translocation renal cell carcinomas
Xp11 translocation renal cell carcinoma
t(6;11) renal cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Succinate dehydrogenase-deficient renal cell carcinoma
Clear cell papillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
Metanephric tumors
Metanephric adenoma
Metanephric adenofibroma
Metanephric stromal tumor
Nephroblastic tumors
Nephrogenic rests
Nephroblastoma
Cystic partially differentiated nephroblastoma
Pediatric cystic nephroma
Mesenchymal tumors
Pediatric
Clear cell sarcoma
Rhabdoid tumor
Congenital mesoblastic nephroma
Ossifying renal tumor of infancy
Adult
Leiomyosarcoma
Angiosarcoma
Rhabdomyosarcoma
Osteosarcoma
Synovial sarcoma
Ewing sarcoma

Angiomyolipoma
Epithelioid angiomyolipoma
Leiomyoma
Hemangioma
Lymphangioma
Juxtaglomerular cell tumor
Renomedullary interstitial cell tumor
Schwannoma
Solitary fibrous tumor
Mixed mesenchymal and epithelial tumors
Adult cystic nephroma/mixed epithelial stromal tumor
Neuroendocrine tumors
Well-differentiated neuroendocrine tumor
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Paraganglioma
Renal hematopoietic neoplasms
Lymphoma
Leukemia
Plasmacytoma
Germ cell tumors
Teratoma
Choriocarcinoma
Mixed germ cell tumors
Metastatic tumors

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discovered incidentally on imaging [7, 8]. However, larger tumors may be symptomatic, causing flank pain and hematuria [7, 8]. Metastatic spread is typically via a hematogenous route, with a general predilection for the renal sinus veins, renal vein, and vena cava [9, 10]. The 5-year survival ranges from 43% to 89%, depending on the stage at presentation [11, 12]. Clear cell RCCs can have a large variability in size and typically occur as a solitary mass. Multifocal or bilateral disease presents in less than 5% of cases and can be associated with hereditary syndromes [13].

Clear cell RCC has a golden-yellow appearance due to the abundance of lipids within the cells. These tumors generally form a well-circumscribed mass with a pseudocapsule (Fig. 2.1). Areas of necrosis, hemorrhage, and/or cystic change are not uncommon. Clear cell RCC arises within the renal cortex and often has a pushing border. Sometimes gross involvement of the renal sinus or renal vein is apparent. Microscopic examination shows diverse morphology. Tumor cells can appear in sheets, alveolar or acinar patterns (Fig. 2.2). Clear cell RCC has a characteristic network of thin vessels which creates a “lace-like” pattern. As the name suggests, tumor cells have clear cytoplasm due to the presence of lipids and glycogen that are dissolved during tissue processing. Higher-grade tumors may have more eosino-

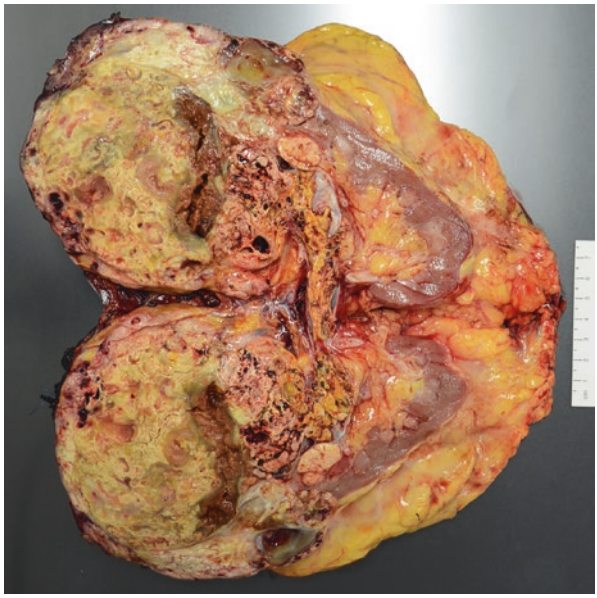

Fig. 2.1 Gross image of a large clear cell renal cell carcinoma with extension of tumor into the perinephric fat

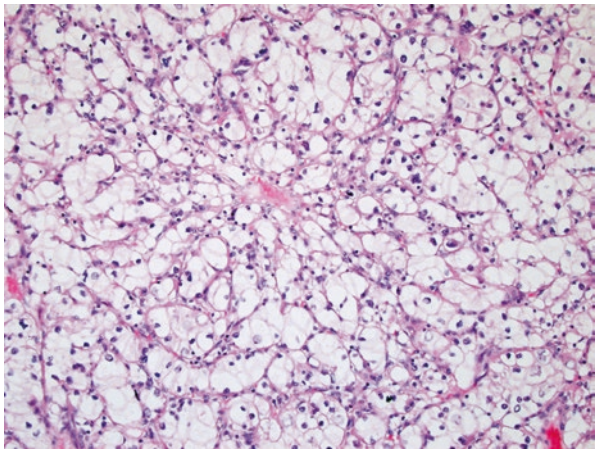

Fig. 2.2 H&E, high magnification, clear cell renal cell carcinoma

philic cytoplasm. Nucleoli range from absent to strikingly prominent, which determines the grade of the tumor per the ISUP nucleolar grading system [5]. Sarcomatoid or rhabdoid features may be present, which conveys a poor prognosis.

The majority of clear cell RCCs demonstrate mutations involving the tumor suppressor gene von Hippel-Lindau (*VHL*) on the short arm of chromosome 3 (3p25-26) [14]. This mutation can arise in both sporadic clear cell RCC as well as in patients with the VHL syndrome [6]. The *VHL* gene produces a protein that interacts with an E3 ubiquitin ligase complex, which targets hypoxia-inducible factors (HIFs) for polyubiquitination and proteasomal degradation. HIFs are transcription factors that

activate genes such as vascular endothelial growth factor (*VEGF*), a promoter of angiogenesis. The absence of functional VHL allows HIFs to escape degradation and thereby contribute to tumorigenesis. Promoter region methylation is a common mechanism by which the *VHL* gene is silenced [14]. Allelic losses on chromosome 14q, loss of 4p, and loss of 9p have been associated with a poor prognosis [14]. In addition, genes involved in chromatin remodeling such as *PBRM1*, *SETD2*, and *BAP1* have been shown to predict survival [14]. The tumor's immunophenotype shows nuclear expression for PAX8, which is seen in nearly all renal epithelial tumors [15–17]. CAIX, vimentin, CD10, and pan-cytokeratin will also be positive in the majority of cases [16, 17].

Papillary Renal Cell Carcinoma

Papillary RCC is the second most common malignant renal tumor, comprising approximately 15% of RCCs in adults [3, 4, 13]. The 5-year survival of papillary RCC is generally considered better than clear cell RCC, ranging from 57% to 85% [11, 12]. Multifocality is more common in papillary RCC compared to clear cell RCC [13]. The majority of papillary RCCs occur sporadically; however, these tumors can be seen in some hereditary syndromes, such as familial papillary RCC syndrome [6, 13]. Papillary RCC has several known predisposing factors including end-stage renal disease with scarring and acquired cystic kidney disease [18].

Papillary RCC usually appears well-circumscribed and friable on gross examination. These tumors range in color from tan to brown and may show areas of hemorrhage, necrosis, or cysts. Microscopically, papillary RCC is composed of numerous fibrovascular cores lined by malignant cells. Foamy macrophages and psammomatous calcifications may be present. Spontaneous hemorrhage has been reported as a presenting feature in 8% of cases [3, 4]. In some cases with previous hemorrhage, hemosiderin can be found entrapped within the cytoplasm of tumor cells, which can be a helpful feature distinguishing these tumors on needle biopsy. The ISUP nucleolar grading system has been validated for papillary RCC [19].

Classically, papillary RCC has been divided into two categories (type 1 and type 2) based on specific morphologic features [18, 20]. Type 1 papillary RCC is defined by fibrovascular cores lined by a single layer of nuclei with scant cytoplasm (Fig. 2.3). These tumors tend to have a more basophilic appearance at low power due to the high nuclear/cytoplasmic (N:C) ratio. Type 2 papillary RCC is defined by fibrovascular cores lined by more than one cell layer with pseudostratified nuclei and abundant eosinophilic cytoplasm (Fig. 2.4). Due to the lower N:C ratio, these tumors tend to look more eosinophilic at low power. Type 2 RCC tends to be of higher grade than the type 1 tumors. It was thought in the past that type 1 papillary RCC had a better prognosis compared to type 2 tumors. However, this concept has been challenged in recent studies [21, 22]. In addition, several new molecularly distinct tumors with papillary features have been recognized since the original subtype classification of papillary RCCs [3, 4]. Assigning a particular subtype can also be challenging to

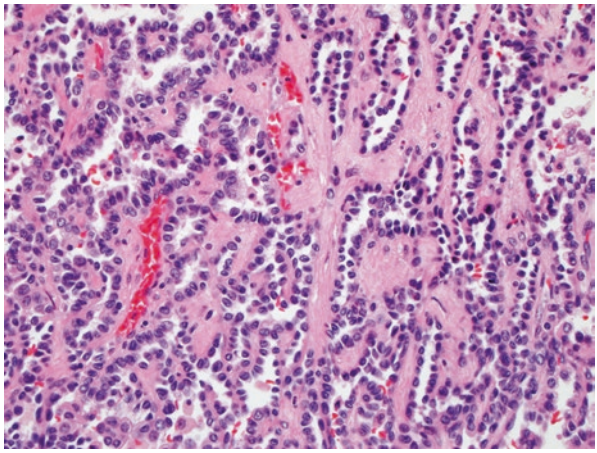

Fig. 2.3 H&E, high magnification, papillary renal cell carcinoma, type 1

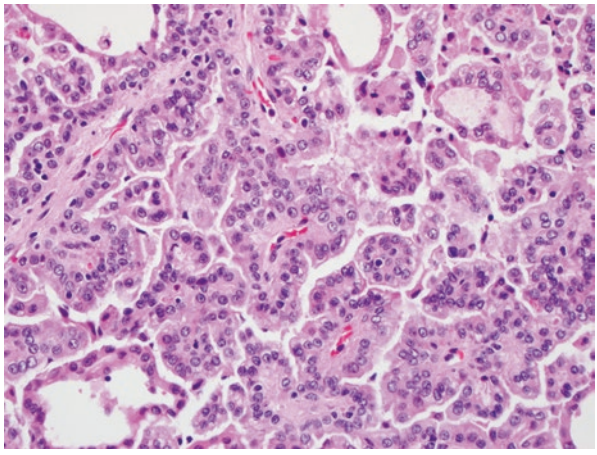

Fig. 2.4 H&E, high magnification, papillary renal cell carcinoma, type 2

pathologists in that many tumors have features of both type 1 and type 2 morphologies. A recent analysis showed distinct molecular differences between type 1 and type 2 tumors; however, type 2 tumors were discovered to be heterogeneous [23]. This raises the question of whether there truly is a distinct type 2 tumor. As such, subtyping papillary RCC remains controversial. Regardless of subtype, it is recommended that papillary RCC be given an ISUP nucleolar grade [3–5]. Oncocytic papillary RCC should no longer be identified as a specific subtype.

Several mutations have been associated with papillary RCC including MET, SETD2, NF2, and BAP1 [23–25]. Gains of chromosomes 7 and 17 are common, especially in type 1 tumors [24, 25]. Type 2 tumors frequently have loss of chromosome 9p and alterations in CDKN2A [25]. Loss of the Y chromosome has also been frequently reported in papillary RCC [14]. Immunohistochemistry will typically show positivity in tumor cells for CK7, AE1/AE3, CAM5.2, EMA, AMACR, vimentin, and CD10 [15, 17].

Chromophobe Renal Cell Carcinoma

Chromophobe RCC accounts for approximately 5% of all cases of RCC [3, 26–28]. Chromophobe RCC has a better prognosis than both clear cell RCC and papillary RCC. The 5-year cancer-specific survival has been reported from 78% to 100% [26–28]. Poor prognostic features include high pathologic stage, sarcomatoid features, lymphovascular invasion, and necrosis [28]. Chromophobe RCC should not be graded, as the innate nuclear atypia does not portend to a worse prognosis. Patients with Birt-Hogg-Dubé syndrome have high incidence of chromophobe RCC as well as hybrid oncocytic/chromophobe tumors (HOCTs) [29]. Birt-Hogg-Dubé syndrome is associated with mutations in the folliculin (*FLCN*) gene and is inherited in an autosomal dominant manner. This syndrome is also associated with fibrofolliculomas, pulmonary cysts, and spontaneous pneumothorax.

Chromophobe RCCs are well-circumscribed, unencapsulated tumors that are classically tan-brown and homogenous. Chromophobe RCCs tend to be large at presentation, with one study reporting an average size of 8 cm [26]. Tumor cells grow in solid sheets with variable oncocytic cytoplasm and classic perinuclear halos (Fig. 2.5). Cells have thick plant-like cell membranes, irregular "raisinoid" nuclei, and binucleation, which create a resemblance to koilocytes. Chromophobe RCCs show strong, diffuse positivity for CK7 and diffuse cytoplasmic staining for Hale colloidal iron, which can help distinguish them from oncocytomas [15, 30]. The genetic profile of chromophobe RCC is variable. Studies have reported losses of chromosomes Y, 1, 2, 6, 10, 13, 17, and 21. Mutations of TP53 and *PTEN* and rearrangements in the *TERT* promoter region have also been identified [31].

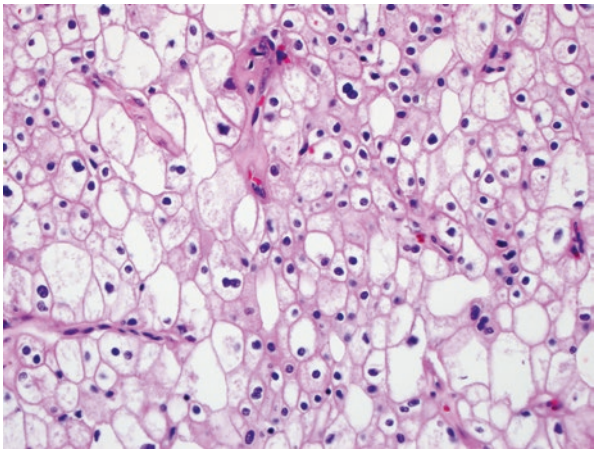

Fig. 2.5 H&E, high magnification, chromophobe renal cell carcinoma

Clear Cell Papillary Renal Cell Carcinoma

Clear cell papillary RCC is a low-grade renal tumor recently recognized by the World Health Organization [4, 32–40]. Previously this tumor was mistaken for conventional clear cell RCC and is more common than once thought, with two studies finding it to be the fourth most common variant of RCC [38, 40]. Although clear cell papillary RCC has an indolent biologic behavior, some cases occur with other synchronous malignant RCCs [32–35]. Clear cell papillary RCC is found in association with end-stage renal disease, and one study showed an association with African American race [37, 38].

Most tumors are small, encapsulated, and variably solid and cystic. Almost all cases are organ confined at presentation. As its name suggests, clear cell papillary RCC contains cells with clear cytoplasm as well as papillary and tubular structures. Clear cell papillary RCC has low-grade nuclei that show reverse polarity, with nuclei arranged in a linear fashion at the luminal surface (Fig. 2.6).

Tumor cells will show strong diffuse staining for PAX8 and CK7 and lack of staining for AMACR [41]. CAIX shows diffuse positivity with an absence of membranous staining along the luminal surface of cells, creating a "cup-shaped" appearance [36]. *VHL* gene mutations and trisomy of chromosomes 7 and 17 are not seen in clear cell papillary RCC [39].

Hybrid Oncocytic/Chromophobe Tumor

HOCTs are indolent renal tumors that have features of both chromophobe RCC and benign oncocytomas [29, 42–45]. It is thought that HOCTs are a distinct entity, rather than a malignant progression of oncocytoma to chromophobe RCC [42, 43, 45]. These tumors are seen in adult patients and can arise sporadically or be seen in

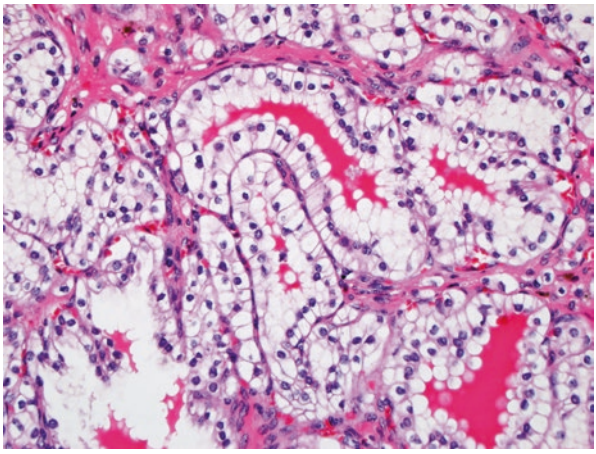

Fig. 2.6 H&E, high magnification, clear cell papillary renal cell carcinoma

association with oncocytosis (Fig. 2.7) or in patients with Birt-Hogg-Dubé syndrome. Sporadic HOCTs tend to be solitary, while those associated with Birt-Hogg-Dubé syndrome and oncocytosis are often multifocal and bilateral. Most of these tumors present at a low pathologic stage and have an indolent behavior [45].

Sporadic HOCTs form well-circumscribed, tan-brown masses that may have a central scar, similar to oncocytomas. Tumor cells have overlapping histologic features seen in oncocytoma and chromophobe RCC. The cells have mild cytologic atypia and abundant eosinophilic cytoplasm. Binucleate cells and perinuclear cytoplasmic clearing are common; however raisinoid nuclei are absent. Tumor cells grow in sheets with occasional small tubules. HOCTs associated with Birt-Hogg-Dubé syndrome will have areas of classic chromophobe RCC and oncocytoma within the same tumor. Chromophobe cells with wrinkled nuclei and perinuclear halos can be found within the fibromyxoid background typically associated with oncocytomas (Fig. 2.8). HOCTs will be positive for CK7 and CD117 [42, 43]. Sporadic HOCTs have been found to have abnormalities of chromosomes 1, 2, 6, 9,

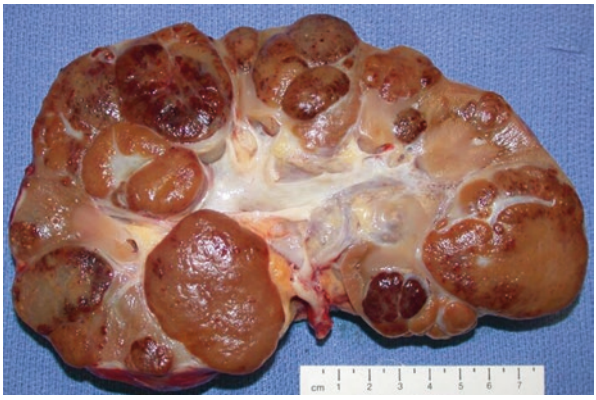

Fig. 2.7 Gross image of a kidney with oncocytosis showing numerous mahogany brown nodules

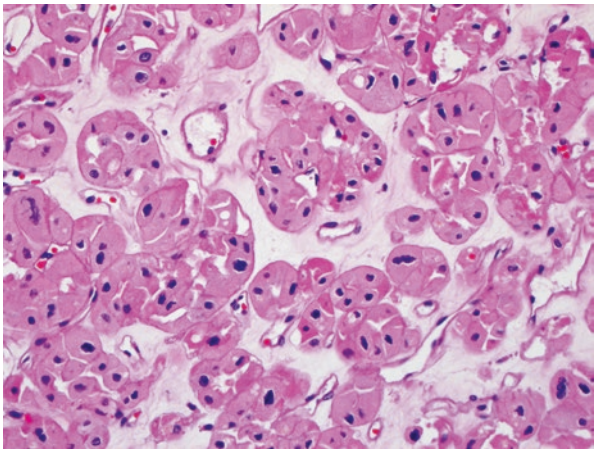

Fig. 2.8 H&E, high magnification, hybrid oncocytic/chromophobe tumor

10, 13, 17, 20, 21, and 22 [43, 46]. Monosomy of chromosome 20 is the most common mutation, which is a rare finding in oncocytoma and chromophobe RCC [3]. Oncocytosis-associated HOCTs and those associated with Birt-Hogg-Dubé syndrome have a non-specific genetic phenotype.

Collecting Duct Carcinoma

Collecting duct carcinoma (CDC) is a rare, aggressive, malignant renal tumor [47–49]. Most patients with CDC are symptomatic and present with high stage and metastatic disease [49]. These tumors have a poor response to chemotherapy and immunotherapy [49].

CDC arises from the medulla and appears as a firm, gray-white mass. Hemorrhage and necrosis are a common finding. Unlike conventional RCC, which is typically well-circumscribed, CDCs have an irregular infiltrative border. Criteria for the diagnosis of CDC includes at least some involvement of the medulla, predominance of tubule formation, a desmoplastic stromal reaction, and exclusion of other RCC subtypes as well as urothelial carcinoma [3]. CDCs should have significant cytologic atypia and a high mitotic rate with atypical mitotic figures. Lymphovascular and renal sinus invasion are common. CDCs have a morphologic overlap with renal medullary carcinoma, urothelial carcinoma, and metastatic carcinomas to the kidney.

Immunohistochemistry can be useful in confirming the diagnosis of CDC. Tumor cells should be positive for PAX8 and negative for GATA3 and p63 and show loss of INI1 [47, 48]. CDCs have a variable genetic profile. DNA losses and loss of heterozygosity have been reported on multiple chromosomes [50]. In addition, studies have shown amplifications of *HER2/neu* and mutations involving *INI1* [50, 51].

Renal Medullary Carcinoma

Renal medullary carcinoma (RMC) is an aggressive malignant renal tumor that is associated with sickle cell trait [41, 52–54]. Most patients present with metastatic disease and the prognosis is exceptionally poor [41, 52–54]. It is thought that RMC occurs in the medulla where the microenvironment is particularly susceptible to sickling of red blood cells and ischemic damage. Chronic reparative changes promote carcinogenesis, particularly via *HIF-1α*, TP53, and *VEGF* mutations [54].

RMC forms a poorly circumscribed mass centered in the renal medulla. Tumors are usually gray-white and firm. Areas of necrosis are common. Tumor cells form tubules and glands that are high-grade with marked cytologic atypia (Fig. 2.9). Tumor cells often produce mucin. The background shows a pronounced myxoid, desmoplastic reaction, and inflammation that is often predominated by neutrophils.

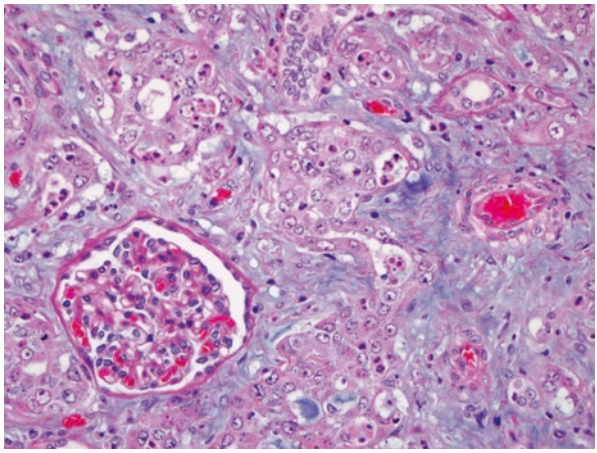

Fig. 2.9 H&E, high magnification, renal medullary carcinoma

Tumor cells show positivity for PAX8, CK7, and CAM5.2 and loss of INI1 [54]. The tumor's genetic profile involves mutations in genes involved in the hypoxia-induced signaling pathways, including *HIF-1α* [54]. Loss of heterozygosity involving *INI1* has also been reported [54].

MiT Family Translocation Renal Cell Carcinomas

The MiT group of transcription factors include, among others, TFE3 and TFEB. RCCs with either a *TFE3* or *TFEB* gene aberrations are collectively known as the MiT family translocation renal cell carcinomas [55–59]. Among this group of RCCs, those with *TFE3* (located at the Xp11.2 locus) alterations are the most common [59]. The *ASPSCR1* (*ASPL*) and *PRCC* genes are the most common fusion partners with *TFE3*, resulting in either the t(X;17)(p11;q25) or the t(X;1)(p11;q21) translocation, respectively [57]. The second, less common, group within the MiT family translocation RCCs are those that show fusions of the *TFEB* gene, located at chromosome 6p21, with the *MALAT1* gene on chromosome 11q12, forming a t(6:11)(p21;q12) fusion [3].

MiT family translocation RCCs have a tendency to disproportionally affect younger patients, representing about 40% of pediatric RCCs [57, 59]. However, about 1–4% of RCCs in adults are MiT family translocation RCCs [56]. Given that RCCs are much more common in adults than children, the absolute numbers of MiT family translocation RCC are actually higher in adults [57]. MiT family translocation RCCs are associated with prior exposure to cytotoxic chemotherapy [55]. The prognosis for these tumors appear to be similar to clear cell RCC but worse than papillary RCC [55]. While data is currently limited, the MiT family translocation RCCs with the *TFEB-MALAT1* fusion appear to behave in a more indolent manner than those with *TFE3* alterations [56]. Both the TFE3- and TFEB-associated MiT family translocation RCCs have the potential to recur many years after initial diagnosis [55].

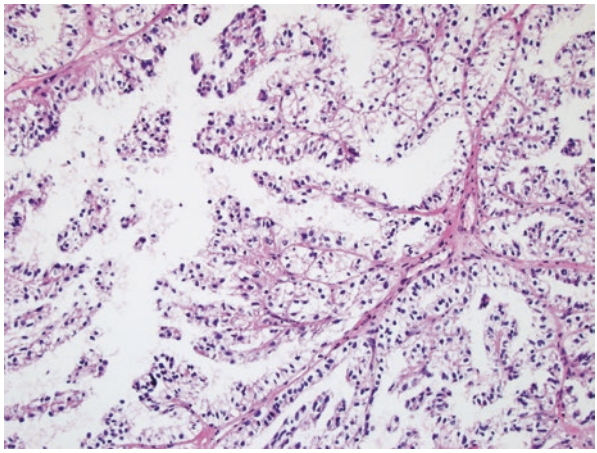

Fig. 2.10 H&E, high magnification, Xp11.2 translocation renal cell carcinoma

MiT family translocation RCCs have no distinguishing gross characteristics and are often similar to the conventional type of RCC. While there can be considerable histologic overlap between the TFE3 and TFEB types, there are some differences. Those with *TFE3* translocations often show mixtures of nested and papillary architecture with variable clear and eosinophilic cells with prominent nucleoli (Fig. 2.10). Psammoma bodies are often present [55, 57]. Those with *TFEB* translocations may show a biphasic tumor composed of small and large epithelial cells among basement membrane material. Melanin pigment can be seen in some MiT family translocation RCCs.

MiT family translocation RCCs are positive for PAX8 and CD10 but are typically negative for CK7 [54]. Unlike other forms of RCC, MiT family translocation RCCs can express cathepsin K and often can express the melanocytic markers HMB-45 and Melan-A [59]. Unlike melanoma, MiT family translocation RCCs are negative for S100 protein and MITF. Both the TFE3 and TFEB fusion products target similar segments of DNA, resulting in transcription of similar downstream targets, such as cathepsin K, HMB-45, and Melan-A [59]. The activation of these targets also explains the presence of melanin pigment in some tumors.

Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) was formally known as multilocular cystic renal cell carcinoma [3, 4, 60–62]. MCRNLMP is a rare renal tumor that typically presents as a solitary mass. Most tumors are discovered incidentally on imaging and are considered to be of low malignant potential as there are no reports of metastatic disease or disease recurrence.

These tumors are entirely composed of multiple cystic spaces. The presence of a solid tumor component excludes the diagnosis of MCRNLMP. Cyst walls and septa are lined by low-grade, clear cells. Individual cells or small groups of clear cells should be present within the septa, but these foci should lack expansile growth. MCRNLMP should not have necrosis, vascular invasion, or sarcomatoid features. Clear cell RCC with cystic degeneration, cystic nephroma, and tubulocystic renal cell carcinoma can mimic MCRNLMP and needs to be excluded.

Tumor cells are positive for PAX8 and CAIX, similar to clear cell RCC [63]. Deletions of chromosome 3p are present in the majority of cases [64].

Mucinous Tubular and Spindle Cell Carcinoma

Mucinous tubular and spindle cell carcinoma (MTSC) is a rare renal tumor typically seen in middle-aged women [3, 65, 66]. This tumor has an association with end-stage renal disease and nephrolithiasis. Most patients present with organ-confined disease. Although these tumors are thought to have a good prognosis, there have been reported cases of metastatic disease [65, 66].

MTSC tends to be well-circumscribed and can grow to be large in size. Tumors are often homogenous tan-gray and have a mucoid appearance. Tumor cells are low-grade and arranged in long, tightly packed tubules that can lie in parallel or show branching (Fig. 2.11a). The background stroma contains abundant extracellular mucin (Fig. 2.11b). Tubules classically transition into the spindle component, which is also low-grade (Fig. 2.11c). MTSC with high-grade features, necrosis, mitoses, or sarcomatoid change is rarely seen.

Tumor cells show positivity for PAX8, CK7, EMA, AMACR, and E-cadherin [65, 66]. These tumors have a variable genetic profile, with losses and gains of multiple chromosomes reported [65, 66]. Gains in chromosome 7 and 17 and loss of chromosome Y have not been described in MTSC, making this tumor distinct from papillary RCC [65, 66].

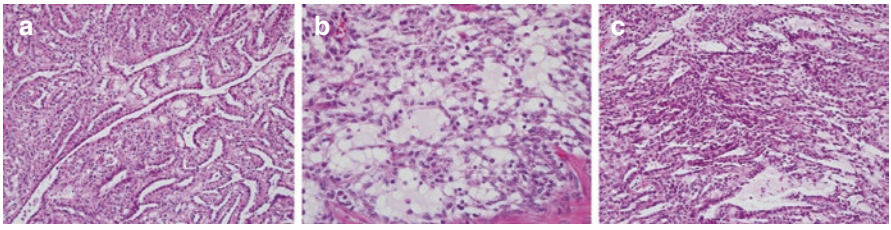

Fig. 2.11 H&E, high magnification, mucinous tubular and spindle cell carcinoma, (**a**) tubule component, (**b**) mucinous component, and (**c**) spindle cell component

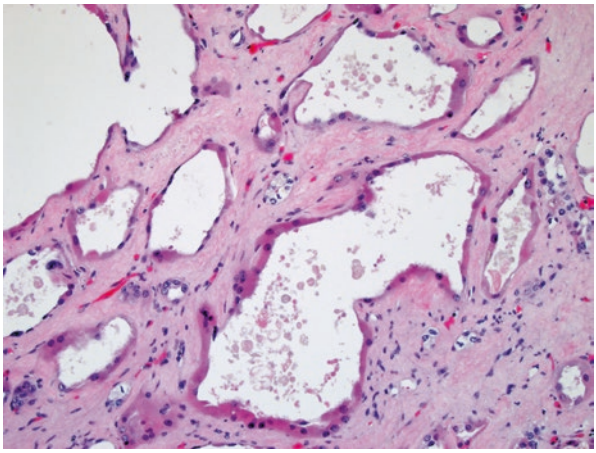

Fig. 2.12 H&E, high magnification, tubulocystic renal cell carcinoma

Tubulocystic Renal Cell Carcinoma

Tubulocystic RCC is a newly recognized renal tumor by the WHO [3, 4]. Tubulocystic RCC is thought to have an indolent biologic behavior with rare cases of metastases reported in the literature [67].

Tubulocystic RCC presents as a well-circumscribed mass composed of multiple cysts. These tumors are typically small (around 4 cm) and organ confined. The tubules are small to medium sized and are lined by a single layer of flat to cuboidal cells (Fig. 2.12). Hobnail cells are usually present. Tubulocystic RCC has high-grade nuclear features with large nucleoli, which help distinguish it from benign tumors such as cystic nephroma. Similar to papillary RCC, tubulocystic carcinoma has gains in chromosome 7 and 17 and loss of chromosome Y [68, 69].

Acquired Cystic Kidney Disease-Associated Renal Cell Carcinoma

Acquired cystic disease (ACD)-associated RCC is another newly recognized renal tumor by the WHO [3, 4]. This malignant tumor is the predominant subtype of RCC arising in the setting of end-stage renal disease and its associated acquired cystic kidney disease [70, 71]. As opposed to other tumors that can be seen in patients with end-stage renal disease and the general population, this tumor is only found in the setting of acquired cystic kidney disease. The incidence of the tumor increases with the time spent on dialysis [70, 71]. ACD-associated RCC is often multifocal and bilateral. Most tumors are small and are thought to have an indolent clinical outcome. However, this is likely confounded by the early detection of these tumors due to frequent imaging in patients with chronic kidney disease. Sarcomatoid features and metastases have been reported in the literature [70, 71].

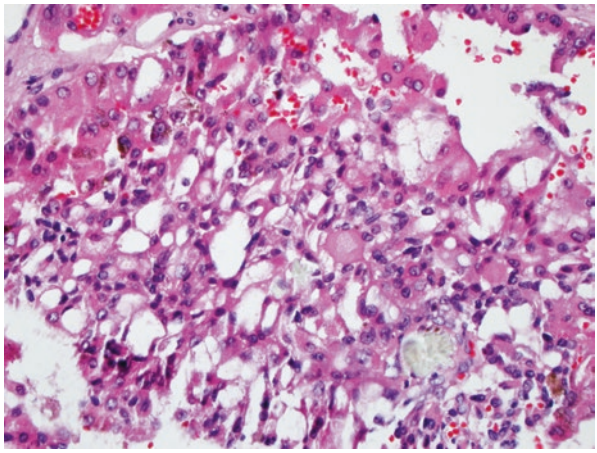

Fig. 2.13 H&E, high magnification, acquired cystic kidney disease-associated renal cell carcinoma

ACD-associated RCC forms a well-circumscribed tan-yellow mass that can arise within a renal cyst or be associated with the renal parenchyma. Necrosis and hemorrhage can be present. The background kidney will be atrophic with multiple small cortical cysts. This tumor can have several morphologic patterns including papillary, tubulocystic, and solid. The classic growth pattern shows a cribriform−/sieve-like appearance with the presence of calcium oxalate crystals (Fig. 2.13). However, calcium oxalate crystals may not always be present and the lack of this finding does not exclude the diagnosis. Tumor cells are high-grade with prominent nucleoli and abundant eosinophilic cytoplasm.

On immunohistochemistry, ACD-associated RCC shows positivity for CD10, RCC marker, and AMACR [70]. CK7 is typically negative in contrast to papillary RCC [70]. This tumor has a variable genetic profile; however the most common abnormalities include gains in chromosomes 3, 7, and 16 [70]. Gains of the sex chromosomes have also been reported [70]. Mutations in the *VHL* gene have not been identified [70].

Hereditary Leiomyomatosis and Renal Cell Carcinoma

Hereditary leiomyomatosis and RCC (HLRCC) is an autosomal dominant syndrome that arises in patients with a germline mutation of fumarate hydratase [72–74]. The mutation causes an increase in fumarate, which impairs the function of HIF prolyl hydroxylase. This leads to increased levels of HIF1α. Patients develop cutaneous and uterine leiomyomas as well as RCC. This RCC subtype is a newly recognized classification by the WHO [3, 4]. These tumors tend to be aggressive and have a poor prognosis.

RCCs associated with the hereditary leiomyomatosis and RCC syndrome can grow to a large size, and extrarenal extension is common. Both cystic and solid

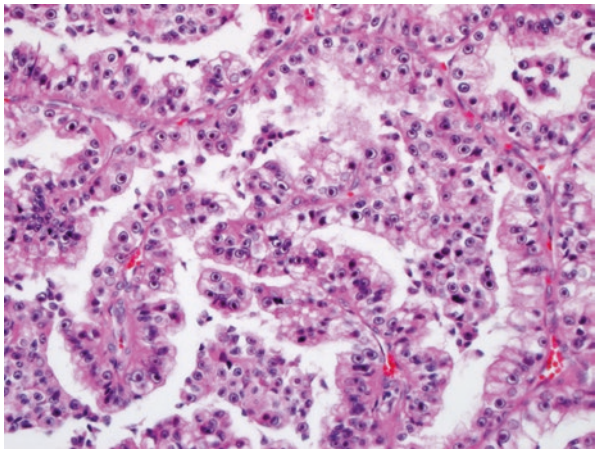

Fig. 2.14 H&E, high magnification, hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma

growth have been reported. Tumor cells can be arranged in tubular, solid, or papillary patterns. Tumor cells are large with prominent nucleoli and abundant eosinophilic cytoplasm. Previously, many of these tumors were classified as type 2 papillary RCC due to the overlapping morphology. Classically, tumor cells have a large eosinophilic nucleolus with cytoplasmic clearing around the nucleolus, creating a cytomegalovirus viral inclusion look (Fig. 2.14). Immunohistochemistry will show loss of fumarate hydratase staining in tumor cells and overexpression of S-(2-succino)cysteine [72–74].

Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

Succinate dehydrogenase (SDH)-deficient RCC is a newly recognized malignant renal tumor by the WHO [3, 4]. This is a rare tumor that comprises less than 1% of all RCCs. Most patients present in early adulthood with the mean age in the fourth decade of life. SDH-deficient RCC is typically hereditary, and the vast majority of cases arise in the setting of a germline mutation on one of the SDH genes [75, 76]. The most commonly involved gene is *SDHB*. Knockout of the SDH genes leads to dysfunction of mitochondrial complex II [75, 76]. Patients have an increased risk of paraganglioma, gastrointestinal stromal tumor, and pituitary adenoma. It is recommended that all patients with SDH-deficient RCC be offered genetic testing for a germline mutation.

Most tumors form a well-circumscribed mass that is organ confined on presentation. Multifocal and bilateral disease is found in up to 30% of patients [75, 76]. Tumor cells have eosinophilic cytoplasm and inconspicuous nucleoli. Solid, nested, and tubular growth patterns can be seen. The classic histologic feature of this tumor is cytoplasmic vacuoles or eosinophilic inclusions that can impart a bubbly appearance to the cells. However, this finding can be found only focally in some tumors.

Higher-grade nuclear features, sarcomatoid change, and necrosis have been reported and suggest a worse prognosis.

Tumor cells are positive for PAX8 and typically negative for CD117 and CK7 [75, 76]. Neuroendocrine markers should be negative, and loss of staining for SDHB by immunohistochemistry is required for the diagnosis.

Nephroblastoma (Wilms Tumor)

Nephroblastoma is the most common childhood renal malignancy [77–80]. It accounts for 90% of all newly diagnosed childhood renal tumors and is the fourth most common overall cancer in this age group. Nephroblastoma is thought to originate from remnants of metanephric tissue, known as nephrogenic blastemal rests. Most patients present at an average age of 2–4 years with a non-painful, palpable abdominal mass. Some children may be symptomatic with abdominal pain, hematuria, fever, hypertension, or an acute abdomen. Most tumors are unilateral and organ confined at presentation, with approximately 5% occurring bilaterally. Advances in chemotherapy have greatly improved the prognosis for patients with nephroblastoma, with an overall survival >90%. Nephroblastoma is associated with a genetic syndrome in 10% of cases. WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) and Denys-Drash syndrome (Wilms tumor, pseudohermaphroditism, and mesangial sclerosis) have *WT1* gene mutations. Beckwith-Wiedemann syndrome (asymmetric growth with hemihypertrophy, macroglossia, omphalocele, and visceromegaly) arises from mutations in the *WT2* gene. Patients with a germline mutation present at an earlier age and are more likely to have bilateral disease.

Nephroblastoma presents as a well-circumscribed, encapsulated mass. The cut surface is soft, homogenous, and gray to tan-pink in color. The presence of hemorrhage, cystic change, and necrosis is common. Classically, tumor cells show triphasic differentiation consisting of blastemal, stromal, and epithelial components (Fig. 2.15). The blastemal component is composed of small blue cells with closely packed nuclei, coarse chromatin, and scant cytoplasm. The epithelial component consists of primitive tubules with elongated nuclei. The stroma contains spindled cells, with some cases showing soft tissue differentiation. Nephroblastoma will have a high mitotic index. Many cases are associated with perilobar or intralobar nephrogenic rests. It is thought that nephrogenic rests are preneoplastic in nature and the risk of malignant transformation is higher for intralobar rests. Anaplasia is defined as markedly enlarged nuclei (3x the size of blastemal nuclei) with hyperchromasia and hyperdiploid (multipolar) mitotic figures. Diffuse anaplasia is associated with *TP53* gene mutations, resistance to chemotherapy, disease recurrence, metastases, and death.

On immunohistochemistry, tumor cells show staining for WT1 and CD56 [79, 80]. The majority of tumors arise from sporadic mutations on the *WT1* gene (chromosome 11p13) or the *WT2* gene (chromosome 11p15). Abnormalities in other

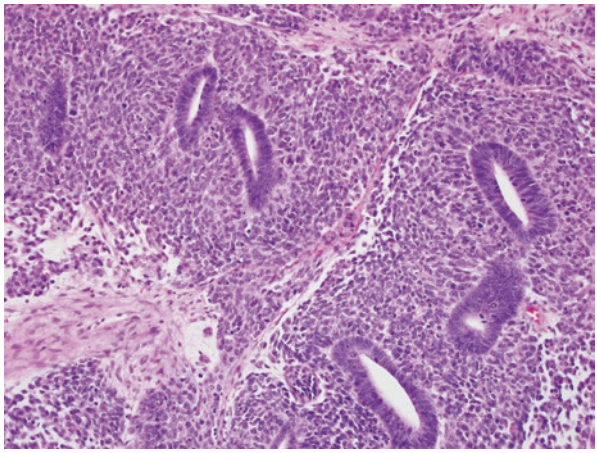

Fig. 2.15 H&E, high magnification, nephroblastoma

genes may also be seen including *WTX*, *CTNNB1*, and *TP53* [79, 80]. Nephroblastomas with loss of heterozygosity at 1p and 16q are associated with a poor prognosis [79, 80].

Benign Renal Tumors

Oncocytoma

Oncocytoma is the most common benign renal tumors, accounting for approximately 9% of all renal cortical neoplasms [81–85]. Most oncocytomas are incidentally discovered on imaging and are otherwise asymptomatic. While capable of local extension, oncocytomas are incapable of metastatic spread.

Oncocytomas present as solid, well-circumscribed masses that classically have a mahogany brown cut surface and the presence of a central stellate scar. A central scar is not diagnostic of oncocytoma, as this feature has been described in malignant renal tumors. Oncocytomas can have foci of hemorrhage, but the finding of necrosis, clear cells, papillary structures, or mitoses excludes this diagnosis. Rare cases have been reported to invade the perinephric fat or the renal vein, a finding that should not be mistaken for malignancy [82]. Tumor cells are uniform with abundant eosinophilic cytoplasm. The tumor grows in small, solid nests within a fibromyxoid background (Fig. 2.16). Cases can also show tubular, cystic, or solid growth.

Oncocytomas will show positivity for CD117 on immunohistochemistry, and CK7 should be negative or only focally positive [83]. This is in contrast to chromophobe RCC, a common diagnostic differential, which is diffusely positive for CK7 [81, 83]. Multifocal oncocytomas and oncocytosis are associated with Birt-

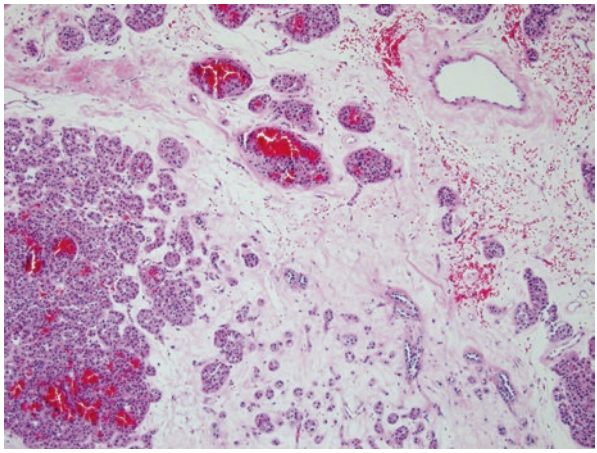

Fig. 2.16 H&E, high magnification, oncocytoma

Hogg-Dubé syndrome. Genetic mutations include loss of chromosomes Y, loss of chromosome 1, rearrangements of 11q13, and deletion of chromosome 14 [84].

Angiomyolipoma

Angiomyolipoma (AML) is a renal tumor that is a member of the perivascular epithelioid cell tumor family [86–89]. The majority of AMLs are benign; however, those with epithelioid features can have malignant behavior [87]. Most tumors are small and can be managed with active surveillance. However, larger tumors (>4 cm) can spontaneously bleed and cause significant morbidity [86]. AMLs are also capable of local invasion. Pregnancy and hormonal therapy have been known to cause increased growth.

AMLs typically present as an unencapsulated, well-circumscribed mass. The color of the cut surface varies with the content of fat present in the lesion. Fat-poor tumors appear tan-white to pink, while those that are fat-rich are more yellow. As the name suggests, AMLs are composed of three components: thick-walled vessels, smooth muscle, and adipose tissue (Fig. 2.17). The diagnosis of fat-poor lesions should be reserved for tumors that contain <25% fat. Hyalinization, cystic change, or calcifications have also been reported. Epithelioid cells may be present in a minority of cases. The presence of ≥70% atypical epithelioid cells, ≥2 mitoses per 10 high power fields, atypical mitotic figures, and necrosis is associated with increased risk of malignant behavior.

Tumor cells will show positivity for SMA, desmin, HMB-45, and Melan-A [88]. Fat-poor tumors are typically negative for Melan-A [88]. Although the majority of AMLs occur sporadically, this tumor presents in up to 90% of patients with tuberous sclerosis complex (TSC), an autosomal dominant syndrome caused by germline mutations of *TSC1* on 9q34 and *TSC2* on 16p13 [88]. Renal AMLs associated with TSC are often multifocal and bilateral. Mutations of *TSC2* can also be seen in sporadic AML. AML is also associated with lymphangioleiomyomatosis.

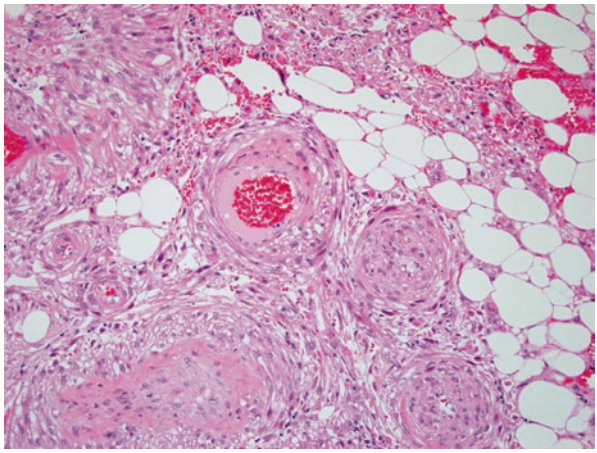

Fig. 2.17 H&E, high magnification, angiomyolipoma

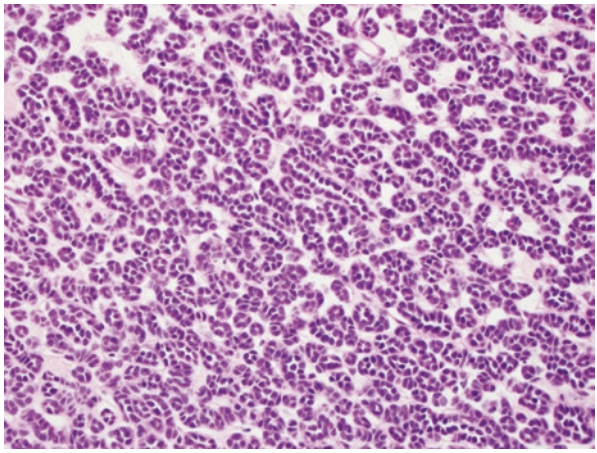

Fig. 2.18 H&E, high magnification, metanephric adenoma

Metanephric Adenoma

Metanephric adenoma is a benign kidney tumor with morphologic resemblance to the fetal kidney [90–92]. It affects a wide age range of patients and is more common in women. Metanephric adenoma is typically an incidental finding but can be associated with hematuria, flank pain, abdominal mass, or polycythemia [90, 92]. Metanephric adenoma is the kidney tumor most likely to cause polycythemia via secretion of erythropoietin [90].

Grossly, metanephric adenomas are solitary, well-circumscribed tan to gray tumors typically 3–6 cm in size. Microscopically, they resemble the fetal metanephric kidney. Tumor cells are arranged in tightly packed acini with inconspicuous lumens set in a scant loose stroma (Fig. 2.18). Acini can focally be elongated with intraluminal tufts forming glomeruloid and short papillary structures. Psammoma

bodies are common. The neoplastic cells are small with fine, evenly distributed chromatin, inconspicuous nucleoli and scant cytoplasm. Mitotic activity and necrosis should be absent.

By immunohistochemistry, the cells show characteristic expression of WT1 and CD57 [91]. They are negative for CK7 and racemase and are diploid for chromosomes 7 and 17 [91].

Mixed Epithelial and Stromal Tumor Family

The mixed epithelial and stromal tumor (MEST) family includes the adult cystic nephroma (which is predominantly cystic) and the MEST (which has cystic and solid areas) [93–95]. Adult cystic nephromas are now recognized to be a separate entity from pediatric cystic nephromas, which have *DICER1* mutations [95]. Most tumors are benign; however malignant transformation has been reported in the literature [93, 94].

These tumors are always solitary, unilateral masses with variable cystic and solid components. Most are well-circumscribed and unencapsulated. The cut surface shows thin-walled cysts with white, firm solid areas. The epithelial component consists of cysts, glands, and tubules. Some glands may have an endometrioid or tubal appearance. Less commonly, intestinal and urothelial morphology has been reported. The cysts are lined by flat to cuboidal epithelium, with hobnail cells being a common finding (Fig. 2.19). Stromal cellularity is variable and in many cases stromal condensation is seen around the epithelial component. The stroma can be composed of blue, spindle cells, creating an ovarian-like appearance. Smooth muscle metaplasia is also a common finding. Cytologic atypia, mitotic activity, necrosis, and hemorrhage are rare.

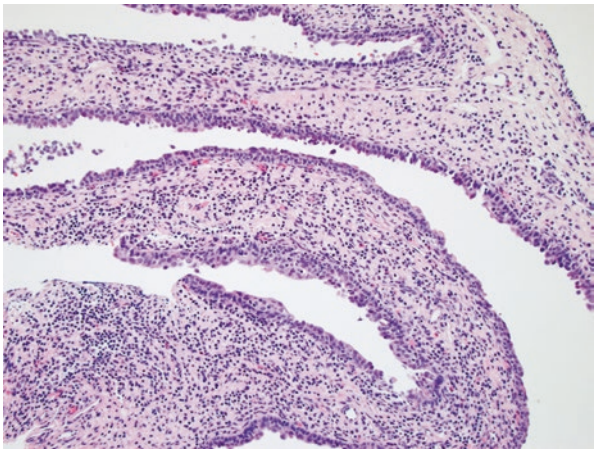

Fig. 2.19 H&E, high magnification, mixed epithelial and stromal tumor

Tumors of the MEST family show immunohistochemical staining for actin, desmin, CD10, estrogen receptor, and progesterone receptor in the stromal component [95]. Inhibin and calretinin may be positive in cases with luteinized stroma [95].

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