Renal Cystic Diseases and Renal Neoplasms: A Mini-Review

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The past two decades have witnessed recognition of several new types of renal cell carcinoma, each with distinct cytogenetic abnormalities. Included are several genetic and acquired cystic kidney diseases associated with development of renal cell carcinoma, the topic of this review. The risk in patients with autosomal dominant polycystic kidney disease is not accurately known but may be slightly increased. The risk for patients with von Hippel-Lindau disease is substantial, and death from renal cancer is common. For patients with tuberous sclerosis complex, the challenge is recognition of the occasional malignancy arising in a field of many benign tumors. Patients with end-stage kidney disease and acquired cystic kidney disease may develop a variety of renal cell carcinoma types. Progress in understanding the molecular basis of renal cyst formation and neoplastic disease has fostered development of targeted therapies that now hold promise for a group of neoplasms whose cure was traditionally dependent on surgical approaches.

R
enal cell carcinomas (RCCs) comprise 2 to 3% of all cancers in the United States (1). Approximately 58,000 new cases of renal cancer (including renal and pelvic cancer) will be diagnosed this year (2). The incidence of RCC ranges from 5 to 10 cases/100,000 population, with the rate being 1.6 times higher in men than in women. There are significant differences in the rate of RCC worldwide. The rate is substantially higher in industrialized nations, partially attributable to known risk factors for RCC. Smoking and industrial compounds are estimated to account for 40 to 50% of cases (1,3,4). Relevant to this manuscript, end-stage kidney disease (ESKD), acquired cystic kidney disease (ACKD), and two genetic renal cystic diseases pose additional risk for RCCs, although their contribution to the total pool of patients is small (1,5–8).

There has been an explosion of information about RCCs over the past two decades. A host of new types (Table 1) have been identified, validated by the presence of distinct cytogenetic abnormalities that explain a historically confusing variety of histologic features previously lumped together as RCCs (1,9–13). Table 2 lists the three most common types of RCCs that comprise 95% of cases; frequency, survival differences, and major cytogenetic abnormalities are also provided (9–13). There is a growing imperative to accurately classify RCC type. Advances in understanding the genetic and molecular events in renal neoplasia is leading to promising targeted therapies for neoplasms whose cure was traditionally dependent on surgical approaches (14–30).

Results and Discussion

The association between renal cortical cysts and RCCs has long attracted the attention of physicians; Sturm in 1875 (31) and Brigidi and Severi in 1880 (32) first postulated an association between renal cysts and RCC. Since these early theories, it is apparent that there are several permutations on the renal cysts and RCC theme that merit separation (33–40). These are noted in Table 3 with comments on their significance. Awareness of these possibilities is important when imaging studies show both cysts and RCC.

In cysts with a mural nodule, cystic tumor necrosis, and intrinsically cystic neoplasms, the surrounding kidney is characteristically noncystic. However, if multiple cysts are present, a cystic renal disease with a neoplastic diathesis should be entertained. Imaging of the contralateral kidney and obtaining pertinent clinical data and family history should be initiated. Four renal cystic diseases that may convey a risk for development of RCCs are the topic of this review and are discussed in order of incidence (Table 4).

Autosomal Dominant Polycystic Kidney Disease

Walters and Braasch (41) are usually cited as the first to mention an association between autosomal dominant polycystic kidney disease (ADPKD) and RCCs, although their 1934 paper focused on surgical issues with only a single sentence that mentioned that 1 of 85 patients had RCCs. The literature on this association is sparse and largely populated by single case reports (7). There are two small series of three cases each (42,43). The best approximation of a population-based study of the incidence of RCCs in ADPKD is a Japanese questionnaire study by Hatano et al. (44), who collated data from 507 hospitals on 5721 patients with RCCs. Renal cystic diseases were identified in 233 patients, and 3 patients had “polycystic kidney disease.” Unfortunately, the dominator, or pool of ADPKD patients from which the cases in these three studies were drawn, was not provided, precluding determination of incidence.

Evidence to support a tumor diathesis in ADPKD is largely circumstantial. Compared with sporadic RCC, RCCs in ADPKD develop at a younger age (47 versus 61 yr), is more often...
bilateral (12 versus 2 to 6%), and is multicentric (30 versus 5%; Figure 1A) (43). A potential precursor lesion, intracystic papillary tuft-like proliferation, is identified in 25% of cases, although these are cytologically bland and a proliferative continuum from benign to malignant lesions as occurs in the entities to follow is lacking (Figure 2A) (45).

There is also circumstantial evidence against a risk of RCCs in ADPKD. Death from RCCs is notably absent from most lists of morbidity and mortality in ADPKD (46). Furthermore, cancers arising in ADPKD are more likely to be reported because of their rarity. Possibly more pertinent, some reported patients have had the contiguous gene syndrome (discussed later), "unilateral or

Table 1. Uncommon RCCs and intrinsically cystic neoplasms

<table>
<thead>
<tr>
<th>I. Uncommon RCCs</th>
<th>II. Intrinsically Cystic Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilocular cystic renal cell carcinoma</td>
<td>A. Malignant</td>
</tr>
<tr>
<td>Collecting duct carcinoma</td>
<td>Multilocular cystic renal cell carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Tubulocystic carcinoma</td>
</tr>
<tr>
<td>Translocation carcinomas (six types)</td>
<td>B. Benign</td>
</tr>
<tr>
<td>Tubulocystic carcinoma</td>
<td>Cystic nephroma</td>
</tr>
<tr>
<td>Mucinous tubular spindle cell carcinoma</td>
<td>Mixed epithelial and stromal tumor</td>
</tr>
<tr>
<td>Hereditary renal cell carcinomas (multiple types)</td>
<td>Cystic partially differentiated nephroblastoma</td>
</tr>
<tr>
<td>Multilocular cystic renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Clear cell papillary renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Acquired cystic kidney disease associated renal cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Three most common types of RCC

<table>
<thead>
<tr>
<th>Carcinoma Type</th>
<th>Frequency</th>
<th>5-yr Survival</th>
<th>Major Genetic Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell renal cell carcinoma</td>
<td>70–80%</td>
<td>55–60%</td>
<td>Chr 3p loss</td>
</tr>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>10–15%</td>
<td>70–90%</td>
<td>Trisomy 7, 17, others</td>
</tr>
<tr>
<td>Chromophobe renal cell carcinoma</td>
<td>3–5%</td>
<td>95%</td>
<td>Loss Y Chr in males</td>
</tr>
</tbody>
</table>

Table 3. Cysts, cystic neoplasms, cystic renal diseases, and RCC

<table>
<thead>
<tr>
<th>Relationship between Cyst and Carcinoma</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple cyst and renal cell carcinoma</td>
<td>Coincidental association in 1% cases</td>
</tr>
<tr>
<td>Cyst with mural nodule of renal cell carcinoma</td>
<td>Extremely rare, few case reports</td>
</tr>
<tr>
<td>Cystic tumor necrosis</td>
<td>5–7% cases, usually high grade tumors</td>
</tr>
<tr>
<td>Inherently cystic renal neoplasms</td>
<td>Both malignant and benign occur (Table 1)</td>
</tr>
<tr>
<td>Renal cystic diseases and renal cell carcinomas</td>
<td>Several types, risk of RCC is substantial</td>
</tr>
</tbody>
</table>

Table 4. Cystic renal diseases with risk of RCCs

<table>
<thead>
<tr>
<th>Cystic Disease</th>
<th>Incidence</th>
<th>Mutated Gene/Protein</th>
<th>Cancer Risk</th>
<th>Cancer Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>1:1000</td>
<td>PKD1/poly CF1</td>
<td>Not known</td>
<td>Papillary</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>1:30–50,000</td>
<td>PKD2/poly CF2</td>
<td>60% of patients</td>
<td>Clear cell</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>1:10,000</td>
<td>VHL/pVHL</td>
<td>2–3% of patients</td>
<td>Clear cell</td>
</tr>
<tr>
<td>End stage kidney disease ± acquired cystic kidney disease</td>
<td>Proportional to dialysis duration</td>
<td>TCS1/hamartin, TCS2/tuberin</td>
<td>Diverse, dependent on tumor type</td>
<td>Usual types, Two new types</td>
</tr>
</tbody>
</table>

There is also circumstantial evidence against a risk of RCCs in ADPKD. Death from RCCs is notably absent from most lists of morbidity and mortality in ADPKD (46). Furthermore, cancers arising in ADPKD are more likely to be reported because of their rarity. Possibly more pertinent, some reported patients have had the contiguous gene syndrome (discussed later), “unilateral or
early PKD,” or are poorly illustrated, raising legitimate questions regarding the cystic disease present. Although the actual risk of malignancy in ADPKD is not known, it is not clearly increased.

**Tuberous Sclerosis Complex**

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with an incidence of 1:10,000 (47–53). Tuberous sclerosis develops from inactivating mutations of TSC1 or TSC2, which are tumor suppressor genes that encode for hamartin and tuberin, respectively. In TSC, dysgenic lesions develop in the brain, skin, heart, lungs, retina, and kidney. Renal involvement develops in 50 to 80%, consisting of renal cysts and neoplasms (Table 5) (54–67).

Cysts, although frequently occurring in TSC, are usually few
in number and more common with TSC2 (53). Diffusely cystic kidneys identical to ADPKD develop in 5% of TSC2 patients and are known as the contiguous gene syndrome (Figure 1B) (68–74). This syndrome results from dual mutations of TSC2 and PKD1, adjacent genes on chromosome 16. The contiguous gene syndrome is important because renal failure develops at an early age from polycystic kidney disease, usually before age 30, and patients with contiguous gene syndrome have the greatest risk of renal malignancy, which also develops at an early age.

The cysts in TSC with the contiguous gene syndrome are often distinctive, lined by large often “hyperplastic” eosinophilic cells (Figure 2B). Renal neoplasms include angiomyolipoma (AML), and two renal cancers: CC-RCC and a variant of AML known as epithelioid AML (epAML). Angiomyolipoma is an unusual mesenchymal neoplasm composed of several tissue types as reflected in its name. It is a member of a group of neoplasms derived from the perivascular epithelioid cell, a cell that has no known normal cellular counterpart. Collectively, these tumors are known as perivascular epithelioid cell-omas (75,76). They may arise in a variety of organs and in soft tissue, and both benign and malignant forms occur.

epAML, an uncommon variant of AML, is composed of large eosinophilic cells. It develops in patients with TSC or may occur sporadically (55,67). The incidence of malignancy is not known because of the rarity of the tumor and variation in diagnostic criteria. However, ~30 to 50% of reported cases of epAML have been malignant (55,67,75,76). Both regular AML and epAML express a variety of melanocytic markers and are negative for cytokeratin and other epithelial markers. These important immunophenotypic features permit separation of epAML from histologically similar appearing RCCs. Most reports of malignancy arising in TSC did not use immunostaining for cytokeratin and melanocytic markers, limiting certainty as to which type of malignancy was actually present. Although renal cancers affect only 2 to 3% of TSC patients, because benign AMLs are so common, the challenge is to recognize a cancer in the setting of multiple benign AMLs.

von Hippel-Lindau Disease

von Hippel-Lindau (VHL) disease is an autosomal dominant disorder with an incidence of 1:35 to 50,000. VHL disease results from germline mutations or deletions of the VHL gene, a tumor suppressor gene located on chromosome 3p25–26 (14,77–81). The protein product, pVHL, has been localized to the primary cilium, placing it within a group of hereditary cystic diseases known as ciliopathies that includes ADPKD (82–84). Carriers of the VHL mutation are subject a second inactivating event of the wild-type VHL allele, predisposing to tumor formation.

Renal involvement in VHL consists of multiple, bilateral clear cell-lined cysts in 70 to 80% and multifocal and bilateral clear cell (CC) RCC in 40 to 60% of patients histologically identical to sporadic CC-RCC (Fig. 1C) (77–81). In VHL disease, the number of solid tumors, incipient tumors, and neoplastic cysts in nephrectomy specimens can be impressive; their number is dependent on the thoroughness of examination as exemplified by two pathologic studies of nephrectomies (Figure 2C). Poston et al. (79) studied 12 kidneys from VHL patients and identified 116 cystic and solid lesions; 65 were deemed malignant. Chauveau et al. (80) examined 46 kidneys from 29 VHL patients and identified 195 solid RCCs and 138 cystic lesions that ranged from benign cysts to cystic RCCs. Despite the high incidence of

Table 5. TSC: selected epidemiologic studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>Study Details</th>
<th>No. of Patients</th>
<th>AML</th>
<th>Cysts</th>
<th>RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rakowski</td>
<td>53</td>
<td>2006</td>
<td>US, MRI, CT</td>
<td>167</td>
<td>82 (49%)</td>
<td>43 (26%)</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>O’Callaghan</td>
<td>52</td>
<td>2004</td>
<td>US</td>
<td>179</td>
<td>86 (48%)</td>
<td>37 (21%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Cook</td>
<td>50</td>
<td>1996</td>
<td>US</td>
<td>139</td>
<td>68 (49%)</td>
<td>44 (32%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Webb</td>
<td>49</td>
<td>1994</td>
<td>US</td>
<td>21</td>
<td>14 (66%)</td>
<td>3 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

RC, renal cancer (includes renal cell carcinoma and malignant epAML); US, ultrasound; CT, computerized tomography; MRI, magnetic resonance imaging.

Table 6. Incidence of RCC in ESKD and ACKD

<table>
<thead>
<tr>
<th>First Author</th>
<th>Reference</th>
<th>Year</th>
<th>Study Details</th>
<th>No. of Patients</th>
<th>ARCD</th>
<th>RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller</td>
<td>86</td>
<td>1989</td>
<td>Autopsy</td>
<td>155</td>
<td>58%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Gulaniker</td>
<td>87</td>
<td>1998</td>
<td>US/CT</td>
<td>206</td>
<td>31%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Farivar-Mohseni</td>
<td>95</td>
<td>2005</td>
<td>US/CT</td>
<td>852</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Kojima</td>
<td>94</td>
<td>2006</td>
<td>US/CT</td>
<td>2024</td>
<td>1.7%</td>
<td></td>
</tr>
<tr>
<td>Denton</td>
<td>90</td>
<td>2002</td>
<td>US-neph</td>
<td>266</td>
<td>33%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Schwarz</td>
<td>96</td>
<td>2007</td>
<td>US-neph</td>
<td>561</td>
<td>23%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Takahashi</td>
<td>89</td>
<td>1993</td>
<td>Neph</td>
<td>50</td>
<td>8.0%</td>
<td></td>
</tr>
</tbody>
</table>

US, ultrasound; CT, computerized tomography; Neph, nephrectomy.
RCC and close cancer surveillance, RCC remains the leading cause of death; one third of VHL patients die of metastatic RCC.

**ESKD and ACKD**

The first association between RCC and ESKD with ACKD was reported by Dunhill et al. in 1977 (85), who described 6 cases in 14 ACKD patients at autopsy (85). This high incidence is definitional; their series included only advanced cases of ACKD. Numerous studies of ACKD in the dialysis population have shown that the incidence of ACKD is proportional to dialysis interval, with close to 100% of patients affected by 10 yr of dialysis (85–94). Renal transplantation seems to reduce the incidence of ACKD (95). A significant concern with ESKD and ACKD is development of RCC, a risk that also increases with duration of dialysis (Table 6) (86–96). Screening for ACKD and RCC is recommended both by the American Society for Transplantation and the European Renal Association-European Dialysis and Transplant Association for patients at high risk or who have been on long-term dialysis, respectively, although an agreed on definition of high risk or long term is lacking (97–99). In a recent study of 561 transplant recipients, Schwarz et al. (96) recommended that all transplant patients have annual ultrasound screening of their native kidneys. Additional recommendations for those with ACKD were proposed based on Bosniak category. It is important to note, however, that ACKD is not a prerequisite for a neoplasia (Figure 3). Kojima et al. (94) reported on 2624 dialysis patients; they identified RCC in 44 patients. Thirty-five patients had ACKD, but nine patients had ESRD without ACKD.

Numerous studies have compared sporadic RCCs to RCCs developing in ESKD/ACKD (86–96). The neoplasms in ESKD/ACKD compared with sporadic cases of RCC are more often smaller, multifocal, bilateral, and lower stage and have a papillary histology. Furthermore, the tumors are more often indolent, with higher 5-yr survivals. The presumption of a favorable prognosis, however, should be viewed with caution. In a study of tumor doubling volumes, Takebayashi et al. (100) found that, although most tumors grew at a rate of 0.5 to 1 cm/yr, 25% of cases showed rapid growth of 6 cm, or more, per year. Thus, all neoplasms in ESKD/ACKD are not biologically equivalent in keeping with their histologic and genetic diversity noted below.

As experience with RCCs in ESKD/ACKD has accumulated and pathologic features have been more critically analyzed, a great degree of heterogeneity was appreciated that reflects cytogenetic differences (101–103). A broad spectrum of epithelial neoplasms is now recognized in ESKD/ACKD, highlighted in a recent report by Tickoo et al. (104). They identified 52 patients with ESKD and RCC; 39 had ACKD and 13 had ESKD without ACKD, again showing that cystic disease is not a prerequisite for neoplasms. The tumors types identified fell into two categories. One group of 27 cases contained RCCs identical to the cancers arising in sporadic cases. The second group of 39 cases consisted of two unique tumors: ACKD-associated RCC and clear cell papillary RCC.

The first neoplasm, ACKD-RCC, is a tumor composed of large eosinophilic cells arranged in a tubulocystic architecture pattern (104–108). Although this histology is not particularly unique, the presence of numerous birefringent calcium oxalate crystals notably sets this tumor apart from other RCCs (Figure 4A). Although,
cytogenetic data are limited to a single report, two of three cases had a “distinctive” cytogenetic profile with gains in chromosomes 1, 6, 10, and 17 (108). The third was cytogenetically normal.

The second tumor, originally identified in ESKD, is called clear cell papillary RCC; it contains clear cells similar to CC-RCC but in a papillary arrangement, an exclusionary feature for a diagnosis of CC-RCC (Figure 4B) (104,109,110). Genetic studies showed that the 3p mutation of CC-RCC is not present, establishing this tumor as a cytogenetically unique neoplasm (111). Since the initial description of this tumor, it has been identified in patients without ESKD, indicating a more widespread occurrence (109,110). Although follow-up information is limited, two cases of ACKD RCC have metastasized, whereas metastases have not been reported in clear cell papillary RCC.

**Genetic and Molecular Basis of RCC in Genetic Cystic Diseases and Targeted Therapies**

TSC and VHL disease are both tumor suppressor–associated disorders resulting in renal cysts and solid tumors (20). The VHL gene at chromosome 3p25 is affected in both VHL disease and in sporadic CC-RCC. Somatic mutations or deletions of the VHL gene occur in 60% of sporadic CC-RCC (13–19). Clear cell RCC with VHL mutations have launched our understanding of molecular events in sporadic CC-RCC and in cancers arising in cystic renal diseases. pVHL is a master regulator protein with two active isoforms, pVHL (30) and pVHL (19), involved in cell cycle control and regulation of the hypoxia-inducible factor (HIF) pathway (Figure 5). Cells lacking pVHL increase expression of genes encoding for factors involved with angiogenesis, cell proliferation, and apoptosis (Figure 5).

Molecular events in RCC arising in TSC implicate a role for the hamartin-tuberin complex that regulates the mammalian targets of rapamycin (mTOR) pathway and is also involved with HIF as shown in Figure 5 (17,22,29,30). In VHL disease, proteosome removal of HIF is reduced, whereas in TSC, the production of HIF is enhanced. Mutations of TSC1 and TSC2 in animals have been shown to result in renal tumors associated with upregulation of HIF 1α and 2α (22). The TSC gene function may also provide a link between ADPKD and neoplasia because polycystin 1 interacts with tuberin, thereby again potentially affecting mTOR and HIF expression (Figure 5) (22,29). Inhibitors of mTOR and angiogenesis now represent promising therapy in certain forms of RCC and have shown efficacy in the treatment of AML (23–29). In patients with advanced stage clear RCC, partial responses with prolongation of survival have been reported.

**Conclusion**

The classification of RCC has evolved from a highly inclusive approach in the 20th century, where morphologically heterogeneous tumors were lumped into a single nosologic entity called RCCs, to a plethora of entities whose separation initially predicated on morphologic grounds has been validated on cytogenetic differences. Risk factors identified for RCCs seem to offer the potential for reducing the incidence of RCCs because some are controllable, specifically smoking and industrial exposures. Ironically, the incidence of RCC is steadily increasing by 2 to 3%/yr, reflecting an increase in detection rate of small tumors discovered incidentally. Fortunately, in parallel with this increase in incidence, the size and stage of tumors has decreased, and outcomes similarly have improved (112).
This review addresses uncontrollable risk factors, the dysregulated environment of hereditary and acquired cystic renal diseases. Of the three genetic cystic diseases discussed, the renal cancer risk for patients with ADPKD is not known. Conversely, the renal cancer risk for patients with VHL disease is substantial, and death from this disease is common despite close surveillance. For patients with TSC, the risk of renal cancer is far less than in VHL disease. However, the challenge is recognition of the occasional malignancy arising in a field of many benign tumors. Patients with ESKD are at substantial risk of renal carcinomas of the usual types and for two neoplasms that seem unique to, or often associated with, patients with ACKD and patients with ESKD, respectively.

Progress in understanding the initiating molecular events in cyst formation and renal neoplasia shows therapeutic promise in affecting cyst formation and in treatment of associated cancers. With advances in molecular therapies, cognizance of the broad spectrum of RCCs possible and their diagnostic nuances is crucial to insure correct tumor classification. As the menu of targeted therapies grows and efficacy improves, renal tumor diagnosis will rely more heavily on molecular diagnostic approaches to avoid misclassification and, thereby, optimize therapeutic strategies.

Disclosures

None.

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