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Review

An overview of renal cell cancer: Pathology and genetics

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ABSTRACT

Renal cell carcinoma is a group of malignancies arising from the epithelium of the renal tubules. The pattern of somatic mutations in kidney tumors has been extensively investigated. In the current 2004 WHO classification, the molecular background of a renal tumor has become, in addition to histopathology, a major criterion for tumor classification. The goal of this review is to discuss morphology and genetics of adult renal epithelial cancer included in the 2004 WHO classification and to mention renal tumor types, which are not considered in the current WHO classification. Further, pathologic considerations with clinical and prognostic implications are provided.

1. The WHO classification of renal cancer

The term renal cell cancer refers to a heterogeneous group of cancers derived from renal tubular cells. In the last years, pathological and basic cancer research has characterized different renal tumor entities [1,2]. The current WHO renal cancer classification from 2004 combines morphological and genetic characteristics and recognizes some variations of renal cancers with different immunophenotypes or molecular changes with clinical implications [3] (Table 1). These tumor subtypes have different prognosis [4,5] and the response to novel therapies maybe different [6].

Clear cell renal carcinoma is the most frequent renal tumor subtype [7]. These tumors have a very vascular tumor stroma, frequently resulting in hemorrhagic areas. The typical yellow tumor surface is due to the lipid content of the cells; cholesterol, neutral lipids and phospholipids are also abundant (Figs. 1 and 2). Some clear cell renal cell carcinomas have a cystic appearance. This may be due to the presence of necrosis (pseudo-cysts). Presence of tumor necrosis is associated with increased aggressive behavior of the tumors. Some clear cell renal cancer form genuine neoplastic cysts. Cases with complete cystic appearance and without a solid tumoral component are defined as *multilocular cystic renal cell carcinoma* [8]. This subtype has an excellent prognosis and is regarded a low-malignant carcinoma subtype of clear cell renal cancer. Sarcomatoid changes can also occur in clear cell renal carcinoma and is associated with poor prognosis [5,9]. Most renal cell carcinomas have little inflammatory response, but sometimes an intense lymphocytic or neutrophilic infiltrate with natural killer cells is present [10] and there is an association between a strong lymphocytic infiltration and worse outcome [11]. Clear cell renal cell carcinomas most commonly metastasize hematogeneously via the vena cava primarily to the lung. Retrograde metastasis along the paravertebral veins, the vena testicularis/vena ovarii, intra-renal veins or along the ureter may also be a route of metastasis. Clear cell renal cell carcinoma is well known for its metastasis to unusual sites and late metastasis, even after 10 years or more. All clear cell kidney tumors are considered malignant tumors, independent of the tumor size [3].

Papillary renal cell carcinomas comprise approximately 10% of renal cell carcinoma [5,12,13]. The age distribution of papillary renal cell carcinoma is similar to clear cell renal cell carcinoma with reported mean age at presentation ranging from 50 to 65 years [14]. Papillary renal cell carcinomas frequently contain necrosis. In some tumors, a pseudo-capsule is identified. Bilateral and multifocal tumors are more common in papillary renal cell carcinoma than in other renal malignancies. The histology is characterized by epithelial cells forming papillae and tubules (Fig. 3). The tumor papillae contain a delicate fibro-vascular core. Aggregates of macrophages are frequently present. Psammoma bodies are common. Two morphological types of papillary renal cell carcinomas have been described [15]. Type 1 tumors with papillae covered by small cells with scanty cytoplasm (Fig. 3A). Type 2 tumor cells are often of higher nuclear grade with eosinophilic cytoplasm and pseudostratified nuclei (Fig. 3B). Type 1 tumors are more frequently multifocal. Sarcomatoid differentiation is also seen in papillary renal cell carcinoma and is associated with poor prognosis. Papillary renal cell carcinomas entirely composed by oncocytes have been described [16]. This subset of papillary tumors shows clinical-pathologic features different from type 1 and type 2 papillary renal cell carcinomas and has been proposed as a third group of papillary renal tumors.

Chromophobe renal cell carcinoma accounts for approximately 5% of renal cancer. They have a better prognosis than clear cell renal cancer [17,18]. Mortality is less than 10%. Rarely, sarcomatoid

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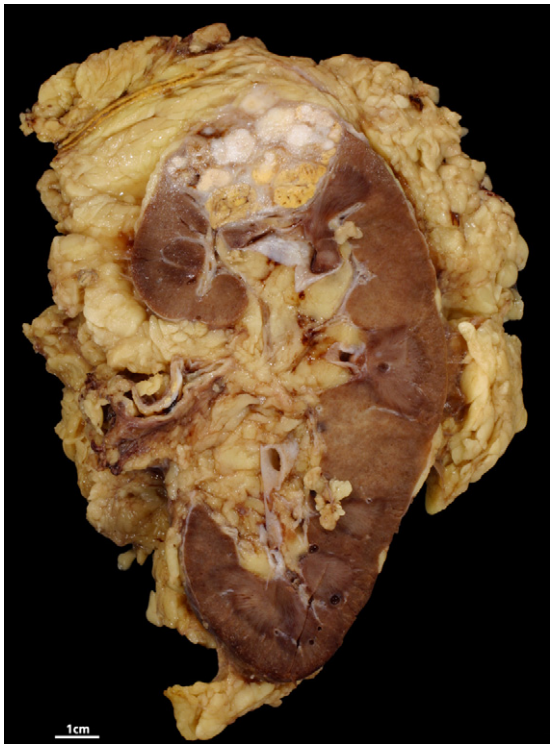

Fig. 1. Gross appearance of clear cell renal cancer. Bright yellow color in some areas is due to lipid and cholesterol content of tumor cells.

transformation does occur and is a diagnostic sign of poor prognosis [19]. Cases of chromophobe renal cancer have documented distant metastasis into lung, liver and pancreas. It has been suggested that liver metastasis is more frequent in chromophobe renal

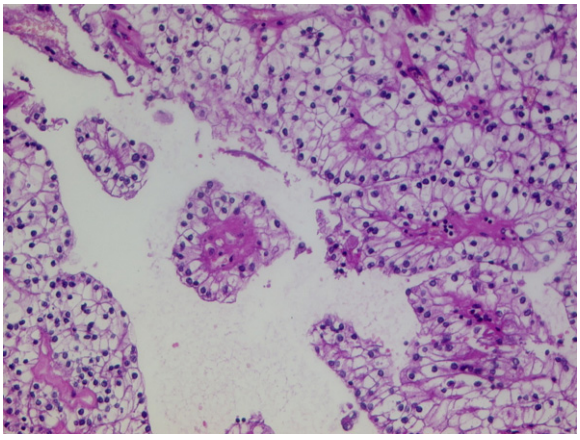

Fig. 2. Microscopic appearance of clear cell renal cancer with classic pattern resembling vegetable cells.

Table 1
WHO histological classification of RCC.

Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

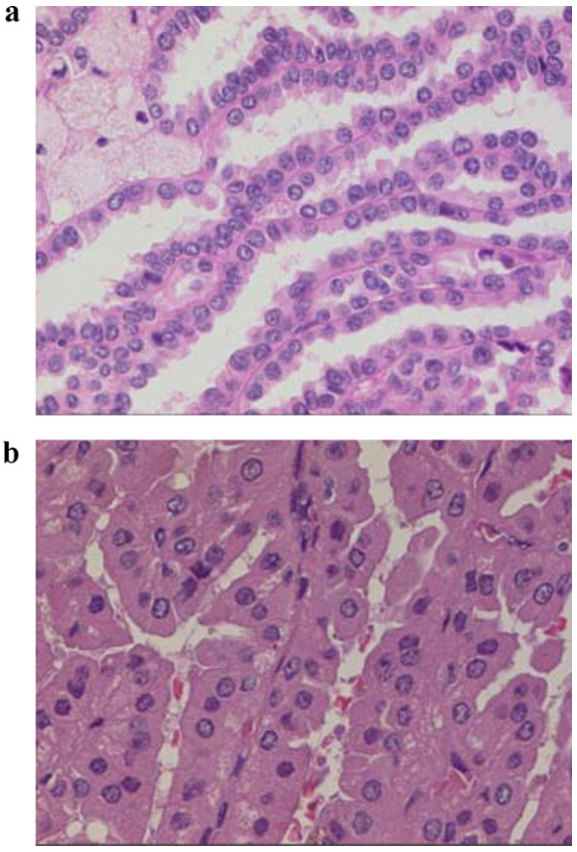

Fig. 3. (A) Papillary renal cell cancer type 1. Tumor cells are relatively small and cuboidal. There are some foam cells. (B) Papillary renal cell cancer type 2. Tumor cells are larger with eosinophilic cytoplasm.

cancers than in other histological subtypes [20]. The cut surface of chromophobe renal cell carcinoma appears homogeneously gray or gray-brown (Fig. 4). The tumor is characterized by large polygonal cells with reticulated cytoplasm and prominent cell membranes. Some cells are irregular and multinucleated. Perinuclear halos are common. A diagnostic hallmark is a diffuse cytoplasmic staining reaction with hales colloidal iron staining [21]. The eosinophilic variant of chromophobe renal carcinoma is purely composed of eosinophilic cells. Electron microscopically, the cytoplasm is characterized by glycogen deposits and numerous vesicles. The major differential diagnosis of chromophobe renal carcinoma is renal oncocytoma. *Renal oncocytoma* is considered to be a benign neoplasm [22]. It has been postulated that eosinophilic chromophobe renal cell cancer originates from renal oncocytoma, and represents the malignant form of this tumor. However, this hypothesis has not been proven. The so-called hybrid tumors share histopathological characteristics of chromophobe carcinoma and oncocytoma.

Collecting duct carcinoma is a very rare subtype of renal cell carcinoma, accounting for about 1% of all renal cancer types. This tumor type is extremely aggressive with frequent metastasis already at presentation [23–25]. These tumors are usually located in the central region of the kidney and have a gray-white appearance with irregular borders. They often display infiltration of peri-renal and renal sinus fat. Metastasis to regional lymph nodes, lung, liver, bone and adrenal glands are comment. Histologically, collecting duct cancer is characterized by a tubulo-papillary architecture with a characteristic desmoplastic stroma reaction. *Renal medullary carcinoma* is a rapidly growing tumor of the renal medulla associated almost exclusively with sickle cell trait. This is an extremely rare tumor. The majority of cases show sickled erythrocytes [26,27].