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

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Introduction

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 foc. 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 had 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.

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 lesion), 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 used for cytookeratin 7 (OV-TL 12/30, 1:800, DAKO, Glostrup, Denmark) and p16 were performed in one tumor using Vysis CDP- N2A/CEP probe kit (Abbott Molecular, Wiesbaden, Germany). Pretreatment using VP-2000 Processor (Abbott Molecular, Tokyo, Japan) was performed according to the manufacturer’s protocol and hybridization was carried out using the ThermoBrite (Abbott Molecular, Tokyo, Japan).

Table I. Clinical summary of ACD-RCC

<table>
<thead>
<tr>
<th>CASE</th>
<th>AGE</th>
<th>SEX</th>
<th>SYMPTOMS</th>
<th>HD DURATION</th>
<th>STAGE</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>M</td>
<td>incidentally found</td>
<td>17 years</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>incidentally found</td>
<td>14 years</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>incidentally found</td>
<td>12 years</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>M</td>
<td>incidentally found</td>
<td>20 years</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>M</td>
<td>incidentally found</td>
<td>17 years</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>F</td>
<td>incidentally found</td>
<td>26 years</td>
<td>IV</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>incidentally found</td>
<td>4 years</td>
<td>I</td>
</tr>
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</table>

ACD – acquired cystic disease; HD – hemodialysis

Table II. Macroscopic findings of ACD-RCC

<table>
<thead>
<tr>
<th>CASE</th>
<th>TUMOR SIZE</th>
<th>COLOR</th>
<th>HEMORRHAGE</th>
<th>NECROSIS</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3.2 cm</td>
<td>light brown</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>3.5 cm</td>
<td>light brown</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>3.2 cm</td>
<td>brown</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>7.5 cm</td>
<td>red brown</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>5.3 cm</td>
<td>light brown</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>8.5 cm</td>
<td>yellow</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>7.0 cm</td>
<td>brown</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table II. Macroscopic findings of ACD-RCC

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 micropapillary 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 foc (Fig. 2D). Artyphal cysts consisting of stratified atypical cells with eosinophilic cytoplasm and papillary adenoma were observed.
in two cases. Necrosis and lymphovascular invasion were observed in four cases and one case, respectively. Pseudocapsular formation and intrarenal metastasis were absent in all cases. In non-neoplastic area, rhabdoid-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-hundred 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 5 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. suggested [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 cases.
Chromophobe generally show positivity for AMACR and negativity for CDKN2A/p16, neoplastic cells of ACD-RCC report on molecular targeted therapy of ACD-RCC 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 phenotype. CDKN2A/p16 gene may be involved in the pathogenesis of ACD-RCC.

The authors declare no conflict of interest.

References

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Fig. 4. Fluorescence in situ hybridization findings. The loss (arrows) of CDKN2A/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 is involved in the pathogenesis of ACD-RCC.