Abstract: The incidence of end-stage renal disease has increased owing to the greater prevalence of patients with chronic kidney disease and diabetes mellitus. End-stage renal disease is usually accompanied by acquired cystic disease and is a risk factor for renal cell carcinoma. The present review discusses the etiology of renal cell carcinoma in end-stage renal disease patients, focusing on two unique renal cell carcinoma histological subtypes: acquired cystic disease-associated renal cell carcinoma and clear cell papillary renal cell carcinoma. Acquired cystic disease-associated renal cell carcinoma occurs almost exclusively in patients who underwent hemodialysis, especially long-term (>10 years) hemodialysis. Its histology is distinctive: a cribriform or sieve-like architecture with intra- or intracystic lumina; tumor cells containing abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli; and most notably, calcium oxalate crystal deposition. Recognition of the crystals is critical for diagnosing acquired cystic disease-associated renal cell carcinoma. Acquired cystic disease-associated renal cell carcinoma typically has an indolent clinical course, except in cases with sarcomatoid components. Clear cell papillary renal cell carcinoma also has an indolent course (no cases involving metastasis have been reported to date), and its features resemble those of both clear cell renal cell carcinoma and papillary renal cell carcinoma. Unlike acquired cystic disease-associated renal cell carcinoma, which occurs only in end-stage renal disease patients, clear cell papillary renal cell carcinoma occurs in non-end-stage renal disease patients as well. Additional renal tumors in end-stage renal disease patients include anastomosing hemangiomas. Long-term hemodialysis worsens the prognosis of end-stage renal disease patients with renal cell carcinoma, regardless of its original histological subtype, presumably by inducing oxidative stress and sarcomatoid transformation.

Key words: acquired cystic kidney disease, end-stage renal disease, hemodialysis, pathology, renal cell tumor.

Introduction

Owing to more patients with chronic kidney disease and diabetes mellitus, especially in developed countries, and fewer donors for renal transplantation, the incidence of ESRD has increased. Patients with ESRD have a high risk of cancer, and ESRD is a confirmed risk factor for RCC. Prolonged dialysis might also predict RCC. Whether renal hyperplastic cysts and adenomas undergo malignant transformation is still unclear. The number of cysts in patients with ACKD might decrease after renal transplantation, whereas the risk of RCC might not. Although the number of RCC cases in ESRD patients is increasing, it is still relatively low, with only small non-comparable studies of dialysis and kidney transplant patients providing etiological, clinical and pathological data.

Native renal tumors in ESRD patients have distinct clinical and pathological features and outcomes. Such tumors include CCPRCCs, anastomosing hemangiomas and ACD-associated RCCs, which are specific to ESRD patients. To aid urologists and pathologists, the present review provides up-to-date information about RCCs in ESRD patients, including their diagnosis.
Incidence

The incidence of RCC is 3–24-fold higher in ESRD patients and kidney transplant recipients, especially those with ACKD, than in the general population, including transplant recipients with a native kidney. Patients with ESRD are diagnosed with RCC at younger ages than those without ESRD, and the male-to-female ratio for RCC is higher in patients with ESRD or kidney transplants than those without.3,9 Male sex, older age, ESRD caused by obstruction, tuberous sclerosis, focal segmental glomerulosclerosis and acquired renal cysts are independently associated with RCC.19

Etiology

What causes RCC in ESRD patients is difficult to determine owing to the presence of numerous carcinogenic factors in these patients. Oxidative stress is thought to promote carcinogenesis in various organs, including the kidneys. It has been shown to cause mitochondrial DNA mutations and DNA hypermethylation in RCCs in ESRD patients. Furthermore, as postulated by Hori et al., oxidative stress, uremic toxins and exposure to as yet unidentified substances might cause ACD, and hypermethylation, genetic mutations and loss of heterozygosity might subsequently induce carcinogenesis. However, it is unclear which histological RCC subtypes are affected by oxidative stress, as the histological classifications used by Hori et al. are outdated. A recent study showed that peroxiredoxins, thioredoxin and Y-box-binding protein-1 impede carcinogenesis in patients with ACD-associated RCC by reducing oxidative stress in the early stage. Collectively, these findings suggest that oxidative stress is a critical inducer of carcinogenesis in ESRD patients. Oxalate crystals, which are commonly found in ACD-associated RCCs (see Pathology), might promote carcinogenesis by inducing oxidative stress and consequent DNA alterations.23

Histological subtypes of RCC include clear cell RCC, papillary RCC and chromophobe RCC. The molecular features of these subtypes appear to differ from those of conventional RCCs, although the molecular data for ESRD patients are limited. For example, VHL gene mutations, which underlie von Hippel–Lindau syndrome, a major cause of clear cell RCC, rarely occur in RCCs in ESRD patients.27,28

Pathology

Distribution of the RCC subtypes and effect of hemodialysis

Notably, the distribution of the RCC subtypes was similar in ESRD and non-ESRD patients during the first decade in which hemodialysis was carried out. However, it is now known to differ somewhat. Papillary RCC and chromophobe RCC, for example, are more frequent in ESRD patients than non-ESRD patients.20

RCC subtype distribution in ESRD patients depends on the overall duration of hemodialysis (Table 1). An exception is clear cell RCC, which is the most common histological type in ESRD patients regardless of hemodialysis duration. RCCs tend to show sarcomatoid changes during long-term hemodialysis, especially when it exceeds 20 years.4,5,13 We confirmed this trend in a study of 315 patients with RCC and ESRD (Kondo et al., submitted for publication). Collectively, these findings suggest that hemodialysis-associated toxicities, such as those causing continuous long-term oxidative stress, elicit numerous genetic changes that promote RCC development, including sarcomatoid transformation, in ESRD patients.

Unique histological RCC subtypes in ESRD patients

ACD-associated RCC

RCCs in ESRD patients were first described by Dunnill et al. in 1977, and the histological features of the six RCCs in that study appeared to resemble those of clear cell and papillary RCCs. In 1980, Konishi et al. described four RCCs in ESRD patients; one was “composed of clear and eosinophilic granular cell (sic) arranged in solid alveolar, papillotubular and lacework fashion (sic)”. Interestingly, this tumor appeared to contain calcium oxalate crystals (Fig. 1d,e). This tumor is presumably the first reported ACD-associated RCC in the English literature. Despite additional reports of ACD-associated RCC, most genitourinary pathologists except Japanese pathologists did not recognize this entity until the study by Tickoo et al. in 2016. ACD-associated RCC was categorized as a new entity by the WHO in 2016.

ACD-associated RCCs usually occur within a cyst in a background of multiple cysts. They are sometimes multifocal and bilateral, and usually well circumscribed, except in cases with sarcomatoid components. The cut surface is typically tan to yellow or brown with dry features (Fig. 1a), and sometimes hemorrhagic and necrotic.

Most ACD-associated RCCs have multiple histological patterns (alveolar, tubular, papillary, cystic and solid) to some degree. They characteristically have a cribriform or sieve-like architecture, with intra- or intracyclic lumina (Fig. 1b). The tumor cells usually have abundant eosinophilic cytoplasm and round to oval nuclei with prominent nucleoli (Fig. 1c). Mitotic figures are rarely seen. The presence of calcium oxalate crystals showing multicolored

Table 1  Distribution of histological types of RCCs in patients with and without ESRD according to the duration of hemodialysis, compared with those of non-ESRD patients

| Duration of hemodialysis | Total (%) | <10 years (%) | ≥10 years (%) | Reference |
|-------------------------|-----------|---------------|--------------|-----------|
| Histological type       |           |               |              |           |
| Clear cell RCC          | 47 (39.2) | 27 (63.0)     | 20 (26.0)    | 65–70     |
| Papillary RCC           | 15 (12.5) | 5 (11.6)      | 10 (13.0)    | 10–15     |
| ACD-associated RCC      | 46 (38.3) | 7 (16.3)      | 39 (50.6)    | 0         |
| RCC associated with     | 2 (1.7)   | 2 (4.7)       | 0 (0.0)      | 4.1       |
| Xp11.2 translocations   | 2 (1.7)   | 1 (2.3)       | 1 (1.3)      | <1        |
| Others                  | 8 (6.7)   | 1 (2.3)       | 7 (9.1)      | <10       |

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birefringence under polarized light is one of the most distinguishing histological features of ACD-associated RCC (Fig. 1d,e). Calcium oxalate crystals are often observed in the stroma as well as the tumor, and interestingly, are sometimes associated with multinucleated giant cells resulting from foreign body reactions. Their recognition is critical for diagnosing ACD-associated RCC.

ACD-associated RCCs might have sarcomatoid or rhabdoid components, especially in cases involving long-term hemodialysis (Fig. 1f). Hence, long-standing oxidative stress and accumulated DNA damage or hypermethylation could contribute to the sarcomatoid transformation of these tumors.

Immunohistochemically, ACD-associated RCC tumor cells express RCC marker, CD10, AMACR, glutathione S-transferase-alpha and BerEP4, but not cytokeratin 7, E-cadherin, high-molecular-weight cytokeratin or MOC31. Cytogenetic studies show a gain of chromosomes 3, 7, 12, 16, 17, 20 and Y.

RCCs and non-RCC tumors in ACKD patients contain numerous cysts similar to those in ACD-associated RCCs. The cysts are lined by atypical cells with eosinophilic cytoplasm, and have flat, papillary or cribriform proliferation patterns and cytogenetic abnormalities, including a gain of chromosomes 3, 7, 12, 16, 17, 20 and Y. Although the atypical cell proliferation might indicate pre-malignancy, as suggested by some studies, there is no direct evidence of ACD-associated RCCs arising from cysts.

**CCPRCC**

CCPRCC was initially reported as an ESRD-specific RCC by Tikoo et al. Although the CCPRCC is thought to be rare, recent studies show that it is the fourth most common RCC, after chromophobe RCC. Most CCPRCCs occur sporadically and, therefore, are apparently unrelated to ESRD. CCPRCC was categorized as a new entity in 2016 by the WHO.

Macroscopically, CCPRCCs are usually small and well circumscribed with a well-developed tumor capsule (Fig. 2a,b). Many CCPRCCs show cystic features. They are typically organ-confined and neither hemorrhagic nor necrotic. Microscopically, they contain three components: epithelial clear cells arranged in a tubular, nested fashion; angiomyomatous stroma; and capillary-sized interconnecting vascular channels closely associated with the epithelial cell clusters. The nuclei of most CCPRCCs are arranged horizontally aside from the basement membrane; this arrangement (termed “keyboard-like”) is a characteristic feature of CCPRCC (Fig. 2c). Nuclei are usually small, round and uniform with minimum atypia.
corresponding to Fuhrman (or WHO/ISUP) grade 1 or 2. The tumor cells usually contain various amounts of fibrous and/or smooth muscle stroma.

Immunohistochemically, the epithelial cells are positive for epithelial membrane antigen, cytokeratin 7, AE1/AE3, CAM5.2, vimentin and CA IX, but not AMACR, RCC marker or TFE3; some cases show CD10 positivity. Interestingly, CA IX has a unique “cup-like shape” staining pattern, namely, tumor cell membrane staining without an atypical surface (Fig. 2d). Unlike clear cell and papillary RCCs, CCPRCCs do not gain chromosome 7 or 17, or have deletions in chromosome 3p or VHL gene mutations.

Owing to morphological, immunohistochemical and genetic similarities, CCPRCC is thought to be related to clear cell tubulopapillary RCC.

Before the first report of CCPRCC, Michel et al. proposed a new tumor type, termed “RAT”. RATs contain an epithelial clear cell component and a prominent leiomyomatous stroma. The epithelial cells form adenosomatous tubular structures with blister-like apical snouts. RATs and CCPRCCs have similar immunohistochemical (e.g. epithelial membrane antigen, cytokeratin 7, vimentin and CA IX positivity; CD10 variable positivity; and AMACR, RCC marker and TFE3 negativity) and genetic (no VHL gene mutations, DNA hypermethylation or loss of heterozygosity at chromosome 3p) features. Interestingly, some tuberous sclerosis-associated RCCs show RAT-like features.

Whether CCPRCCs and RATs are the same entity or different entities is still being debated. In support of the former, their morphological and immunohistochemical characteristics are similar, and both have benign clinical courses. In support of the latter, their morphological, immunohistochemical and genetic characteristics are not identical.

Despite the inclusion of “carcinoma” in their name, CCPRCCs are regarded as benign or unlikely to become malignant, as no recurrences or tumor-related deaths have been reported.

Macroscopic, microscopic, immunohistochemical and cytogenetic characters of clear cell RCC, papillary RCC, ACD-associated RCC and CCPRCC are listed in Table 2.

**Miscellaneous renal tumors in ESRD patients**

Vascular tumors, such as hemangiomas and angiosarcomas, rarely occur in the kidney. However, a recent report details a unique histological type of kidney hemangioma termed “anastomosing hemangioma”. Interestingly, anastomosing hemangiomas often occur in ESRD patients, as well as non-ESRD patients. Most are small, with a diameter usually <2 cm (range 0.3–3.5 cm). They are well circumscribed and mahogany brown-colored with hemorrhage, and have spongy features. They are located in the medulla and often abut the fat in the renal sinus.

Microscopically, anastomosing hemangiomas have a loosely lobulated architecture with medium-caliber vessels and anastomosing sinusoidal capillary-sized vessels with scattered hobnail endothelial cells within a framework of non-endothelial supporting cells. This sieve-like arrangement shows structural similarity between splenic sinusoids and angiosarcomas; hence, anastomosing hemangiomas might be misdiagnosed as angiosarcomas, despite their benign clinical features. The non-endothelial supporting cells have blunt features and no mitoses in their nuclei, which aid in preventing overdiagnosis. Immunohistochemically, they always express representative endothelial markers, such as CD31 and CD34 (Fig. 3d). Recognition of both its sieve-like arrangement and blunt cell morphology is important for accurate diagnosis of anastomosing hemangioma. The etiology and incidence of this disease are not well-documented because of its rarity.
Angiomyolipomas and minute capsular leiomyomas have also been reported in ESRD patients. However, the relationship between these tumors and ESRD is unclear because of their low incidence in ESRD patients.

**Stage**

RCCs in ESRD patients usually have a lower T stage, a lower Fuhrman (or WHO/ISUP) nuclear grade, and fewer lymph nodes and/or distant metastases than do RCCs in non-ESRD patients. ESRD patients tend to have more medical checkups, including ultrasonography, computed tomography and magnetic resonance imaging, than do healthy people. We suggest that the frequency of screening facilitates the detection of RCC at an early stage, resulting in a relatively favorable outcome and clinical and pathological status in ESRD patients.

**Prognosis**

RCCs generally have a better prognosis in ESRD than non-ESRD patients. However, owing to the limited follow-up periods, outcomes cannot be precisely predicted at present. Recent studies identified long-term hemodialysis as an unfavorable prognostic factor for RCC in ESRD patients; this reflects potential sarcomatoid transformation of RCCs in such patients, particularly those who undergo hemodialysis >20 times (Table 1).

The adjusted hazard ratios for overall graft loss and death with a functioning graft are higher among kidney transplant...

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**Table 2** Gross, microscopic and immunohistochemical features of clear cell RCC, papillary RCC, ACD-associated RCC and CCPRCC

|                      | Clear cell RCC                                      | Papillary RCC                                      | ACD-associated RCC                              | CCPRCC                                    |
|----------------------|-----------------------------------------------------|---------------------------------------------------|-------------------------------------------------|-------------------------------------------|
| **Gross**            | Usually well circumscribed, pseudocapsule, golden yellow | Usually well circumscribed, gray to yellow, hemorrhage and necrosis (sometimes) | Well circumscribed with cyst, yellow or brownish | Well circumscribed and encapsulated, cystic, color is variable |
| **Microscopic**      | Nested, alveolar, papillary                          | Papillary, tubulopapillary                        | Papillary, cribriform, sieve-like                | Papillary and/or tubulocystic             |
| **Architecture**     | Nested, alveolar, papillary                          | Papillary, tubulopapillary                        | Papillary, cribriform, sieve-like                | Papillary and/or tubulocystic             |
| **Nucleus**          | Variable                                            | Round-to-oval                                     | Inconspicuous (type 1), conspicuous (type 2)    | Inconspicuous                            |
| **Nucleolus**        | Variable                                            | Inconspicuous (type 1), conspicuous (type 2)      | Usually conspicuous                             | Usually conspicuous                       |
| **Cytoplasm**        | Clear (sometimes basophilic)                        | Clear (type 1), eosinophilic (type 2)             | Eosinophil                                      | Eosinophil                               |
| **Others**           |                                                     | Psammoma body, macrophage (type 1)               | Oxalate crystal                                 | Oxalate crystal                           |
| **Immunohistochemistry** |                      |                                                   |                                                 |                                           |
| **CK7**              | Negative                                            | Positive                                          | Negative                                        | Positive                                  |
| **AMACR**            | Negative/focal                                       | Positive                                          | Positive                                        | Negative                                  |
| **CD10**             | Positive                                            | Positive                                          | Positive                                        | Negative                                  |
| **CA IX**            | Positive                                            | Focal                                             | Positive                                        | Positive (cup-shaped)                     |
| **RCCMa**            | Positive                                            | Positive                                          | Positive                                        | Negative                                  |
| **Gain**             | 5q                                                  | 7, 17                                             | 3, 7, 12, 16, 17, 20, Y                         | 7, 17                                     |
| **Loss**             | 3p                                                  | Y                                                 | 3p                                              |                                           |

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Fig. 3 Morphological features of anastomosing hemangiomas. (a) Gross and (b) semi-gross features of anastomosing hemangiomas. A tumor located in the renal sinus fat adjacent to the renal medulla. (c) A representative photograph showing anastomosing sinusoidal vessels with scattered hobnail endothelial cells (sieve-like arrangement). (d) The tumor cells are positive for CD31.
patients with versus without a prior cancer.\(^{59}\) Incident cancer after kidney transplantation is a significant risk factor for death in patients with a functioning graft, accounting for the majority of deaths in these patients.

**Conclusions**

There are several RCC subtypes in ESRD patients, including ACD-associated RCC and CCPRCC, which are histologically unique. The RCCs in ESRD patients have distinct clinical features, which differ from those in non-ESRD patients. Because RCCs are becoming more common in ESRD patients, their precise recognition and appropriate diagnosis by both pathologists and urologists is required.

**Conflict of interest**

None declared.

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Editorial Comment

Editorial Comment to Renal tumors in end-stage renal disease: A comprehensive review

According to the 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs, succinate dehydrogenase-deficient renal cell carcinoma (RCC), hereditary leiomyomatosis and RCC syndrome-associated RCC, tubulocystic RCC, acquired cystic disease (ACD)-associated RCC and clear cell papillary RCC (CCPRCC) were newly added to the classification. Furthermore, multicellular cystic RCC and translocation RCC associated with Xp11.2 or 6p21 were reclassified as multicellular cystic neoplasm of low malignant potential and Mit family translocation RCC, respectively. Foshat et al. reviewed the pathogenesis, morphology and clinical characteristics of ACD-associated RCC, and describe dissimilar clinical and pathological features compared with clear cell RCC and papillary RCC.1 Tsuzuki et al. also report features of ACD-associated RCC, CCPRCC and miscellaneous renal tumors in patients with end-stage renal disease, focusing on characteristics for histological diagnosis.2 There is little information on diagnostic imaging, most likely because these reviewers expound the findings from the perspective of pathologists. The incidence of ACD increases in patients with long-term hemodialysis and the risk of developing tumor angiomyoadenomatous tumor and featuring polysomy 7 and 17 and a mutation in the von Hippel-Lindau gene: report of a hybrid tumor and a few comments on renal angiomyoadenomatous tumor and papillary renal tumors with clear cell. Ann. Diagn. Pathol. 2011; 15: 213–6. 52. Hes O, Comperat EM, Rioux-Leclercq N. Clear cell papillary renal cell carcinoma, renal angiomyoadenomatous tumor, and renal cell carcinoma with leiomyomatous stroma relationship of 3 types of renal tumors: a review. Ann. Diagn. Pathol. 2016; 21: 59–64. 53. Denl KF, Schildhaus HU, Comperat E et al. Clear cell papillary renal cell carcinoma and renal angiomyoadenomatous tumor: two variants of a morphologic, immunohistochemical, and genetic distinct entity of renal cell carcinoma. Am. J. Surg. Pathol. 2015; 39: 889–901. 54. Brown JG, Folpe AL, Rao P et al. Primary vascular tumors and tumor-like lesions of the kidney: a clinicopathologic analysis of 25 cases. Am. J. Surg. Pathol. 2010; 34: 942–9. 55. Montgomery E, Epstein JI. Anastomosing hemangiosarcoma of the genitourinary tract: a lesion mimicking angiosarcoma. Am. J. Surg. Pathol. 2009; 33: 1364–9. 56. Buttner M, Kufer V, Brunner K, Hartmann A, Amann K, Agaimy A. Benign mesenchymal tumours and tumour-like lesions in end-stage renal disease. Histopathology 2013; 62: 229–36. 57. Kryvenko ON, Haley SL, Smith SC et al. Haemangiomas in kidneys with end-stage renal disease: a novel clinicopathological association. Histopathology 2011; 65: 109–18. 58. Tsuzuki T, Sassa N, Gotoh M et al. Re: Yann Neuzillet, Xavier Tillou, Romain Mathieu, et al. Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. Eur. Urol. 2011; 60: 366–73; e35–6. 59. Lim WH, Badve SV, Wong G. Long-term allograft and patient outcomes of kidney transplant recipients with and without incident cancer – a population cohort study. Oncotarget 2017; 8: 77771-82.