Renal Cell Carcinoma Associated With End-stage Renal Disease and Acquired Cystic Disease of the Kidney

Chin-Chen Pan*
Department of Pathology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

*Corresponding author. Department of Pathology, Taipei Veterans General Hospital, 201, Shih-Pai Road, Section 2, Taipei 11217, Taiwan. E-mail: ccpan@vghtpe.gov.tw

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1. Introduction

Patients with end-stage renal disease (ESRD), especially those with acquired cystic disease of the kidney (ACDK) secondary to long-term dialysis, are at increased risk for renal cell carcinoma (RCC). ACDK usually occurs in 10–20% of patients who have been on dialysis (both peritoneal and hemodialysis) for up to 3 years, in 40–60% up to 5 years, and more than 90% at more than 10 years. Approximately 3–7% of patients with ACDK develop RCC with a risk that is reportedly as high as 100 times compared to that in the general population. In earlier literature, the most common type of RCC arising in the background of ACDK was considered to be papillary RCC. However, with more extensive analyses, that concept has changed dramatically. Although the usual types of RCC as those seen in the general population can occur in ESRD patients with or without ACDK, the common histologic types of RCC that are associated with ESRD and ACDK nowadays are reported to be two specific variants. One subtype has only been described in patients with ACDK, and is hence designated “acquired cystic disease (ACD)-associated RCC” in most reports. The other subtype, designated “clear cell papillary RCC”, occurs chiefly in patients with ESRD, not necessarily in the setting of ACDK.

2. Incidences

Tickoo et al. studied 66 ESRD kidneys (52 of which had ACDK) and found a total of 261 grossly identifiable tumors and numerous additional microscopic tumors in the kidneys. ACD-associated RCC was recognized as the most common type, accounting for 36% of dominant masses in all ESRD kidneys, as well as 46% in ACDK. Clear cell papillary RCC was identified in 23% of all ESRD kidneys regardless of whether or not they showed features of ACDK. Other major usual types including papillary RCC, clear cell RCC and chromophobe RCC accounted for 18%, 15% and 8% of dominant masses in ESRD, respectively.

2.1. ACD-associated RCC

ACD-associated RCCs are observed exclusively in the background of ACDK. It has not been reported in non-cystic ESRD and patients without ESRD. It may be detected in patients with clinical renal masses, but more often present as an incidental finding in nephrectomies performed for other non-tumorous situations. Grossly, they are usually small and may be found within cysts. Multifocality and bilateralism are not uncommon.

Histologically, ACD-associated RCCs show a spectrum of morphologic features, but the presence of eosinophilic (oncocytic) cells with at least Furman grade 3 nuclei, and cribriform as well as tubulocystic patterns, are consistent findings (Figure 1A). Areas with papillary, alveolar, solid or diffuse patterns may also be seen, and sometimes variable proportions of the tumor may have clear cell cytology. Given the occasional presence of papillary structure and large eosinophilic cells with prominent nucleoli resembling those seen in type 2 papillary RCC, it is plausible that ACD-associated RCC was classified as papillary RCC before ACD-associated RCC was recognized as a distinct entity. Nevertheless, the distinct cribriform and microcystic (sieve-like) growth patterns have never been observed in usual papillary RCCs.

One peculiar feature of ACD-associated RCC is the presence of intratumoral oxalate crystals (CaOx) (Figure 1B). Thus, the appellation “oxalate phenotype” was created for this tumor. CaOx is also observed in renal tubules in
non-neoplastic renal parenchyma of ACDK. However, the impact of intratumoral CaOx on tumor cells is not clear. CaOx may act as a mitogen at lower concentrations but may cause cell necrosis or apoptosis at higher concentrations. In the context of ESRD, CaOx is thought to promote cyst and tumor formation through both mechanical obstruction of renal tubules and regulation of tubular cell cycles. However, the crystals rarely induce foreign body reaction and the proliferation activity as measured by Ki67 labeling index is not significantly high in ACD-associated RCC. These features imply that CaOx deposition may not have a great impact on tumor cell kinetics.

The segment of renal tubule that ACD-associated RCC originates from has not been elucidated. ACD-associated RCCs are diffusely immunoreactive for alpha-methylacyl-CoA racemase, CD10, RCC marker, vinculin, glutathione S-transferase-alpha, BerEP4 and pan-cytokeratin AE1/3, and variably reactive for epithelial membrane antigen, vimentin, and low molecular weight cytokeratin. The tumors usually do not express or only focally express CK7, high molecular weight cytokeratin, e-cadherin and kidney specific cadherin at a low level.4,5,7,8 ACD-associated RCCs are labeled by proximal markers at a higher rate than distal ones, suggesting a probable proximal tubule origin.

The atypical cysts in ACDK are most likely precursors of ACD-associated RCC. Histologically, the lining epithelium of “atypical cysts” often has eosinophilic cytoplasm and large nucleoli similar to that of ACD-associated RCC. Occasionally, there is multilayering of the cystic epithelium with formation of papillary tufts or nodular lesions. Keeping in line with this speculation, Cheuk et al.9 observed a gradual increase in chromosome gains along with proliferation of the cystic lining epithelium, leading to multiple chromosomal trisomies and polysomies in the carcinoma. The accumulative cytogenetic abnormalities lend credence to a hypothesis of “adenoma-carcinoma” sequence for the emergence of the tumor.

There are only a few published studies to date on genetic abnormalities in ACD-associated RCC. Cossu-Rocca et al.7 examined three cases using fluorescence in situ hybridization with centromeric probes for chromosomes 1, 2, 6, 10 and 17. They did not find any chromosomal losses but they demonstrated multiple chromosomal gains in two cases. Our recent study demonstrated non-random chromosomal gains clustered on chromosomes 3, 7, 16, Y and, less frequently, 17. We also examined the genotypes of simultaneously multifocal tumors within the affected kidneys. The chromosomal aberrations in all multifocal tumors were not identical for the same kidney or for the same patient, indicating a “field effect” that induces multifocal neoplastic transformation of renal tubular cells.8

2.2. Clear cell papillary RCC

Clear cell papillary RCC was first described by Tickoo et al.5 in their report of a systematic survey of tumors associated with ESRD. The tumors were mostly well circumscribed and enveloped by a thin capsule. Microscopically, the tumors showed a mixed papillary, solid-acinar, tubular and microcystic pattern. Irrespective of the architecture, the tumors were almost entirely composed of cells with clear cytoplasm (Figure 2A). Immunohistochemically, the tumor cells were diffusely positive for CK7 (Figure 2B) but negative for CD10 and alpha-methylacyl-CoA racemase.5,10 Since clear cell RCCs do not show papillary pattern and they are generally negative for CK7, while papillary RCCs are mostly positive for CD10 and alpha-methylacyl-CoA racemase, the tumor did not belong to either category; thus, the hybrid term “clear cell papillary RCC” was coined. It should be noted that clear cell papillary RCC is a distinct entity from clear cell RCC and papillary RCC. The tumor is not considered a hybrid or composite tumor comprising clear cell RCC and papillary RCC.

Unlike ACD-associated RCC, clear cell papillary RCCCs also arise in the kidneys of non-cystic ESRD. Recently, it was claimed that such tumors are not exclusive to ESRD as tumors with similar morphology were reported in the normal kidneys of the general population.10 The scenario has become more perplexing since a group of European pathologists proposed a new entity called
“renal angiomyoadenomous tumor” to describe morphologically overlapping tumors that develop in normal kidneys.11 The debate persists as to whether they belong to the same category of renal tumors.12

The cytogenetic data about clear cell papillary RCCs are limited. Fluorescence *in situ* hybridization analysis of seven clear cell papillary RCCs showed that they all lacked the gains of chromosome 7 and losses of chromosome Y that are typical of papillary RCC. Only one tumor showed a gain of chromosome 17. Deletion of 3p, usually seen in clear cell RCC, was not detected.10 However, the seven tumors were all taken from normal kidneys rather than ESRD kidneys; therefore, the representativeness of those findings is questioned. Our own experience showed trisomy of chromosomes 7 and 17 in one case. Collection of more cases is necessary before a conclusion can be drawn.

### 3. Prognosis

The biologic behavior of RCCs in ESRD is reported to be less aggressive than that of RCCs in sporadic or non-ESRD settings. Only rare cases have been reported that show sarcomatoid changes and metastases.5,13 A possible reason for this less aggressive behavior may be that these patients are usually under constant medical care, with radiological evaluations possibly picking up most tumors quite early.

### 4. Conclusion

Over the past few years, the field of renal tumor pathology has burgeoned with newly defined entities. More and more previously “unclassified” RCCs have gained definitive classifications. The recognitions of ACD-associated RCC and clear cell papillary RCC are good examples of this process. These new entities should not be taken as merely an academic exercise that is interesting to pathologists alone, but rather seen as progress that may have eventual clinical implications. The association of these tumors with ESRD also provides clues as to the histogenesis of RCC that may shed light on further investigations into RCCs.

### References


Figure 2  (A) Mixed papillary and acinar pattern in clear cell papillary renal cell carcinoma. (B) The tumor is diffusely immunoreactive for CK7.