6 Familial Forms of Renal Cell Carcinoma and Associated Syndromes

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Chapter

Familial renal cell carcinoma (FRCC) is a hereditary renal neoplasm presenting within more than one member of a family. FRCC is uncommon and accounts for approximately 1–4 % of renal cancers [1]. In contrast to sporadic renal cell carcinomas (RCCs), FRCCs usually occur at a relatively young age and present as multiple tumors in both kidneys. In addition, patients may develop neoplastic disease in other nonrenal organs, such as the skin, lungs, uterus, and central nervous system. The majority of FRCCs are autosomal dominant diseases with variable penetrance [2]. Specific genetic alterations have been identified in most FRCCs, and the majority of these alterations are known to be involved in metabolic pathways that regulate oxygen, iron, glucose, and energy levels. Environmental or lifestyle factors may also play a role in the oncogenesis in FRCC [3]. It is important to identify these diseases, as this can help assess the cancer risk and extrarenal manifestation risk of individual family members and plan for cancer screening and prevention. In addition, appropriate psychosocial support and counseling may be provided to affected family members.

FRCC is a heterogeneous disease comprised of a number of syndromes. Each syndrome/subtype exhibits distinct genetic alterations, pathologic characteristics, and clinical features. In this chapter, we will primarily discuss five major hereditary syndromes that are associated with FRCCs: von Hippel-Lindau syndrome, hereditary papillary RCC, hereditary leiomyomatosis and RCC, Birt-Hogg-Dubé syndrome, and tuberous sclerosis syndrome (Table 6.1). A number of other heritable syndromes may also be associated with FRCC and are briefly discussed here, including the hyperparathyroidism-jaw tumor syndrome, PTEN hamartoma, and constitutional chromosome 3 translocations [4–6].

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Table 6.1 Major hereditary syndromes associated with renal cell neoplasms

Syndrome (abbreviation)	Gene (protein)	Chromosome location	Renal pathology	Other clinical manifestations
Von Hippel-Lindau (VHL) syndrome	*VHL* (pVHL)	3p25	Clear cell RCC, cystic renal cell carcinoma, renal cysts	Central nervous system hemangioblastomas, pheochromocytomas, pancreatic cysts, neuroendocrine tumors; endolymphatic sac tumors; epididymal and broad ligament cystadenomas
Hereditary papillary RCC (HPRCC)	*MET* (HGFR)	7q31	Papillary type 1 RCC	None
Hereditary leiomyomatosis and RCC (HLRCC)	*FH* (pFH)	1q42-43	Papillary type 2 RCC; often solitary	Uterine leiomyomas and leiomyosarcoma, cutaneous leiomyomas
Birt-Hogg-Dubé (BHD) syndrome	*FLCN* (Folliculin)	17p11.2	Hybrid oncocytic RCC, chromophobe RCC, clear cell RCC, oncocytoma, oncocytosis	Cutaneous papules, lung cysts, spontaneous pneumothoraces
Tuberous sclerosis (TS) syndrome	*TSC1* (hamartin)	9q34	Angiomyolipoma, papillary RCC, hybrid oncocytic RCC	Facial angiofibromas, periungual fibromas, shagreen patches, cardiac rhabdomyomas, lung and kidney cysts, cortical tubers
	TSC2 (tuberin)	16p13		
Succinate dehydrogenase mutation	*SDHB* (pSDHB)	1p36	B – solid and cystic tumors, variable pathology, oncocytic and clear cell RCC	Paragangliomas/pheochromocytomas, GIST, pituitary adenomas, pulmonary chondromas
	SHDC (pSDHC)	1q23	C – solid tumors, clear cell RCC, low grade	
	SDHD (pSDHD)	11q23	D – solid tumors, clear cell RCC	
Cowden/PTEN hamartoma tumor syndrome	*PTEN* (pPTEN)	10q23	Variable pathology, including clear cell, chromophobe, and papillary RCC	Breast, thyroid, and endometrial cancer, mucocutaneous lesions, acral keratoses, facial trichilemmomas, papillomatous papules, macrocephaly, Lhermitte-Duclos disease, benign thyroid conditions, mental retardation, GI hamartomas, lipomas, fibromas, breast fibrocystic disease
Microphthalmia transcription (MiT) family translocations	Fusion chimeric proteins with TFE3 or TFEB	Xp11.2	Solid or cystic tumors, variable architecture RCC	None
		t(6;11)		
Microphthalmia-associated factor mutation	*MITF* (pE318K)	3p14	Solid or cystic tumors, clear cell and papillary RCC	Melanoma
Chromosome 3 translocation	Fusion chimeric protein	t(3;8)	Clear cell RCC	None
BRCA1-associated protein-1 (BAP1) mutation	*BAP1* (pBAP1)	3p21	Solid and cystic tumors, high-grade clear cell RCC	Uveal/cutaneous melanoma, mesothelioma

Von Hippel-Lindau

Introduction

Von Hippel-Lindau (VHL) syndrome is a hereditary disease with an autosomal dominant pattern. The VHL incidence is estimated to about 1:36,000 [7]. Patients usually develop characteristic neoplasms in multiple organs, including clear cell RCC, capillary hemangioblastomas of the central nervous system and retina, pheochromocytoma, pancreatic tumors, and inner ear tumors [7]. The mean age of RCC onset in patients with VHL syndrome is 37 years, which is much earlier than that for sporadic RCC (61 years).

VHL disease is caused by germline mutations of the *VHL* gene, which is located on the short arm of chromosome 3 (3p26-25) [8]. The *VHL* gene is a relatively small tumor suppressor gene with a coding sequence of 639 nucleotides on three exons [9]. The VHL protein is responsible for proteomic degradation of hypoxia-inducible factors (HIFs) [10]. HIF-1α and HIF-2α regulate a number of downstream genes, including vascular endothelial and platelet-derived growth factors (VEGF and PDGF), transforming growth factor-α (TGF-α), erythropoietin, glucose transporter protein-1, carbonic anhydrase IX, and C-mesenchymal-epithelial transition factor (c-MET) [2]. These downstream genes are involved in the cell cycle, angiogenesis, and tumorigenesis. Mutations of the *VHL* gene, which may occur in any exon, are most commonly missense mutations, but nonsense mutations such as deletions, insertions, and translocations may also occur. The germline mutation is found in nearly all VHL families [11]. The type of mutation is associated with the clinical presentation of VHL disease. Somatic VHL alterations are also common in sporadic clear cell RCCs, but they are usually absent in papillary, chromophobe, or collecting duct RCCs.

Clinical Presentation

The earliest manifestations of VHL are usually not related to renal pathology. Central nervous system (CNS) hemangioblastomas, including retinal hemangioblastomas, can present as vision loss or neurologic symptoms as early as age 1 [7]. Other early manifestations in specific families include pheochromocytoma and pancreatic cysts, with ages of onset as young as 5 having been reported. Renal tumors have been noted as early as the teenage years, but generally present in the 4th decade of life on routine screening exams or with gross or microscopic hematuria. Overall some 25–60 % of VHL patients develop renal tumors, renal cysts, or cystic renal cell carcinomas; these are often bilateral and multifocal, as with most all forms of FRCC. Therefore, screening efforts for renal tumors in individuals affected by VHL generally start at age 18, when annual axial imaging (CT or MRI) is recommended.

Pathology

Grossly, the tumors often present as multiple, well-circumscribed, bright yellow masses in both kidneys. There are often numerous cysts containing clear fluid in the kidneys. Some patients may develop up to 600 microscopic tumors and over 1000 cysts in each kidney [12]. Microscopically, the tumors are typically composed of clear cell RCC, which is characterized by nests or sheets of tumor cells with clear cytoplasm separated by a delicate vascular network (Fig. 6.1a). The tumor may show focal papillary, tubular, or cystic features (Fig. 6.1b). The renal cysts are usually lined by a single layer of tumor cells with clear cytoplasm, sometimes forming small tufts and papillary structures (Fig. 6.1c). In addition, multiple, small, incipient tumors (under 0.5 cm in the largest dimension), which are also composed of clear cell RCC, are often scattered in the renal parenchyma (Fig. 6.1d).

The immunohistochemical profile of VHL-associated RCC is similar to that of sporadic clear cell RCC. They usually show strong positive immunoreactivity for carbonic anhydrase IX (CAIX) and CD10 and are negative or focally positive for cytokeratin 7 (CK7). The reactivity for alpha-methylacyl-CoA racemase (AMACR) is variable. Deletion of chromosome 3p is also

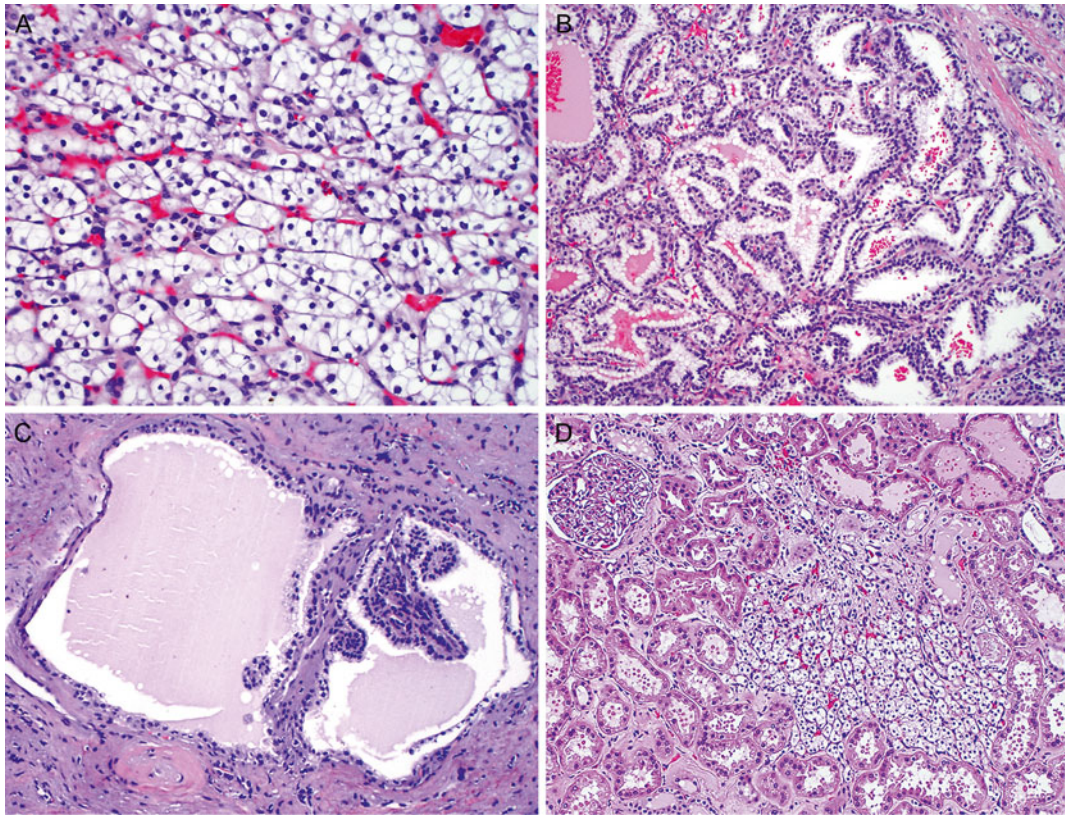

Fig. 6.1 Renal cell carcinoma in von Hippel-Lindau syndrome. The tumor is typically the clear cell type, which is characterized by small nests of tumor cells with clear cytoplasm separated by a delicate vascular network (**a**). Tumor cells may form papillae and tubules (**b**). Renal cysts are lined by a single layer of clear tumor cells, forming small tufts and papillae (**c**). Small tumors (less than 0.5 cm) of clear cell RCCs are common (**d**)

common in VHL-associated RCC (82 %), at a level similar to that observed in sporadic clear cell RCC (80 %) [13].

VHL-associated RCC may have focal areas of tubular, papillary, and cystic structures lined by tumor cells with clear cytoplasm, which mimics clear cell papillary RCC (CCPRCC). CCPRCC is a new entity that has not been included in the current WHO classification [14]. However, unlike VHL-associated RCC, CCPRCC is characterized by positive immunoreactivity for CK7 and negative reactivity for AMACR and CD10. Furthermore, while VHL-associated RCC frequently exhibits 3p deletion, CCPRCC lacks 3p deletion but may exhibit chromosome 7 or 17 abnormalities in a subset of cases [13].

Treatment

Historically many patients with VHL underwent radical nephrectomy, but renal parenchymal-sparing treatments are generally preferred in this and most other FRCC syndromes. Given the proclivity of most patients with VHL to form multiple and bilateral clear cell renal cell carcinomas over their lifetime, nephron-sparing should be entertained whenever oncologically feasible. Partial nephrectomy is now the standard extirpative approach to all but the largest renal tumors, and percutaneous ablation (with radiofrequency or cryotherapy) can also be offered to patients in lieu of radical nephrectomy unless the solid tumors have grown too large for such modalities [15]. A 3 cm size

threshold prior to intervention for solid renal masses has been studied in order to limit the number of interventions in patients with some forms of FRCC such as VHL [16]. Data to date suggest that the metastatic potential of lesions less than 3 cm in diameter in VHL is close to zero, so solid renal masses in VHL, invariably clear cell RCC, are routinely observed until they grow. At that point, partial nephrectomy is performed if feasible, as well as enucleation of all smaller tumors and cysts that can be handled safely. If percutaneous ablation is chosen, only the 3 cm+ tumor is ablated and the smaller lesions are followed.

Hereditary Papillary Renal Cell Carcinoma (HPRCC)

Introduction

HPRCC is an inherited renal tumor syndrome characterized by an autosomal dominant trait with a high penetrance [17]. Affected individuals are at a high risk of developing a large number of tumors in both kidneys. This syndrome chiefly affects the kidney, and no extrarenal involvement has been reported to be associated with HPRCC. The tumors are invariably composed of papillary type 1 RCC. The onset of HPRCC is usually late in most patients, in the 6th to 8th decades of life, but a few cases of early onset have been reported [18].

HPRCC is commonly associated with germline mutations in the proto-oncogene MET, which is located at chromosome 7q31 [19]. MET encodes a transmembranous protein kinase, hepatocyte growth factor receptor [20]. Normally, hepatocyte growth factor receptor binds and activates MET tyrosine kinase, which in turn phosphorylates a number of signal transduction proteins. The MET tyrosine kinase plays an important role in cell proliferation and differentiation. Missense mutations in the MET tyrosine kinase domain lead to ligand-independent constitutive activation of the MET protein [21]. The aberrant activation of the MET protein leads to phosphorylation of signal transducers and adaptors, resulting in cancer development. *MET* somatic mutations have also been reported in some patients with sporadic papillary type 1 RCC [22].

Clinical Presentation

Solid papillary renal tumors are the only clinical manifestation of this form of FRCC, and therefore these tumors are picked up incidentally, by screening of families known to be affected or on workup for gross or microscopic hematuria. These tumors are invariably solid (though some cysts have been noted in affected individuals) and enhance only minimally compared to other solid renal tumors: +10–30 Hounsfield units on contrast CT or +15 % on contrast MRI [23]. No mature routine screening recommendations for mutation carriers exist, though abdominal imaging by CT or MR is generally recommended every 2 years.

Pathology

Typically, there are numerous tumors in bilateral kidneys, which may number in the hundreds to thousands on gross examination. Histologically, the renal tumors are composed of papillary type 1 RCC, which is characterized by papillae lined with a single layer of small tumor cells with scant amphophilic cytoplasm and low nuclear grade (Fig. 6.2a). Papillae may coalesce to impart solid growth patterns with glomeruloid structures (Fig. 6.2b). There is a variable amount of foamy histiocytes and psammomatous calcification in the papillary cores (Fig. 6.2c). Necrosis and hemosiderin deposits may be found. Clear cell changes may be present, especially in areas adjacent to necrosis. A large number of small papillary renal neoplasia that are identical to sporadic renal papillary adenomas are frequently seen in the renal parenchyma (Fig. 6.2d).

It is difficult, if not impossible, to distinguish HPRCCs from sporadic papillary type 1 RCCs based on pathologic analysis, as they share similar histologic and immunohistochemical features

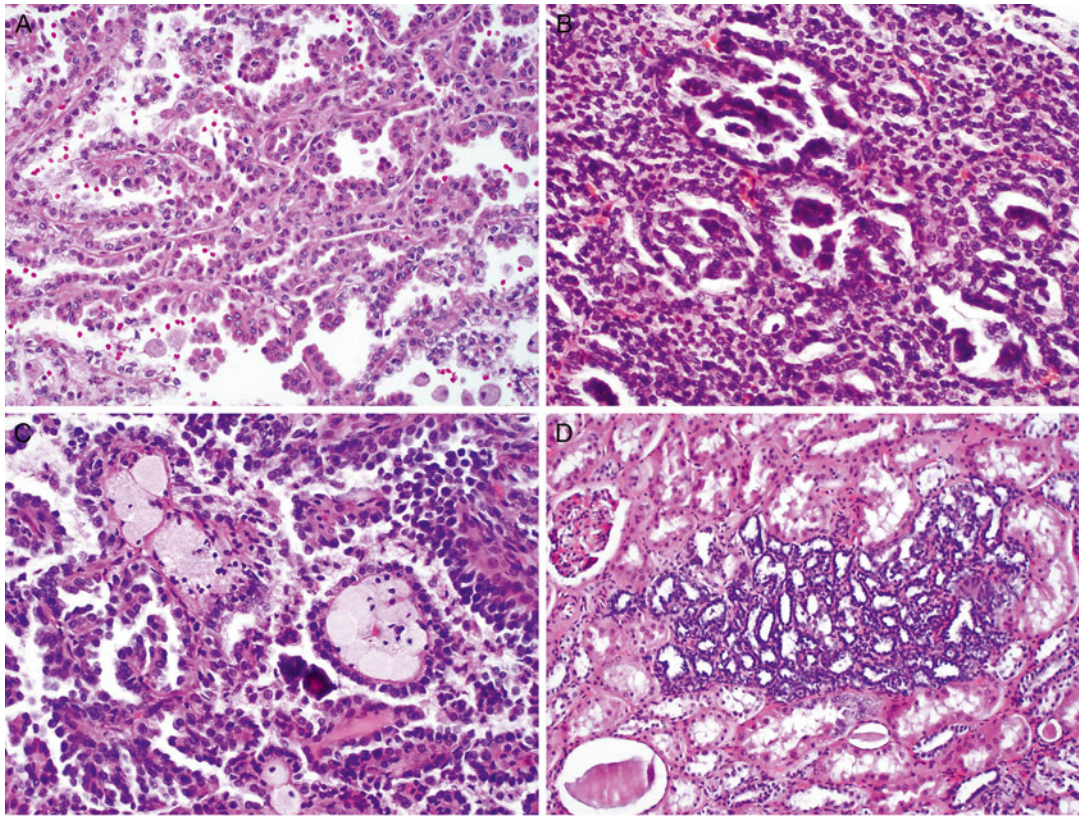

Fig. 6.2 Hereditary papillary renal cell carcinoma. The tumor is invariably a papillary type 1 RCC, which is characterized by papillae lined with a single layer of tumor cells with low nuclear grade (**a**). Papillae may coalesce a solid growth pattern with glomeruloid structures (**b**). Foamy histiocytes and psammomatous calcification are observed in the papillary cores (**c**). A large number of renal papillary adenomas are frequently seen in the grossly normal renal parenchyma (**d**)

[24]. A diagnosis of HPRCC may be entertained when a patient presents with a large number of papillary type 1 RCC and a family history of renal tumor. The diagnosis of HPRCC can be further supported by identifying the germline MET mutations on DNA sequencing.

Treatment

Type I papillary RCCs typically grow slowly and have low metastatic potential. They are therefore generally managed observationally until the 3 cm threshold for intervention is reached, as for many other forms of FRCC. The options of radical nephrectomy, partial nephrectomy, and percutaneous ablation are similarly offered for these tumors.

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

Introduction

HLRCC is an autosomal dominant cancer syndrome with a high penetrance [25]. These patients are at risk of developing papillary type 2 RCC, cutaneous and uterine leiomyomas. In affected patients, the penetrance of RCC is approximately 20–30 %, whereas the penetrance of cutaneous and uterine leiomyomas is much higher: 76 % of individuals and 100 % of women at a mean age of 25 years or 30 years [25–27]. Occasionally patients may develop leiomyosarcoma in the uterus. The median age of patients at onset of RCC is 36–44 years, which is much earlier than

when sporadic kidney cancer manifests. The onset of leiomyomas occurs at a relatively young age: at 10–47 years for cutaneous leiomyomas and 18–52 years for uterine leiomyomas.

The gene responsible for HLRCC is fumarate hydratase (*FH*), a tumor suppressor which is located on chromosome 1 (1q42.3-q43) [25–27]. Germline mutations in *FH* gene have been found in 85 % of the HLRCC patients. The majority of germline mutations are missense mutations, although truncation and whole-gene deletion may occur. A "second hit" or somatic inactivation of the remaining *FH* allele is usually required to cause functional loss of FH protein. Because the FH protein regulates the conversion of fumarate to malate in the citric acid (Krebs) cycle, the inactivation of this protein increases the level of fumarate, which competitively inhibits the HIF prolyl hydroxylase [28]. Subsequently, the HIF level increases, influencing the expression of the downstream genes. There is no evidence to support a relationship between the *FH* gene mutation and sporadic RCC.

Clinical Presentation

This is a disorder with cutaneous, uterine, and renal manifestations, only the latter being cancerous. Patients generally develop cutaneous leiomyomata (trunk and extremity) in their 20s, and these can be painful. Females almost always develop multiple, large uterine leiomyomata during their young adulthood, which typically become quite symptomatic though rarely cancerous. In addition, some 10–16 % of affected patients also develop papillary RCC type 2 renal tumor [29]. These cancers are very aggressive, highly malignant, and quite different in behavior from most other papillary RCC and even from many clear cell RCC. Unlike other forms of FRCC, these tumors grow so rapidly that a patient will often present with just one large (and symptomatic) tumor despite their hereditary predisposition to multiple and bilateral tumors.

Pathology

Renal Cancer

On gross examination, HLRCC tumors are typically solitary and unilateral, unlike tumors of other hereditary RCC syndromes, which are characterized by bilateral distribution of multiple renal tumors. HLRCC tumors are usually large, tan, and firm with necrosis. Microscopically, HLRCC usually exhibits a large number of papillae covered by large tumor cells with abundant eosinophilic cytoplasm (Fig. 6.3a), as is seen in papillary type 2 RCC. The most characteristic feature of HLRCC is the presence of a large nucleus with a very prominent inclusion-like nucleolus that is surrounded by a clear halo, resembling cytomegalovirus nuclear inclusions (Fig. 6.3b). The tumor may also have solid, tubular, or tubulopapillary growth patterns (Fig. 6.3c). The tumor is often associated with desmoplastic and cystic changes, mimicking collecting duct carcinoma (CDC), but CDC lacks the characteristic nucleolar features of HLRCC. Furthermore, CDC is positive for CK7 and ULEX on immunostaining, while HLRCC is often negative or only focally positive for CK7 and negative for ULEX-1. Occasionally, the tumor may develop sarcomatoid dedifferentiation (Fig. 6.3d). The tumors often present at an advanced stage with invasion into renal vein, renal sinus, and perinephric soft tissue [30]. Recent studies have shown that the presence of *S*-(2-succino)-cysteine (2SC) positivity by immunohistochemical analysis predicts genetic alterations of the *FH* gene in patients and that this immunoreactivity is generally absent in non-HLRCC-related tumors [31, 32].

Leiomyomas of the Skin and Uterus

Cutaneous leiomyomas often appear as multiple, firm nodules ranging from 0.2 to 2.0 cm in the largest dimension. Microscopically, cutaneous leiomyomas are composed of anastomosing bundles of smooth muscle cells with inconspicuous nuclei. Uterine leiomyomas often present as

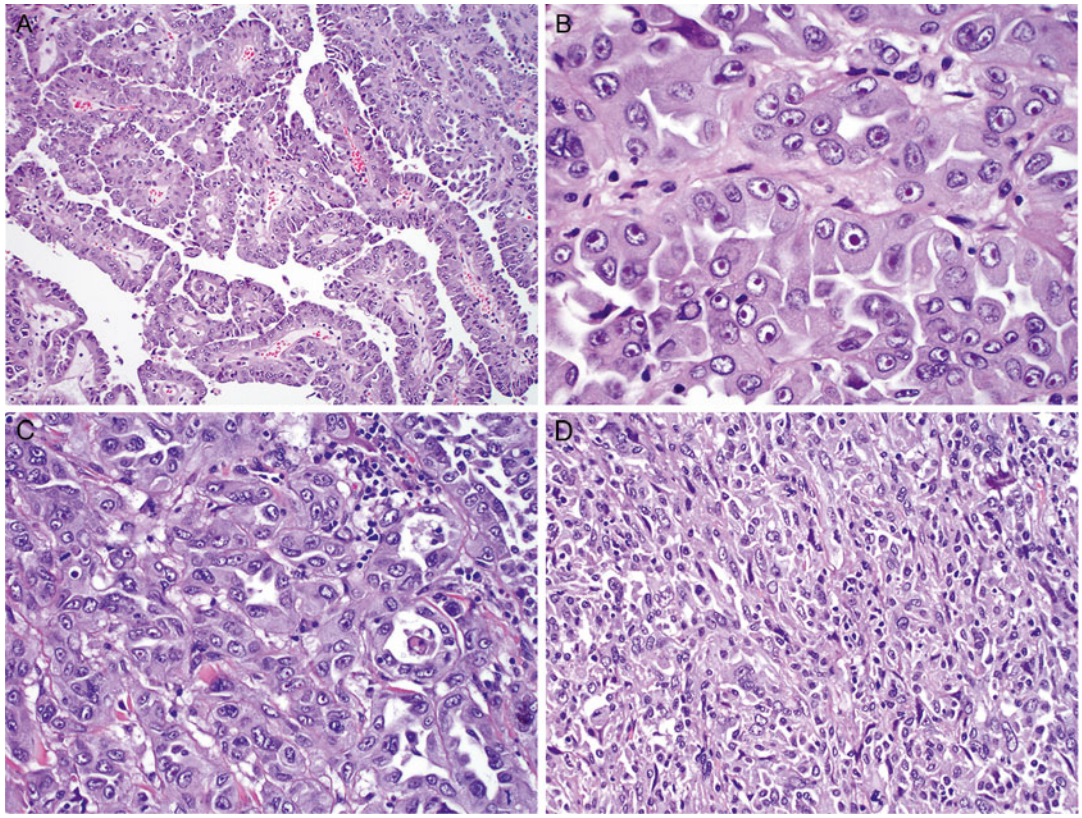

Fig. 6.3 Hereditary leiomyomatosis and renal cell carcinoma. The tumor typically appears like papillary type 2 RCC, which is composed of papillae covered by large tumor cells with a high nuclear grade and abundant eosinophilic cytoplasm (**a**). The most characteristic feature is the presence of a large nucleus with a prominent inclusion that is surrounded by a clear halo (**b**). The tumor may have solid, tubular, or tubulopapillary growth patterns (**c**). The RCC may develop focal sarcomatoid dedifferentiation (**d**)

numerous, well-circumscribed, and firm masses. Histologically, most leiomyomas are composed of whorled, interlacing fascicles of uniform, fusiform smooth muscle cells. A small number of patients develop uterine leiomyosarcomas [33], which are usually large and fleshy with poorly defined margins. The leiomyosarcomas are usually hypercellular with conspicuous nuclear atypia and increased mitotic activity.

Treatment

Prompt surgical management is recommended for HLRCC patients with a renal mass of any size. Unlike other forms of FRCC, where it is generally prudent to wait until a renal tumor grows to 3 cm prior to intervening, HLRCC renal tumors are treated on diagnosis. While there are not enough data to recommend nephron-sparing vs. radical nephrectomy for these tumors, prompt and aggressive treatment is warranted for these patients. Unfortunately, given that this syndrome has only recently been characterized, more than half of patients already had locally advanced or metastatic disease at presentation in the initial series [34].

Birt-Hogg-Dubé (BHD) Syndrome

Introduction

BHD syndrome is a rare autosomal dominant cancer syndrome with incomplete penetrance [35]. Renal tumors occur in 14–34 % of affected individuals with an onset commonly in the 6th

decade of life (ranging 31–73 years). The majority of the renal tumors that develop are hybrid oncocytic tumors (50 %), chromophobe RCCs (33 %), or oncocytomas (5 %), but clear cell and papillary RCCs have occasionally been seen as well [36]. More than half of patients with BHD syndrome also have multifocal oncocytosis in the surrounding renal parenchyma [36].

BHD syndrome is caused by germline mutations in the folliculin gene (*FLCN*) [37], which is located at chromosome 17p11.2 [38]. These mutations can be insertions, deletions, or nonsense mutations. The *FLCN* gene, which functions as a tumor suppressor gene, requires mutations in both alleles to be inactivated. Usually, one allele has a germline mutation and the other allele has a somatic mutation. FLCN protein forms a complex with interacting proteins, which regulates the mammalian target of rapamycin (mTOR) signaling pathway via AMP-activated protein kinase (AMPK) [39]. Mutations in the *FLCN* gene may also be involved in the development of a number of sporadic RCCs [40].

Clinical Presentation

BHD is a hereditary disorder predisposing patients to benign skin lesions, lung cysts and spontaneous pneumothorax, and renal tumors. BHD patients develop asymptomatic cutaneous fibrofolliculomas and other benign skin lesions during their young adulthood—skin-colored papules typically distributed over the nose, face, neck shoulders, and back. Benign lung cysts develop in the lung bases most typically, and these lead to spontaneous pneumothorax in many patients over time (~50× compared to the general population). BHD patients also have a 7× incidence of renal tumor compared to unaffected relatives and tend to present in their 5th decade of life [41]. As for any renal tumor, they may be found incidentally, on screening exams, or may present with hematuria or flank symptomatology. Screening for renal tumor is recommended every 2 years at least given that some patients with BHD have indeed died from metastatic RCC.

Pathology

Patients with BHD syndrome often have multiple, well-circumscribed, tan or brown tumors in both kidneys (Fig. 6.4a). The average size of the largest tumor at presentation was 5.7 cm (ranging 1.2–15 cm), and the average number of tumors was 5.3 per kidney (ranging 1–28 cm) in the initial series [36]. Various histologic characteristics have been reported for patients with this syndrome. Half of the renal tumors are hybrid oncocytic tumors, which usually demonstrate features of both oncocytomas and chromophobe RCCs (Fig. 6.4b). Oncocytic hybrid renal tumors are usually positive for CD117 and focally positive for CK7 (Fig. 6.4c). Another common feature of hybrid renal oncocytic tumors is a mixture of oncocytic cells with abundant eosinophilic cytoplasm and clear cells with no prominent irregularity of the nuclear membrane (Fig. 6.4d). Other tumors may include chromophobe RCC (34 %), clear cell RCC (9 %), oncocytoma (7 %), or papillary RCC (2 %). Most patients (56 %) also exhibit renal oncocytosis in the grossly normal renal parenchyma. Metastatic disease is rare and occurs only occasionally in patients with renal tumors larger than 3 cm.

Skin and Other Lesions

Several skin lesions are associated with the BHD syndrome [41]. The most characteristic is fibrofolliculoma, a benign tumor associated with the hair follicle. Fibrofolliculomas usually appear as skin papules on the neck, upper chest, upper back, and face. Histologically, these tumors show a proliferation of follicular epithelium surrounded by a perifollicular fibrous sheath. The stroma surrounding the epithelium may be densely fibrous or loose. Alcian blue may demonstrate the presence of abundant mucin. Trichodiscomas and acrochordons are also frequently associated with BHD syndrome. Pulmonary cystic lesions are present in 24 % of patients with BHD syndrome; these lesions may rupture, leading to spontaneous pneumothorax

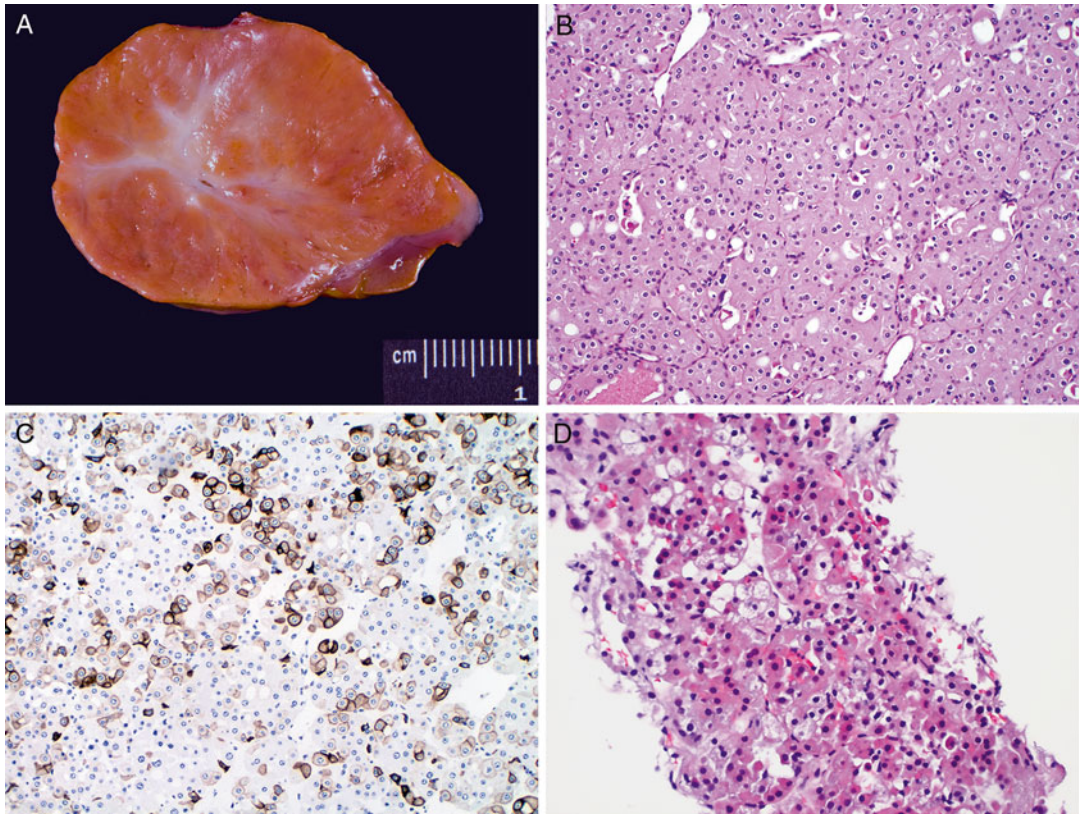

Fig. 6.4 Renal cell carcinoma in Birt-Hogg-Dubé syndrome. The tumor is usually well circumscribed and tan or brown in color (**a**). The most common histologic feature is a hybrid oncocytic tumor, which shows features of both oncocytomas and chromophobe RCCs (**b**) and focal immunoreactivity for CK7 (**c**). Another hybrid renal tumor is composed of oncocytic cells with abundant eosinophilic cytoplasm and clear cells with no prominent nuclear membrane irregularity (**d**)

[42]. Multiple lipomas and mucosa papules have also been described for patients with BHD syndrome. A large number of other tumors may also occur in these patients, but a causal relationship between the syndrome and these tumors has not been proven [42].

Treatment

BHD renal tumors are treated and followed per 3 cm FRCC guideline. As most of these tumors are indolent (oncocytic hybrid tumors, oncocytoma) or of low malignant potential (chromophobe RCC), they may be followed until they reach 3 cm in diameter or become symptomatic in order to minimize repeated procedures on an affected kidney. Given that there is an increased incidence of clear cell RCC in BHD, no renal mass in a BHD patient can be considered completely benign, and partial nephrectomy, percutaneous ablation, or radical nephrectomy are all considered on individual bases in these patients [43].

Tuberous Sclerosis (TS) Syndrome

Introduction

Affecting 1 in 6000 live births in the United States, TS syndrome is a relatively common genetic disease [44]. The syndrome encompasses neoplastic diseases that can affect virtually any organ in the body but particularly the brain, kid-

ney, lungs, eyes, and skin [45]. TS syndrome is transmitted in an autosomal dominant fashion and has variable penetrance. The characteristic renal tumor is angiomyolipoma (AML), which is present in 60–80 % of individuals with TS syndrome and represents the most common cause of TSC-related mortality in adults [46].

TS syndrome is associated with the mutations of two tumor suppressor genes, tuberous sclerosis complex 1 and 2 (*TSC1* and *TSC2*) [47, 48]. *TSC1* is located at chromosome 9q34 and encodes the protein hamartin, and *TSC2* is located at chromosome 16p13.3 and encodes the protein tuberin. Hamartin and tuberin bind and form a complex that downregulates the mTOR signaling pathway [49]. Mutations of *TSC1* or *TSC2* inactivate hamartin and tuberin, respectively, leading to upregulation of the mTOR signaling pathway. The majority of genetic mutations in TSC are sporadic and not inherited.

Clinical Presentation

TS patients develop multiple, bilateral AML in their kidneys at an early age and have a slightly higher incidence of RCC over their lifetime as well (see below). Unlike in sporadic cases where AML are more commonly found in women, a majority of TS patients whether male or female develop renal AML by age 30. These are found incidentally, or on imaging for symptoms, which are generally related to bleeding from these very vascular tumors. Bleeding complications related to AML typically occur once a lesion grows to over 4 cm in diameter [50] and present either as gross hematuria or perinephric hematoma that may lead to hemodynamic instability. Infiltration by AML may also result in mass effect and hypertension and contribute to eventual renal failure.

Pathology

Unlike sporadic AMLs, AMLs of the TS syndrome are characterized by multiple, well-circumscribed, small tumors in bilateral kidneys. Most AMLs present in the renal parenchyma, but some may be located on the renal capsule. Sometimes AMLs may involve other organs. The gross appearance depends on the relative proportion of tumor components. Microscopically, AMLs are composed of three typical components in various proportions: blood vessel, spindle cells, and adipose tissue (Fig. 6.5). Vessels typically have an eccentrically thickened wall with spindle cells spun off the wall. Epithelioid AMLs are reported to be more frequent in TS than in sporadic settings. Approximately 20–30 % of patients with TS develop renal cortical cysts. Renal cell carcinoma may occur in 2–4 % of patients. The most common RCC in TSC exhibits

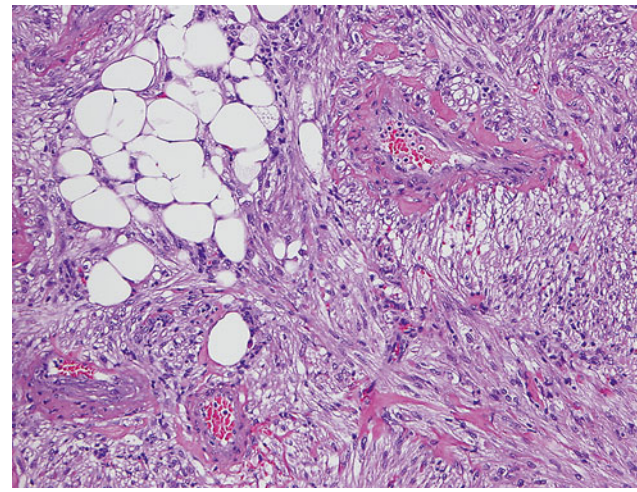

Fig. 6.5 Angiomyolipoma in tuberous sclerosis syndrome. The tumor is typically composed of blood vessels, smooth muscle spindle cells, and adipose tissue

papillary features and uniformly lacks succinate dehydrogenase subunit B expression, prompting the novel term "TSC-associated papillary RCC" [51]. Another RCC associated with TSC is featured by hybrid oncocytic tumor and chromophobe RCC.

Patients with TS syndrome often develop neoplastic disease in multiple organs [52]. The typical skin lesions include facial angiofibromas, periungual fibromas, shagreen patches, and hypopigmented macules. Central nervous system lesions include subependymomas and giant cell astrocytomas. Patients may develop cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis, and retinal hamartomas.

Treatment

The management of renal AML in TS is usually noninvasive, with selective angioembolization used for most bleeding or preemptively for significantly enlarging lesions. Partial nephrectomy has been performed for larger lesions, while nephrectomy has been performed for severely affected renal units. More recently, molecular exploration of the TSC pathways described above has led to trials of mTOR inhibitors in patients with TS. Everolimus is being used successfully to shrink AML in TS patients over a 1-year interval, with promising results of 30–80 % shrinkage of renal lesions in an ongoing study [53, 54].

Succinate Dehydrogenase Mutation

Similar to FH in HLRCC, succinate dehydrogenase (SDH) is a critical enzyme in the Krebs cycle and electron transport chain, and its mutation shifts the cells towards aerobic glycolysis, resulting in rapid growth and proliferation. The enzyme is made of four subunits, SDHA, SDHB, SDHC, and SCHD, and mutations in the latter three predispose to aggressive RCC. These patients also present with paragangliomas (PGL) and pheochromocytomas (PCC), gastrointestinal stromal tumors (GIST), pituitary adenomas, and pulmonary chondromas. The kidney tumors can be cystic or solid and may present with variable pathology, including oncocytic features in SDHB-associated tumors. The low grade of clear cell tumors on histopathology may be deceptive, for they behave aggressively, metastasizing early. Given the potential for multifocality and lifelong risk for metachronous tumor development, the recommendation for these patients, when feasible, is nephron-sparing surgery with lifelong surveillance [55].

Cowden/PTEN Hamartoma Tumor Syndrome

A number of syndromes with differing phenotypical manifestations have been associated with mutations in *PTEN* gene, and of these, more than 300 mutations are associated with Cowden syndrome [56]. PTEN is a tumor suppressor, and its mutated form allows dysregulated activation of PI3K/AKT pathway and resultant activation of mTOR pathway. Besides increased risk for development of RCC, Cowden syndrome is associated with increased risk for breast, endometrial, and thyroid malignancy. Pathognomonic phenotypic features include mucocutaneous lesions such as acral keratosis, facial trichilemmomas, and papillomatous papules. Other nonmalignant conditions associated with this syndrome include macrocephaly, Lhermitte-Duclos disease, benign thyroid conditions, mental retardation, GI hamartomas, lipomas, fibromas, and breast fibrocystic disease. Due to its low penetrance, patients may not have a convincing history of familial RCC; however, the phenotype of the associated dermatologic features and macrocephaly, along with the presence of other cancers, should raise the suspicion for *PTEN* mutation. Histopathology of the kidney tumors associated with this syndrome is variable, and papillary, chromophobe, and clear cell variants of RCC have been described. The biologic behavior of these tumors is not different than their sporadic histopathologically matched counterparts; however, obtaining genetic diagnosis may allow selection of targeted therapy, should surgery not be an option.

Microphthalmia Transcription (MiT) Family Translocations

This includes a variety of chromosomal translocations which result in fusion proteins activating the MET receptor with uncontrolled proliferation and downstream mTOR pathway activation [57–59]. The largest family is the Xp11.2 translocations/*TFE3* fusions with several genes including *ASPL*, *PRCC*, *PSF*, *NonO*, and *CLTC*. Another less common subtype involves t(6;11)(p21;q12)/*alpha-TFEB* gene fusion. The Xp11.2 is the most common etiology for RCC in pediatric population, comprising about 50 % of total neoplasms. Although rare in adult population, these translocations account for 15 % of RCC in patients younger than 45 years of age. There is speculation that these cancers are associated with exposure to chemotherapy. Interestingly, whereas in children these tumors may have indolent course, in adults they are very aggressive and tend to metastasize early, showing propensity for retroperitoneal lymph node involvement. There is no consensus about architectural uniformity in these tumors, but they tend to be diagnosed by TFE3 and TFEB staining and fluorescent in situ histochemistry (FISH). Grossly they may be cystic or solid and may resemble clear cell or papillary morphology with psammoma bodies and hyaline nodules. The treatment recommendation is partial or radical nephrectomy with regional lymphadenectomy and lifelong surveillance.

Microphthalmia-Associated Factor (MITF) Mutation

Most recently a germline mutation in MITF, which is another member of the family of MiT transcription factors, was identified in families which have RCC and melanoma. This missense mutation at the Mi-318K locus of MITF gene stimulates transcription of genes affecting multiple oncogenic pathways, including *MET* and *HIF1A*. These tumors are of variable architecture, and the prognosis remains under investigation [60].

BAP1 Mutation

BAP1 (BRCA1-associated protein-1) is an enzyme that functions as both an effector and regulator of breast cancer gene 1 (*BRCA1*). Its function is implicated in multiple pathways, including cell cycle regulation, protein trafficking, chromatin modulation, and DNA repair. Individuals with *BAP1* mutation have increased susceptibility for early onset clear cell RCC, along with cutaneous and uveal melanomas and mesothelioma. This is a new member of familial RCC attributable to genetic mutation, and more studies are needed to ascertain the prognosis of BAP1-associated renal tumors [61].

Chromosome 3 Translocation

This is a balanced germline translocation between chromosome 3 and 8, which includes multiple genes important for renal cell cancer development, including *VHL*, *BAP1*, *PBRM1*, and *SETD2*. These patients can present with multifocal cystic and solid clear cell RCC, similar to VHL; however, the age of onset is later, usually in 4th or 5th decade of life [60]. The later age of onset can be explained by the 3-step tumorigenesis model, which includes inheritance of the constitutional translocation, loss of the derivative chromosome carrying the 3p segment as a result of chromatid separation, and, finally, a somatic mutation that renders the tumor suppressor gene inactive. There are no other malignancies associated with this genotype.

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