

Review

Genetic alterations and histopathologic findings in familial renal cell carcinoma

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Summary. Renal cell carcinoma is increasing in frequency in the United States and is often detected late in the course of disease due to nonspecific symptoms. A subset of renal cell carcinoma is attributable to familial or hereditary syndromes, including von Hippel-Lindau and Birt-Hogg-Dubé syndromes, among others. Understanding of the molecular alterations in patients with familial syndromes may provide some insight into the underlying mechanisms of disease initiation and progression. This review describes the various subtypes of renal cell carcinoma and the familial syndromes associated with these tumors.

Key words: Kidney, Kidney cancer, Pathology, Neoplasia, Review

Introduction

Renal cell carcinoma (RCC) comprises 2% of adult malignancies (Landis et al., 1999), and affects approximately 150,000 people per year worldwide (Chow et al., 1999). The majority of RCCs affect persons over the age of 40 years, and the risk of RCC is highest in industrialized countries, and environmental influences such as tobacco use and exposure to arsenic compounds appear to affect the development of this cancer (Smith et al., 1992; Parkin et al., 1994; Kurtio et al., 1999). Additional proposed risk factors include obesity, estrogens, and asbestos, although definitive evidence has not been established for these agents (Lindblad et al., 1995; Mellemegaard et al., 1995; Pesch et al., 2000). Even though an increasing number of RCC cases are detected incidentally by imaging procedures, the incidence of RCC in the United States appears to be increasing independent from early detection (McCredie, 1994; Chow et al., 1999).

RCC arises from the epithelial cells of the renal

tubule. Most commonly, RCC is identified incidentally during a workup for unrelated conditions. The cases of RCC that are symptomatic, however, may demonstrate a wide spectrum of symptoms (Ritchie and Chisholm, 1983). The classically described presentation of flank pain, flank mass, and hematuria occurs in less than half of all patients afflicted by RCC (Gibbons et al., 1976). Frequently, nonspecific symptoms, including fatigue, weight loss, and abdominal pain, dominate the clinical picture. On occasion, patients may present with paraneoplastic syndromes, including hypercalcemia, gynecomastia, and polycythemia (Kim et al., 2003). Although many patients do well following surgical resection, approximately 20% ultimately die from their disease due to local recurrence or distant metastases (Goetzl et al., 2004).

Although originally grouped as a single entity, RCC has been subsequently subclassified into various subtypes based on distinguishing morphologic and molecular features (Thoenes et al., 1986; van den Berg et al., 1993; Moch et al., 2000). The current World Health Organization (WHO) classification of RCC distinguishes clear cell (conventional), papillary, chromophobe, and Xp11 translocation RCC, as well as carcinoma of the collecting ducts of Bellini. Papillary adenoma and oncocytoma are also common neoplasms of the kidney that demonstrate a more indolent course.

Approximately 1 to 4% of all RCCs occur as part of a familial syndrome (Pavlovich and Smith, 2004), such as von Hippel-Lindau (VHL) syndrome, and Birt-Hogg-Dubé syndrome. Patients with these syndromes often present with additional cutaneous and systemic manifestations of the underlying disease process, although occasionally renal cell carcinoma is the initial or only finding. In the majority of these heritable syndromes, the underlying genetic alteration is known, allowing an insight into the underlying molecular mechanisms influencing renal cell carcinoma pathogenesis.

This review will describe the subtypes of RCC commonly encountered in familial renal cell carcinoma syndromes, emphasizing morphologic, cytologic, and

molecular features, followed by a review of specific heritable syndromes associated with the development of various forms of RCC.

Clear cell (conventional) RCC

Comprising the most common subtype of RCC, clear cell RCC has been previously termed “granular cell tumor”, “Grawitz tumor”, and “hypernephroma” in the literature (Storkel et al., 1997). Clear cell RCC is a malignant, primarily solitary lesion arising within the cortex of the kidney. The proposed cell of origin is the proximal renal tubule cell. In patients with von Hippel-Lindau disease or constitutional chromosome 3 translocation, clear cell RCCs may be multifocal and bilateral, and demonstrate an earlier age of onset (Kovacs et al., 1989; Neumann et al., 1998).

Gross examination reveals a rounded, fairly well-circumscribed yellow-orange lesion with multifocal hemorrhage and necrosis. Microscopic examination demonstrates a variety of histologic patterns, including alveolar, solid, and acinar patterns surrounded by thin-walled vessels. The cells typically demonstrate clear cytoplasm, reflecting the dissolution of lipid and glycogen within histologic preparations. Occasionally, eosinophilic granular cytoplasm may be detected. Nuclear features are scored via the Fuhrman grading system (Fuhrman et al., 1982), which yields prognostic information (Srigley et al., 1997; Zisman et al., 2001) within each pathologic stage and is scored as follows: Grade I, small, uniform nuclei; Grade II, granular open chromatin without conspicuous nucleoli; Grade III, prominent nucleoli identified at 10x magnification; Grade IV, nuclear pleomorphism and macronucleoli. The highest grade identified within the lesion carries the overall RCC grade.

Cytology of RCC as obtained by fine needle aspiration (FNA) demonstrates short papillary groups, “floral” type cellular arrangements, and occasionally metachromatic basement membrane-like material. The individual cells may contain clear, granulated, or multivacuolated cytoplasm, most notably demonstrated by Diff-Quik stain. Nuclei often demonstrate low nuclear/cytoplasmic ratios. A prominent, cherry-red nucleolus may be present in lesions of higher grade. Attempts at grading should be performed on the cytologic specimen, with the caveat that the entire lesion has not been sampled. Sarcomatoid change is evidenced by a dimorphic population consisting of high grade epithelial carcinoma and spindle or strap-like cells.

Multilocular cystic renal cell carcinoma is composed of cells morphologically identical to grade I clear cell RCC, but demonstrates only multiple cystic structures (Murad et al., 1991). This lesion is categorized separately within the WHO classification scheme.

The diagnosis of clear cell RCC, like other subtypes of RCC, is based primarily on morphologic features. Clear cell RCC immunolabels with the RCC antibody (McGregor et al., 2001), which can be helpful in

distinguishing metastatic lesions with clear cell features. Other immunostains for CD10 (Avery et al., 2000), epithelial membrane antigen (EMA; Taki et al., 1999), cytokeratins (Pitz et al., 1987; Delahunt and Eble, 1997), and parvalbumin (Martignoni et al., 2001) have been examined, although no definitive labeling panel has been designed to distinguish RCC subtypes.

Deletions of chromosome 3p have been detected by fluorescence in situ hybridization (FISH), loss-of-heterozygosity (LOH) analysis, and CGH analysis, and have been proposed to be an early event in the pathogenesis of clear cell RCC (Zbar et al., 1987; Presti et al., 1991, 1998). Specific regions of chromosome 3 deletions include gene locus 3p25-26 spanning the VHL gene, 3p21-22, and 3p13-14 (Yamakawa et al., 1991; Latif et al., 1993; Shuin et al., 1994; van den Berg et al., 1996; Velickovic et al., 1999). The VHL locus is also affected in clear cell RCC by mutation and DNA methylation (the VHL pathway is discussed under familial renal cell carcinoma; Dulaimi et al., 2004). Additional loci affected by LOH that demonstrate a worsened prognosis include 9p, 14q, 17p and 10q (Oda et al., 1995; Wu et al., 1996; Kondo et al., 2001; Presti et al., 2002).

Patient survival correlates well with pathologic staging, with increasing stage characterized by large size, extension into the renal vein or invasion into the sinus or perirenal fat. The microscopic finding of sarcomatoid differentiation portends a poor overall survival, especially when sarcomatoid differentiation comprises greater than 50% of the specimen (Moch et al., 2000). Metastatic spread of clear cell RCC often occurs hematogenously to the lungs and bone, although lymphatic spread may also occur. Unusual sites, including the thyroid gland, heart, spleen, and pancreas may be involved by clear cell RCC metastases many years after initial diagnosis.

A comparison of clear cell RCC with other renal neoplasms is provided in Table 1.

Papillary renal cell carcinoma

Papillary RCC is a malignant neoplasm that presents similarly to clear cell RCC and is primarily distinguished on a pathologic basis (Mancilla-Jimenez et al., 1976; Mydlo and Bard, 1987; Kuroda et al., 2003b). Although frequently sporadic, papillary RCC may rarely be found as a component of hereditary papillary renal cancer, hereditary leiomyomatosis and RCC, and Birt-Hogg-Dubé syndromes. Frequently solitary, this subtype of RCC is more commonly multifocal and bilateral than other subtypes of RCC (Renshaw and Corless, 1995). Papillary RCC is proposed to arise from cells of the proximal renal tubule.

On gross examination, papillary RCC appears well-circumscribed and yellow-brown with multiple regions of hemorrhage and necrosis. Commonly, cystic degeneration and papillary structures may be identified. Microscopic examination reveals papillary or

tubopapillary structures; occasionally, more solid forms of papillary RCC may be identified containing a glomeruloid-like growth of cells. The fibrovascular cores in these lesions contain macrophages with occasional cholesterol clefts, hemosiderin-laden macrophages, and calcifications. Similar to clear cell RCC, the Fuhrman system is utilized for nuclear grade. Uncommonly, sarcomatoid differentiation may be identified, which predicts a poorer outcome.

On cytologic analysis, specimens appear cellular and contain papillary structures lined by a single layer of uniform tumor cells with a high nuclear/cytoplasmic ratio and fine, granular chromatin. Frequently, foamy and hemosiderin-laden macrophages are identified within the papillae. On occasion, psammoma bodies may be identified.

In recent years, papillary RCC has been subdivided into type 1 and type 2 lesions based on cellular morphology and patient outcome, although this classification remains somewhat controversial (Delahunt and Eble, 1997; Delahunt et al., 2001; Allory et al., 2003). Type 1 lesions contain a single layer of small cells with little cytoplasm that rest on the underlying fibrovascular cores, whereas type 2 lesions contain pseudostratified cells with abundant eosinophilic cytoplasm and nuclear atypia. Overall, type 2 lesions demonstrate poorer patient survival.

In contrast to the clear cell RCC, chromosome 3 alterations are more infrequent in papillary RCC (Morrissey et al., 2001; Velickovic et al., 2001). The most common alterations, in contrast, are trisomy 7 and 17 and loss of chromosome Y (Kovacs et al., 1991). Specific loss at 9p13 has been associated with poorer survival in patients with papillary RCC (Schraml et al., 2000).

A similar morphologic, but benign, lesion that commonly arises in the kidneys of elderly persons and patients on hemodialysis is the papillary adenoma. These lesions are less than 5 mm in diameter and demonstrate low nuclear grade. Papillary adenomas contain similar genetic alterations as those found in papillary RCC.

Chromophobe renal cell carcinoma

Chromophobe RCC accounts for only 5% of renal cell carcinomas and demonstrates only rare distant metastases and a mortality rate of less than 10%, emphasizing the importance of distinguishing this subtype of RCC. Chromophobe RCC appears to arise from the intercalated cells of the renal collecting duct and may occur in association with Birt-Hogg-Dubé syndrome (Pavlovich et al., 2002). In general, chromophobe RCC presents with similar features to clear cell RCC (Kuroda et al., 2003a).

Gross examination of chromophobe RCC reveals a slightly lobulated, light brown cut surface with small areas of hemorrhage. A distinguishing characteristic is the transition to a gray coloration of the lesion following fixation. Microscopic examination identifies tumor cells admixed with broad septa and thick-walled, hyalinized blood vessels. These cells are an admixture of large, polygonal cells with pale cytoplasm and prominent cell membranes with smaller cells containing a granular, eosinophilic cytoplasm. Binucleated cells are occasionally seen. Nuclei commonly demonstrate a wrinkled appearance with perinuclear halos. A Hale's colloidal iron stain reveals a blue cytoplasmic staining pattern of the lesional cells. As in other subtypes of RCC, sarcomatoid differentiation portends a poorer prognosis.

Cytology of chromophobe RCC parallels the features identified in surgical specimens. Typically, polygonal cells with either pale or granular cytoplasm and coarse, granular chromatin are present. Occasionally, perinuclear halos, binucleation, and cytoplasmic metachromatic hyaline globules may be present. These cells are positive by Hale's colloidal iron stain.

Despite the good prognosis generally associated with chromophobe RCC, these lesions demonstrate a surprisingly extensive loss of chromosomes, including -1, -2, -6, -10, -13, -17, and -21 (Speicher et al., 1994; Bugert and Kovacs, 1996; Brunelli et al., 2004). In

Table 1. Comparison of key features distinguishing subtypes of sporadic renal neoplasms.

RENAL NEOPLASM	GROSS DESCRIPTION	MICROSCOPIC DESCRIPTION	GENETICS
Clear cell RCC	Yellow-orange Hemorrhage, necrosis Well-circumscribed	Acinar, alveolar, solid patterns Clear cytoplasm Fuhrmann graded nuclei	3p deletions <i>VHL</i> mutation LOH of 9p,14q,10q
Papillary RCC	Yellow-brown Well-circumscribed	Papillary, tubulopapillary Type 1 vs type 2 morphology Foamy macrophages	Trisomy 7, 17 Loss of chromosome Y
Chromophobe RCC	Lobulated, light brown Gray following fixation Well-circumscribed	Mixture of pale and pink cells Distinct cell borders, binucleated Hyalinized vessels, septae	Extensive chromosome loss, including 1, 2, 6, 10, 13, 17, and 21
Oncocytoma	Mahogany-brown, Well-circumscribed Central scar	Nests, acini, tubular structures Eosinophilic, granular cytoplasm	Mixed population of normal and abnormal karyotypes; t(5;11)(q35;q13); loss of chromosomes 1, 14; 11q13 rearrangements

addition, mutations of *p53*, *LOH* of *10q23.3* in the region of *PTEN*, and telomere shortening have been reported in these lesions (Holzmann et al., 1993; Contractor et al., 1997; Sukosd et al., 2001).

Oncocytoma

Oncocytomas are benign neoplasms that are proposed to arise from the intercalated cells of the kidney. These neoplasms occur sporadically, as well as part of the Birt-Hogg-Dubé syndrome (Pavlovich et al., 2002). Similar to the malignant renal neoplasms, these lesions occur in adult patients.

Oncocytomas are commonly incidental findings discovered on radiologic workup for other disease processes. A classic radiologic finding of oncocytoma is a central scar.

On gross examination, oncocytomas appear well-circumscribed, mahogany-brown lesions with a central scar in approximately one-third of cases. On microscopic analysis, these lesions contain nests, acini or tubular structures comprised of round to polygonal cells with dense eosinophilic cytoplasm. The nuclei appear uniform with variably prominent nucleoli, although rare pleomorphic cells with degenerative atypia and cells with a paucity of cytoplasm may be identified.

On cytologic analysis, a monomorphous population of large polygonal or rounded cells with finely granular cytoplasm is identified. The nuclei are bland with fine, granular chromatin. As oncocytic cells may be identified in a variety of renal lesions, including clear cell RCC and oncocytic carcinoma, these lesions should be designated as an oncocytic neoplasm only.

Genetic analysis reveals a mixture of cells that contain normal and abnormal karyotypes. Rarely, loss of chromosome 1 and 14 and translocation of t(5;11)(q35;q13) (van den Berg et al., 1995; Presti et al.,

1996; Herbers et al., 1998). In a small set of oncocytomas, rearrangements of 11q13 have recently been reported (Jhang et al., 2004).

Familial renal cell carcinoma

Familial renal cell carcinoma accounts for approximately 1 to 4% of all RCCs diagnosed (Pavlovich and Schmidt, 2004). Although the majority of patients with one of the familial syndromes are often diagnosed based on other systemic findings, an occasional patient may initially present with renal disease. In general, RCCs arising in the context of heritable syndromes occur at younger ages and are often bilateral and multiple, in contrast to the sporadic forms, which are often solitary. Furthermore, the genetic abnormalities underlying familial renal neoplasms are often distinct from those identified in sporadic forms, with the exception of 3p loss, which encompasses the VHL gene locus (Latif et al., 1993), in clear cell RCC.

The major forms of familial renal cell carcinoma include von Hippel-Lindau (VHL) syndrome, hereditary papillary renal cancer, hereditary leiomyomatosis and RCC, Birt-Hogg-Dubé syndrome, and constitutional chromosome 3 syndrome. A rare form of familial renal cancer is hyperparathyroidism-jaw tumor syndrome.

von Hippel-Lindau (VHL) syndrome

Germline mutations of the VHL gene on 3p25-26 lead to the VHL syndrome, characterized by clear cell RCC, renal cysts, hemangioblastomas of the central nervous system and retina, pheochromocytoma, pancreatic cysts and neuroendocrine tumors, inner ear tumors, and cystadenomas of the epididymis and broad ligaments (Shuin et al., 2004). The major cause of mortality in these patients is metastatic clear cell RCC

Table 2. Familial renal cancer syndromes.

SYNDROME	CHROMOSOME	GENE	INHERITANCE	RENAL LESION(S)	ADDITIONAL MANIFESTATIONS
Von Hippel-Lindau	3p25	VHL	AD 1:40,000*	Clear cell RCC, renal cysts	CNS, retinal hemangioblastomas, inner ear tumors, pancreatic endocrine tumors and cysts, cystadenomas of the broad ligament and epididymis
Hereditary papillary renal carcinoma	7q31	c-MET	AD	Type 1 papillary RCC	None
Hereditary leiomyomatosis and RCC	1q42-43	FH	AD	Type 2 papillary RCC	Cutaneous and uterine leiomyomas, uterine leiomyosarcomas
Birt-Hogg-Dubé	17p11.2	BHD	AD	Chromophobe, clear cell, papillary RCC, oncocytomas	Facial fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, multiple lipomas
Constitutional chromosome 3 translocation				Clear cell RCC	None
Hyperparathyroidism jaw tumor	1q25-32	HRPT2	AD	Papillary RCC, mixed epithelial/stromal tumors	Parathyroid tumors, mandibular and maxillary fibroosseous lesions

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(Shen et al., 2000).

The *VHL* gene encodes a tumor suppressor molecule that appears to mediate cell cycle regulation and angiogenesis. Under normal conditions, *VHL* is widely expressed in epithelial and nervous tissues, where it has been proposed to regulate hypoxia-inducible factor (HIF) and HIF-1 β (Sakashita et al., 1999; George and Kaelin, 2003). Under normoxic conditions, *VHL* undergoes hydroxylation at one to two proline residues, allowing it to undergo ubiquitination and subsequent targeted degradation. Under hypoxic conditions, hydroxylation and ubiquitination does not occur, allowing HIF to enter the nucleus and induce transcription of hypoxia-inducible genes, such as vascular endothelial growth factor (VEGF) and erythropoietin (Maxwell et al., 1999). Additional functions of *VHL* have been recently described, including participation in the assembly of the extracellular fibronectin matrix, exit of the cell cycle, epithelial cell differentiation and downregulation of CXCR4, a chemokine receptor implicated in metastatic spread (Ohh et al., 1998; Staller et al., 2003).

Alterations of the *VHL* gene include missense and nonsense mutations, deletions, and splice site mutations (Neumann and Bender, 1998). Patients with *VHL* mutations are further subdivided into type 1, 2A, and 2B types, related to the presence or absence of pheochromocytoma and RCC, as well as the specific underlying mutation.

Hereditary papillary renal carcinoma (HPRC)

HPRC demonstrates multiple, bilateral type 1 papillary RCCs without additional systemic manifestations of disease. Activating mutations of the *MET* oncogene, which encodes a receptor tyrosine kinase that binds hepatocyte growth factor (HGF), underlie the pathogenesis of this disorder (Jeffers et al., 1997; Schmidt et al., 1997, 1998). Under normal conditions, the *MET* gene product regulates cellular proliferation and cell migration in response to HGF. Mutation of the *MET* gene underlies progression and metastatic spread of numerous epithelial carcinomas, including breast and colon cancer (Ma et al., 2003).

Hereditary leiomyomatosis and renal cell cancer (HLRCC)

Multiple bilateral type 2 papillary RCCs, cutaneous and uterine leiomyomas, and early onset uterine leiomyosarcoma defines the HLRCC syndrome.

The genetic alteration underlying this syndrome includes missense and splice site mutations of the *FH* gene, which encodes a mitochondrial and cytosolic protein (Tomlinson et al., 2002; Alam et al., 2003). Mitochondrial *FH* participates in the Krebs cycle to convert fumarate to malate; the function of cytosolic *FH* has not been elucidated (Tomlinson et al., 2002). To date, no correlation between *FH* mutation and phenotype

of patients with HLRCC has been identified. Inactivation of the *FH* gene has been implicated in the activation of the HIF hypoxia pathway and upregulation of hypoxia-inducible genes, similar to the activated pathway in *VHL* gene mutations, although the types of RCC identified in these syndromes are different.

Biallelic germline mutations of the *FH* gene have also been described and has been associated with the *FH* deficiency syndrome (Kiuru et al., 2001; Alam et al., 2003), characterized by developmental delay, neurologic impairment, fumaric aciduria, and reduced *FH* enzymatic activity throughout the body; these patients have an implied risk for the development of type 2 papillary RCC.

Birt-Hogg-Dubé syndrome (BHD)

BHD syndrome predisposes patients to the development of facial fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and multiple forms of RCC, including oncocytomas and chromophobe, clear cell, and papillary RCC.

Multiple genetic alterations predispose to the BHD syndrome, including frameshift mutations and LOH (Nickerson et al., 2002; da Silva et al., 2003; Khoo et al., 2003). The BHD gene encodes folliculin, a highly conserved protein of unknown function that does not share significant homology to known human proteins.

Constitutional chromosome 3 translocations (CC3)

Patients with the CC3 syndrome are predisposed to the development of multiple, bilateral clear cell RCCs without additional systemic manifestations. The multiple genetic abnormalities underlying this syndrome are unified by heritable patterns of clear cell RCC associated with breakpoints along the p and q arms of chromosome 3 (Cohen et al., 1979; Bodmer et al., 2002). The involvement of the *VHL* gene in the development of renal cancer in CC3 patients is controversial, and to date, no CC3 patient has developed systemic manifestations associated with the *VHL* syndrome.

Hyperparathyroidism-jaw tumor (HPT-JT) syndrome

Patients with HPT-JT syndrome demonstrate an increased risk for the development of fibroosseous lesions of the maxilla and mandible, as well as parathyroid tumors, papillary RCC, and mixed epithelial and stromal tumors of the kidney (Chen et al., 2003). Mutations of the *HRPT2* gene, which encodes parafibromin, underlies the HPT-JT syndrome, although the function of this gene product is unclear (Carpten et al., 2002).

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