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AWARD REVIEW

Recent classification of renal epithelial tumors

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Abstract The recent classification of renal tumors is based on genetic evidence as well as on histologic features. Malignant tumor includes clear cell renal carcinoma (RCC), multilocular cystic RCC, papillary RCC, chromophobe RCC, carcinoma of the collecting duct of Bellini, renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions and mucinous tubular and spindle cell carcinoma. Benign tumor is subdivided into papillary adenoma, renal oncocytoma and metanephric adenoma. Recently, new disease entities such as acquired cystic disease-associated RCC, clear cell papillary RCC and renal carcinoma with t(6;11)(p21:q12) have been discovered. In this article, we briefly review and introduce the clinical, morphological and genetic features of these tumor entities.

Keywords Renal cell carcinoma · WHO classification · Renal cell carcinomas subtypes · Pathology and genetics

Introduction

The classification of renal tumor had been traditionally determined according to the morphological difference including the cytological appearance and architecture of tumor cells. However, the genetic characteristics in various tumors have been elucidated. Therefore, recent classification has been performed on the basis of genetic difference as well as morphological difference [1]. In addition, some new disease entities have been proposed recently. In this article, we review the overview of renal tumor classification and introduce these tumor entities briefly. Morphological, immunohistochemical and genetic features of each subtype of renal tumors are summarized in Table 1.

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Clear cell renal cell carcinoma

This tumor accounts for 80 % of all renal neoplasms. Grossly, the tumor is well circumscribed, but large tumor may show the infiltrating growth. The tumor capsule is usually absent. The cut surface of the tumor show the golden-yellow in color, but hemorrhage or necrosis may be often observed. Histologically, the tumor proliferates with alveolar, solid, tubular or cystic patterns (Fig. 1). The cytoplasm exhibits the clear cell cytology reflecting abundant glycogen and fat in low grade tumors but granular cell cytology in high grade tumor. Immunohistochemically, neoplastic cells are usually positive for CA9, RCC Ma, CD10 and PAX2, but negative or focally positive for cytokeratin 7 [1, 2]. Genetically, abnormalities such as mutation or methylation of *von Hippel–Lindau* (*VHL)* gene located at the chromosome 3p25 or loss of chromosome 3p have been frequently found [1–5]. The prognosis of this tumor depends on nuclear grade [1].

Multilocular cystic renal cell carcinoma

This tumor comprises 4 % of clear cell RCC [2]. Grossly, the tumor is well circumscribed with capsular formation and multicystic appearance, but there is no expansile nodule. Microscopically, the cyst wall is lined by neoplastic cells with clear cytoplasm (Fig. 2). The Fuhrman nuclear grade usually corresponds to grade 1 [6, 7]. The deletion of chromosome 3p is observed in most tumors using LOH or FISH analysis and *VHL* gene mutation was

Table 1 Features of each subtype of renal tumors

Tumor subtype	Morphology	Immunohistochemistry	Genetic features
Clear cell RCC	Solid, alveolar, tubular, clear cell	CA9, CD10, RCC Ma	*VHL,* loss of ch 3p
Multilocular cystic RCC	Multicysts lining by clear cell, low-grade nuclei	CA9, CD10, CK7	*VHL,* loss of ch 3p
Papillary RCC	Basophilic to amphophilic (type1), eosinophilic (type 2), foamy macrophages	CK7(type 1 > 2), AMACR, CD10, RCC Ma	*MET(type 1)*, gain of ch 7 and 17, loss of ch Y
Chromophobe RCC	Pale and eosinophilic cells, solid, nested, tubular	CK7, CD82, Parvalbumin, Ksp-cadherin	Loss of ch 1, 2, 6, 10, 13, 17, 21
Collecting duct carcinoma	Solid, acinar, tubular, papillary, cribriform, high grade	HMWCK, UEA-1, CK19	No consistent abnormalities
Xp11.2 RCC	Solid alveolar, papillary, voluminous cells, hyaline nodules, psammoma bodies	TFE3, Cathepsin K	Translocation involving *TFE3* gene
MTSCC	Elongated tubules, spindle cells, low-grade nuclei, mucin	CK7, CK19, AMACR	Loss of ch 1, 4, 6, 8, 11,13, 14, 15, 22
Papillary adenoma	Papillary, tubulopapillary, low-grade nuclei	CK7, AMACR	Gain of ch 7 and 17, loss of ch Y
Oncocytoma	Solid nests, organoid, granular, eosinophilic	Parvalbumin, Ksp-cadherin	Normal, loss of ch Y and 1, ch 11q13 alteration
Metanephric adenoma	Small acini, papillary, glomeruloid, blue cells, psammoma bodies	WT1, CD57	Loss of ch 2p13

RCC renal cell carcinoma, *MTSCC* mucinous tubular and spindle cell carcinoma, *ch* chromosome

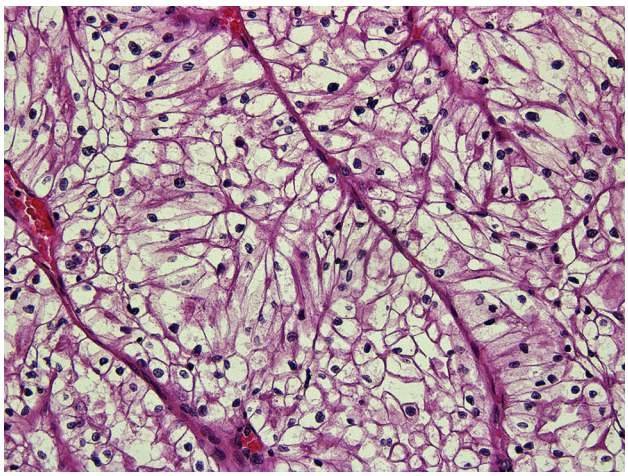

Fig. 1 Microscopic finding of clear cell renal cell carcinoma (RCC). The acinar growth of clear cells is seen with delicate vascular network in the stroma

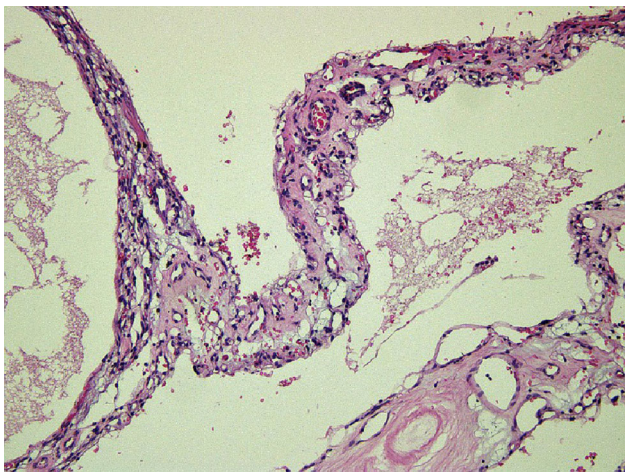

Fig. 2 Microscopic finding of multilocular cystic RCC. Multilocular cystic growth pattern lining by neoplastic cells with clear cytoplasm is seen

identified in 25 % of MCRCC. As the majority of this tumor is incidentally discovered, patients pursue a favorable clinical course [7].

Papillary renal cell carcinoma

This tumor type comprises 10–15 % of all renal neoplasm [1, 2]. Macroscopically, the tumor form well-circumscribed mass and the pseudocapsule may be seen. The cut surface shows yellow or brown in color according to the amount of abundant foamy macrophages or hemorrhage. Microscopically, the tumor is subdivided into two categories. The first is type 1 and the tumor is composed of small neoplastic cells with scant amphophilic to basophilic cytoplasm and low nuclear grade (Fig. 3a). The second is type 2 and the tumor consists of columnar cells with eosinophilic cytoplasm and high nuclear grade. In type 2, nuclear pseudostratification is often observed (Fig. 3b) [8, 9]. Psammoma bodies or foamy macrophages may be seen in the stroma. Immunohistochemically, the positive for cytokeratin 7, AMACR, CD10 and RCC Ma is frequent. However, the positive for cytokeratin 7 is more frequent in type 1 than type 2 [1, 2]. Recently, the oncocytic variant is

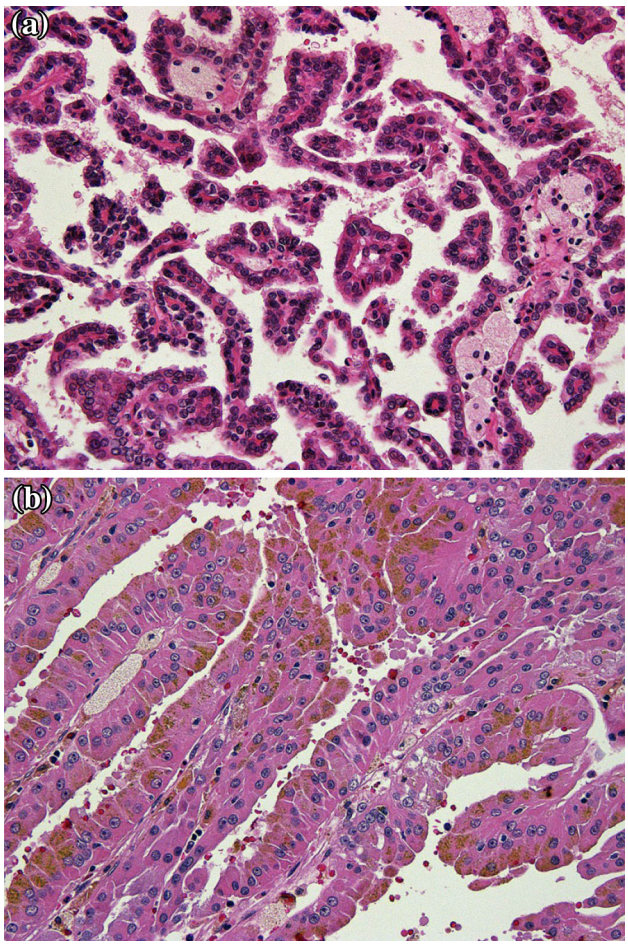

Fig. 3 Microscopic findings of papillary RCC. **a** Type 1. Cuboidal tumor cells with amphophilic to basophilic scant cytoplasm, proliferating with a papillary architecture. **b** Type 2. Papillary configuration of columnar neoplastic cells with eosinophilic cytoplasm and nuclear pseudostratification is observed

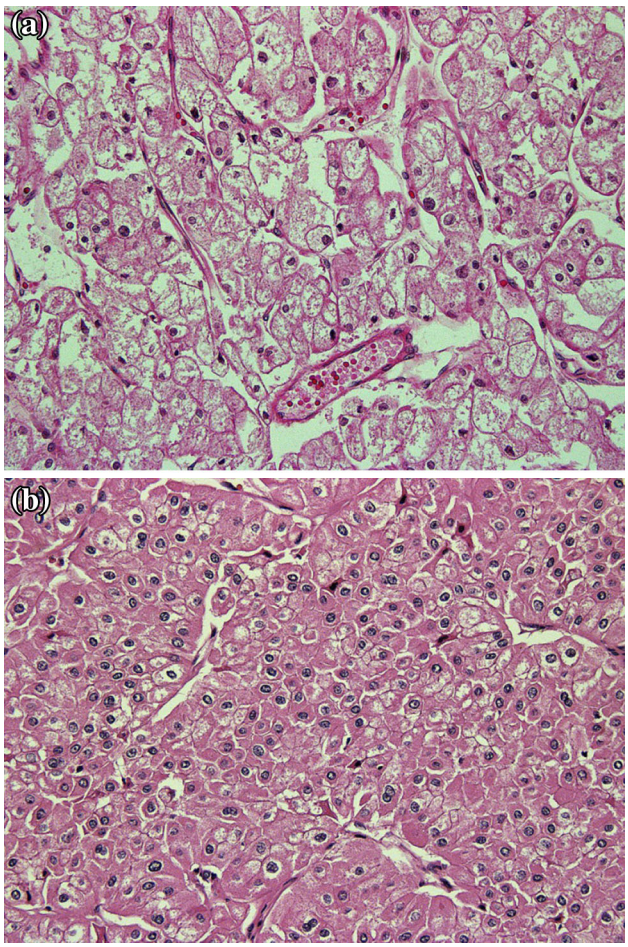

Fig. 4 Microscopic findings of chromophobe RCC. **a** Typical variant. The compact solid sheets of pale cells with distinct cell border and shrunken nuclei are noted. **b** Eosinophilic variant. The tumor cells with eosinophilic cytoplasm and perinuclear halo show the solid sheet growth pattern

identified. The tumor cells show the oncocytic cytoplasm and nuclei located along the luminal sides without pseudostratification. The prognosis of type 1 tumor is more favorable than that of type 2 tumor. This difference seems to depend on the nuclear grade.

Chromophobe renal cell carcinoma

The incidence of this tumor type accounts for 5 % of all renal neoplasms. The gross picture shows well-demarcated mass without capsules. The cut surface of the tumor shows beige or pale-tan in color [1, 2]. Microscopically, the tumor is subdivided into two categories. In the typical variant, tumor cells predominantly consist of pale cells with finely reticular cytoplasm and distinct cell border (Fig. 4a). In eosinophilic variant, eosinophilic cells are predominant and account for more than 80 % (Fig. 4b). Nuclear outline is irregular and nuclei often show the shrunken pattern. Binucleation or perinuclear halo is usually seen [10–12]. At contrast, renal oncocytoma has round and centrally located nuclei and lack perinuclear halo. Immunohistochemically, tumor cells show the diffuse positivity for cytokeratin 7 with membranous accentuation, but CA9 is usually negative. CD10 is generally negative, but may be positive in tumors with aggressive clinical courses. Cytogenetically, losses of chromosomes 1, 2, 6, 10, 13, 17 and 21 are noted. The prognosis of chromophobe RCC is better than that of clear cell RCC, but tumors with sarcomatoid change and extensive necrosis may show the aggressive clinical course [1, 2].

Carcinoma of the collecting duct of Bellini

The incidence of this tumor comprises less than 1 % of all renal cancers. Grossly, the tumor is located in the medulla and form the whitish mass with irregular border [1, 2]. Microscopically, the various growth patterns such as

tubular, solid, papillary, cribriform or hobnail are observed (Fig. 5). Intracytoplasmic mucin may be identified in some cases. The identification of dysplasia in the collecting duct surrounding the tumor may become the diagnostic clue for collecting duct carcinoma [13–15]. According to the previous reports, there are no consistent specific genetic abnormalities for this tumor category. The prognosis of this tumor is worse, the two-thirds of patients die of cancer within 2 years after disease discovery [1, 2].

Renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions

The tumor generally affects pediatrics and young adults, and accounts for approximately 1 % of all renal neoplasm in adults. The tumor shows the well-demarked mass without capsular formation. The cut surface of the tumor demonstrates the tan-yellow in color and hemorrhage or necrosis may be often observed. Microscopically, voluminous neoplastic cells with clear to eosinophilic cells proliferate with alveolar or papillary configuration in *ASPL-TFE3* RCC. In the stroma, psammoma bodies or hyaline nodules are occasionally seen (Fig. 6). In *PRCC-TFE3* RCC, tumor cells show the less abundant cytoplasm and the stroma exhibits few psammoma bodies or hyaline nodules. Immunohistochemical labeling for TFE3 in the nuclei is a useful tool for this tumor. In addition, CD10, RCC Ma and AMACR are usually positive. The genetic fusion of *TFE3* to some genes including *ASPL, PRCC, PSF, NonO* and *CLTC* has been identified to date. In prognosis, adult cases may pursue more aggressive clinical course than pediatric patients [1, 2, 16, 17].

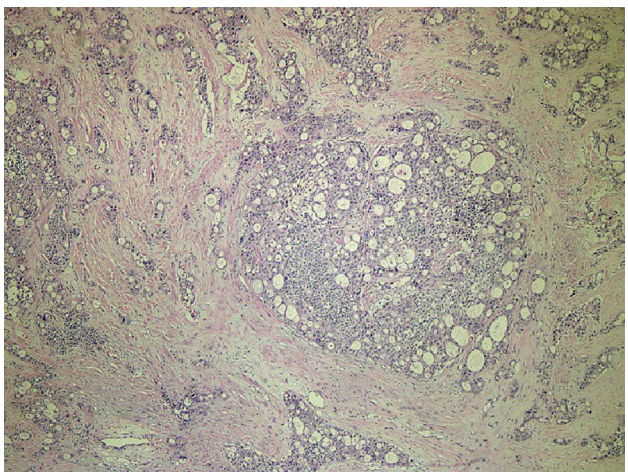

Fig. 5 Microscopic finding of carcinoma of the collecting duct of Bellini. Tumor cells proliferate with tubular, cribriform and solid pattern in the desmoplastic stroma

Mucinous tubular and spindle cell carcinoma

The gross features of this tumor is generally well defined and the cut surface impart gray–white to tan or yellow color. Histologically, the tumor consists of tubules with frequent elongation and spindle cell with low cytologic atypia in the mucin deposition of the stroma (Fig. 7). Papillary configuration may be present. Immunohistochemically, tumor cells are usually positive for cytokeratin 7 and AMACR. CD10 is negative but may be focally positive. The positivity for RCC Ma varies from a case to a case. Cytogenetically, losses of chromosomes 1, 4, 6, 8, 13, 14, 15 and 22 are observed [18]. Most cases show the indolent clinical behavior, but some aggressive cases have recently been reported [1, 2, 19].

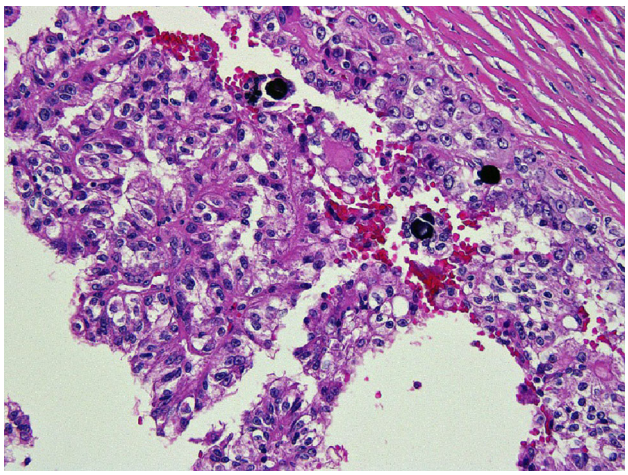

Fig. 6 Microscopic finding of renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions. The papillary growth with the admixture of clear and eosinophilic cells is seen with hyaline nodules and psammoma bodies in the stroma

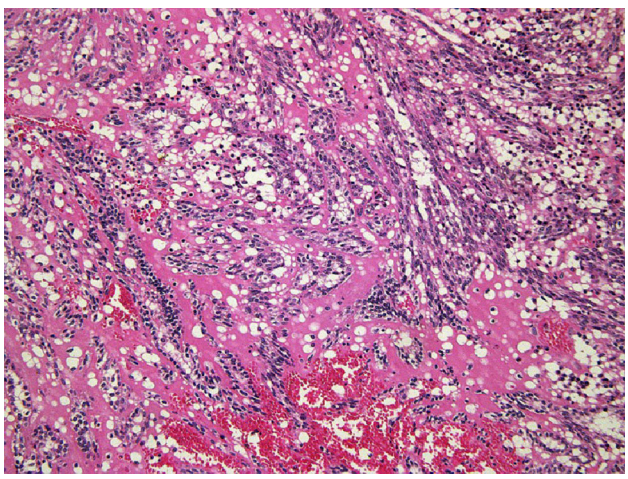

Fig. 7 Microscopic finding of mucinous tubular and spindle cell carcinoma. Elongated tubules and low-grade spindle cells proliferate on the myxoid background

Papillary adenoma

According to the definition of the recent WHO classification, papillary adenoma is the tumor consisting of papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller. Most tumors are incidentally found in the kidney removed by nephrectomy because of renal tumor or at autopsy. Genetically, gain of chromosomes 7 and 17 and loss of chromosome Y are observed. This tumor is considered as a precursor of papillary RCC [1, 2].

Oncocytoma

The tumor accounts for 5 % of all renal neoplasm. The gross features of this tumor show well-circumscribed, non-encapsulated mass and the cut surface shows mahogany–brown color. One-third of tumors may exhibit central scar. Histologically, the tumor with oncocytic cytoplasm proliferates with solid compact nest, acinar or organoid pattern in the edematous or hyalinized stroma (Fig. 8). Nuclei show round shape and are centrally located in the cytoplasm. Nuclear chromatin is evenly distributed. In molecular aspect, loss of chromosomes 1 and Y or chromosome 11q13 alteration may be observed. This tumor is benign [1, 2, 20–22].

Metanephric adenoma

This tumor occurs in children and adults with a female predilection. Macroscopically, the tumor is well defined but not encapsulated. Histologically, the tumor consists of small acini and tubules with scant cytoplasm. Papillary configuration or glomeruloid bodies may be focally seen (Fig. 9). In the stroma, hyalinization or psammoma bodies are often observed. Immunohistochemically, tumor cells are positive for WT1 and CD57. The clinical course is generally favorable [1, 2, 23–25].

Newly identified entities

Acquired cystic disease-associated renal cell carcinoma

This tumor exclusively occurs in patients with acquired cystic disease receiving long-term dialysis. Histologically, various growth patterns including, papillary, tubular, solid and microcystic architectures are seen. The tumor cytoplasm is generally deep eosinophilic or oncocytic (Fig. 10). The stroma contains the oxalate crystals that are highlighted by a polarized microscope. Immunohistochemically, tumor cells are positive for AMACR but negative for cytokeratin 7 [2, 26–28]. The prognosis is generally favorable because patients receiving dialysis receive a periodical medical examination. However, some cases with sarcomatoid change or rhabdoid features have been reported to date [27–30].

Clear cell papillary renal cell carcinoma

This tumor occurs in both patients with end-stage kidney disease or patients without renal dysfunction or failure. Gross picture of this tumor shows well-circumscribed mass with capsule and cystic formation. Histologically, tumor cells with clear cell cytoplasm usually show the marked papillary growth (Fig. 11). Tubules or acini of tumor cells may be noted. Immunohistochemically, neoplastic cells are positive for cytokeratin 7 but negative for AMACR.

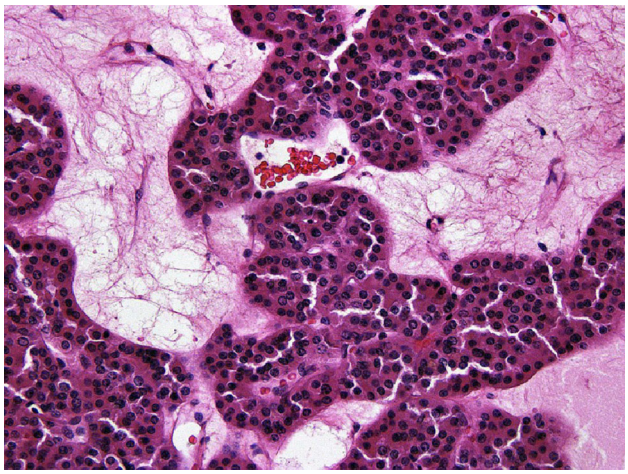

Fig. 8 Microscopic finding of renal oncocytoma. The organoid pattern of tumor cells with oncocytic cytoplasm is seen in the edematous stroma. Nuclei are round and centrally located in the cytoplasm

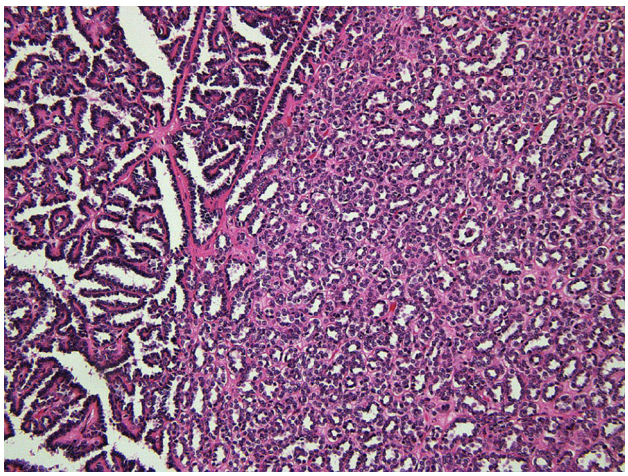

Fig. 9 Microscopic finding of metanephric adenoma. The small acinar or papillary architecture of tumor cells with scant cytoplasm is noted

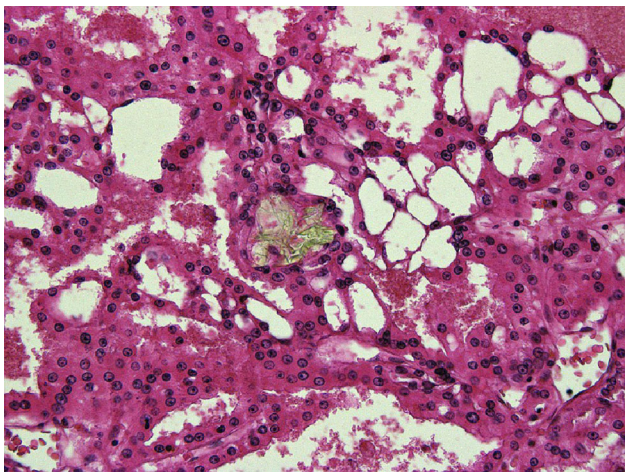

Fig. 10 Microscopic finding of acquired cystic disease-associated RCC. Microcystic pattern of neoplastic cells with oncocytic cytoplasm is seen in the stromal deposition of oxalate crystals

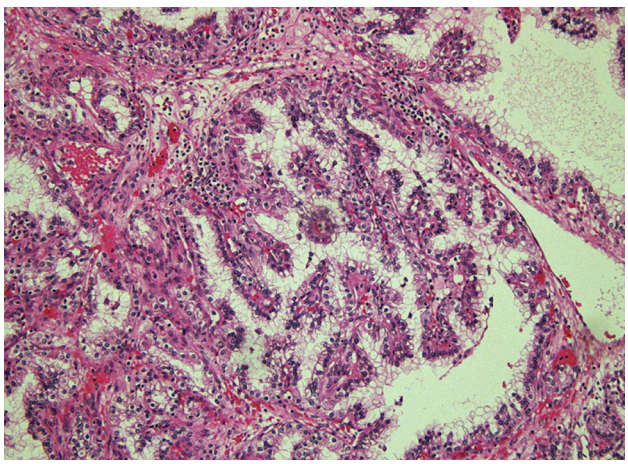

Fig. 11 Microscopic finding of clear cell papillary RCC. The papillary projection lined by neoplastic cells with clear cytoplasm is observed

Genetically, this tumor has no characteristics of clear cell or papillary RCC. The clinical behavior is generally indolent because of the frequent low stage [2, 31, 32].

Renal carcinoma with t(6;11)(p21:q12)

This tumor generally affects children and young adults but some adult cases have been reported. Macroscopically, satellite nodules are often observed around the main tumor. Microscopically, the tumor is composed of large neoplastic cells and small neoplastic cells surrounding basement membrane materials, giving rise to the rosette-like morphology (Fig. 12). Immunohistochemical expression of TFEB in nuclei is an available diagnostic tool. The fusion between *TFEB* gene and *alpha* gene is genetically found [2, 33–35].

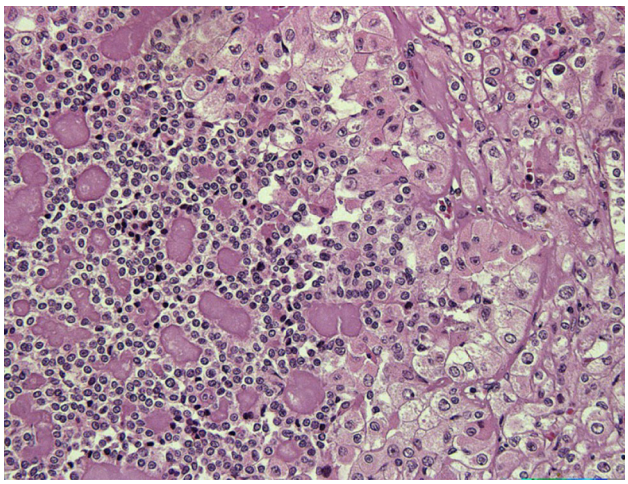

Fig. 12 Microscopic finding of renal carcinoma with t(6;11)(p21;q12). The tumor consists of the admixture of large and small neoplastic cells. The basement membrane materials are surrounded by small cells

Future perspectives

Several additional new disease entities including renal cancer with anaplastic lymphoma kinase gene fusion have been proposed [36–39]. The advance of the molecular targeted therapy in RCC will be expected in the near future.

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