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Original Article

Clear cell papillary renal cell carcinoma − An indolent subtype of renal tumor

Wei-Jen Chen [a], Chin-Chen Pan [b,e], Shu-Huei Shen [c,f], Hsiao-Jen Chung [a,d,g], Chih-Chieh Lin [a,d,g], Alex T.L. Lin [a,d,g], Yen-Hwa Chang [a,d,g,*]

[a] *Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[d] *Department of Urology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[e] *Department of Pathology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[f] *Department of Radiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[g] *Shu-Tien Urological Science Research Center, Taipei, Taiwan, ROC*

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Abstract

Background: Clear cell papillary renal cell carcinoma (CCPRCC) is a new but rare tumor entity as listed in the World Health Organization 2016 renal tumor classification. Around 360 cases have been reported in the English literature to date, and only one tumor with sarcomatoid change was reported to develop distant metastasis. In the present study, we aim to review the clinical course and analyze the treatment outcome of CCPRCC in our institution.

Methods: We retrospectively collected patients diagnosed with CCPRCC between January 2008 and September 2016 in our institute. The clinical features, pathology slides, and clinical outcomes were reviewed.

Results: Twenty-five patients were collected during the study period, with a mean age at diagnosis of 62.8 years (range 35−85 years). Three patients developed the tumor in their native kidney following a kidney transplant, and three patients were diagnosed by needle biopsy before cryoablation therapy due to high surgical risk. The mean follow-up time was 49.7 months (range 12−119 months). During the follow-up period, all patients were alive without local recurrence or distant metastasis. All tumor specimens in our series expressed cytokeratin 7 (CK7) diffusely in immunohistochemistry staining. One patient was diagnosed with pT3a cN0M1, Fuhrman grade 3 CCPRCC with renal vein invasion and lung metastasis in 2010 on the basis of the histologic pattern and immunoreactivity for CK7. The clinical course was not compatible with any of the reported cases in the literature, so the kidney specimen was re-examined using whole-exome sequencing. The diagnosis was then revised to clear cell renal cell carcinoma.

Conclusion: Our series confirmed that CCPRCC has an indolent clinical behavior. When the diagnosis is made in a high-grade renal tumor, it should be carefully re-confirmed using cytogenetic or genomic methods.

Keywords: Clear cell papillary renal cell carcinoma; Cytokeratin 7 immunoreactivity; Whole-exome sequencing

1. Introduction

Clear cell papillary renal cell carcinoma (CCPRCC) is a new entity as listed in the World Health Organization 2016 renal tumor classification.[1] It was first reported in patients with end-stage renal disease (ESRD) in 2006[2], and was named "clear-cell papillary renal cell carcinoma of end-stage kidneys" according to its

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* Corresponding author. Dr. Yen-Hwa Chang, Department of Urology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: yhchang@vghtpe.gov.tw (Y.-H. Chang).

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pathological features and the patient's renal disease background. However, the majority of cases subsequently reported were in normal kidneys. These tumors have distinct pathological immunohistochemical staining features. Morphologically, CCPRCC exhibits a clear cytoplasm with variable tubular/acinar, papillary, and cystic architecture, and the tumors show strong positive staining for cytokeratin 7 (CK7).[3–8]

The published literature to date indicates that CCPRCC has an indolent clinical behavior with low-grade cytology, no lymph node metastasis, no local recurrence, and no distant metastasis, except for one case reported by Diolombi et al. who was diagnosed with sarcomatoid pT3 CCPRCC with skeletal and lung metastasis in 2015.[9]

In this study, we aim to review the clinical course and analyze the treatment outcome of CCPRCC patients in our hospital.

2. Methods

The first case of CCPRCC in our hospital was diagnosed in 2008. From January 2008 to December 2016, 765 patients were newly diagnosed with primary renal cell carcinoma (RCC), of whom 25 (3.3%) had CCPRCC. The medical charts, imaging studies, and pathology slides were retrospectively reviewed under patient agreement. All of the patients were regularly followed for at least 12 months. Among them, 22 patients received nephrectomy (including: radical nephrectomy in five patients and partial nephrectomy in 17 patients), and the other three patients were diagnosed by biopsy before cryoablation therapy. All of the pathology slides were reviewed by the same pathologist (C.C. Pan). Tumor size was evaluated by assessing the tumor diameter of the nephrectomy specimen or by computed tomography (CT) in the patient who received cryoablation therapy. All tumors were staged according to the American Joint Committee on Cancer (AJCC) Staging Manual 8th edition.

3. Results

3.1. Clinical findings and outcomes

The clinical characteristics of our patients with CCPRCC are summarized in Table 1. There were 11 men and 14 women, with a median age at diagnosis of 62.8 years (range 35–85 years). The mean tumor size was 2.6 cm (range 0.5–6.2 cm). Three patients received cryotherapy after a biopsy confirmed CCPRCC due to a poor general condition. In the other 22 patients who received surgical resection, four had end-stage

Table 1
Patient characteristics.

Case	Age (year)	Gender (Male/Female)	Operation	If ESRD status at diagnosis (Yes/No)	Tumor laterality	Tumor number	Size (cm)	Fuhrman grade	Stage	Follow-up time	Other tumor in the resected kidney
1	39	F	ORN, bilateral	LDKT[b]	Bilateral	3[a]	2	2	pT1a	119m	
2	67	F	RAPN	No	Left	1	3.1	2	pT1a	76m	
3	35	M	OPN	No	Right	1	5	2	pT1b	76m	
4	60	F	LRN	Yes	Right	1	0.6	2	pT1a	74m	ACKD-RCC
5	68	F	LPN	No	Right	1	2.1	2	pT1a	70m	Renomedullary interstitial cell tumor
6	71	M	RAPN	No	Right	1	2.8	2	pT1a	67m	
7	61	M	RAPN	No	Left	1	1.2	2	pT1a	62m	
8	56	F	ORN, bilateral	DDKT[c]	Right	1	3.3	2	pT1a	57m	
9	60	F	RAPN	No	Left	1	2.4	2	pT1a	56m	
10	61	M	RAPN	No	Right	1	1.5	2	pT1a	53m	ccRCC
11	72	M	OPN	No	Right	1	1.1	2	pT1a	52m	Papillary adenoma
12	35	F	OPN	No	Left	1	3.5	2	pT1a	51m	
13	67	M	ORN, bilateral	LDKT[d]	Right	1	1.5	2	pT1a	47m	
14	77	F	Bx + cryo	No	Left	1	3.7	2	cT1a	64m	
15	42	F	OPN	No	Right	1	2.3	3	pT1a	32m	
16	57	F	OPN	No	Left	1	1.8	2	pT1a	24m	
17	72	M	RAPN	No	Left	1	3.5	2	pT1a	44m	
18	68	M	Bx + cryo	No	Left	1	2.2	2	cT1a	42m	
19	51	M	RARN	Yes	Left	2	0.5	2	pT1a	32m	ccRCC
20	75	F	RAPN	No	Left	1	6.2	2	pT1b	32m	
21	84	F	Bx + cryo	No	Left	1	2.8	2	cT1a	31m	
22	64	M	RAPN	No	Right	1	2.1	2	pT1a	24m	
23	63	M	OPN	No	Right	1	3.1	2	pT1a	23m	
24	85	F	OPN	No	Right	1	1.5	2	pT1a	22m	
25	81	F	OPN	No	Left	1	6	2	pT1b	12m	

ESRD = end stage renal disease; ACKD-RCC = acquired cystic kidney disease-associated renal cell carcinoma; ORN = open radical nephrectomy; OPN = open partial nephrectomy; RAPN = robot-assisted partial nephrectomy; Bx + cryo = biopsy then cryoablation; LDKT = living donor kidney transplant; DDKT = deceased donor kidney transplant.

[a] One tumor (1.2 cm) was at left kidney; Two tumors (2 cm, 1.5 cm) were at right kidney. The above three tumors were all CCPRCCs.

[b] Case 1: diagnosed 29 months after living donor kidney transplant. The graft kidney function was normal.

[c] Case 8: diagnosed 55 months after deceased donor kidney transplant. The graft kidney function was normal.

[d] Case 13: diagnosed 30 months after living donor kidney transplant. The graft kidney function was normal.

renal disease, of whom three had received a kidney transplant before CCPRCC was diagnosed in the native kidneys. One patient had multiple (three) CCPRCCs over bilateral kidneys. Three patients had other types of synchronous RCC; one with acquired cystic kidney disease-associated RCC, and the others with ccRCC. All CCPRCCs were localized and low grade (pT1ã pT1b, Fuhrman grade 2), and all of the patients are currently alive with no evidence of disease.

One patient (not included in our series) had a prior diagnosis of CCPRCC with lung metastasis and underwent cytoreductive nephrectomy in June 2010. He received multiple treatment modalities and died 3 years and 8 months after the nephrectomy. Since the clinical course was not compatible with any of the reported cases in the literature, we re-examined his kidney specimen using whole-exome sequencing, and revised his diagnosis to ccRCC. This patient will be discussed in detail later in this article.

3.2. Pathological features

Grossly, CCPRCCs are tan-white to yellow in color, well circumscribed, and well encapsulated (Fig. 1A). The tumor size in most cases is less than 4 cm. Microscopically, CCPRCCs have variable tubular, acinar, papillary and cystic architecture[10] (Fig. 1B). Typically, the tumor cells are composed of cuboidal or columnar cells with a clear cytoplasm and round nuclei, and aligned in a linear manner away from the basal aspect of the cells. All of the tumor cells have cytoplasm with a low nuclear grade (Fuhrman grade 1 or 2).

CK7 is the most important immunohistochemical stain for CCPRCC. All tumors in our series expressed CK7 diffusely (Fig. 1C), which is compatible with other reported series.[3–8]

3.3. Case presented with advanced stage

This 62-year-old man presented with a chronic cough for 6 months before a CT scan revealed a 9.5-cm left renal tumor with renal vein tumor thrombus and bilateral lung metastases in 2010. He underwent cytoreductive nephrectomy with a pathological diagnosis of pT3aN0 Fuhrman grade 3 clear cell papillary RCC. Following an uneventful recovery from surgery, he was enrolled in the RECORD-II trial and randomized to receive bevacizumab (BEV, 10 mg/kg q2w) plus interferon (6 MIU tiw) treatment since July 2010 with a best response of stable disease. However, he discontinued BEV due to grade 3 proteinuria in March 2011 and was withdrawn from the study due to grade 3 neutropenia in July 2011. He shifted to sunitinib 50 mg/day with progressive disease at 3 months. He then received everolimus 5 mg bid in November 2011 for 6 months with progression of disease. He underwent video-assisted thoracoscopic resection of the lung metastatic lesion in July 2012, and received gamma-knife radiosurgery for brain metastatic lesions in October 2012. After metastasectomy, systemic treatment was shifted to axitinib in July 2013. However the disease progressed, and he died of the disease in January 2014.

Grossly, the nephrectomy specimen (Fig. 2A) contained a soft tan tumor measuring 9.5 × 8.5 × 8 cm in the upper pole.

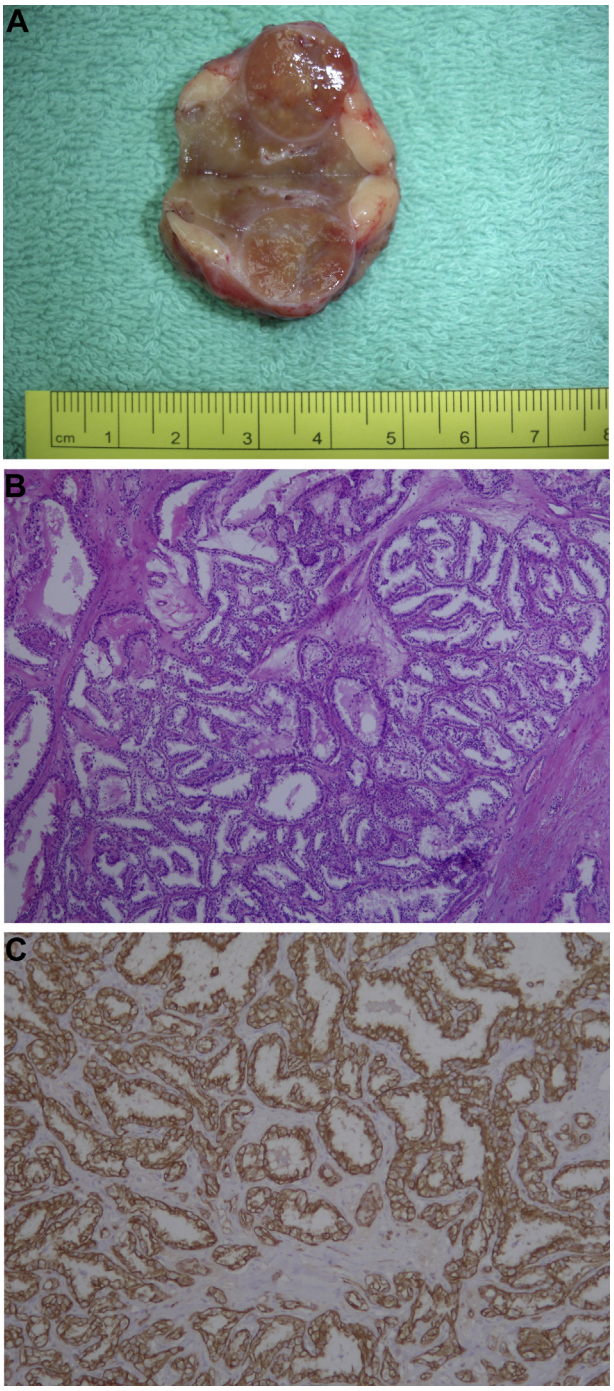

Fig. 1. (A) Gross specimen of a CCPRCC (B) Typical H&E stain of CCPRCC (C) Immunohistochemical stain of typical CCPRCC showed strong positive for CK7.

The tumor had not invaded the pelvis and was confined by a capsule. Microscopically, the tumor was composed of clear tumor cells in papillary and tubulocystic patterns with focal reverse polarity of the nuclei and apical snouts (Fig. 2B and C). Part of the tumor revealed a Fuhrman grade 3 nuclear pattern. The tumor had invaded the renal vein, but not the pelvis or perirenal soft tissue. Necrosis was present. The tumor cells were immunoreactive for CK7 (Fig. 2D) and focally weakly positive for CD10 and RCC markers. α-methylacyl

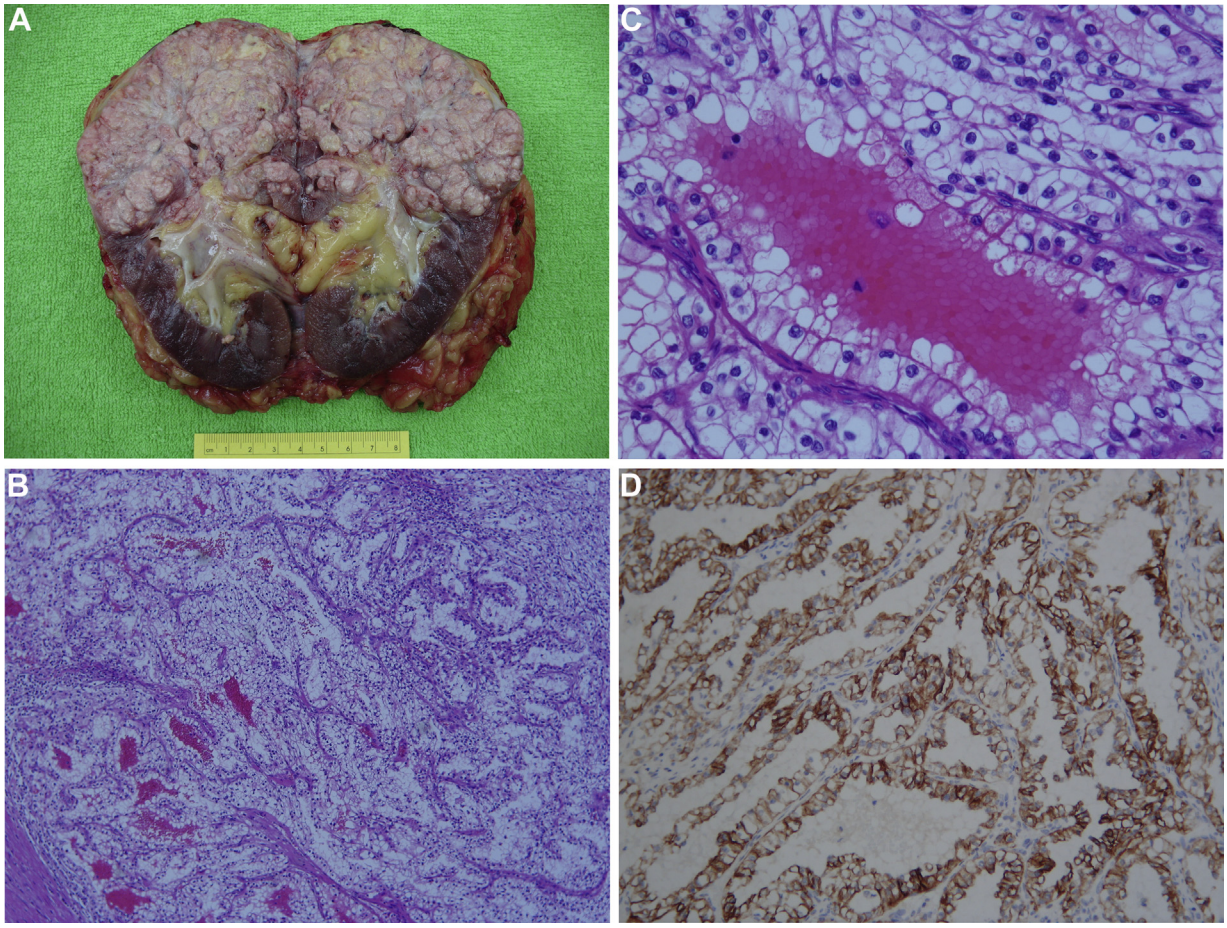

Fig. 2. Representative pictures of the nephrectomy specimen: (A) A soft tumor at upper pole (B) mixed acinar and papillary patterns with clear cytoplasm (C) focal area revealing reverse polarity of nuclei and apical snouts (D) cytoplasmic immunoreactivity for CK7.

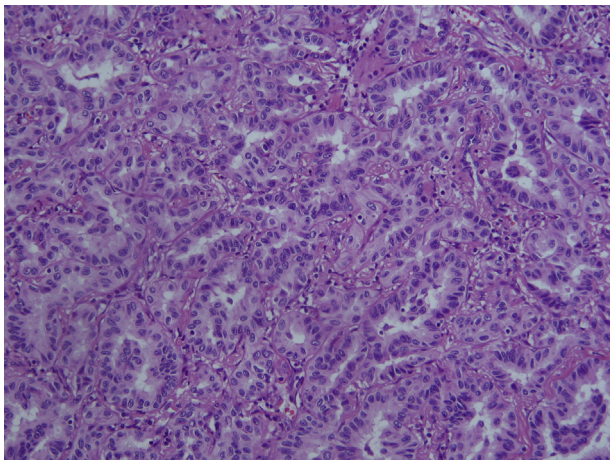

Fig. 3. Microscopic view of the lung metastasis.

coenzyme A racemase (AMACR) and transcription factor E3 (TFE3) markers were negative. He was initially diagnosed with CCPRCC on the basis of the histologic pattern and immunoreactivity for CK7.

With regards to the lung metastasis specimen (Fig. 3), sections of the left lower lobe lobectomy specimen showed multiple metastatic carcinomas, composed of pleomorphic cells with clear to pink granular cytoplasm arranged in papillae, glands and small solid nests. The morphology and immunoprofile was compatible with the previous kidney tumor.

The diagnosis was made at a time when the biological behavior was not fully understood. However, according to the later literature, no cases of metastatic CCPRCC had been reported, and all tumors were composed of low nuclear grade. Therefore, we re-examined the kidney specimen using whole-exome sequencing, which revealed 3p loss; 7 gain; *von Hippel–Lindau (VHL) gene* exon 2, A358G, and R120G mutations (Fig. 4), thus favoring ccRCC, and the diagnosis was revised.

4. Discussion

CCPRCC is regarded to be a unique subtype of renal parenchymal neoplasia that is distinct from other renal tumors.[1] During the time period of our series (from January 1, 2008 to December 31, 2016), a total of 25 cases of CCPRCC were identified, accounting for 3.3% (25/765) of all newly diagnosed primary RCC in our hospital, which is compatible with the 2.9%[5] and 4.3%[7] reported in previous studies.

CCPRCC developed in patients with acquired cystic kidney disease and ESRD. It was first described as “CCPRCC in

Fig. 4. Whole-exome sequencing of the kidney tumor detected 3p loss; 7 gain; *von Hippel–Lindau* (*VHL*) *gene* exon 2, A358G, R120G mutation.

end-stage kidneys" in 2006 by Tickoo et al.[2] However, further studies revealed that this kind of tumor could also affect normal kidneys. In our series, ESRD was associated with CCPRCC in only 4 cases (15.4%).

Four of our cases were diagnosed with CCPRCC in the native kidney after renal transplantation. Patients who receive solid organ transplants are known to be at a higher risk of cancer, which is thought to be due to chronic immune suppression. Transplant patients have also been reported to have a 10- to 100-fold higher risk of RCC growth in the native kidneys than the general population,[11] with reported incidence rates of RCC growth in native kidneys after kidney transplant of 0.8% in an American series[12] and 1.3% in a Chinese series.[13] The most common RCC subtype in native kidneys in renal transplant patients is ccRCC, followed by papillary RCC. No data is available on the incidence of CCPRCC in native kidneys after kidney transplant due to the rarity of the tumor. Only one case has been reported in the English literature,[14] with no tumor recurrence in 21 months of follow-up. In our series, four patients developed CCPRCC after kidney transplant, and they were followed for at least 4 years with no evidence of disease. RCC has been shown to be more aggressive in renal transplant recipients compared to the general population.[15,16] However, the clinical outcomes of CCPRCC in the renal transplant recipients in our series also seemed to be indolent even though the patients were immunosuppressed. This unique finding needs to be validated in a larger series with longer follow-up period.

Three main RCC subtypes which should be considered in the differential diagnosis of CCPRCC are ccRCC, papillary RCC, and translocation RCC. According to the typical microscopic tumor morphology and CK7 staining pattern, CCPRCC can be differentiated from ccRCC, papillary RCC, and translocation RCC in most cases. For more challenging cases, other IHC stain or molecular markers can provide more information for differentiation among these subtypes. The immunoreactivity of CK7 can be used to differentiate CCPRCC from ccRCC, since ccRCC is negative for CK7 stain. Microscopically, like papillary RCC, CCPRCC also contains tubular or papillary architecture, but the clear cytoplasm is not characteristic in papillary RCC. In challenging cases, although papillary RCC is also positive for CK7 stain, the absence of carbonic anhydrase IX stain and the positive AMACR stain can help differential diagnosis papillary RCC

from CCPRCC.[8] The nuclear features of translocation RCC are heterogeneous, and usually presented with high Fuhrman nuclear grade. The CK7 stain of translocation RCC is usually weak.[8]

Based on the current evidence, cryoablation therapy for small renal tumors (<4 cm) is suggested as an alternative treatment option in the elderly, those with multiple comorbidities, and those who are not candidates for surgery.[17,18] A tumor biopsy before energy ablative therapy is mandatory. In patients diagnosed with CCPRCC from a biopsy specimen, cryoablation therapy seems to be more reasonable due to the indolent nature of the disease. In our series, three patients with a cT1a tumor received cryoablation therapy, and none had tumor recurrence at a median follow-up period of 35.7 months (range 31−64 months). Active surveillance as the initial management option for small renal masses has been evaluated in recent years.[19] We suggest that especially for high surgical risk patients with biopsy-confirmed cT1a CCPRCC, active surveillance may also be considered as a treatment option.

The only case of sarcomatoid CCPRCC with metastasis was reported in 2015.[9] The authors used fluorescence in situ hybridization to confirm the absence of a 3p deletion, trisomy 7 or 17 and a common clonal origin of sarcomatoid transformation. We identified one patient (not included in the series) initially diagnosed in 2010 with metastatic CCPRCC with high nuclear grade. However, the pathology report was revised to ccRCC based on the results of whole exome sequencing. According to the available data, clinicians should be cautious before making the diagnosis of CCPRCC in patients with high nuclear grade or metastatic tumors. Additional confirmation using cytogenetic or genomic methods for differentiation is necessary.

Our study is limited by being a retrospective review. However, our series present the largest single institute series in an Asian population, with a long follow-up period (mean 49.7 months). In addition, we reported three patients with CCPRCC after kidney transplant and three who received cryoablation therapy. Based on our findings, CCPRCC has an indolent behavior even if the patients are immunosuppressed or if they receive less invasive therapy. Microscopically, CCPRCC is considered to be a tumor of low malignant potential,[20] as all tumors in our series were of low nuclear grade. Whenever the diagnosis is made in a high grade renal tumor, it should be carefully re-confirmed by either cytogenetic or molecular genetic methods.

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