Original paper

Acquired cystic disease-associated renal cell carcinoma: a clinicopathological study of seven cases

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The disease entity of acquired cystic disease (ACD)-associated renal cell carcinoma (RCC) has been recently incorporated into the international renal tumor classification. However, there are a few descriptions on clinicopathologic features. We performed a clinicopathologic study of seven cases with ACD-RCC. All tumors were incidentally found. Histologically, the tumor consisted of microcystic or cribriform pattern of neoplastic cells with deeply eosinophilic to oncocytic cytoplasm in the stroma of oxalate crystal deposition. Three cases contained the area of sarcomatoid transformation, of which one case also demonstrated rhabdoid phenotype foci. Six among seven patients had a hemodialysis history of more than 10 years and two patients showing the dedifferentiation had a hemodialysis history of more than 20 years. The follow-up duration ranged from 18 to 107 months with a mean of 59.1 months. Regarding the outcome, four patients were alive without disease. One patient was alive with metastasis 10 months after the operation. No patient died of disease. Finally, ACD-RCC generally pursues a favorable clinical course, but tumors with a hemodialysis history of more than 20 years may cause the dedifferentiation such as sarcomatoid change or rhabdoid features and this phenomenon may lead to worse clinical outcome.

Key words: acquired cystic kidney, renal cell carcinoma, pathology, prognosis.

Introduction

The disease entity of acquired cystic kidney-associated renal cell carcinoma (ACD-RCC) has been recently established [1, 2, 3, 4, 5, 6, 7] and incorporated into the recent International Society of Urologic Pathology and World Health Organization Classification [8, 9]. However, there are a few descriptions on the clinical outcome of ACD-RCC [3, 10]. In this article, we examined the clinicopathologic study of seven cases with ACD-RCC.

Material and methods

During April 2005 and December 2016, seven cases with ACD-RCC have been selected for this study.

Three cases have been previously reported [11, 12, 13]. Clinical finding (sex, age, symptoms, hemodialysis duration and stage) macroscopic findings (tumor size, color, necrosis and hemorrhage), microscopic findings (multiplicity, sarcomatoid change, rhabdoid phenotype, Fuhrman Grade, and other lesions) and therapy/outcome (surgery, adjuvant therapy, follow-up duration and clinical outcome) were retrospectively evaluated for each case. The disease-free survival of ACD-RCC was compared with that of clear cell RCC (24 cases) or chromophobe RCC (7 cases), using Kaplan-Meier method and the long-rank test. All p values were two sided and a $p < 0.05$ was considered to be significant. This study (no. 151) was approved by the ethical committee of Kochi Red Cross Hospital. For the immunohistochemistry, tissue sections were cut and stained with Ventana Benchmark Ultra autostainer (Ventana Medical Systems, Tucson, AZ). Primary antibodies against cytokeratin 7 (OV-TL 12/30, 1 : 800, DAKO, Glostrup, Denmark and AMACR(P504S) (13H4, 1 : 100, DAKO, Glostrup, Denmark) were employed in the present study. Fluorescence *in situ* hybridization (FISH) for p16 was performed in one tumor using Vysis CDKN2A/CEP probe kit (Abott Molecular, Wiesbaden, Germany). Pretreatment using VP-2000 Processor (Abott Molecular, Tokyo, Japan) was performed according to the manufacturer's protocol and hybridization was carried out using the ThermoBrite (Abott Molecular, Tokyo, Japan).

Results

Clinical features

Clinical characteristics are summarized in Table I. The patients consisted of five men and two women. The age of patients ranged from 38 to 78 years with a mean age of 52.9 years. No patient presented any symptoms such as hematuria, abdominal pain or mass and all tumors were incidentally found in the periodical imaging analysis on the follow-up of hemodialysis. The duration of hemodialysis ranged from 4 to 26 years with a mean of 15.7 years. The TNM stage was composed of five cases in stage I, one in stage III and one in stage IV. The cause of chronic renal failure was hypertension in three cases, and diabetes mellitus in one case. The cause of the remaining cases was uncertain.

Pathological findings

Macroscopic findings

Macroscopic features are summarized in Table II. The size of tumors ranged from 2.2 to 8.5 cm with a mean size of 5.0 cm. The cut surface of the tumor showed light brown in three cases (Fig. 1), brown in two cases, red brown in one case and yellow color in one case. Hemorrhage and necrosis were identified in three and two tumors, respectively.

Microscopic findings

Microscopic features are summarized in Table III. In all cases, the tumor histologically consisted of microcystic (Fig. 2A) or cribriform pattern of neoplastic cells with deeply eosinophilic to oncocytic cytoplasm on the background of oxalate crystal deposition (Fig. 2B). Three cases contained the area of sarcomatoid transformation (Fig. 2C) and one case demonstrated rhabdoid phenotype foci (Fig. 2D). Atypical cysts consisting of stratified atypical cells with eosinophilic cytoplasm and papillary adenoma were observed

Table I. Clinical summary of ACD-RCC

Case	Age	Sex	Symptoms	HD duration	Stage
1	38	M	incidentally found	17 years	I
2	78	F	incidentally found	14 years	I
3	66	M	incidentally found	12 years	I
4	72	M	incidentally found	20 years	III
5	47	M	incidentally found	17 years	I
6	56	F	incidentally found	26 years	IV
7	63	M	incidentally found	4 years	I

M – male; F – female; HD – hemodialysis

Table II. Macroscopic findings of ACD-RCC

Case	Tumor size	Color	Hemorrhage	Necrosis
1	3.2 cm	light brown	+	–
2	3.5 cm	light brown	–	–
3	2.2 cm	brown	–	–
4	7.5 cm	red brown	+	+
5	5.3 cm	light brown	+	–
6	8.5 cm	yellow	–	+
7	5.0 cm	brown	–	–

+, present; –, absent

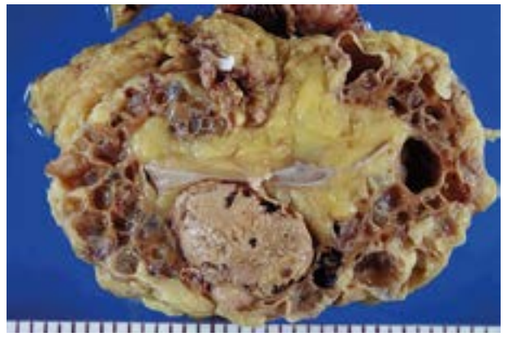

Fig. 1. Macroscopic findings. The background kidney demonstrates multicystic pattern, namely acquired cystic disease. On the cut surface, the tumor is well circumscribed and shows light brown color

in two cases. Necrosis and lymphovascular invasion were observed in four cases and one case, respectively. Pseudocapusular formation and intrarenal metastasis were absent in all cases. In non-neoplastic area, thyroid-like appearance associated with chronic pyelonephritis was observed in all cases.

Immunohistochemical results

In five cases, immunohistochemistry was performed. Neoplastic cells in all cases were diffusely positive for AMACR, but negative for cytokeratin 7.

Prognosis

Therapy, follow-up duration and clinical outcome are summarized in Table IV. All tumors were resected by radical nephrectomy. Adjuvant therapy was performed in one patient (Case 6). The follow-up was available with five patients. The follow-up duration ranged from 18 to 107 months with a mean of 59.1 months. Regarding the outcome, four patients (Cases 3, 4, 5, 7) were alive without disease and one patient (Case 6) presented with metastasis to rib, lung at the operating time and underwent interferon therapy postoperatively. Subsequently, she developed the metastasis to para-aortic lymph nodes and received VEGF/PDGF inhibitor (sorafenib). She was alive with disease at 18 months after the operation. No patient died of the disease. Compared with disease-free survival of clear cell RCC or chromophobe RCC, there was statistically no difference between that of ACD-RCC (Fig. 3).

FISH findings

Two-hundreds thirty-seven neoplastic cells of one tumor (Case 6) were counted and p16 loss was observed in 24.2% of all tumor cells (Fig. 4).

Discussion

Based on the present study, tumors with ACD-RCC tend to be incidentally discovered during the periodical follow-up. Therefore, the periodical examination of bilateral kidneys with ACD seems to be very important to find the early renal tumors. We recommend the computed tomography scan examination once per a year.

On gross examination, tumors are generally well circumscribed and show the brown, red brown to light brown color on the cut surface. Hemorrhage or necrosis may be occasionally observed. Histologically, as observed in the present study, the tumor is characterized by microcystic or cribriform growth pattern of deeply eosinophilic to oncocytic cells and Fuhrman Grade 2 to 3 and oxalate crystal deposition in the stroma [3, 4, 5, 6, 7, 8, 9]. Papillary growth, clear cell change or foamy cell change may be noted. In some cases, ACD-RCC may be identified multiply and this phenomenon was also observed in the present study [3]. Additionally, other lesions such as clear cell RCC, papillary RCC, papillary adenoma, or atypical cysts may be often associated, as observed in the present study. We suggest that atypical cysts may be precursor lesions of ACD-RCC. It is well known that the frequency of ACD-RCC is positively associated with hemodialysis duration of more than 10 years [10, 14, 15]. Sarcomatoid change was demonstrated in three cases of the present study [11, 13]. This transformation may be related to the long-term, more than 20 years, hemodialysis, as Sassa *et al*. suugested [10]. In the present study, two cases of Stage III or IV had a hemodialysis history of more than 20 years. Therefore, our result supports Sassa's hypothesis. However, rhabdoid change seems to be rare in ACD kidney [13]. Regarding the therapy of ACD-RCC, radical nephrectomy is the standard therapy. However, partial resection may be one option in some feasible cas-

Table III. Microscopic findings of ACD-RCC

Case	ACD-RCC Multiplicity	Sarcomatoid change	Rhabdoid phenotype	Fuhrman Grade	Other lesions
1	–	–	–	2	–
2	–	+, 10%	–	4	–
3	–	–	–	2	CCP-RCC, ACs
4	+	–	–	3	CRCC, PRCC
5	–	+, 1%	–	4	–
6	+	+, 90%	+,1%	4	PA, ACs
7	–	–	–	3	PA

+, present; –, absent; CRCC – clear cell renal cell carcinoma; PRCC – papillary renal cell carcinoma; CCP-RCC – clear cell papillary renal cell carcinoma, PA – papillary adenoma; AC – atypical cysts

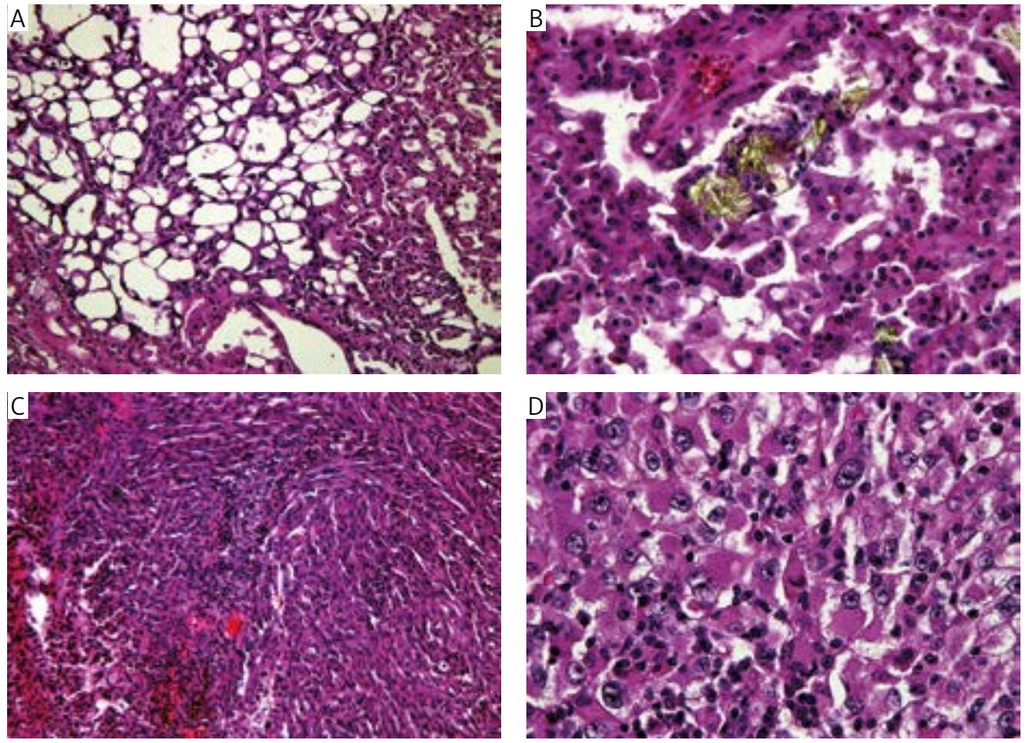

Fig. 2. Microscopic findings. A) Neoplastic cells with deeply eosinophilic to oncocytic cytoplasm proliferate with microcystic or cribriform pattern. B) Oxalate crystals deposit in the tumorous stroma. C) Sarcomatoid change. Spindle neoplastic cells with marked cytologic atypia proliferate. D) Rhabdoid features. Tumor cells show the abundant eosinophilic cytoplasm with eccentric nuclei

Table IV. Therapy, follow-up duration and outcome of ACD-RCC

Case	Surgery	Adjuvant therapy	Follow-up duration	Outcome
1	RN	NA	lost	–
2	RN	NA	lost	–
3	RN	NP	51 months	AWOD
4	RN	NP	69 months	AWOD
5	RN	NP	107 months	AWOD
6	RN	IFN, VEGF/PDGF-I	18 months	AWD
7	RN	NP	63 months	AWOD

RN – radical nephrectomy, NA – not available; NP – not performed; IFN – interferon; VEGF/PDGF-I, vascular endothelial growth factor/platelet-derived growth factor-inhibitor; AWOD – alive without disease; AWD – alive with disease

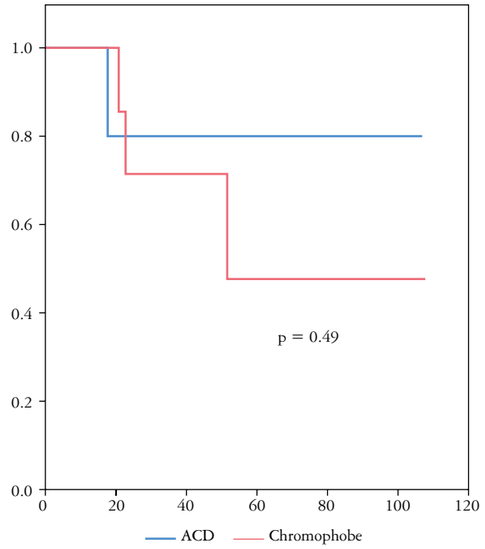

Fig. 3. The comparison of disease-free survival of ACD-RCC and chromophobe RCC. There is no significant difference in survival rate between two tumors

es. We speculate that VEGF/PDGF inhibitor may be one option for advanced stage tumors. There is no report on molecular targeted therapy of ACD-RCC because of the scarce cases with advanced stage. Immunohistochemically, neoplastic cells of ACD-RCC generally show positivity for AMACR and negativity for cytokeratin 7 [16]. Napsin A may express in this subtype [17]. Cytogenetic study of ACD-RCC frequently showed the numerical abnormalities of chromosomes 3 and 16 with gains of chromosomes 7 and 17 [18, 19, 20, 21, 22]. We have suggested that loss of chromosome 9 or 14 may be related to the dedifferentiation of ACD-RCC such as sarcomatoid change or rhabdoid morphology [11, 13]. Tajima *et al.* have suggested that pronounced polysomy of chromsomes 3 and 16 or p53 mutation may be associated with sarcomatoid change [22]. The prognosis of ACD-RCC seems to generally be favorable unless the proportion of dedifferentiation is predominant. Some investigations have suggested that loss of *CDKNA2/p16* gene at chromosome 9p21 may be related to aggressive behavior in clear cell RCC [23, 24]. However, the abnormality of *CDKN2A/p16* gene seems to be not involved in the pathogenesis of metanephric adenoma [25]. In this study, we suggest that the loss of *CDKN2A/p16* gene may be involved in the pathogenesis of ACD-RCC. Further examination in a large scale study will be required in order to elucidate the role of *CDKN2A/p16* gene in ACD-RCC.

In conclusion, most cases of ACD-RCC is incidentally found in the periodical follow-up imaging.

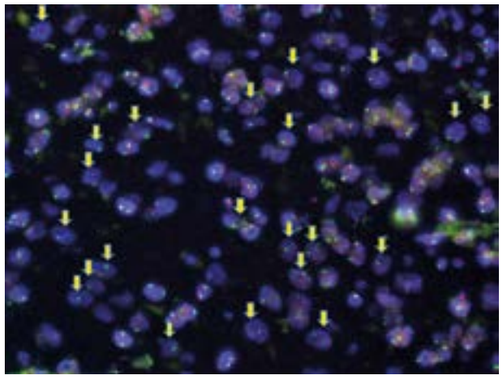

Fig. 4. Fluorescence *in situ* hybridization findings. The loss (arrows) of *CKDN2A/p16* gene is observed

ACD-RCC frequently occurs in patients having a long-term hemodialysis history of more than 20 years. The further long-term hemodialysis history of more than 20 years can lead to the dedifferentiation such as sarcomatoid change or rhabdoid phenotype. *CDKN2A/p16* gene may be involved in the pathogenesis of ACD-RCC.

The authors declare no conflict of interest.

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