Multilocular cystic renal cell carcinoma with focus on clinical and pathobiological aspects

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Summary. Multilocular cystic renal cell carcinoma (MCRCC) accounts for approximately 1 to 2% of all renal tumors. This tumor is currently classified as a subtype of clear cell RCC. Clinically, the majority of these tumors are incidentally found. Macroscopically, the tumor is well demarcated and consists of various-sized cysts. The fibrous septa are generally thin and there is no discernible expansile nodule. Microscopically, the cyst walls are lined with tumor cells with clear to occasionally slightly eosinophilic cytoplasm. The Fuhrman nuclear grade is generally low and usually corresponds to grade 1. The deletion of chromosome 3p was identified in most tumors using FISH analysis and VHL gene mutation was identified in 25% of MCRCC. As MCRCC generally exhibits a low stage of TNM classification, the great majority of these tumors have a favorable clinical course. To date, there are no reports of metastasis, vascular invasion or sarcomatoid change in MCRCC. Accordingly, nephron sparing surgery is first recommended as a therapeutic strategy.

Key words: Multilocular cystic renal cell carcinoma, Clear cell renal cell carcinoma, Chromosome 3p, VHL gene mutation

Introduction

Multilocular cystic renal cell carcinoma (MCRCC) was introduced as a distinct entity for the first time in 1982 (Lewis et al., 1982). The diagnostic criteria of MCRCC historically have changed minimally. In 1991, Murad et al. defined MCRCC as tumors in which solid typical RCC areas exhibited less than 10% of the total mass. Subsequently, Corica et al. proposed a cutoff point of 25%. Eble and Bonsib (1998) considered tumors without grossly visible expansile nodule expanding the septa as MCRCC. According to the recent WHO classification, the diagnostic criteria proposed by Eble and Bonsib (1998) considered tumors without grossly visible expansile nodule expanding the septa as MCRCC. According to the recent WHO classification, the diagnostic criteria proposed by Eble and Bonsib, a tumor composed of numerous cysts, the septa of which contain small groups of clear cells indistinguishable from grade 1 clear cell carcinoma, seems to be adapted (Eble, 2004). In this article, we present an overview of this tumor entity with a focus on clinical and pathobiological aspects.

Clinical characteristics

MCRCC is a rare entity, comprising approximately 1 to 2% of all renal tumors (Prasad et al., 2006; Sabhiki et al., 2008; Argawal et al., 2011). There is slight male predominance (Murad et al., 1991; Corica et al., 1999; Suzigan et al., 2006). The majority of tumors are incidentally discovered during radiological scanning (Corica et al., 1999; Nassir et al., 2002; Suzigan et al., 2006; Gong et al., 2008). Some patients may present gross hematuria, flank pain, palpable mass and abdominal discomfort (Corica et al., 1999; Gong et al., 2008). The stages of MCRCC are generally low,
according to the criteria of tumor-node-metastasis (TNM) classification (Murad et al., 1991; Corica et al., 1999; Nassir et al., 2002; Gong et al., 2008). A case of concurrent MCRCC and leiomyoma in the same kidney has been reported (Cheong et al., 2010).

**Imaging findings**

Ultrasound sonography reveals a well-defined multilocular cystic mass composed of serous or complicated fluid. However, ultrasound sonography may downgrade higher Bosniak categories (Nassir et al., 2002). Computed tomography (CT) scan without enhancement discloses that MCRCC consists of separated and variable-sized cysts showing hypodensity and is separated from the non-tumorous renal parenchyma by a fibrous capsule. Septal or wall calcification may be seen in 20% of cases (Prasad et al., 2006). There is no recognizable expansile nodule in the thin septa (Kim et al., 2000). Enhanced CT scan may detect small, slightly enhanced solid areas in some cases (Kim et al., 2000; Nassir et al., 2002). According to Bosniak classification, most cases with MCRCC correspond to category II or III, but even category IV may occur in some cases (Hora et al., 2005; You et al., 2011). Magnetic resonance imaging may show lesional enhancement (Nassir et al., 2002). It seems to be practically impossible for clinicians to establish an accurate diagnosis with imaging examination because multilocular cyst RCC should be strictly distinguished from other entirely cystic diseases, including cystic nephroma, cystic partially differentiated nephroblastoma and tubulocystic carcinoma, after surgery.

**Pathological findings**

**Macroscopic findings**

Tumor size ranges from 1 to 14 cm in the maximum diameter (Suzigan et al., 2006). The tumor is generally a well-demarcated mass composed entirely of various-sized cysts (Fig. 1) (Troung et al., 2003; Halat and MacLennan, 2007). The cysts contain serous, mucoid, gelatinous, proteinaceous or hemorrhagic fluid (Murad et al., 1991; Yamashita et al., 1995; Troung et al., 2003; Imura et al., 2004; Halat and MacLennan, 2007; Agarwal et al., 2011). The fibrous wall or septa are thin and regular, and there are no expansile nodules more than 5mm long (Aubert et al., 2005). Tumor necrosis has never been observed (Brinker et al., 2000; Suzigan et al., 2006). Most patients have unilateral mass with no side predominance (Corica et al., 1999; Suzigan et al., 2006).

**Microscopic findings**

The cysts are histologically lined by cuboidal and flattened epithelial cells with clear to occasionally slightly eosinophilic cytoplasm (Fig. 2A) (Brinker et al., 2000; Koga et al., 2000; Troung et al., 2003; Suzigan et al., 2006). In the septa, small groups of neoplastic cells forming a solid area may be observed (Suzigan et al., 2006). The Fuhrman nuclear classification generally corresponds to grade 1 (Fig. 2B), but may be grade 2 in some cases (Murad et al., 1991; Corica et al., 1999; Brinker et al., 2000; Koga et al., 2000; Nassir et al., 2002; Suzigan et al., 2006; Sabhiki et al., 2008). There are no or few mitotic figures and abnormal mitotic figures have never been seen (Murad et al., 1991). No necrotic focus has been identified in the lesions (Murad et al., 1991; Nassir et al., 2002).

**Histochemical findings**

Periodic acid-Schiff (PAS) and Oil red O stains highlight glycogen and intracytoplasmic lipid in the cytoplasm of tumor cells, respectively (Feldberg and Weiss, 1982). One study using lectin histochemistry has demonstrated that tumor cells react with *peanut agglutinin* (PNA) in many cases (Imura et al., 2004). Although the reactivity to PNA is characteristic to the distal nephron, these results may reflect non-specific reactivity, because this tumor seems to have a close relationship to clear cell RCC that arises from the proximal nephron.

**Immunohistochemical findings**

Neoplastic cells show positivity for CAIX (carbonic anhydrase IX), CD10, RCC Ma and PAX2 (Fig. 3A), but are negative for CD68 (von Teichman et al., 2011; Li et al., 2012). We found the immunoreactivity for adipophilin in the cytoplasm of tumor cells that...
corresponded to lipid droplets (Fig. 3B). This result may reflect a close relationship between MCRCC and clear cell RCC, because adipophilin expression in clear cell RCC has been previously reported (Ostler et al., 2010). Inactivated GSK3β (glycogen synthase kinase 3-β), decreased PTEN expression and PAX2 positivity is observed in the great majority of MCRCCs and these results resemble clear cell RCC. However, the frequency (93%) of strong nuclear positivity of p27 is higher than that (30%) of clear cell RCC (von Teichmann et al., 2011). The MIB-1 index is less than 5% (Aubert et al., 2005).

**Ultrastructural findings**

Ultrastructurally, neoplastic cells have microvilli on the apical lumens and this feature resembles clear cell RCC (Murad et al., 1991; Eble and Bonsib, 1998).

**Flow cytometric findings**

Ploidy studies disclosed diploid DNA content in
more than 90% of cases with MCRCC (Murad et al., 1991; Corica et al., 1999).

**Molecular genetic findings**

In dual color interphase fluorescence *in situ* hybridization analysis with centromeric α-satellite DNA probe for chromosome 3 (CEP3) and subtelomeric probe for chromosome 3p25 (3pTel25), chromosome 3p deletion was observed in 74% of cases with MCRCC and 89% of clear cell RCC (Halat et al., 2010). VHL gene mutation was observed in 25% of tumors with MCRCC (von Teichman et al., 2011) (Fig. 4A). The low rate of tumor cells in MCRCC may contribute to the low frequency of VHL gene mutation in MCRCC compared with clear cell RCC, because the low rate of tumor cells can clearly become an obstacle to molecular studies. Additionally, we found the loss of heterozygosity (LOH) in chromosome 3p in one case with MCRCC (Fig. 4B). These results supply the evidence that MCRCC is a subtype of clear cell RCC from the genetic aspect. However, further examination in a large scale study will be required.

**Differential diagnosis**

MCRCC should be distinguished from clear cell RCC with cystic change, cystic nephroma, mixed epithelial and stromal tumor, tubulocystic carcinoma, angiomylipoma with epithelial cyst (AMLEC), clear cell papillary RCC and von Hippel-Lindau (VHL) disease. Clear cell RCC with cystic change macroscopically has an expansive nodule or thick wall, and histologically may possess a necrotic area (Deshpande et al., 1986; Brinker et al., 2000; Freire and Remer, 2009). In cystic nephroma according to the present WHO classification, the tumor frequently affects infants and adult women and neoplastic cells usually have eosinophilic cytoplasm with hobnail appearance and ovarian-like stroma may be also present (Hartman et al., 1987; Troung et al., 2003; Michal et al., 2004, 2010). Cystic nephroma is immunohistochemically negative for CAIX (Li et al., 2012). Mixed epithelial and stromal tumor often affects middle-aged women. This tumor possesses a solid portion macroscopically and the ovarian stroma is often seen microscopically (Michal et al., 2004). In tubulocystic carcinoma, neoplastic cells demonstrate the marked nuclear atypia that corresponds to Fuhrman nuclear grade 3 (Yang et al., 2008; Zhou et al., 2009). Tubulocystic carcinoma is frequently positive for cytokeratin 7 and AMACR. In AMLEC, Müllerian stroma is often observed beneath the epithelial cells and neoplastic cells are positive for melanosomal antigen (Fine et al., 2006). Clear cell papillary RCC often have a cystic area. Immunohistochemically, tumor cells are diffusely positive for cytokeratin 7, but generally negative for AMACR and CD10 (Gobbo et al., 2008). In VHL disease, renal tumors often multiply and clinical information such as the presence of tumors or cyst in central nervous system or other visceral organs or family history is very important (Bisceglia et al., 2006; Shuin et al., 2006). In Table 1, immunohistochemical profiles in the differential diagnosis of renal cystic neoplasms largely consisting of cysts are summarized.

<p>| Table 1. Immunohistochemical profile of renal neoplasm largely consisting of cysts. |
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RCC, renal cell carcinoma; CN, cystic nephroma; MEST, mixed epithelial and stromal tumor; TC, tubulocystic carcinoma; CAML, cystic angiomylipoma; CPDN, cystic partially differentiated nephroblastoma; NP, not present.

**Fig. 4. A.** The Sequence of part of exon 1 of VHL gene. Arrow shows point mutation, single base substitution C>A at position 194 of CDS resulting in premature STOP codon. **B.** Fragmentation analysis of microsatellite marker D3S1597 (3p). Arrow shows LOH 3p in tumour tissue.
Therapy

Partial nephrectomy, radical nephrectomy or enucleation is performed for the treatment of MC RCC (Nassir et al., 2002; Aubert et al., 2005). When MC RCC is clinically suspected, nephron-sparing surgery should be recommended, whatever its size and when technically feasible (Weiss et al., 1998; Koga et al., 2000; Aubert et al., 2005; Hora et al., 2005; You et al., 2011).

Prognosis

MC RCC has a favorable prognosis (Murad et al., 1991; Brinker et al., 2000; Koga et al., 2000; Imura et al., 2004; Bisceglia et al., 2006; Suzigan et al., 2006; Halat et al., 2010). To date, there are no reports of metastases, vascular invasion or sarcomatoid change of MC RCC (Murad et al., 1991; Kim et al., 2000; Agarwal et al., 2011). Accordingly, some investigators prefer the term of “multicystic renal neoplasm of uncertain malignant potential” for clinicians until more data with long term follow-up is available. The 5-year or 10-year survival rates and non-recurrence rates after surgery range from 97.3 to 100% and from 90.3 to 100%, respectively (Kim et al., 2000; Koga et al., 2000; Nassir et al., 2002; Imura et al., 2004; Suzigan et al., 2006).

Future perspectives

On the basis of previous studies, MC RCC seems to be characterized by low nuclear grade and low stage of TNM classification. However, as this tumor is rare and the tumor volume is generally small (less than 25%), there are a few genetic studies on MC RCC to date (Nassir et al., 2002; Halat et al., 2010). Accordingly, further research in a large scale study will be required in order to clarify the pathogenesis of MC RCC.

References

Mulitlocular cystic RCC


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