

Review

Review of acquired cystic disease-associated renal cell carcinoma with focus on pathobiological aspects

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Summary. Acquired cystic disease (ACD)-associated renal cell carcinoma (RCC) is a recently established entity. In this article, we introduce the general view of this new entity. Macroscopically, the disease exclusively occurs in ACD and may arise as a dominant mass or non-dominant masses. Histologically, the tumor is characterized by a microcystic pattern, neoplastic cells with an eosinophilic or oncocytic cytoplasm and frequent intratumoral oxalate crystal deposition. Prominent nucleoli of tumor cells are often observed. Immunohistochemically, neoplastic cells are generally positive for AMACR but negative for cytokeratin 7. Ultrastructurally, neoplastic cells contain abundant mitochondria in the cytoplasm. Genetically, the gain of chromosomes 3, 7, 17 and abnormality of the sex chromosome were frequently observed in several studies. In conclusion, ACD-associated RCC may be widely recognized as a distinct entity in the near future because this tumor is morphologically and genetically different from other renal tumor entities that have been previously established.

Key words: Acquired cystic disease-associated renal cell carcinoma, Oxalate crystals, Chromosome 3, Sex chromosome

Introduction

Many investigators have considered for a long time that clear cell or papillary renal cell carcinoma (RCC) is a common histological type of renal cancer arising from acquired cystic disease (ACD) (Ishikawa and Kovacs, 1993; Troung et al., 1995, 2003; Kojima et al., 2006). However, a new disease entity of ACD-associated RCC showing characteristic histologic features has been recently established (Sule et al., 2005; Petrolla and MacLennan, 2006; Tickoo et al., 2006). In this article, we introduce the general view of this disease.

Epidemiology

ACD-associated RCC accounts for 36% of renal epithelial neoplasms arising from end-stage renal disease and is now considered to be the most common histological type (Tickoo et al., 2006). We have found that ACD-associated RCC frequently occurs in patients receiving hemodialysis of more than 10 years (Nouh et al., 2009) and it is known that the incidence of ACD-associated RCC increases as the duration of hemodialysis progresses (Enoki et al., 2010).

Pathological findings

Macroscopic findings

Diagnostic criteria for ACD are cystic structures accounting for at least 25% of the renal parenchyma or greater than three cysts per kidney (Pope et al., 1994).

The cut surface of the tumor varies from grey tan to yellowish or brownish and hemorrhage or necrosis is occasionally seen (Enoki et al., 2010).

Microscopic findings

ACD-associated RCC is histologically characterized by typical microcystic growth pattern (Fig. 1A), deeply eosinophilic or oncocyctic cytoplasm and is frequently associated with intratumoral oxalate crystal deposition (Fig. 1B) (Rioux-Leclercq and Epstein, 2003; Sule et al., 2005; Tickoo et al., 2006). Some investigators suggest that many microcysts may be formed by intracytoplasmic vacuoles mainly due to degenerative

change. These crystals are multicolored under polarized microscopic observation. Papillary, tubular, cribriform or solid growth pattern may also be seen. Nuclei are generally round and nuclear grade frequently shows Fuhrman grade 3 but may exhibit Fuhrman 1 or 2 (Sule et al., 2005; Tickoo et al., 2006; Enoki et al., 2010). Clear cell change may be present in some cases. Sarcomatoid change or rhabdoid features may be seen in some cases (Tickoo et al., 2006; Kuroda et al., 2008; Kuroda et al., 2010b). Multiple lesions of ACD-associated RCC can often be identified (Tickoo et al., 2006; Enoki et al., 2010). Atypical cyst, papillary tuft, cribriform lesion and papillary renal adenoma may be precursor lesions of ACD-associated RCC (Hughson et

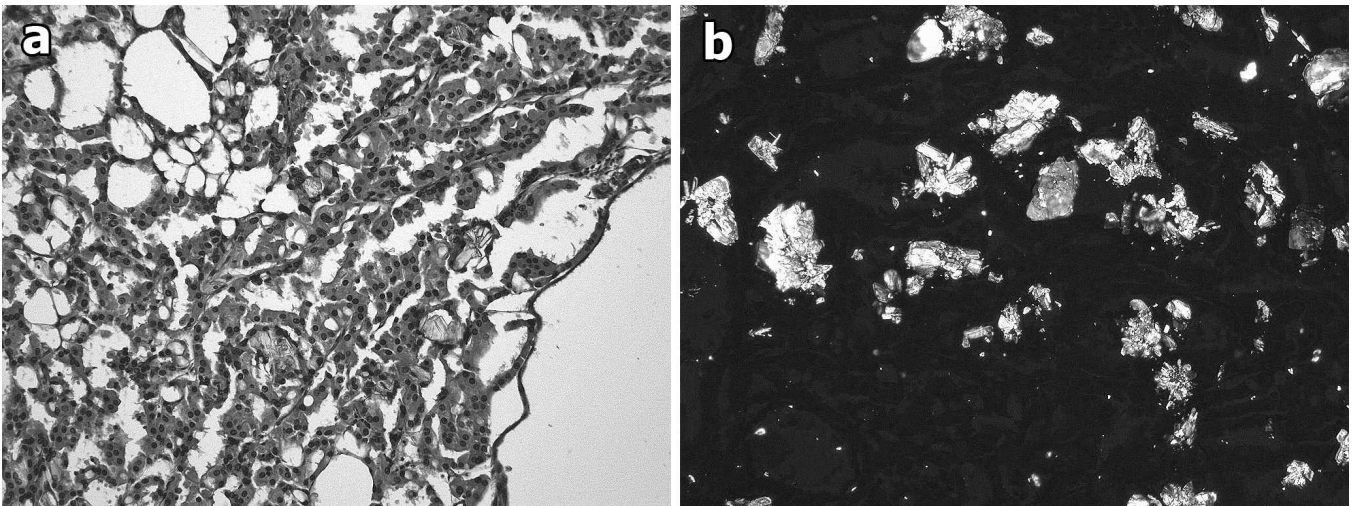


Fig. 1. Microscopic findings. **a.** Microcystic growth pattern of neoplastic cells formed by many Intracytoplasmic vacuoles is seen. **b.** The deposition of oxalate crystals is observed in the stroma under polarized microscopy. x 40

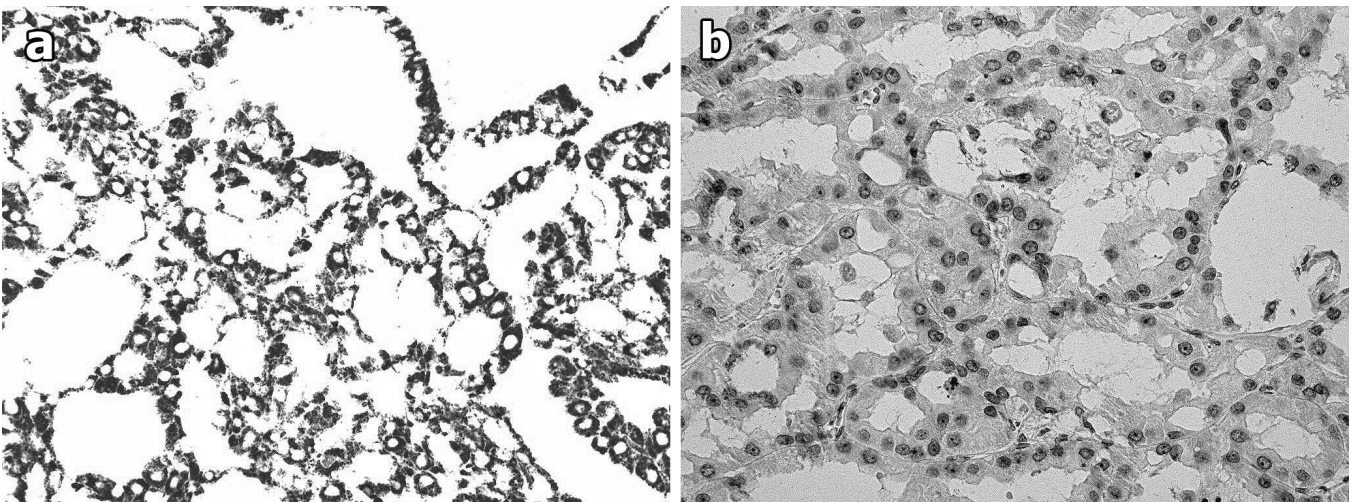


Fig. 2. Immunohistochemical results. **a.** Immunoreactivity for AMACR is observed in the cytoplasm of many tumor cells. **b.** Neoplastic cells show complete lack of staining for cytokeratin 7. x 100

al., 1980, 1986; Cheuk et al., 2002)

Immunohistochemical findings

Neoplastic cells are positive for AMACR (Fig. 2A), CD10, CD57 and vinculin, but negative for cytokeratin 7 (Fig. 2B) and high molecular weight cytokeratin (Tickoo et al., 2006; Enoki et al., 2010).

Ultrastructural findings

Neoplastic cells contain abundant mitochondria in the cytoplasm (Kuroda et al., 2008). Nagy et al. (2003) suggest that the mitochondria-rich morphology in renal tumors arising in end-stage renal disease may be due to mitochondrial DNA alteration.

Differential diagnosis

A differential diagnosis, such as clear cell RCC (granular cell variant), papillary RCC and oncocytoma should be considered. Microcystic or cribriform growth pattern is not prominent in these tumors. Additionally, oxalate crystal deposition in the intratumoral stroma is generally absent in these tumors. Immunohistochemically, AMACR is negative or focally positive for clear cell RCC, and papillary RCC generally demonstrates cytoplasmic labeling for cytokeratin 7 (type 1 > type 2). E-cadherin and CD117 are generally expressed in renal oncocytoma.

Molecular genetic findings

Non-neoplastic renal parenchyma or precursor lesions of ACD-associated RCC frequently show gains of chromosomes 7 and 17 (Cheuk et al., 2002; Hes et al., 2008). Cossu-Rocca et al. (2006) have performed fluorescence *in situ* hybridization (FISH) of three tumors. They found gains of chromosomes 1, 2 and 6 in two tumors, but no losses or gains of chromosomes 1, 2, 6, 10, or 17 were seen in one tumor. Pan et al. (2009) have reported the common gain of chromosomes 7 and 17 in ACD-associated RCC using combined array comparative genomic hybridization (CGH) and FISH analyses, but they have suggested that ACD-associated RCC is different from papillary RCC because the gain of chromosome 3 and the sex chromosome is more frequently observed in ACD-associated RCC than in papillary RCC. Kuntz et al. (2010) have also reported that a gain of chromosome 3 was seen in the study of four tumors in two patients with ACD-associated RCC using array CGH. We have reported that one tumor with ACD-associated RCC showed gains of chromosomes 3, 7 and 16, and a loss of chromosome Y in a G-band karyotype study (Kuroda et al., 2010a). We have also described that the numerical abnormalities of chromosomes 3 and 16, irrespective of gain or loss, frequently occurs in ACD-associated RCC using FISH analysis (Kuroda et al., in press). These chromosomal

abnormalities seem to be different from other renal disease entities, although they may partially share the nature of papillary RCC. Concerning the genetic change of ACD-associated RCC with sarcomatoid change, we have found the loss of chromosomes 1p, 2q11-22, 9 and 14 in one tumor using CGH analysis (Kuroda et al., 2008). Additionally, we have described that the G-band karyotype of ACD-associated RCC with sarcomatoid change and rhabdoid features showed the following changes: 46, X, +X, -Y[1]/43, idem, add(2)(q31), -6, -9, -14, -15, +16, -22, +mar1[6]/46, XY[2]/abnormal cell[11] (Kuroda et al., 2010b).

Prognosis

ACD-associated RCC seems to have a relatively good prognosis because patients with long-term hemodialysis receive periodic follow-up (Sule et al., 2005; Nouh et al., 2010). However, ACD-associated RCC with sarcomatoid change or rhabdoid features may have a metastatic disease (Kuroda et al., 2010b). In contrast, some investigators have reported that some cases behave in a more aggressive fashion than clear cell RCC or other histological types (Tickoo et al., 2006; Enoki et al., 2010).

Perspectives

It is possible that the concept of ACD-associated RCC may be widely accepted in the world because this disease is different from previously established other renal disease entities in both histological and genetic aspects. However, the gene responsible for the tumorigenesis of ACD-associated RCC remains undiscovered. Further examination in a large study will be required in order to characterize this tumor entity.

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