New and emerging renal tumour entities

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Abstract

In this review, we discuss new and emerging renal cell carcinoma (RCC) entities, including anaplastic lymphoma kinase (ALK) RCC, oncocytic variant of chromophobe RCC, atrophic kidney-like renal tumour, biphasic alveolosquamoid RCC, tubulocystic RCC, thyroid-like follicular carcinoma of the kidney, succinate dehydrogenase-deficient RCC, Birt–Hogg–Dubé syndrome-associated renal tumour, hereditary leiomyomatosis/renal cell carcinoma associated RCC, tuberous sclerosis-associated RCC, *PTEN* hamartoma tumour syndrome, clear cell papillary RCC, acquired cystic disease-associated RCC, Xp11.2 RCC, t(6;11) RCC and renal hemangioblastoma. These tumours have clinical, pathological and genetic features distinct from other common RCCs and therefore are important to recognize. Some of them have been recognized as distinct histological subtypes in the 2016 World Health Organization Classification. However, further studies are needed to elucidate their clinicopathologic features and molecular mechanisms.

Keywords Acquired cystic disease-associated RCC; ALK; anaplastic lymphoma kinase; atrophic kidney-like renal tumour; Birt–Hogg–Dubé syndrome-associated renal tumour; clear cell papillary RCC; HLRCC associated RCC; succinate dehydrogenase-deficient RCC; thyroid-like follicular carcinoma of the kidney; translocated associated RCC; tuberous sclerosis-associated RCC; tubulocystic RCC

Introduction

Recently, many new renal tumour entities and new concepts regarding the "established" renal tumour entities have been described and incorporated into the 2012 International Society of Urological Pathology (ISUP) classification of renal tumours.[1] Several entities, including tubulocystic RCC, clear cell papillary RCC, and succinate dehydrogenase (SDH)-deficient RCC, have distinct clinicopathological features and are therefore recognized as new RCC subtypes. Other entities, such as anaplastic lymphoma kinase associated RCC and thyroid like follicular carcinoma of the kidney, are considered emerging RCC entities and additional studies are needed to further elucidate their clinical, pathological and molecular characteristics. Correct diagnosis of these tumours is, however, critical for not only understanding of their pathogenesis but also patient management.

Clear cell papillary renal cell carcinoma

Although initially reported in end-stage kidneys, this tumour is now most commonly sporadic in otherwise normal kidneys.[2–9] It accounts for 1–4.3% of all epithelial neoplasms. The patient's age ranges from 18 to 88 (mean 70) years. There is no gender predilection. Patients are usually asymptomatic.[9] Tumours are usually small.[3–6] Grossly, the tumour shows variable cystic formation with focal solid consistency and the cut surface is white-tan, pale yellow, or red-brown. Histologically, the tumour is composed of clear cells forming a variety of growth patterns including papillary, tubular, acinar, solid and cystic. Branching tubules and papillae are common.[6] Nuclear grade is low, typically ISUP nucleolar grade 1 or 2 in most cases. Nuclei often show linear arrangement away from the basement membrane (Figure 1A).[5–7] Smooth muscle is often identified within the stroma. Immunohistochemically, neoplastic cells are positive for cytokeratin 7 and carbonic anhydrase IX with characteristic "cup-shaped pattern" (Figure 1B), but negative for AMACR, CD10 and RCC Ma.[2–9] TFE3 is consistently negative.[5,7] This tumour shows no genetic characteristics of clear cell RCC or papillary RCC.[3,4] The array CGH analysis showed no chromosomal imbalances.[5] Partial nephrectomy may be best therapeutic option for a solitary lesion. Active surveillance may be considered if a correct diagnosis is rendered on needle core biopsy.[9] Prognostically there has been no reports of local recurrence or distant metastasis.[6–8] Further studies are needed to ascertain its biological behaviour; however, this tumour is best regarded as having an indolent clinical behaviour.

Acquired cystic disease-associated renal cell carcinoma

This tumour of unique morphology occurs exclusively in patients with acquired cystic disease (ACD).[2] ACD-RCC accounts for 36% of renal epithelial tumours in the end-stage kidneys and often in patients on haemodialysis for more than 10 years.[2,10,11] Histologically, it is characterized by cells with deeply eosinophilic cytoplasm forming multiple patterns including microcystic or cribriform. Intratumoral oxalate crystal deposition is characteristic (Figure 2).[2,10–13] The nuclear atypia is usually ISUP Grade 3.[11] Some cases have sarcomatoid or rhabdoid changes which correlate with adverse prognosis.[14,15] Immunohistochemically, tumour cells are positive for AMACR, CD10 and RCC Ma, but negative for cytokeratin 7.[12] Ultrastructurally, tumour cells contain abundant mitochondria.[14] FISH, G-band karyotype and array CGH analysis show gain of chromosomes 3, 7, 16, 17 and sex chromosome.[12,13,16] Hence, this tumour may be closely related to papillary RCC.[12,17] Chromosomal aneuploidy, particularly gain

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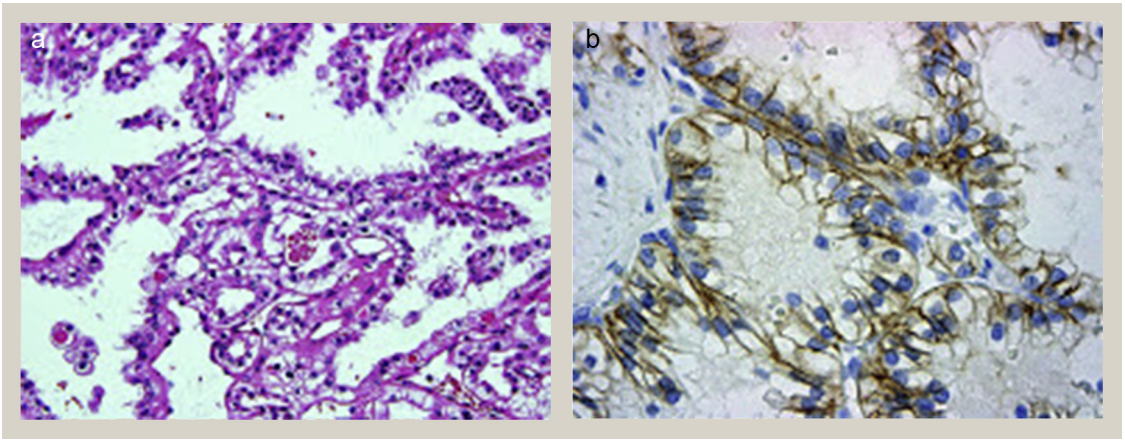

Figure 1 Clear cell papillary renal cell carcinoma. (**a**)Tumour cells with clear cytoplasm form cystic and papillary configuration. Nuclei are polarized away from the basement membrane (Courtesy of Dr. Kawakami F, Kobe, Japan). (**b**) Immunohistochemical stain for CAIX shows cup-shaped pattern (Courtesy of Dr. Watanabe R, Shizuoka, Japan).

of chromosome 3 and 16, may be characteristic of this tumour.[13,18] Radical or partial nephrectomy is usually performed. These tumours seem to have better prognosis than their sporadic counterparts as patients are under intense surveillance for their underlying medical kidney disease with various imaging studies. However, tumours with sarcomatoid or rhabdoid differentiation may behave aggressively.[2,14,15]

Microphthalmia/TFE (MiT) gene family translocation renal cell carcinoma

MiT gene family translocation RCC includes Xp11.2/*TFE3* translocation RCC and t(6;11)/*TFEB* translocation RCC. TFE3 and TFEB both belong to the MiT gene family. Xp11.2/*TFE3* translocation RCC and t(6;11)/*TFEB* translocation RCC share clinical, pathological and genetic features and are therefore grouped together as MiT gene family translocation RCCs.

Xp11.2/TFE3 translocation RCC is characterized by a translocation between the *TFE3* gene at chromosome Xp11.2 and another gene including *ASPL* at 17q25, *PRCC* at 1q21, *PSF* at 1q34, *NonO* at Xq12 and *CLTC* at 17q23.[19–22] Partner genes at chromosomes 3q23, 10q23 and 19q13.1 remain unidentified.[23–25] This tumour generally affects children and young adult and is the most common form of RCC in children. It also occurs in adults and accounts for 1% of all renal tumours in adults.[1,19–23,26–29] Patients may present with haematuria or abdominal mass.[29] A previous exposure to cytotoxic chemotherapeutic agents in childhood may be a risk factor.[30] Grossly, the tumour is well-marginated but unencapsulated. The cut surface displays yellow-tan colour with soft consistency. Histologically, this tumour is characterized by mixed papillary, nested and alveolar growth patterns. Tumour cells have voluminous clear and/or eosinophilic cytoplasm, distinct cell border, and large nuclei with vesicular chromatin and prominent nucleoli (Figure 3). Psammoma bodies or hyaline nodules are often identified in the stroma.[23,26–28] Immunohistochemically, tumours cells underexpress and are usually focally and weakly positive for epithelial markers including keratins and EMA. It shows nuclear positivity for TFE3 protein which seems to be a highly sensitive and specific marker for this tumour (although it is also positive in alveolar soft part sarcoma). However, excessive antigen retrieval or use of concentrated antibody may lead to false positivity in other tumours.[31] Ultrastructurally, rhomboid crystals or dense granules are identified in the cytoplasm of *ASPL-TFE3* RCC.[20,29] FISH using the *TFE3* gene break-apart probe is helpful for establishing the diagnosis.[32] Patients are usually treated with radical or partial nephrectomy.[28] Extended lymphadenectomy is also performed. For metastatic lesions, VEGF or mTOR inhibitors may lead to improved outcome.[29] Adult tumours seem to behave more aggressively than paediatric ones.[26,28,29] Metastasis to lymph nodes is commonly observed.[27–29]

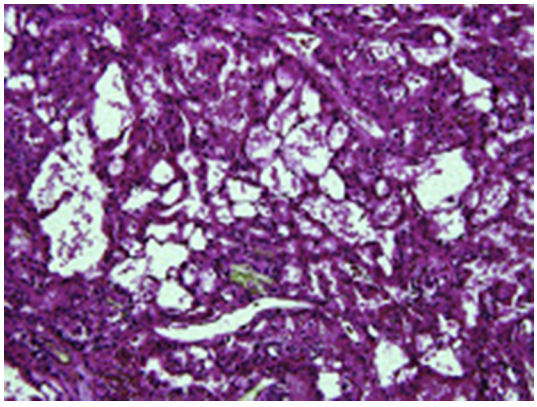

Figure 2 Acquired cystic disease-associated renal cell carcinoma. The tumour cells with deeply eosinophilic to oncocytic cytoplasm form microcystic or cribriform pattern. Intratumoral oxalate crystals are present.

t(6;11)/*TFEB* translocation RCC is characterized by the fusion of *TFEB* gene at chromosome 6p21 to *Alpha* gene at chromosome 11q12. It generally occurs in children and young adults, but has been reported in adults.[27,33–39] It is very rare and accounts for <1% of all renal tumours. The age ranges from 6 to 57 (mean 23) years. There is a slight female preponderance. The tumour ranges from 1 to 20 (mean 6.5) in size.[38] Grossly, the tumour is

