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Prognostic Significance and Nature of Rhabdoid Features in Renal Cell Carcinoma

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Background: Recent reports have indicated that renal cell carcinoma (RCC) with rhabdoid features follows an aggressive clinical course. We investigated the prognostic significance and nature of the rhabdoid component. **Methods:** We retrospectively analyzed the incidence and clinicopathologic characteristics of RCC with rhabdoid features in 174 radical nephrectomy cases. The specimens were examined histologically and immunohistochemically. **Results:** Twelve of the 174 RCC cases (6.9%) showed rhabdoid features. Histologically, all the tumors with rhabdoid features were of the clear cell type. The presence of rhabdoid features was significantly associated with higher Fuhrman's nuclear grade and higher pathologic tumor stage at presentation. Among the 12 patients who showed the rhabdoid component, nine (75%) developed metastasis and seven (58.3%) died of disease-related causes. The presence of rhabdoid features was independently associated with metastasis and disease-related mortality. The rhabdoid cells were positive for vimentin; variably positive for pan-cytokeratin, epithelial membrane antigen, and CD10; and negative for cytokeratin 7, smooth muscle actin, desmin, E-cadherin, and c-Kit. No case showed loss of integrase interactor-1; one was p53 positive, and five were insulin-like growth factor mRNA binding protein 3 positive. The Ki-67 labeling index was 1-25% (mean, 5.5%). **Conclusions:** The rhabdoid component is an independent prognostic factor for metastasis of RCC; therefore, identification of this component is critical.

Key Words: Carcinoma, renal cell; Kidney; Rhabdoid tumor; Prognosis; Metastasis

Rhabdoid tumor of the kidney is a rare and highly aggressive childhood neoplasm, with a mortality rate of 80%.[1,2] This tumor is characterized by rhabdoid cells with large vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm containing globular inclusion bodies reminiscent of rhabdomyoblasts. Such cells are also encountered in otherwise conventional neoplasms of the kidney[1] and other organs, which are classified according to the non-rhabdoid, conventional component.

In general, tumors with rhabdoid features are associated with rapid growth and a poor prognosis. Several reports have indicated the significance of rhabdoid features in otherwise typical renal cell carcinoma (RCC), but the independent significance of this component in relation to prognosis has not been thoroughly evaluated.[3-6] To the best of our knowledge, no study regarding RCC with rhabdoid feature has been reported in Korea. In this retrospective study, we evaluated the incidence and clinicopathologic characteristics of RCC with rhabdoid features to clarify the prognostic significance and nature of the rhabdoid component.

MATERIALS AND METHODS

Cases and clinical data

The study included 174 consecutive patients with RCC who underwent a radical nephrectomy at Dongsan Medical Center between January 1997 and December 2007. Clinical data were obtained from the medical records and pathology reports. All RCC histological slides were screened for the presence of rhabdoid cells as described by Weeks *et al.*[1]: large epithelioid cells with vesicular nuclei, prominent nucleoli, and large paranuclear intracytoplasmic hyaline globules. Cases with a rhabdoid component comprising roughly <5% of the tumor volume were excluded. The tumors were typed histologically according to the 2004 World Health Organization classification and graded according to the Fuhrman's nuclear grading scheme. Further, the pathologic tumor stage was assigned according to the 7th edition of American Joint Committee on Cancer staging manual.

Immunohistochemistry

Paraffin-embedded tissue microarrays were used for immunohistochemistry. A 5-mm-diameter paraffin core was obtained from a representative area of each tumor with the typical rhabdoid feature and arrayed. The following primary antibodies were used: vimentin (1 : 4,000, mouse, BioGenex, San Ramon, CA, USA), pan-cytokeratin (pan-CK; 1 : 2,000, mouse, Dako, Glostrup, Denmark), epithelial membrane antigen (EMA; 1 : 2,000, mouse, Dako), cytokeratin 7 (CK7; 1 : 2,000, mouse, Dako), smooth muscle actin (SMA; 1 : 2,000, mouse, Dako), desmin (1 : 800, mouse, Dako), CD10 (1 : 100, mouse, Novocastra, Leica Microsystems GmbH, Wetzlar, Germany), E-cadherin (1 : 1,200, mouse, Zymed, Invitrogen, Carlsbad, CA, USA), c-Kit (1 : 400, rabbit, Dako), p53 (1 : 1,000, mouse, Novocastra), insulin-like growth factor mRNA binding protein 3 (IMP3; 1 : 300, mouse, Dako), integrase interactor-1 (INI1) (1 : 200, mouse, BD, San Jose, CA, USA), and Ki-67 (1 : 200, mouse, Novocastra).

The immunohistochemical staining procedures were conducted using BenchMark XT with an iVIEW diaminobenzidine (DAB) kit (Ventana Medical Systems Inc., Tucson, AZ, USA) except for IMP3 and INI1, which were immunostained using a Lab Vision Autostainer 360 (Thermo Fisher Scientific, Inc., Fremont, CA, USA) with an Ultravision LP kit (LabVision, Fremont, CA, USA). Briefly, the tissue microarray blocks were cut at 4-μm thickness, deparaffinized in xylene, and rehydrated in a graded series of ethyl alcohol. Endogenous peroxidase activity was quenched by immersing the slides in 3% H_2O_2 for 20 minutes. After rehydration with phosphate-buffered saline (pH 7.4), microwave-mediated epitope retrieval was performed for vimentin, EMA, SMA, CD10, E-cadherin, c-kit, p53, IMP3, INI1, and Ki-67, but sections for pan-CK and CK7 were incubated in protease. The sections were visualized with DAB and counterstained with hematoxylin. Appropriate positive and negative control sections were also used.

The Ki-67 labeling index (percentage of Ki-67-positive nuclei) was determined by assessing the area with maximal staining at ×400 magnifications. The remaining results were graded depending on the percentage of positive cells, irrespective of the intensity of the immunoreactive signal, as follows: no positive cells in the rhabdoid component, 0; positive cells in < 5% of the rhabdoid component, 1; positive cells in 5-50% of the rhabdoid component, 2; positive cells in > 50% of the rhabdoid component, 3. Cases with grade 0 or 1 were considered negative for expression and those with grades 2 to 3 were defined as positive.

Statistical analysis

The relationship of the presence of rhabdoid features with patient age and tumor size was analyzed with the independent t-test. Fisher's exact test was used to analyze the relationship between the presence of the rhabdoid component and gender. The relationships with pathologic tumor stage and Fuhrman's nuclear grade were analyzed by the chi-square test with linear-by-linear association. After an initial screening for associations with metastasis using a univariate analysis, a multivariate analysis with a logistic regression model was conducted by including the significant variables in the univariate analysis. A Kaplan-Meier analysis and the Cox regression model corrected for competing risks were applied to analyze the significant risk factors for disease-related mortality. All statistical analyses were performed using PASW ver. 18.0 (IBM SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

Clinicopathologic characteristics

The male-to-female ratio and age of the 174 patients with RCC were 1.9 : 1 and 19-82 years (mean, 55 ± 12 years), respectively. The tumor size ranged from 1.0 to 17.0 cm (mean, 5.7 ± 2.8 cm). Histologically, 146 (83.9%) tumors were of the clear cell type; others included papillary, chromophobe, Xp11 translocation, mucinous tubular and spindle cell, and unclassified types. RCCs with rhabdoid features were identified in 12 of the 174 (6.9%) cases (Table 1). All RCCs with rhabdoid features were of the clear cell type, comprising 8.2% of the 146 clear cell-type cases, and the rhabdoid component constituted 5-90% of tumor volume. Areas with rhabdoid features were closely associated with clear cell areas with conventional morphology or sarcomatoid changes and were almost always accompanied by necrosis, except in one case. Rhabdoid cells were mostly discohesive and arranged in diffuse sheets as alveolar structures with thin fibrovascular septae or individual cells scattered among conventional tumor cells (Fig. 1). Desmoplasia and a myxoid stroma were observed in two and one case, respectively. Fuhrman's nuclear grade for the rhabdoid component was either 3 (n = 2, 16.6%) or 4 (n = 10, 83.3%). Multinucleated giant cells in rhabdoid foci were observed in 10 of the 12 cases (83.3%).

Follow-up data were available for all 146 patients with clear

Table 1. Clinicopathologic summary of renal cell carcinoma cases with rhabdoid features

Case No.	Age (yr)	Sex	Size (cm)	T stage	Nuclear grade	Volume[a] (%)	Sarcomatoid change/ Necrosis	Ki-67 index (%)	Metastasis	Outcome
1	61	M	5.7	3b	4	30	+/+	1	+	DOD
2	45	M	7.0	1b	4	20	+/+	1	+	DOD
3	45	M	5.3	1b	3	15	-/+	2	+	DOD
4	65	M	8.0	2a	4	40	-/+	6	-	NED
5	55	M	7.0	1b	4	10	-/+	1	+	AWD
6	63	M	10.5	3a	4	5	-/+	17	+	DOD
7	47	M	8	3a	4	40	-/+	8	-	NED
8	61	M	5.8	1b	4	8	-/-	1	-	NED
9	68	M	5.9	3a	4	50	-/+	1	+	AWD
10	47	M	12.5	3a	4	70	-/+	1	+	DOD
11	71	F	6.8	3a	4	60	-/+	25	+	DOD
12	49	M	11.0	3a	3	90	-/+	2	+	DOD

[a] Volume (%) indicates the volume of rhabdoid component in the entire renal cell carcinoma.
M, male; DOD, dead of disease; NED, no evidence of disease; AWD, alive with metastatic disease; F, female.

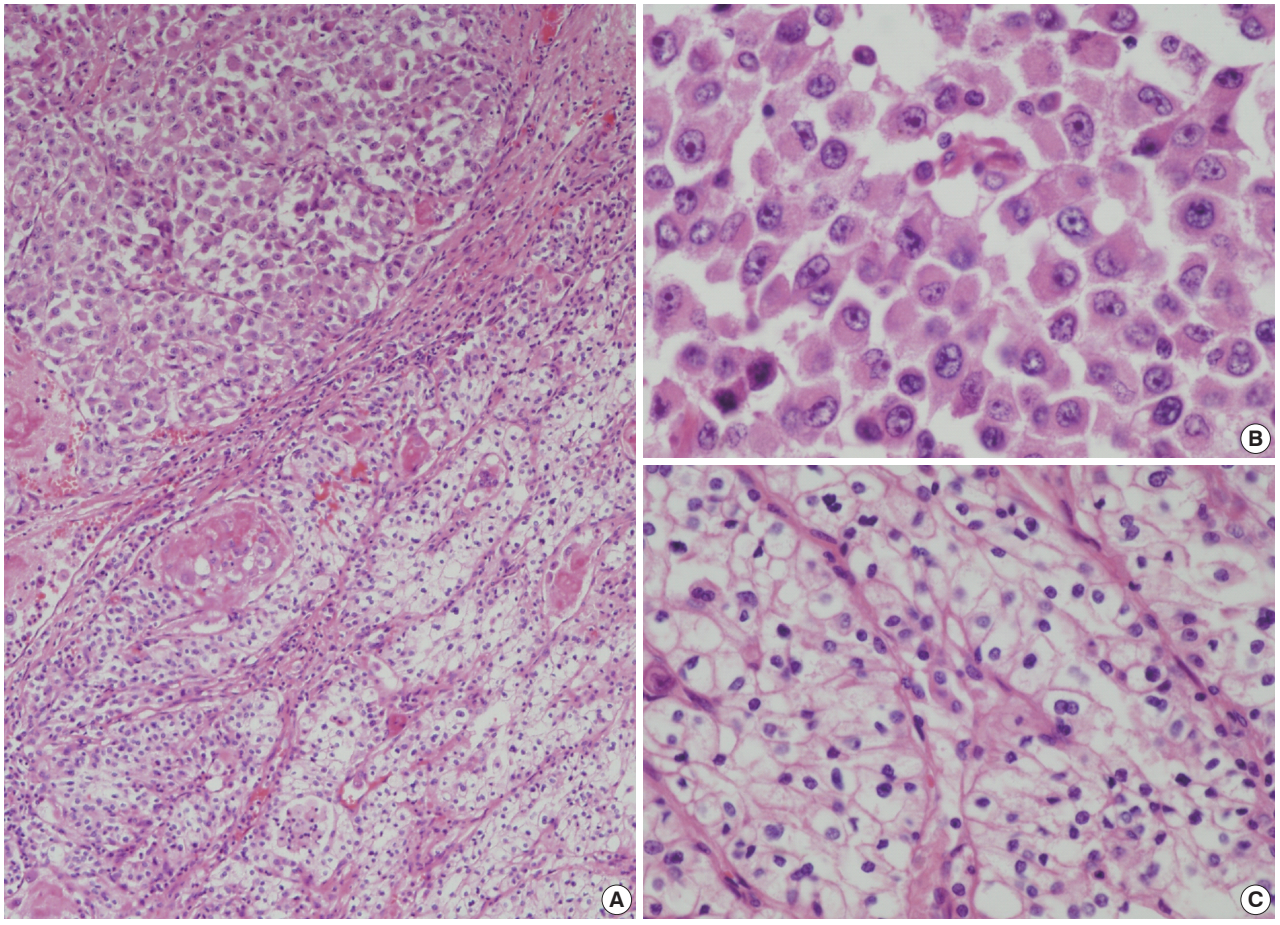

Fig. 1. Radical nephrectomy specimen showing the (A) close association between rhabdoid cells (upper) and clear cells in renal cell carcinoma (lower). (B) The rhabdoid cells exhibit vesicular nuclei, prominent nucleoli, and intracytoplasmic hyaline globules, (C) compared with clear cells.

cell-type RCC (mean duration, 45 ± 31 months; median duration, 37 months; range, 1 to 135 months). At presentation or during follow-up, metastasis developed in 29 of the 146 (19.9%) patients, including nine (75%) with the rhabdoid component. Disease-related death occurred in 21 (14.4%) of 146 patients, including seven (58.3%) patients with rhabdoid features.

Relationship between rhabdoid features and clinicopathologic parameters

The presence of rhabdoid features was positively correlated with larger tumor size ($p = 0.002$), higher pathologic tumor stage ($p = 0.001$), and higher nuclear grade ($p < 0.001$) of the clear cell-type RCCs. No differences in gender or age distribution were observed between the RCCs with and without rhabdoid features (Table 2).

Univariate and multivariate analyses of the clinicopathologic parameters related to metastasis

The presence of metastasis showed a significantly strong association with the presence of rhabdoid features ($p < 0.001$). Metastasis was also significantly associated with higher nuclear grade ($p < 0.001$) and pathologic tumor stage ($p < 0.001$) in the univariate analysis but showed no significant correlation with age or gender (Table 3).

In the multivariate analysis, nuclear grade and pathologic tumor stage were each recategorized into two groups (low vs high) (for nuclear grade, 1 and 2 vs 3 and 4; for pathologic tumor stage, 1 and 2 vs 3). After adjusting for the presence of rhabdoid features, nuclear grade, and pathologic tumor stage, the multivariate analysis showed that the presence of rhabdoid features ($p = 0.004$) and pathologic tumor stage ($p = 0.001$) were significantly associated with metastasis. When the presence of rhabdoid features was used for predicting metastasis, the sensitivity, specificity, positive predictive value, and negative predictive value were 31%, 97%, 75%, and 85%, respectively.

Correlation between disease-related mortality and rhabdoid features

In the Kaplan-Meier analysis (Fig. 2), disease-related mortality was correlated with gender ($p = 0.047$), nuclear grade ($p < 0.001$), pathologic tumor stage ($p < 0.001$), and presence of rhabdoid features ($p < 0.001$).

The multivariate model for disease-related mortality included gender, nuclear grade, pathologic tumor stage, and the presence of rhabdoid features. Nuclear grade and pathologic tumor stage were each recategorized into two groups (low vs high). The outcome was independently associated with the presence of rhabdoid features (hazard ratio [HR], 5.1; 95% confidence interval [CI], 1.8 to 14.5; $p = 0.002$) and recategorized pathologic

Table 2. Relationship between rhabdoid features and clinicopathologic parameters of clear cell-type renal cell carcinoma (RCC)

Clinicpathologic parameters	RCC without rhabdoid features	RCC with rhabdoid features	p-value
No. of pateints	134	12	
Age (yr)	56.2 ± 12 (19-82)	56.4 ± 10 (45-71)	0.959
Male/Female ratio	94/40	11/1	0.18
Pathologic tumor stage			**0.001**
1a	54 (40.3)	0 (0.0)	
1b	34 (25.4)	4 (33.3)	
2a	18 (13.4)	1 (8.3)	
2b	5 (3.7)	0 (0.0)	
3a	23 (17.2)	6 (50)	
3b	0 (0.0)	1 (8.3)	
Tumor size (cm)	5.4 ± 2.5 (1.0-13.8)	7.8 ± 2.3 (5.3-12.5)	**0.002**
Fuhrman's nuclear grade			**< 0.001**
1	3 (2.2)	0 (0.0)	
2	35 (26.1)	0 (0.0)	
3	87 (64.9)	2 (16.7)	
4	9 (6.7)	10 (83.3)	
Metastasis			**< 0.001**
Absent	114 (85.1)	3 (25.0)	
Present	20 (14.9)	9 (75.0)	

The data represent the mean ± standard deviation (range) or the number of patients (%). The bold values indicate a statistically significant difference ($p < 0.05$) by independent t-test (for age and tumor size), chi-square test with linear-by-linear association (for pathologic tumor stage and nuclear grade), and Fisher's exact test (for gender and metastasis).

Table 3. Univariate and multivariate analyses of the clinicopathologic parameters of clear cell-type renal cell carcinoma (RCC) related to metastasis

Variable	Univariate analysis			Multivariate analysis	
	Without metastasis	With metastasis	p-value	OR (95% CI)	p-value
Age (yr)	55.3 ± 11.1	56.0 ± 14.2	0.06		
Gender			0.172		
Female	36 (87.8)	5 (12.2)			
Male	81 (77.1)	24 (22.9)			
Pathologic tumor stage			**< 0.001**	5.9 (2.2-16.0)	**0.001**
1a	47 (87.0)	7 (13.0)			
1b	34 (89.5)	4 (10.5)			
2a	17 (89.5)	2 (10.5)			
2b	5 (100.0)	0 (0.0)			
3a	14 (48.3)	15 (51.7)			
3b	0 (0.0)	1 (100.0)			
Fuhrman's nuclear grade			**< 0.001**		
1	3 (100.0)	0 (0.0)			
2	34 (97.1)	1 (2.9)			
3	73 (82.0)	16 (18.0)			
4	7 (36.8)	12 (63.2)			
Rhabdoid features			**< 0.001**	9.0 (2.0-40.4)	**0.004**
Absent	114 (85.1)	20 (14.9)			
Present	3 (25.0)	9 (75.0)			

Under univariate analysis, the data represent the mean ± standard deviation or the number of patients (%). The bold values indicate a statistically significant difference ($p < 0.05$).
OR, odds ratio; CI, confidence interval.

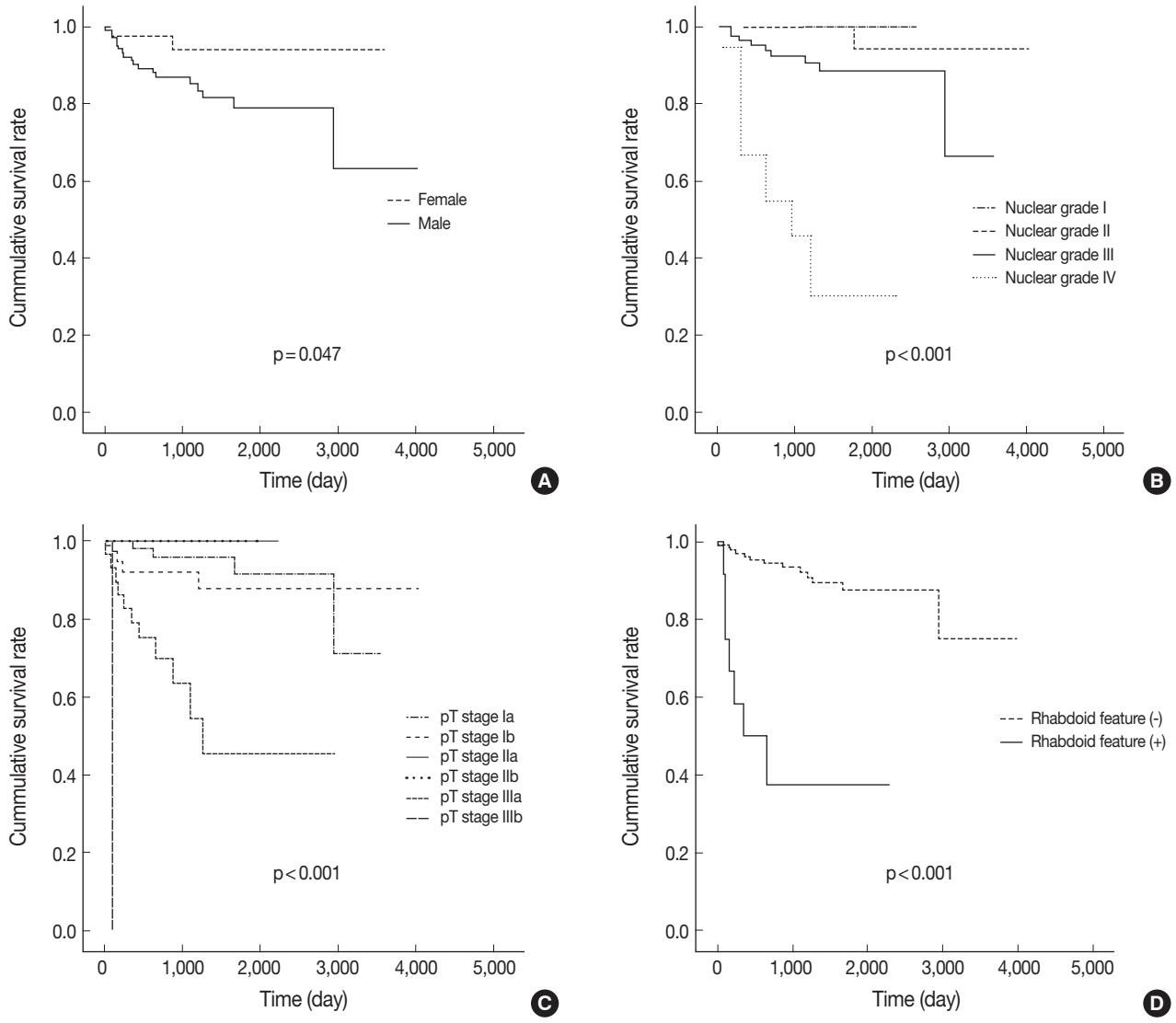

Fig. 2. Kaplan-Meier curves depicting the impact of gender (A), Fuhrman's nuclear grade (B), pT stage (C), and presence of rhabdoid features (D) on the disease-associated mortality of patients (n=146) with clear renal cell carcinoma.

tumor stage (HR, 4.7; 95% CI, 1.9 to 12.0; p=0.001).

Immunohistochemical findings

The results of the immunohistochemical studies are summarized in Table 4. The rhabdoid component showed diffuse or globular cytoplasmic positivity for vimentin (100%) in all 12 cases (Fig. 3). No case showed loss of INI1 (0%). Five were positive for pan-CK (42%), six were positive for EMA (50%), and nine were positive for CD10 (75%). Myogenic markers including SMA and desmin were negative in all cases (0%). CK7, E-cadherin, and c-Kit were also negative in all cases (0%). p53 positivity was observed in one (8%) case, and the Ki-67 labeling index ranged from <1 to 25% (mean, 5.5±2.3%). IMP3 positivity was noted in five (42%) cases. IMP3 immunostaining results of the non-rhabdoid areas were available for seven cases, and all of them were positive for IMP3. Interestingly, the rhabdoid areas were negative for IMP3 in three cases with IMP3-positive non-rhabdoid areas.

DISCUSSION

Malignant neoplasms with rhabdoid features have been reported in various organs including the kidney, urinary bladder, and prostate;[3-6] however, the presence of rhabdoid features in

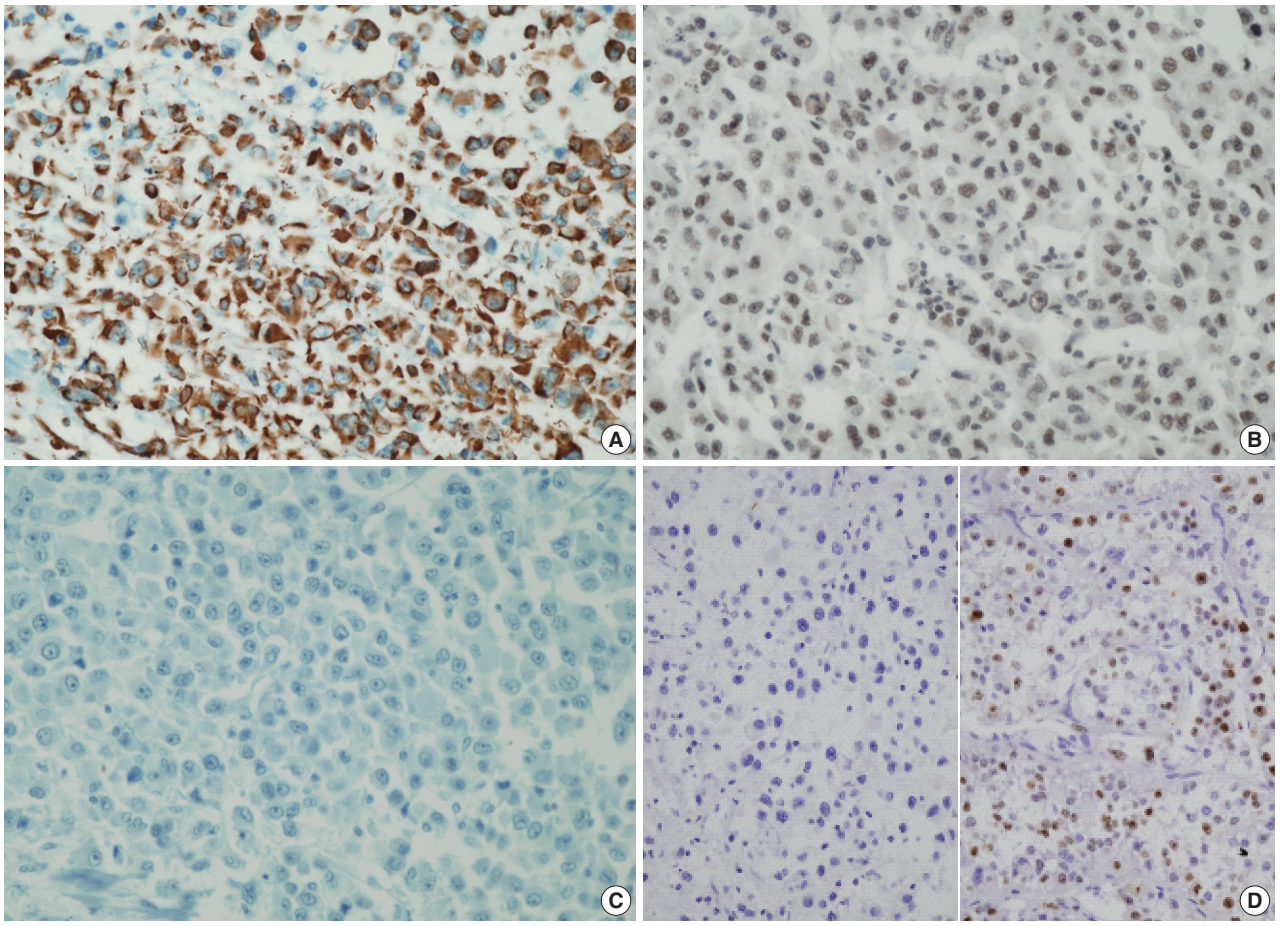

Fig. 3. Specimens showing positive staining for vimentin (A) and integrase interactor-1 (B), and negative staining for p53 (C). The Ki-67 labeling index varied from 1% (left in D) to 25% (right in D).

Table 4. Comparison of immunostaining results of rhabdoid cells in renal cell carcinoma between this study and previous studies

Staining	Present study	Kuroiwa *et al.*[4]	Leroy *et al.*[6]
Vimentin	12/12 (100)	8/8 (100)	14/14 (100)
SMA	0/12 (0)	0/8 (0)	0/14 (0)
Desmin	0/12 (0)	0/8 (0)	0/14 (0)
EMA	6/12 (50)	6/8 (75)	11/14 (78)
Pan-cytokeratin	5/12 (42)		9/14 (65)
CK7	0/12 (0)		
E-cadherin	0/12 (0)		
CD10	9/12 (75)		
p53	1/12 (8)		10/14 (71)
c-Kit	0/12 (0)		1/14 (7)
IMP3	5/12 (42)		
INI1	12/12 (100)		
AE1/AE3		6/8 (75)	
CAM 5.2		4/8 (50)	
HHF-35		0/8 (0)	
Chromogranin		0/8 (0)	

The data represent the positive cases/total cases (%).
SMA, smooth muscle actin; EMA, epithelial membrane antigen; CK7, cytokeratin 7; IMP3, insulin-like growth factor mRNA binding protein 3; INI1, integrase interactor-1.

conventional neoplasms is best characterized in the kidney. Since Gokden *et al.*[3] systematically analyzed RCC with rhabdoid features, several reports have emphasized the poor prognosis associated with the rhabdoid component.[3-6] In neoplasms of other organs such as the stomach, thyroid, meninges, and urinary bladder,[7-10] the rhabdoid component has also been associated with aggressive behavior. In the kidney, rhabdoid features are predominantly associated with clear cell-type RCCs, but there are reports of associations with papillary- and chromophobe-type RCCs, collecting duct carcinoma, renal medullary carcinoma, urothelial carcinoma, synovial sarcoma, and mixed stromal and epithelial tumor.[2-6,11-15] We found a rhabdoid component in 6.9% of the 174 cases in this study, which is comparable to the results of previous studies.[3-6] The reported range of frequency (3.2-7.4%) may be attributed to the selection criteria; one study with the lowest frequency included tumors with rhabdoid features of more than 10% only.[3-6] In our study, the rhabdoid features were associated with clear cell-type RCCs only, and collecting duct carcinoma and renal medullary carcinoma were not in-

cluded. Their incidence among clear cell-type RCCs was 8.2%.

When we investigated the prognostic significance of rhabdoid features in RCC, the presence of rhabdoid cells was associated with poor prognostic factors such as a higher nuclear grade, higher pathologic stage, and accompanying tumor necrosis. In the multivariate analysis, the presence of rhabdoid features was one of the independent risk factors for metastasis. Additionally, the presence of rhabdoid features was independently associated with disease-related mortality. Therefore, the presence of a rhabdoid component should receive special attention and should be included in pathologic reports, as in the case of meningioma.[8,16] Notably, most rhabdoid components were closely associated with necrosis in our study. Leroy *et al.*[6] and Kuroiwa *et al.*[4] reported areas of necrosis adjacent to the rhabdoid component in 13 of 14 (93%) and all eight cases (100%), respectively. Therefore, it is advisable to include necrotic tissue during gross examination to obtain additional prognostic information.

The nature and histogenesis of rhabdoid cells in conventional renal neoplasms have not been clearly defined. Rhabdoid cells generally express vimentin and variably express pan-CK and EMA. Myogenic markers are negative. Our immunostaining results are in agreement with these findings. The protein expression patterns somewhat overlap with those seen in rhabdoid tumors, and, therefore, a possibility of a composite tumor consisting of conventional neoplasm and a rhabdoid tumor can be considered. However, the conserved nuclear expression of INI1 in the present study as well as in other studies supports the view that the development of rhabdoid features in conventional neoplasms is unrelated to the histogenesis of rhabdoid tumor.[17,18] Leroy *et al.*[6] reported that p53 expression is higher in rhabdoid areas than in non-rhabdoid areas, implicating p53 in tumor dedifferentiation; however, we observed p53 expression in only one case. Miyagi *et al.*[19] also reported the lack of p53 expression or mutation in lung adenocarcinoma with rhabdoid features. This contradictory finding in the kidney needs further clarification.

Higher proliferation activity of the rhabdoid component has been reported in the kidney, lung, and meninges.[4,16,19] Kuroiwa *et al.*[4] estimated the proliferation activity of the rhabdoid component as 9.89±8.35%, which is higher than that of the conventional RCC component. In our study, the Ki-67 labeling index was 5.5±2.3%, which was not statistically different from the Ki-67 labeling index of the non-rhabdoid component (data not shown). This disagreement may be attributed to the staining fields (whole slide vs microarray) or organ differences and needs further investigation. Our immunostaining results suggest that the development of rhabdoid features is not related to the histogenesis of rhabdoid tumor and may not be associated with a *p53* mutation or higher proliferation activity.

Factors other than high proliferation activity may contribute to the aggressive behavior of the rhabdoid component, including loss of cell junctions, cell-cell interactions or cell-extracellular matrix (ECM) interaction, and changes associated with ischemia or necrosis. Most rhabdoid cells are scattered individually and are associated with necrosis. The loss of cell junctions or cell-cell and cell-ECM interaction has been regarded as an important step in the process of tumor metastasis.[20,21] We did not study the expression patterns of variable adhesion molecules except E-cadherin; thus, this possibility could not be demonstrated. Necrosis in clear cell-type RCC is considered to be a poor prognostic factor, but the underlying mechanisms have not been clarified.[22,23] IMP3 is an oncofetal protein known to be a good marker for RCC metastasis.[24,25] Interestingly, the frequency of IMP3 expression in the rhabdoid area was lower than in the non-rhabdoid area.

In the kidney, neoplasms with rhabdoid features should be distinguished from rhabdoid tumors and rhabdomyosarcoma. Rhabdoid tumor, a highly aggressive neoplasm of childhood, is predominantly composed of rhabdoid cells. On ultrastructural study, the characteristic cytoplasmic hyaline inclusion is a whorl of intermediate filaments. This tumor has a molecular hallmark: biallelic inactivation of the *hSNF5/INI1* tumor suppressor gene. The loss of INI1 can be demonstrated by immunohistochemical staining[18] and observed in renal and extrarenal rhabdoid tumors, renomedullary carcinomas, and, variably, in epithelioid sarcomas. Rhabdomyosarcomas are very rarely documented in the kidney. They show characteristic striated muscle differentiation and myoglobin and desmin positivity.

In conclusion, the rhabdoid component of RCC was an independent prognostic factor of metastasis; therefore, its identification is critical. The underlying mechanism of the aggressive behavior needs further investigation.

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