

## Original Article

# Clear cell renal cell carcinoma with rhabdoid differentiation: report of 10 Chinese cases supporting a distinctive variant

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**Abstract:** This article describes 10 cases of adult clear cell renal cell carcinoma with rhabdoid differentiation (ccRCC-RD). The lesions all occurred in adult patients (age range 51-77 years, median 56 years), and a marked male predominance (7 males and 3 females) was noted. Six lesions were located in the right kidney, and 4 were located in the left. Histologically, the lesions consisted of rhabdoid areas and classical clear cell RCC areas. The rhabdoid areas occupied 5% to 80% of the kidney in each of the cases. The rhabdoid cells exhibited a round to polygonal shape with globular eosinophilic cytoplasmic inclusions, eccentric pleomorphic vesicular nuclei and prominent nucleoli, which were arranged in large sheets with solid and organoid patterns. One case also exhibited sarcomatoid differentiation. Tumor necrosis was observed in all cases. In all cases, clear cell areas were ISUP grade 3 or 4. The rhabdoid and clear cells exhibited similar immunohistochemical profiles, including CK8/18+, Vimentin+, epithelial membrane antigen (EMA)+, PAX8+, desmin-, and  $\alpha$ -SMA-, which supports the notion that the rhabdoid and clear cells originate from the same clone and do not represent muscle metaplastic differentiation. The mean Ki-67 labeling index was increased in the rhabdoid areas (32%) compared with the clear cell areas (6%). Follow-up data were obtained from 9 cases. Three patients had lung and bone metastasis, 4 patients died from the tumors, and 1 patient had tumor recurrence. Our results indicate that ccRCC with rhabdoid differentiation exhibits aggressive biological behavior and support the notion that ccRCC-RD is a distinctive variant.

**Keywords:** Renal cell carcinoma, clear cell, rhabdoid differentiation

## Introduction

Gokden et al first described renal cell carcinoma (RCC) with rhabdoid features in adults [1]. The term rhabdoid is used to describe cells with histologic morphology that resembles rhabdomyoblasts yet exhibit immunohistochemical and ultrastructural differences. RCC with rhabdoid morphology is a recently described variant that has an aggressive biologic behavior and poor prognosis, which is similar to sarcomatoid RCC [2-6]. The current World Health Organization classification of RCC does not include this phenotype as a distinct histologic entity. The International Society of Urological Pathology (ISUP) 2012 Consensus Conference has identified rhabdoid differentiation as a prognostic parameter for adult RCC,

which indicates an aggressive clinical behavior and poor prognosis [7]. In this article, we describe the clinical and pathobiological features of 10 clear cell RCCs with rhabdoid differentiation (ccRCC-RD).

## Materials and methods

### Case selection

The 10 cases were collected from the consultation and surgical files of the Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China. The clinical demographics, follow-up data and pathological information were obtained from the clinicians and pathology reports that the referring pathologists submitted. Slides were reviewed by two experienced pathologists (W.C.F and Y.X.Q).

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**Table 1.** Clinicopathological data of clear cell renal cell carcinoma with rhabdoid differentiation

Patient	Sex	Age (y)	Presentation	Tumor site	Tumor size* (cm)	pT	Metastasis at diagnosis	Surgery	Follow up (Months)
1	M	56	asymptomatic	Right	9	T2a	No	RN	DOD at 48
2	M	66	malaise and weight loss	Right	7.4	T2a	No	RN	Recur. at 51, AED at 87
3	M	52	flank pain	Left	5	T1b	No	PN	ANED at 42
4	F	51	asymptomatic	Right	12.5	T2b	No	RN and LE	Lung Mets at 7, DOD at 21
5	M	65	flank pain	Left	8	T2a	No	RN and LE	ANED at 25
6	F	69	flank pain	Right	4.5	T1b	No	RN and LE	ANED at 8
7	M	58	left hip pain	Left	7.5	T2a	Bone Mets	RN	Lung Mets at 1, AED at 3
8	M	77	flank pain	Left	7.5	T2a	NA	RN	NA
9	F	56	flank pain	Right	16	T2b	No	RN	DOD at 31
10	M	53	lower limb movement disorder	Right	4.5	T3b	Lung, Bone, LN Mets	RN and LE	DOD at 9

Abbreviations: RN, radical nephrectomy; PN, partial nephrectomy; Recur., recurrence; NA, not available; Mets, metastases; AED, alive with evidence of disease; DOD, dead of disease; ANED, alive with no evidence of disease; LN, Lymph node; LE, lymphadenectomy. \*Largest dimension.

### Immunohistochemical staining

Immunohistochemistry for epithelial membrane antigen (EMA) (1:100; DAKO), cytokeratin (AE1/AE3, dilution 1:100; Dako),  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) (1:200; DAKO), desmin (1:100; DAKO), CD117 (1:600; DAKO), paired box gene 8 (PAX8) (1:800; Proteintech Group), CK8 (1:100; DAKO), CK18 (1:100; DAKO), Vimentin (1:200; Dako), CD10 (1:100; DAKO), carbonic anhydrase IX (CAIX) (1:400; Abcam), RCC (1:100; DAKO), CK7 (1:50; Dako) and Ki-67 (1:100; Dako) was performed according to the instructions. For each antibody, appropriate positive and negative controls were employed throughout the study.

Regarding staining intensity, a score index of 0, 1+, 2+, and 3+ that corresponds to negative, weak, moderate, or strong staining intensity, respectively, was used. A stain was considered positive if greater than 10% of the cells exhibited at least 1+ intensity.

### Results

#### Clinical features

Ten cases of ccRCC-RD were identified from our combined databases. None of these cases had been previously published. The clinical details are summarized in **Table 1**. The study included 7 males and 3 females with a median age of 56 years (range, 51-77 years). Six neoplasms were localized to the right kidney, and 4 were localized to the left. Five patients presented with flank pain. One patient (case 7) presented with left hip pain with physical examination reveal-

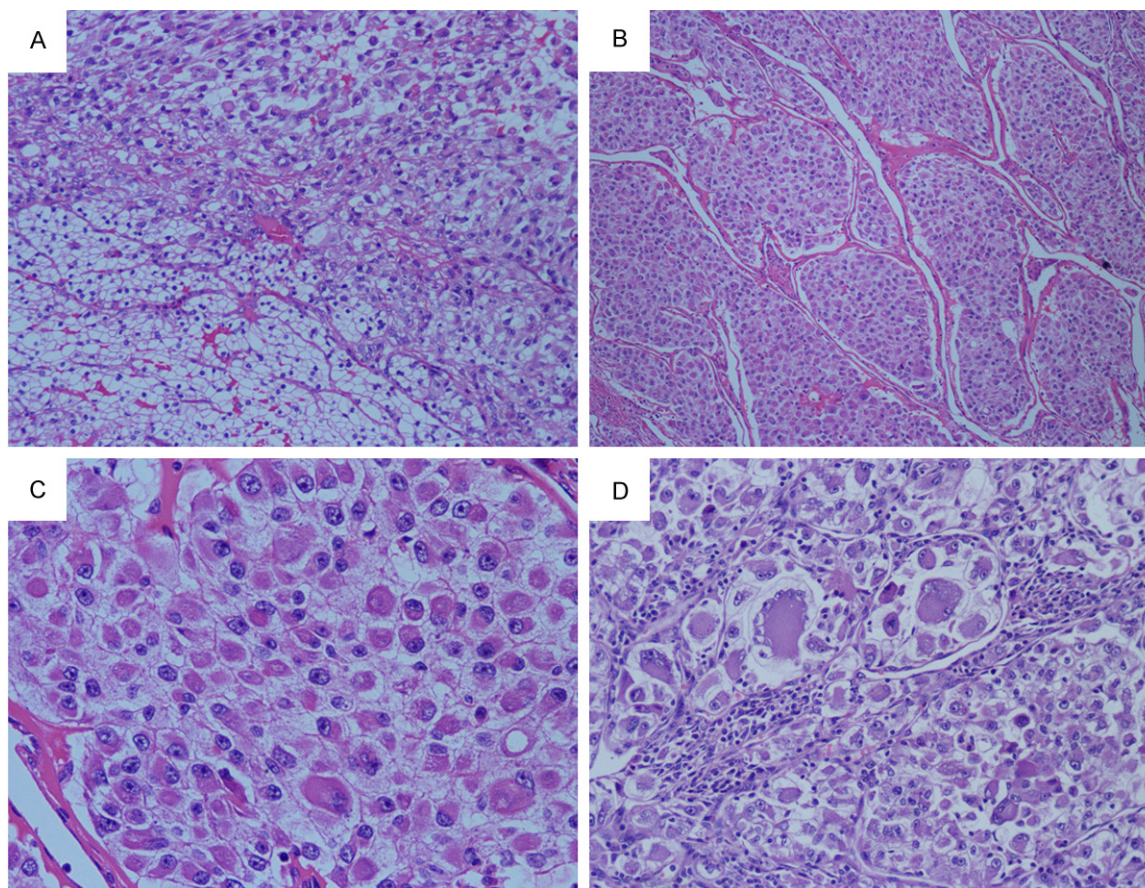
ing a left renal tumor. Two patients were asymptomatic at diagnosis, and their tumors were discovered incidentally by abdominal ultrasonography. One patient experienced malaise and weight loss, and one patient (case 10) presented with lower limb movement disorder due to a RCC bone metastasis.

Imaging revealed renal solid masses that were similar to other renal solid tumors. Necrosis was present in 4 tumors. Cystic foci and calcifications were not present. Positron emission tomography-computed tomography (PET-CT) revealed a radioactive concentration on the left side of the hip, suggesting bone destruction in case 7. Computed tomography (CT) examination revealed a right renal tumor with bone metastasis, lung metastasis, neck and retroperitoneal lymph node metastasis as well as invasion in the inferior vena cava in case 10.

At diagnosis, 2 cases were pT1b, 5 were pT2a, 2 were pT2b, and 1 was pT3b. Regional lymph nodes (hilar, pelvic, and/or para-aortic) were resected in 4 cases. Of these 4 cases, 1 (case 10) exhibited lymph node metastases (pN1) as well as lung and bone metastasis (M1). Radical nephrectomy was performed in 9 patients (90%).

Follow-up data were available for 9 of the 10 patients (**Table 1**). Two patients (cases 1 and 9) died from the disease at 48 and 31 months, respectively, after the operation without preceding metastases. Two patients (cases 4 and 10) died from the disease at 21 and 9 months with lung and bone metastases, respectively. One patient (case 7) had lung and bone metas-

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**Figure 1.** Histological features. A. Transition between rhabdoid and clear cell areas. B. Rhabdoid cells were arranged in an alveolar or organoid growth pattern. C. Rhabdoid cells were round to polygonal with globular eosinophilic cytoplasmic inclusions and eccentric pleomorphic vesicular nuclei as well as prominent nucleoli. D. Note the multinucleated tumor giant cell and lymphocytic infiltrate.

tasis and was alive at 3 months after surgery. One patient had tumor recurrence at 51 months and was alive at 87 months after nephrectomy. Within this group, only 3 patients (cases 3, 5 and 6) were alive with no evidence of disease at 42, 25 and 8 months after the operation, respectively.

### *Pathologic features*

Macroscopically, the largest dimension of tumor ranged from 4.5 to 16 cm (median, 8.0 cm). Most cases exhibited a regular edge, and the individual tumor masses were separated by dense fibrous tissue. Only 3 tumors had areas of poorly marginated growth. The tumors were mostly hard moderate, and solid with a mixed gray white, or gray brown cut surface. Hemorrhage and necrosis were also observed in some cases.

Microscopically, a transition between rhabdoid and classical clear cell RCC areas was noted in

all cases (**Figure 1A**). The rhabdoid component represented 5% to 80% of the tumor volume. Rhabdoid differentiation accounted for  $\leq 10\%$  of the tumor volume in 4 (40%) cases, 10% to 50% in 3 (30%) cases, and  $> 50\%$  in 3 cases (30%). In one case (case 5), a sarcomatoid area with highly atypical spindle cells intermingled with rhabdoid cells was noted. The sarcomatoid component accounted for  $< 5\%$  of the tumor volume. The rhabdoid cells were arranged in large sheets with a solid, alveolar and organoid growth pattern (**Figure 1B**). Rhabdoid cells were round, polygonal, and occasionally spindle shaped with abundant pink cytoplasm and globular eosinophilic cytoplasmic inclusions. Halos of clear cytoplasm around the inclusions were noted in some cells. The nuclei were large round, oval, eccentric, irregular, and vesicular, containing prominent nucleoli (**Figure 1C**). Multinucleate cells were also identified (**Figure 1D**). Multifocal and extensive tumor necrosis was regularly observed in 9 cases (90%). The



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**Table 2.** Histological findings of clear cell renal cell carcinoma with rhabdoid differentiation

Patient	ISUP grade of clear cell component	Capsular invasion	Vascular invasion	Percentage of rhabdoid component	Necrosis	Sarcomatoid component
1	3	absence	absence	5%	absence	absence
2	3	absence	absence	10%	presence	absence
3	3	absence	absence	5%	presence	absence
4	4	absence	presence	20%	presence	absence
5	3	presence	absence	50%	presence	presence, < 5%
6	3	absence	absence	30%	presence	absence
7	3	absence	absence	5%	presence	absence
8	4	absence	absence	60%	presence	absence
9	4	presence	absence	80%	presence	absence
10	4	presence	presence	70%	presence	absence

ISUP grade of the clear cell areas was grade 3 in 6 cases and grade 4 in 4 cases based on the most recent International Society of Urological Pathology (ISUP) grading system [7]. A lymphocytic infiltrate was focally observed in the tumor stroma (**Figure 1D**). Capsular invasion was observed in 3 cases, and vascular invasion was observed in 2 cases. The histological findings are summarized in **Table 2**.

### *Immunohistochemical findings*

All cases exhibited similar immunohistochemical profiles (**Table 3**). Both rhabdoid and clear cell components were positive for AE1/AE3 (9/9 and 7/9, respectively), CK8 (9/9, both), CK18 (8/8, both), EMA (10/10, both) (**Figure 2A**), Vimentin (10/10, both), CD10 (10/10, both) (**Figure 2B**), CAIX (6/6, both), PAX-8 (9/9, both) and RCC (5/7 and 7/7, respectively). In some cases, the staining for AE1/AE3 was focal or negative, whereas CK8, CK18 and EMA exhibited a diffuse and strong pattern of staining. The rhabdoid cells exhibited stronger CK8, CK18 and Vimentin expression than clear cells. However, the clear cells exhibited increased EMA, CD10 and RCC staining intensity compared with the rhabdoid cells. Interestingly, Vimentin, CK8 and CK18 highlighted the presence of globular cytoplasmic inclusions (**Figure 2C, 2D**). All tumor cells were negative for CD117 and CK7. Myogenetic antibodies (desmin and  $\alpha$ -SMA) exhibited negative immunoreactivity in the rhabdoid areas of all ten cases (**Figure 2E**). In the case with sarcomatoid differentiation (case 5), the immunophenotypes of the rhabdoid and clear cell areas were similar, whereas the sarcomatoid areas only expressed Vimentin.

Nuclear Ki-67 immunoreactivity was observed in all 10 cases (**Figure 2F**). In the rhabdoid areas, the Ki-67 index was 10% to 70% (mean 32%). In the clear cells areas, Ki-67 was only detected in 1% to 10% of the tumor cells (mean 6%).

### **Discussion**

Gokden et al [1] was the first to report rhabdoid differentiation in adult RCC. Approximately 75 cases were reported through 2013 [7]. Recently, Przybycin et al presented a clinicopathologic analysis of the largest series (76 cases) of RCC with rhabdoid differentiation [4]. Yang et al reported 10 cases of renal cell carcinoma with rhabdoid differentiation in Chinese adult RCC patients [6]. Based on these studies, the incidence of rhabdoid features ranged from 3% to 7% of RCC cases [7]. These few cases have demonstrated a male predominance (male/female [M:F], 2:1), presenting from the third to eighth decade with a mean age ranging from 52 to 63 years. Our clinical characteristics are consistent with previous reports. Studies have also demonstrated that RCC with rhabdoid morphology exhibits an aggressive clinical behavior and poor prognosis [1-6]. Metastases occur in up to 70% of cases, and the cancer-specific mortality rate is 40% to 50%. The reported sites of distant metastases include the lungs, bone, liver, brain, adrenal glands, diaphragm, skin, and thigh [1-6, 8, 9]. In the present study, three patients had distant metastases. The metastasis sites included the lungs and bone. Four patients died from the tumors. Microscopically, necrosis, a high grade, microvascular invasion, and sarcomatoid differentia-

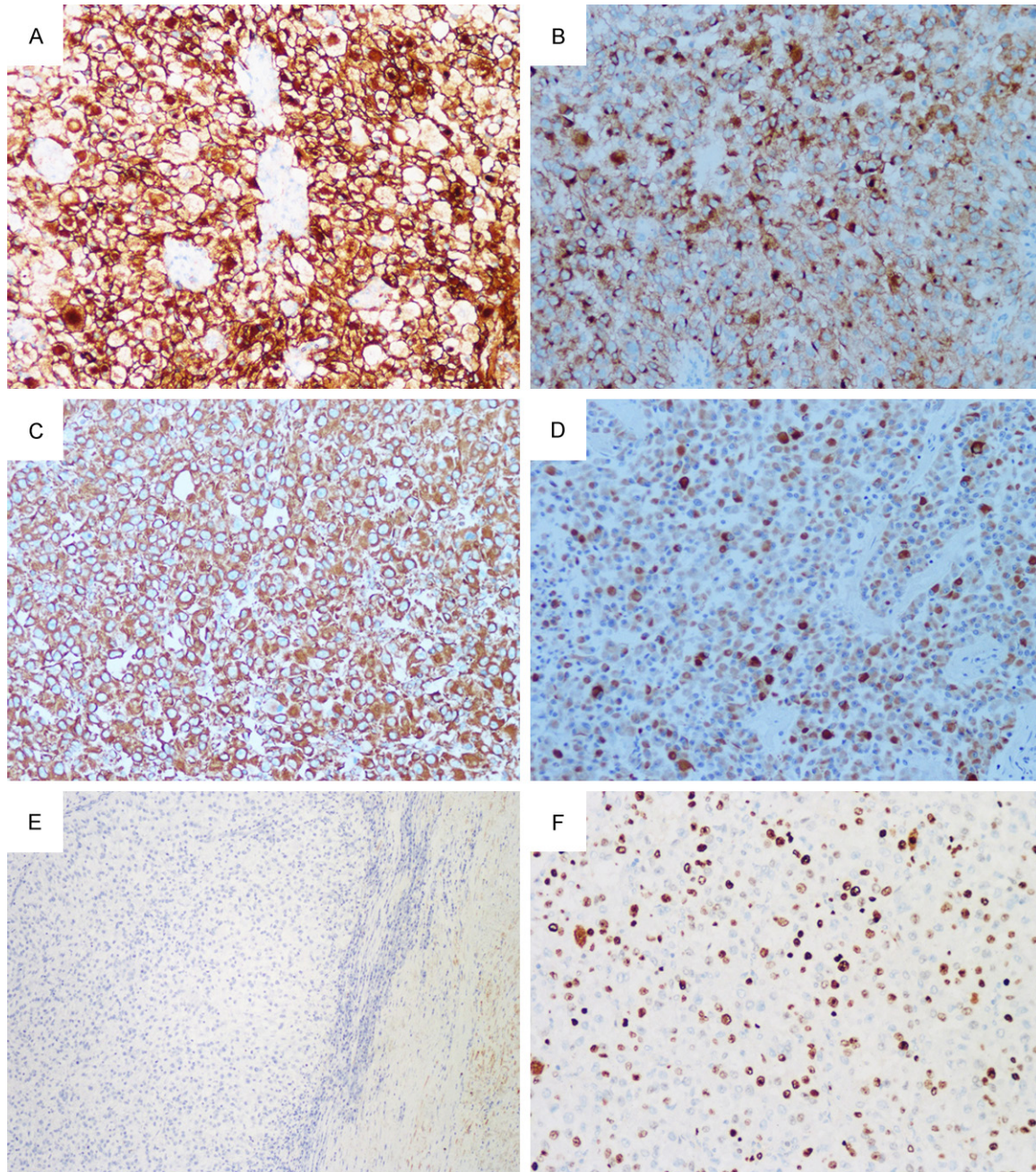
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**Table 3.** Results of immunohistochemical staining in rhabdoid and clear cell components

Case		AE1/ AE3	CK8	CK18	EMA	Vimentin	CD10	CAIX	PAX-8	RCC	Ki-67	CK7	CD117	Desmin	SMA
1	Rhabdoid areas	2+, F	NA	NA	2+	3+	2+	2+	NA	1+	30%	-	NA	-	-
	Clear cell areas	2+, F	NA	NA	3+	3+	3+	2+	NA	2+	10%	-	NA	-	-
2	Rhabdoid areas	2+	3+	3+	3+	3+	3+	NA	3+	2+	40%	NA	NA	-	-
	Clear cell areas	1+	2+	2+	3+	3+	3+	NA	3+	2+	10%	NA	NA	-	-
3	Rhabdoid areas	NA	3+	3+	2+	3+	2+	NA	3+	NA	10%	-	-	-	-
	Clear cell areas	NA	2+	2+	3+	3+	3+	NA	3+	NA	2%	-	-	-	-
4	Rhabdoid areas	2+	3+	3+	3+	3+	3+	NA	3+	-	30%	-	-	-	-
	Clear cell areas	2+	1+	1+	3+	3+	3+	NA	3+	2+	5%	-	-	-	-
5	Rhabdoid areas	2+	3+	3+	3+	3+	1+, F	3+	1+	1+	10%	-	-	-	-
	Clear cell areas	1+	1+	1+	3+	3+	1+, F	3+	1+	2+	1%	-	-	-	-
6	Rhabdoid areas	1+, F	3+	3+	3+	3+	2+	3+	3+	1+	60%	-	-	-	-
	Clear cell areas	1+, F	2+	2+	3+	2+	3+	3+	3+	3+	10%	-	-	-	-
7	Rhabdoid areas	2+	3+	3+	3+	3+	2+	3+	3+	-	30%	-	-	-	-
	Clear cell areas	-	2+	2+	3+	2+	3+	3+	3+	3+	10%	-	-	-	-
8	Rhabdoid areas	2+, F	3+	NA	2+	3+	2+, F	NA	3+	1+	30%	-	-	-	-
	Clear cell areas	2+, F	2+	NA	3+	3+	2+, F	NA	2+	1+	10%	-	-	-	-
9	Rhabdoid areas	2+, F	3+	3+	3+	3+	3+	2+	3+	NA	10%	-	-	-	-
	Clear cell areas	2+, F	3+	3+	3+	3+	3+	2+	2+	NA	1%	-	-	-	-
10	Rhabdoid areas	2+	3+	3+	3+	2+	2+	2+	3+	NA	70%	-	NA	-	-
	Clear cell areas	-	2+	2+	3+	3+	3+	2+	3+	NA	5%	-	NA	-	-
No. of Positive Cases (%)	Rhabdoid areas	9/9 (100)	9/9 (100)	9/9 (100)	10/10 (100)	10/10 (100)	10/10 (100)	6/6 (100)	9/9 (100)	5/7 (71)	10/10 (100)	0/9 (0)	0/7 (0)	0/10 (0)	0/10 (0)
	Clear cell areas	7/9 (78)	9/9 (100)	9/9 (100)	10/10 (100)	10/10 (100)	10/10 (100)	6/6 (100)	9/9 (100)	7/7 (100)	10/10 (100)	0/9 (0)	0/7 (0)	0/10 (0)	0/10 (0)

Abbreviations: F, focal; NA, not available.

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**Figure 2.** Rhabdoid cells demonstrated diffuse and strong expression of EMA (A), CD10 (B), Vimentin (C) and CK18 (D). Desmin exhibited negative immunoreactivity in rhabdoid cells (E). The Ki67 index was approximately 30% (F).

tion were noted. All of these results support views that have been described in various studies, including the notion that rhabdoid differentiation is a prognostic parameter that should be specified in the pathology report, although few cases have been reported.

Although rhabdoid differentiation is typically observed in clear cell RCC, tumors with this

morphology have also been observed in papillary RCC [4, 6], chromophobe RCC [4, 10, 11], collecting duct carcinoma [1], malignant mixed epithelial and stromal tumor of the kidney [12], acquired cystic disease-associated RCC [9], medullary carcinoma [13], hereditary leiomyomatosis and RCC [14]. These findings support the notion that rhabdoid differentiation may be a common pathway of dedifferentiation in



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RCCs. Additionally, frequent observations of “transition areas” wherein rhabdoid cells arise in close association with the cells of the parent RCC have been noted, and the ultrastructural basis of the rhabdoid phenotype is aggregation of paranuclear intermediate filaments and/or paranuclear condensation of organelles rather than true skeletal muscle differentiation [1, 2, 15]. These findings suggest that the rhabdoid cells and clear cells originate from the same clone instead of representing muscle metaplastic differentiation.

In adult RCC, rhabdoid differentiation is characterized by the presence of variably cohesive large epithelioid cells with central eosinophilic intracytoplasmic inclusions; large, eccentric, and irregular nuclei; and prominent nucleoli [1, 2, 7]. Architecturally, most of the rhabdoid areas exhibited a solid growth pattern, consisting of an organoid (78%) and/or a sheet-like (30%) arrangement of the tumor cells. In this study, we used the aforementioned commonly accepted definition of rhabdoid morphology. The proportion of rhabdoid cells ranges from 5 to 90% of the total tumor volume [2, 7, 15]. If a tumor exclusively exhibits rhabdoid morphology, pathologists should designate the tumor as “unclassified carcinoma with a rhabdoid component” [7]. In our study, one of 10 tumors had a small proportion of rhabdoid features. In recent studies, Przybycin et al [4] evaluated 76 RCC with rhabdoid differentiation, 19 (25%) of which were associated with sarcomatoid elements. Then, Zhang et al [16] reported 28 (4%) rhabdoid areas, and Yang et al [6] described 5 cases (50%). These results indicate that rhabdoid areas are constantly associated with high-grade RCC of the sarcomatoid type.

In current study, Vimentin, EMA and CK8/18 appeared to be the most sensitive markers, and this finding is consistent with previous studies [1, 5-7, 17]. AE1/AE3 expression was observed in foci. Vimentin staining highlighted the presence of globular cytoplasmic inclusions. The CD10 staining intensity increased with increasing nuclear grade and was strongest in rhabdoid cells. PAX8, a renal specific transcription factor, was expressed in these cells, and this marker can be used to identify tumors from other sources. Furthermore, no myogenic markers, including desmin and  $\alpha$ -SMA, are expressed in rhabdoid cells. The mean Ki-67 labeling index was increased in the

rhabdoid areas (32%) compared with the clear cell areas (6%), which may also imply a poor prognosis.

RCC with rhabdoid differentiation should be differentiated from renal tumors with rhabdoid features. The identification of a non-rhabdoid component is crucial and may require extensive sampling. High-grade urothelial carcinoma of the renal pelvis is rarely accompanied by rhabdoid features [18, 19]. Identification of urothelial carcinoma *in situ* and immunohistochemical positivity for GATA3, CK20, p63, and uroplakin II plays an important role in achieving an accurate diagnosis. Malignant rhabdoid tumor (MRT) of the kidney rarely occurs in adults [20, 21]. The combined loss of INI-1 with PAX8 expression may help differentiate MRT from RCC-RD, which is supported by a study reporting the absence of INI1 in the latter [22]. Renal epithelioid angiomyolipoma may impart rhabdoid features [23]. The immunohistochemistry of SMA, HMB45 and melan A is useful. A subset of adult renal rhabdoid tumors may be a rhabdoid variant of poorly differentiated synovial sarcoma, and the use of molecular techniques, such as detection of SYT-SSX fusion transcripts, can facilitate accurate diagnosis [24, 25]. Sporadic renal hemangioblastoma is frequently misdiagnosed as RCC. The presence of pericytomatous growth patterns and intracytoplasmic lipid vacuoles strongly suggests hemangioblastoma [26, 27]. S-100 protein,  $\alpha$ -inhibin and neuron-specific enolase (NSE) may be helpful [28, 29]. Additionally, the application of myogenic markers in the immunohistochemical study can distinguish between pleomorphic rhabdomyosarcoma and RCC-R.

### Conclusion

In summary, we present a clinicopathologic analysis of 10 clear cell RCC cases with rhabdoid differentiation in Chinese adults. We support the notion that rhabdoid and classical clear cell RCCs originate from the same clone and exhibit divergent differentiation. Additionally, clear cell RCC with rhabdoid morphology is a distinctive type of dedifferentiation, and the rhabdoid components exhibit high proliferative activity and indicate a poor prognosis.

### Disclosure of conflict of interest

None.

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