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*Original Article*

# Clear cell papillary renal cell carcinoma: a clinicopathologic analysis of 6 cases

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**Abstract:** Clear cell papillary renal cell carcinoma (CCPRCC) is a newly described variant of renal cell carcinoma (RCC) which is composed mainly of cells with clear cytoplasm arranged in cystic and papillary patterns. We report the clinicopathologic features, prognosis and differential diagnosis of 6 Clear Cell Papillary Renal Cell Carcinomas. The clinical information and follow-up data were analyzed. The patients were six males with median age of 52.5 years. Case 1 revealed dense calcification and ossification. Cases 2 and 3 contain a variably prominent smooth muscle stromal component. CA-IX, CK7, PAX-8 and VIM were positive in all cases. TFE3 and AMACR were not expressed in any tumor. CD10 was negative in 5 of 6 cases .The patients were followed for 13~55 months with no local tumor recurrences and tumor metastasis. The CCPRCC was associated with a more favorable outcome. These were low-grade and low-stage renal tumors. No lymph node or distant metastasis of the six tumors.

**Keywords:** Kidney, neoplasia, clear cell papillary renal cell Carcinoma, osseous metaplasia, leiomyomatous stroma

## Introduction

Clear cell papillary renal cell carcinoma (CCPRCC) is a newly described variant of renal cell carcinoma (RCC) and represents a distinct clinical pathological entity [1, 2]. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia has recently endorsed it as a distinct subtype of epithelial tumor and recommended the inclusion of this tumor in the ISUP Vancouver modification of the WHO 2004 histologic classification of RCCs [2]. Herein, for further understanding of this disease, we report the clinical and immunohistochemical phenotypes of 6 papillary renal tumors showing the same peculiar features.

## Materials and methods

### *Cases*

The 6 cases were retrieved from the surgical pathology files of participating institutions. Clinical findings were obtained from medical records. Sections cut at 4-μm thickness were stained with hematoxylin and eosin and the cases were reviewed. Follow-up was available in all the six cases (**Table 1**). In addition to H&E stains, immunohistochemical studies were performed on 6 cases (**Table 2**).

### *Clinical findings/features*

The patients were 6 men; the ages at presentation were 48 years (case 1), 68 years (case 2), 42 years (case 3), 65 years (case 4), and 44 years (case 5), and 57 years (case 6) (median age: 52.5 y). Median age is 52.5 years. And mean age is 54 years. All the six patients had no history of renal disease. None of the six patients was known to have had symptoms related to the tumor. For all the patients, the Computerized Tomography (CT scan) showed renal occupied lesions (**Figure 1**). Laparotomy was performed and the nephrectomy specimen was sent for histopathology.

## Results

### *Gross pathology*

There were three radical nephrectomy specimens and three renal resection specimens. Circumscribed mass were mentioned in all of the gross descriptions. They measured from

**Table 1.** Clinicopathologic findings

| Case No. | Age | Sex | Size (cm) | Fuhrman Grade | Stage | ESRD | Follow-up (month) |
|---|---|---|---|---|---|---|---|
| 1 | 48 | M | 3.0 | G1 | pT1 | No | NED (14) |
| 2 | 68 | M | 1.6 | G1 | pT1 | No | NED (23) |
| 3 | 42 | M | 5.0 | G2 | pT1 | No | NED (13) |
| 4 | 65 | M | 2.2 | G1 | pT1 | No | NED (55) |
| 5 | 44 | M | 3.0 | G2 | pT1 | No | NED (15) |
| 6 | 57 | M | 2.0 | G2 | pT1 | No | NED (17) |

ESRD, end-stage renal disease; M, man; W, woman; NED, no evidence of disease.

**Table 2.** Immunohistochemical findings

| Case No | AMACR | CA IX | CD10 | CK 7 | TFE3 | VIM | pax-8 |
|---|---|---|---|---|---|---|---|
| 1 | Neg | +++ | Neg | ++ | Neg | +++ | +++ |
| 2 | Neg | +++ | -/+ | +++ | Neg | +++ | +++ |
| 3 | Neg | +++ | Neg | +++ | Neg | +++ | +++ |
| 4 | Neg | +++ | Neg | +++ | Neg | +++ | +++ |
| 5 | Neg | +++ | Neg | +++ | Neg | +++ | +++ |
| 6 | Neg | +++ | Neg | +++ | Neg | +++ | +++ |

Neg, indicates negative; -/+, 1% to 25% positive; +, 26% to 50% positive; ++, 51% to 75% positive; +++, 76% to 100% positive.

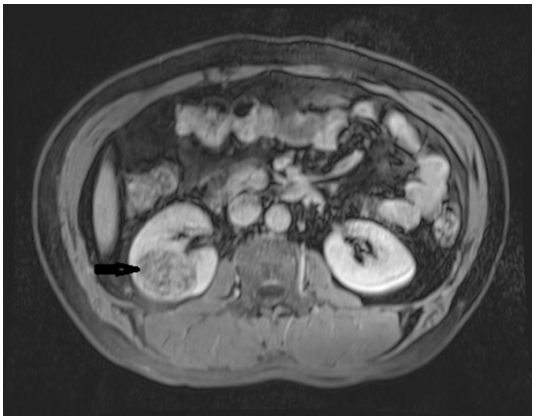

**Figure 1.** The Computerized Tomography (CT scan) showed renal occupied lesions, as indicated by the black arrow.

1.6 to 5.0 cm in maximum diameter. The lesions of 2 cases bulge on the renal capsule, but did not wear out (case 5, case 6). The renal vein and adrenal gland is normal and free of tumor.

*Microscopic examination*

All tumors were well circumscribed with a well defined, thin, fibrous capsule and were composed histologically of cells with clear cytoplasm arranged in papillary patterns (**Figure 2**). Some clear cell papillary structures were associated with cysts lined by epithelial cells with clear cytoplasm. The papillae had prominent fibro-vascular cores and were covered with a single layer of clear cells with predominantly apical nuclei, exhibiting low-grade nuclear pleomorphism. In case 1, we found massive osseous metaplasia and calcification (**Figure 3**). Other 2 cases (case 2 and case 3) show a characteristic of angioleiomyomatous stroma (**Figure 4**). Both tumors had a variously thick capsule formed by a layer of bands of smooth muscle. These were low-grade and low-stage renal tumors. No lymph node or distant metastasis of the six tumors.

*Immunohistochemistry*

The results of the immunohistochemical procedures are summarized in **Table 2**. CA-IX, pax-8 (**Figure 5**) and VIM were positive in all cases. Carbonic anhydrase IX (CA-IX) were expressed in cup-shaped distribution (**Figure 6**). CK7 was diffusely expressed in case 4 and in 50% to 90% of the cells in the other cases. In addition, the tumor cells stained negative for a-methylacyl-CoA racemase (AMACR); CD10 was negative in 5 of 6 cases; in case 2, about 10% of cells expressed CD10. TFE3 were not expressed in any tumor.

## Discussion

Clear cell papillary renal cell carcinoma (CCPRCC) was composed mainly of cells with clear cytoplasm arranged in cystic and papillary patterns [1, 2]. It is one of the forms of renal cell carcinoma associated with end-stage renal disease, and was previously described in clear cell papillary renal cell carcinoma of end-stage kidneys [3]. However, tumors with similar features have been reported in kidneys not affected by end-stage renal disease [4]. We analyzed 6 cases of this group of renal epithelial tumors that showed distinct morphologic features. In our study, 5 tumors occurred in normal kidneys, only 1 tumor (case 4) arose in a background of renal cyst.

Gross examination of case 1 revealed dense calcification and ossification. Histopathological examination of the tumor contained mature

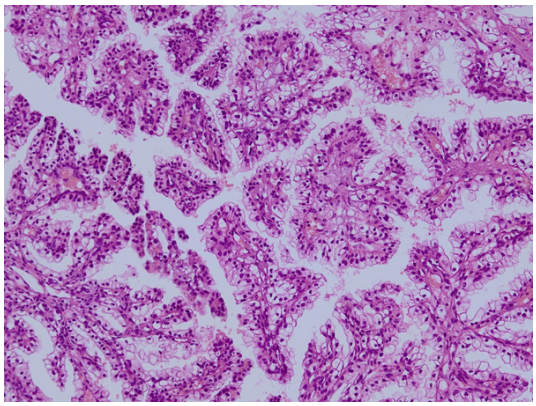

**Figure 2.** The tumor were composed histologically of cells with clear cytoplasm arranged in papillary patterns (original magnification, ×100).

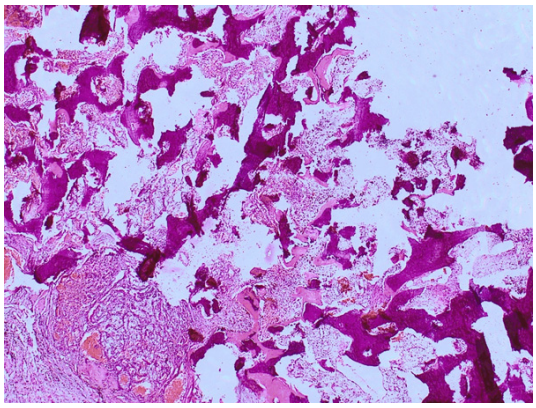

**Figure 3.** There were massive osseous metaplasia and calcification in Case 1 (original magnification, ×20).

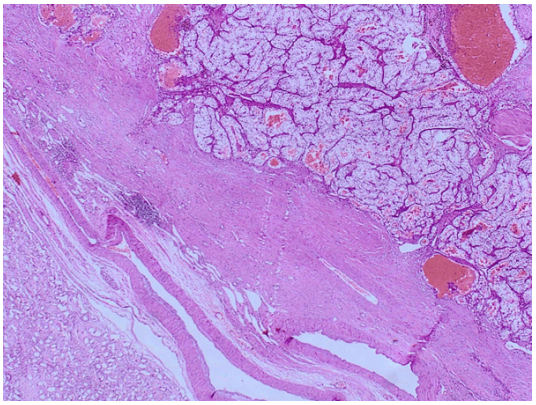

**Figure 4.** Case 2 and case 3 show a characteristic of angioleiomyomatous stroma (original magnification, ×20).

bony tissue. Although calcification is a well-recognized feature of renal tumors, they are rarely

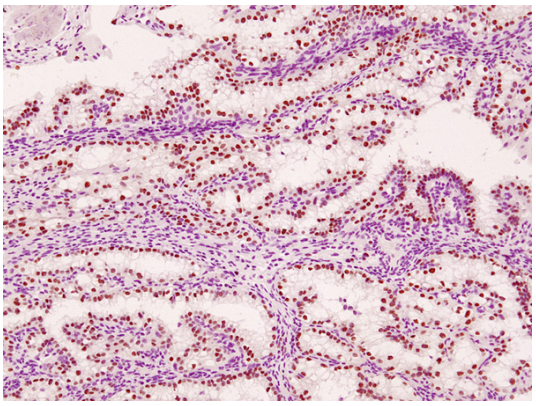

**Figure 5.** The positive staining for PAX-8 was brown in the nucleus (original magnification, ×100).

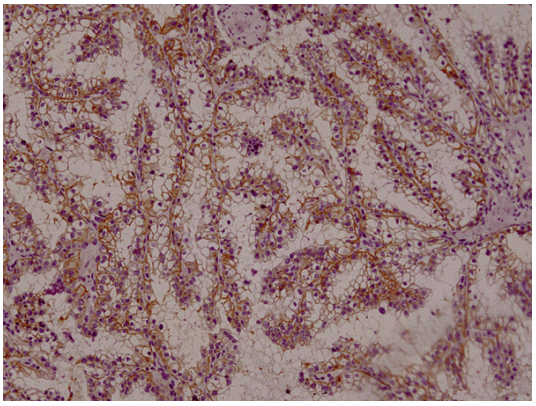

**Figure 6.** CA9 is diffusely expressed in the tumor (original magnification, ×100).

ossified. Daniel reported that 10.3% of RCCs had calcified foci, based on a review of 2,709 renal masses at the Mayo Clinic [5]. Moreover, reports of histopathologically confirmed osseous metaplasia or bone formation within RCC are rare [6]. To our knowledge, the presence of osseous metaplasia in CCPRCC was first reported in our study.

The mechanism of ossification is unclear, although it might involve a metaplastic or reparative response either in the tumor or in the surrounding tissue, the production of bone by tumor cells, or the ossification of a preexisting mucin or calcium deposit [7]. Osseous metaplasia may occur secondary to ischemia, necrosis, or inflammation in the tumor or surrounding tissues [7]. The prognostic significance of ossification in CRCC remains unclear because of the limited number of cases reported to date. However, several studies demonstrated that

ossification is a significant prognostic marker for patients with RCC [7, 8] and is usually representative of an early stage without invasion or metastasis [8]. Cribbs et al. reported a clear cell renal carcinoma with ossification which no recurrence or metastasis was observed from a follow-up of 25 years [9]. Therefore, RCC with osseous metaplasia implies a more favorable prognosis, although this is contradicted by some reports, suggesting that ossification is actually associated with high-grade tumors and a poor prognosis [10]. Due to the limited follow-up available, long time results should be viewed for a following up of a longer time.

Cases 2 and 3 contain a variably prominent smooth muscle stromal component. The leiomyomatous tissue often entirely encased patches of tubular structures, or it formed only small leiomyomatous islands within the epithelial component. Whether or not this leiomyomatous stroma is part of the neoplastic proliferation has not been firmly established. Petersson F et al. [11] studied the clonality status of 14 renal cell carcinomas and found the leiomyomatous stromal component in all analyzable (8/14) cases to be polyclonal and therefore reactive rather than neoplastic. They propose that the non-neoplastic leiomyomatous stromal component is likely derived from smooth muscle cells of large caliber veins located at the peripheral capsular region or within the collagenous septae of the tumors. The leiomyomatous stroma in renal cell carcinomas is polyclonal and not part of the neoplastic process. Leiomyomatous stroma is not specific for CCPRCC. It can be seen also in otherwise typical clear cell RCCs [12].

The CCPRCC was associated with a more favorable outcome. Evidence of biological aggressiveness, such as perirenal or renal sinus invasion, vascular invasion, tumor necrosis, and sarcomatoid dedifferentiation, has not been observed in these tumors. All the 6 patients in this study, showed no evidence of disease after a mean follow-up period of 23 months. More than 80 earlier reported cases for which data were available, including 6 cases in this study, have been categorized as pathologic stage category pT1, and only 2 tumors were pT2 [3, 4, 13-15]. All have exhibited low-grade nuclear features (Fuhrman grade 1 or 2). These observations suggest that clear cell tubulopapillary renal cell carcinomas may be biologically indolent tumors; however, further follow-up studies are needed to better define their clinical behavior.

CCPRCC are easily distinguishable from the tumors, including CCRCC with secondary papillary formation PRCC with clear cell changes, composite CCRCC and PRCC, or unclassified RCC with both clear cell and papillary components. As none of these tumors were CK7 positive and AMACR negative [16], they often exhibit pathologic features of aggressive RCC, including Fuhrman grade 3 and 4 nuclei, coagulative necrosis, vascular invasion, lymph node metastasis, and sarcomatoid differentiation, none of which is seen in CCPRCC.

In summary, clear cell papillary RCCs are typically small, biologically indolent tumors [17, 18]. No lymph node or distant metastasis of these tumors has been reported to date in the literature. In the recent ISUP classification, the term of “low malignant potential” similar to that of multilocular cystic RCC has been proposed on the basis of these indolent clinical features [18]. We are going to keep following the six patients.

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## Disclosure of conflict of interest

None.

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