Int J Clin Exp Pathol 2016;9(12):12896-12900
www.ijcep.com /ISSN:1936-2625/IJCEP0038332

Original Article

Clinicopathologic features of clear cell papillary renal cell carcinoma: our experience of 11 cases

Jia-Yi Liu[1*], Yao Li[1*], Jia-Zi Shi[1*], Wei-Ping Wang[1], Yi Gao[1], Jie Wang[1], Yi Bao[1], Hua-Mao Ye[2], Jia-Xuan Liu[3], Xing-Ye Chen[4], Yi-Sha Gao[4], Bing Liu[1*], Lin-Hui Wang[1]

Departments of [1]Urology, [3]Pathology, Changzheng Hospital, Second Military Medical University, Shanghai, China; Departments of [2]Urology, [4]Pathology, Changhai Hospital, Second Military Medical University, Shanghai, China. [*]Equal contributors.

Received August 21, 2016; Accepted August 29, 2016; Epub December 1, 2016; Published December 15, 2016

Abstract: Objective: Clear cell papillary renal cell carcinoma is a new recognized subtype of renal cell carcinoma and has not been widely known by clinician and pathologist. The aim of the present study is to investigate the clinicopathologic features of CCPRCC to improve the understanding of this disease. Methods: Included in this study were eleven patients with CCPRCCs between January 2013 and December 2015. The morphologic and immunohistochemical features were studied along with clinical and follow-up information retrospectively. Results: The patients were 8 men and 3 women, mean age 61.5 years. Nine tumors were stage pT1a and the other two were stage pT1b, with a mean diameter of 2.5 cm. CK7 and CAIX were both positive in all cases they were performed on, while negative reactions occurred in majority cases for CD10 (9/11) and TFE3 (9/9). During a mean follow-up period of 16.4 months, no patient developed local recurrences, distant metastasis or cancer death. Conclusion: CCPRCCs are typically small, biologically indolent tumors without recurrence or metastasis. More attention should be paid to its accurate classification and identification from other more aggressive RCCs.

Keywords: Kidney, renal cell carcinoma, clear cell papillary renal cell carcinoma, immunohistochemistry, prognosis

Introduction

Clear cell (tubule) papillary renal cell carcinoma (CCPRCC) is a recently described renal neoplasm, in which the tumor cells are characterized by clear cytoplasm lining cystic, tubular, and papillary structures. International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia has recommended it as a distinct subtype of renal epithelial tumor and suggested a relevant inclusion in the WHO 2004 histological classification of RCCs [1, 2]. However, quite a number of urologists and even some pathologists still know little about this subtype of RCCs, which may be attributed to its recent recognition and few relevant studies. Herein, we studied the clinicopathologic features of 11 cases for further understanding of this disease.

Materials and methods

Following the approval of our Institutional Review Board (IRB) of Changzheng hospital (Second Military Medical University, SMMU), the electronic medical record system was queried to identify all patients with CCPRCCs dating from January 2013 to December 2015. All patients were informed of the involved procedures, and they were provided with written consent before the review of clinical information and pre-existing sections stored at Department of pathology. The pathological re-diagnosis of these cases was reviewed by three experienced pathologists (CXY, LJX and GYS). Prior to analysis, patient information was anonymized and de-identified.

Pathologic parameters including gross appearance of the tumor, size, location, multi-focality, Fuhrman nuclear grade, pathologic stage, were retrieved from the pathology reports. The results of immunohistochemical studies were also reviewed. All sections were studied using a fluorescence microscope (BX-51, Olympus, Japan). Immunostaining was considered positive when diffuse positivity was observed in

Table 1. Clinicopathologic findings of 11 cases of CCPRCC

Case	Age	Sex	Laterality	Grade (Fuhrman)	Size (cm)	Stage	ESRD	Tumor-related death	Follow-up (mo)	Tumor recurrence	Metastasis
1	61	M	Right	2	2.5	pT1a	No	No	28	No	No
2	57	M	Right	2	4.5	pT1b	No	No	22	No	No
3	53	M	Left	2	5	pT1b	No	No	16	No	No
4	63	M	Right	2	2	pT1a	No	No	15	No	No
5	64	M	Right	2	1.3	pT1a	No	No	12	No	No
6	61	M	Left	2	2	pT1a	No	No	11	No	No
7	58	M	Left	1	1.5	pT1a	No	No	7	No	No
8	84	F	Left	1	1.5	pT1a	No	No	7	No	No
9	51	F	Left	1	2	pT1a	No	No	7	No	No
10	82	F	Right	2	2.6	pT1a	No	No	34	No	No
11	42	M	Left	2	2.5	pT1a	No	No	9	No	No

ESRD indicates end-stage renal disease.

Table 2. IHC staining profile of 11 cases of CCPRCC

Case	CK7	CAIX	CD10	TFE-3	Other IHC
1	NA	+	-	NA	
2	+	+	-	-	PAX8(+)
3	+	+	+	-	EMA(+), PAX8(+)
4	+	+	-	-	
5	NA	+	-	-	
6	+	+	+	-	
7	+	+	-	-	Vimentin(+)
8	+	+	-	-	Vimentin(+), EMA(+), PAX8(+)
9	NA	+	-	-	
10	+	NA	-	NA	Vimentin(+), E-cadherin(+), EMA(+)
11	+	NA	-	-	Vimentin(+), CD117(-), E-cadherin(+), EMA(+)

CD indicates cluster of differentiation; PAX8, Paired box gene 8; EMA, Epithelial membrane antigen. NA, Not available.

more than 90% tumor cells. Staining was considered negative if fewer than 5% of tumor cells were labeled.

Results

Clinical findings

Detailed clinicopathologic characteristics of all patients were summarized in **Table 1**. Eleven patients (8 male and 3 female), pathologically diagnosed as CCPRCC, were included in the present study between January 2013 and December 2015, which accounted for 1.1% of all RCCs at the same period. The mean age was 61.5 years old (range, 42-82 years). No history of chronic kidney disease, tumor, or other diseases was observed in all patients. Treatment consisted of 8 partial nephrectomies and 3 radical nephrectomies. During a mean follow-up period of 16.4 months (range, 7 to 34 months), no tumor recurrence, metastasis, or cancer-related death was observed.

Pathological features

All tumors were localized in a single kidney (left 6, right 5) with a mean diameter of 2.5 cm (range, 1.3-5.0 cm). Coexisted clear cell RCC was observed in one case. Fuhrman nuclear grade ranged from Grade 1 (3/11) to Grade 2 (8/11). According to the World Health Organization (WHO) 2004 classification, nine patients presented with pT1a disease (≤4 cm) and two patients presented with pT1b disease (N4 and 7 cm). In the present study, the tumors were remarkably similar to each other and had a cystic or mixed cystic/solid appearance. Well encapsulated tumors with a predominant solid architecture and tan cut surface were also recognized. None of the tumors demonstrated the characteristic golden-yellow color of clear cell RCC. Histologically, all cases exhibited representative morphologic features of CCPRCC as previously described, such as clear cells with low nuclear grade, variable papillary, tubular/acinar, and cystic architecture, and a representative linear arran-

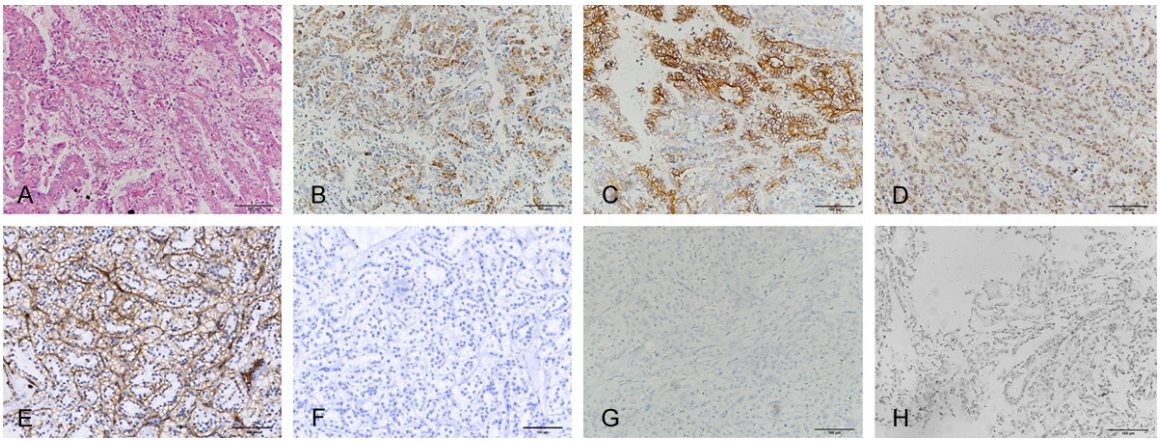

Figure 1. Histological and immunohistochemical features of CCPRCC. Typical CCPRCC tubulopapillary architecture (A); Positive immunostaining for CK7 (B), CAIX (C), PAX-8 (D), Vim (E); Negative immunostaining for CD10 (F), RCC (G), TFE-3 (H).

gement of nuclei away from the basal aspect of cells. All tumors were restricted to a well-defined fibrous capsule and composed of cells with clear cytocharacteristic plasma arranged in papillary structures. Papillary and cystic architecture were present at least focally in all tumors. The papillae were covered by small to medium-sized cubiform cells with plentiful clear cytoplasm. Neither necrosis nor mitotic figure was observed.

Immunohistological features

All tumors showed remarkable uniformity in their immunohistological pattern (**Table 2**). CK7 (8/8) and CAIX (9/9) were both positive in all cases they were performed on, while CD10 was negative in majority cases (9/11). TFE3, a relevant marker in the differential diagnosis of CCPRCC with translocation RCC, was consistently negative in 9 stained cases (**Figure 1B-H**).

Discussion

Clear cell papillary renal cell carcinoma is a neoplasm composed of variable mixtures of cystic, branched tubular and papillary components. Shen et al. [3] has reported that clear cell papillary renal cell carcinoma was the fourth (12/290, 4.1%) most common histological type of renal cell carcinoma in their 290 cases. While in other studies, the proportion of CCPRCC was 1% or even less, which implied that partial of the CCPRCC cases may be probably misdiagnosed as clear cell RCC or papillary RCC [4]. In order to strengthen the understanding of CCPRCC and differentiation from other RCCs, we analyzed a series of CCPRCC with distinct clinical, morphologic and immunohistological features.

The age is similar to that for other RCCs in general (mean 60 y, range, 18 to 88 y) as ISUP has recommended [2]. A slight male predominance (8/11) was observed in the present series. This has been reported in several studies, thus large-scale studies are wanted to further determine this [3, 5-12]. All patients were asymptomatic except one suffered from backache, which was consistent with previous reported [3, 4, 11, 13]. CCPRCC was once regarded to be associated with end-stage kidney disease (ERSD) [2, 14]. In our study, no ESRD was observed in any case, which demonstrated that CCPRCC may also occur without ERSD [4, 7, 11, 15-17].

Histologically, all tumors were localized in a single kidney (left 6, right 5) with a mean diameter of 2.5 cm (range, 1.3-5.0 cm), which is consistent with the previous opinion that CCPRCCs are usually unicentric, unilateral, and small [2]. All cases exhibited typical morphologic features of CCPRCC as previously described including clear cells of low nuclear grade, variable papillary, tubular/acinar, and cystic architecture, and a characteristic linear arrangement of nuclei away from the basal aspect of cells [2, 18-22]. However, according to ISUP, cases with typical morphology, but no typical immunohistochemical profile, cannot be definitively diagnosed CCPRCC [2]. Previous researches have suggested the immunehistochemical features of CCPRCC [2-4, 9, 17, 23-26]. Almost all tumor cells show diffuse and

intense staining with CK7, and a membranous distribution pattern with CAIX. Vimentin (Vim) and paired box gene 8 (PAX8) are also positive in most cases, while CD10 and TFE-3 are negative. In this study, an immunehistochemical panel was applied for differential diagnosis between CCRCC, PRCC and CCPRCC. As expected, most cases exhibited positive for CK7 (8/8) and CAIX (9/9), and negative for CD10 (9/11) and TFE-3 (9/9), which further confirmed previous reports. All of these are necessary to distinguish CCPRCC from other RCCs, including CCRCC with secondary papillary structure, PRCC with clear cell changes, composite CCRCC and PRCC, or unclassified RCC with both clear cell and papillary components. Most CCRCC tend to be positive for CD10 and CAIX, negative for the CK7. As for the PRCC, CD10 and CK7 usually exhibit positive, while CAIX show negative.

During the mean follow-up period of 16.4 months, no evidence of biological aggressiveness, such as peritoneal or renal sinus invasion, vascular invasion, tumor necrosis, and sarcomatoid dedifferentiation, was observed in any case, which indicated that CCPRCC may be biologically indolent with a more favorable outcome. Considering its indolent biological behavior, we deeply believe that it is necessary to distinguish CCPRCC from other RCC subtypes. Once diagnosed as CCPRCC, patients will suffer from less psychological burden after surgery. What's more, excessive post-operation visits will be avoided, thus reduce the economic burden. There's no doubt it is good news for patients, especially those in less developed countries.

Although the present study was a retrospective case series with a mean follow-up period of 16.4 months, we still believe that CCPRCCs are typically small, biologically indolent tumors. More attention should be paid to its accurately classification and identification from other more aggressive RCCs. Definitely, large scale studies with longer follow-up and further investigation of the molecular pathogenesis are urgently wanted.

Acknowledgements

This work has been supported by National Natural Science Foundation of China (81272817).

Disclosure of conflict of interest

None.

Address correspondence to: Lin-Hui Wang and Bing Liu, Department of Urology, Changzheng Hospital, Second Military Medical University, Shanghai, China. E-mail: wanglinhuicz@163.com (LHW); 13501616398@163.com (BL)

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