Case Report

Clear Cell (Tubulo) Papillary Renal Cell Carcinoma: A Case Report and Literature Review of a Recently Recognized New Entity

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Clear cell (tubulo) papillary renal cell carcinoma (CCPRCC) is a newly established entity in renal tumor classification. Here we report a case of CCPRCC in a 61 year old male with long history of hypertension, chronic renal failure, and one year history of dialysis. Grossly the tumor is multicystic. Microscopically, bland appearing tubules and occasional small papillae with low grade nuclei are noted. The characteristic linear arrangement of nuclei deviating from basal aspect of the lumens is prominent. Immunohistochemically, the tumor cells are positive for CK7, high-molecular weight cytokeratin (HMWK), CA-IX (cup-shape pattern), and negative for AMACR and CD10. The histology and immunophenotype all qualify this tumor as CCPRCC. The diagnostic criteria and the related differential diagnoses are also discussed.

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Key Words: *clear cell (tubule) papillary renal cell carcinoma, diagnostic criteria, immunophenotype, cup-shape pattern of CA-IX*

INTRODUCTION

Clear cell (tubulo) papillary renal cell carcinoma (CCPRCC) was recently established as one of five new distinct renal tumor entities by The Classification Working Group of the International Society of Urological Pathology in a consensus conference held at Vancouver, Canada.[1] The other four entities are tubulocystic renal cell carcinoma, acquired cystic disease-associated renal cell carcinoma, the MiT family translocation renal cell carcinoma, and hereditary leiomyomatosis renal cell carcinoma syndrome-associated renal cell carcinoma.[1]

CCPRCC comprises about 1% of all renal cell neoplasms.[2] The majority of cases have been reported as sporadic, although cases associated with end-stage renal disease are also well-documented.[3] The age of presentation ranges from 18-88 years old (mean 60 years old), and there is no gender or race predilection.[4]

To be classified into this entity, both morphologic features and immunohistochemistry (IHC) patterns have to be satisfied for a candidate tumor.[1] Morphologically, the tumor must be composed of 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. Immunohistochemically, the tumor cells should have a profile of CK7+, CA-IX+, high-molecular weight cytokeratin (HMWK)+, CD10-, and AMACR-. Furthermore, CA-IX should present as cup-shaped distribution, that is, diffuse membranous distribution with the absence of staining along the luminal borders of the tumor cells.[1]

Clinically, although the number of cases in the literature with extended follow-up information is small, CCPRCC seems indolent in behavior, with no metastasis reported so far.[1,5]

Here we report a case of CCPRCC in a 61 year old male patient with history of hypertension, end stage renal failure, acquired renal cystic disease, and dialysis for one year. The morphology and IHC pattern of the renal tumor are well-fit for the diagnostic criteria for CCPRCC.

CASE REPORT

Patient History

The patient was a 61 year old male with a long history of hypertension and subsequent chronic renal failure. He started dialysis one year ago. Two years ago ultrasound found hypoechoic areas in upper pole measuring 1.4 x 1.3 cm and in the lower pole measuring 0.5 x 0.6 cm in the right kidney. Benign cysts were suggested. Three months ago a computed tomography (CT) was conducted to evaluation patient's newly onset hematuria. Complex poorly demarcated right renal upper pole lesion measuring 2 x 2 cm and lower pole

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lesion measuring 2.8 x 2.9 cm in size were found. With the uncertainty of the diagnosis, a right nephrectomy was performed.

Methods

Immunohistochemical stainings of the renal tumor were performed on 10% formalin fixed, paraffin embedded tissue sections by using the avidin-biotin-immunoperoxidase method, with 3-amino-9-ethyl carbazole as the chromogen and hematoxylin as the counterstain. The following monoclonal antibodies were used: CK7, CD10, HMWK, AMACR, and CA-IX.

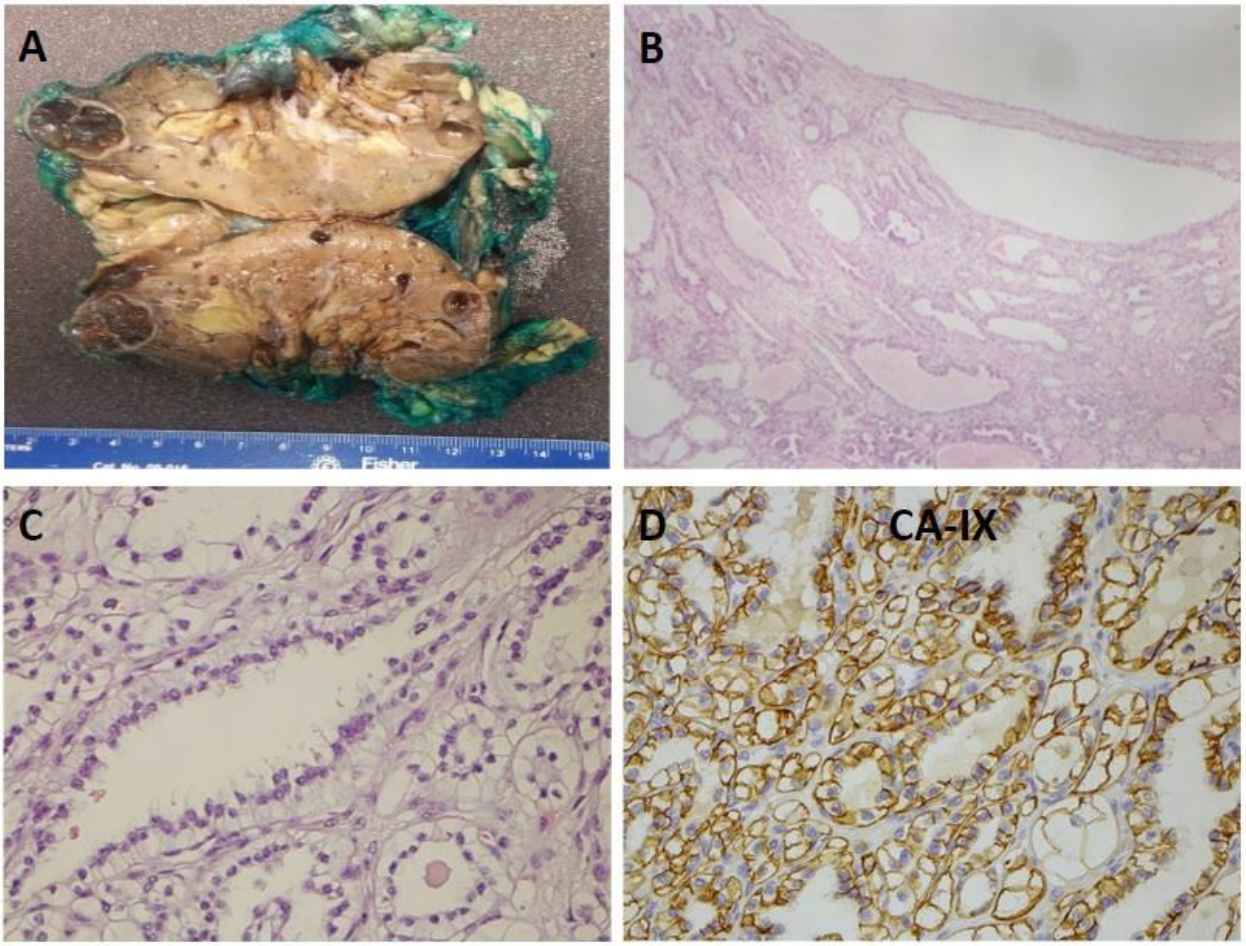

Figure 1. Gross, microscopic and CA-IX immunostaining pattern for CCPRCC. **A.** Gross specimen of the tumor-containing kidney. The tumor is cytic. **B.** Low power view of the tumor (X50). The tumor contains cysts, tubules, papillae and focal solid sheets. **C.** High power view of the tumor (X400). The characteristic linear arrangement of nuclei away from the basal aspect is prominent (arrow). **D.** The characteristic cup-shape pattern of CA-IX immunostaining of the tumor cells (arrow).

RESULTS

Grossly the right kidney was partially covered in fat, measuring 13 x 8 x 4.5 cm and weighing 157 grams. Sectioning the specimen reveals 3 cysts filled with yellow gelatinous material and are hemorrhagic, ranging in size from 3 to 0.9 cm in greatest dimension. The cysts are located in the upper and lower poles and mid-posterior aspect of the specimen. All three cysts are confined to the kidney. Representative sections were submitted for microscopic examination.

Microscopically, the mid-posterior lesion turns out benign renal cyst. However, the upper and lower pole cysts present as complex cysts with papillae, tubules and focal acinar formation. The tumor cells are clear cell in nature, with low grade nuclei and inconspicuous nucleoli (Fuhrman grade 1). The papillae are largely lined with single layer of tumor cells. Characteristically, the nuclei of the tumor cells form a linear arrangement and deviate toward the luminal side. The pseudocapsules of the cysts are intact. There is no tumor necrosis, foamy macrophages or lymphovascular invasion seen.

Immunohistochemically, the tumor cells are positive for CK7, HMWK, CA-IX, but negative for CD10 and AMACR. The CA-IX is uniquely cup-shaped, with membrane surrounding except luminal side.

Based on the histology and immunostaining pattern, this tumor is classified as CCPRCC.

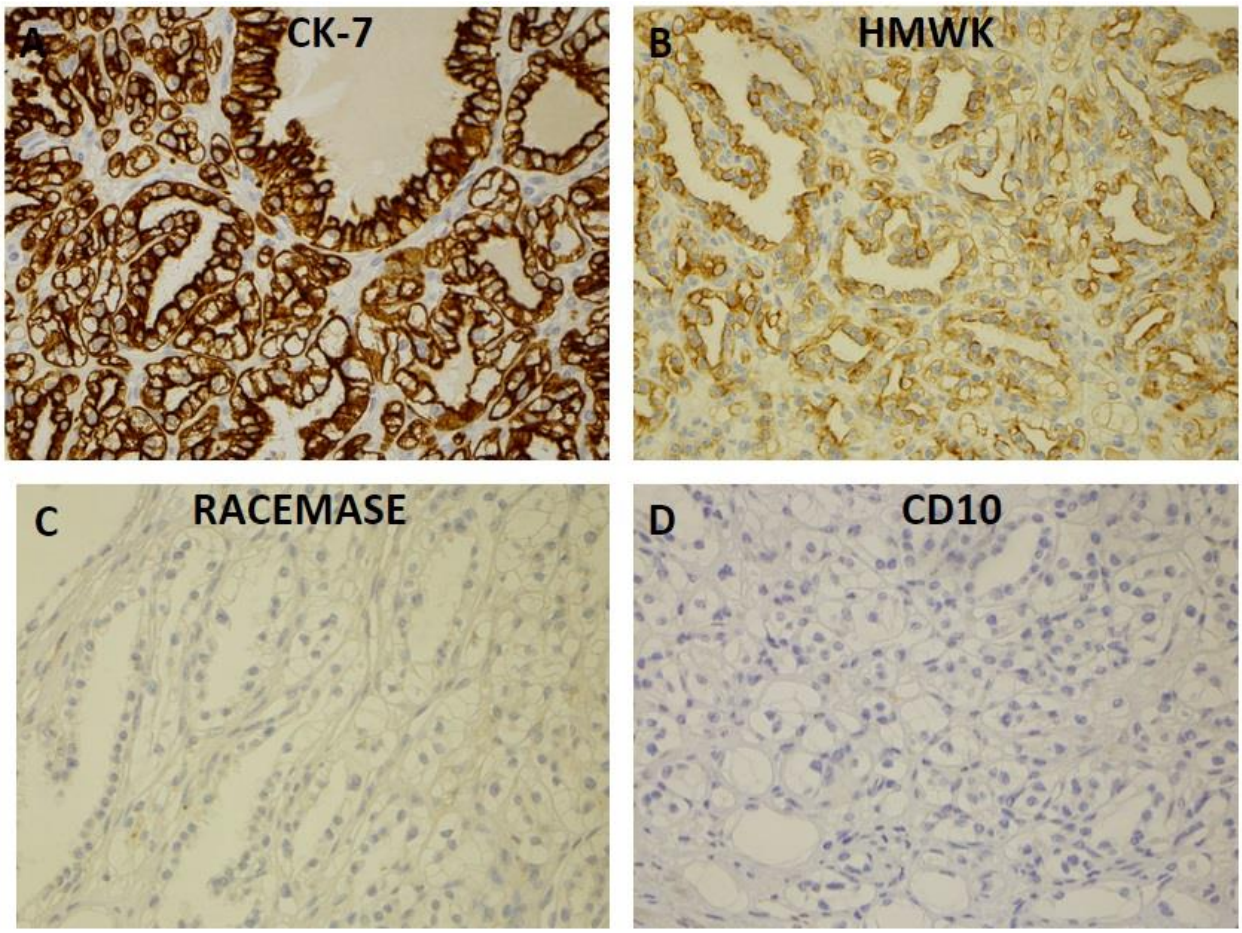

Figure 2. The immunostaining pattern for CCPRCC. The tumor cells are positive for CK-7 (**A**), HMWK (**B**), but negative for Racemase (**C**) and CD10 (**D**).

DISCUSSION

CCPRCC is a newly classified renal cell carcinoma (RCC).[1] This tumor was originally described in a background of end stage renal disease and acquired cystic kidney diseases, although it has subsequently been reported in normal kidneys.[3,5,6] CCPRCC comprises about 1% of all renal cell neoplasms, with an age range and gender distribution similar to RCC in general.[7] CCPRCC is low grade in nature.[1,4] There is no metastasis from a CCPRCC been reported so far, suggesting of the likelihood that this tumor is less aggressive than other RCC subtypes. Indeed, some experts who participated in the classification conference even suggested to down-regulate this tumor to the category of "neoplasm with low malignant potential".[1]

CCPRCC is usually small and encapsulated. The tumor may be solid, white tan, pale yellow or reddish brown, but typical bright or golden-yellow heterogeneous appearance of clear cell RCC is not present. The cystic component is usually located at the periphery of the tumor, near its junction with renal parenchyma, and may be angulated, flattened, or irregular. Bilaterality and multifocality have been documented, especially in cases arising from a background of cystic kidney diseases.

Histologically, CCPRCC is composed of an admixture of cysts, tubules, acinar glands, papillae and even solid sheets. Although the characteristic linear arrangement of the low grade nuclei away from the basal aspect (so-called inverted polarity) is fairly unique to CCPRCC, the classification committee strictly requires the immunostaining pattern should be satisfied simultaneously.[1] That is, the tumor cells must have an immunophenotype of CK7+, HMWK+, CD10-, AMACR-, and a cup-shaped CA-IX. The importance of this requirement will be further discussed in differential diagnosis.

At the molecular genetic level, CCPRCC is distinct from clear cell and papillary RCC. CCPRCC lacks deletion of 3p25, VHL mutation, hypermethylation of VHL promoter, and other recurrent copy number changes seen in other types of RCCs, such as trisomies of chromosome 7 and 17. However, low copy gains of chromosome 7 or 17 have been

documented in a few cases, and loss of heterozygosity of the VHL locus also has been reported in one patient.[1,5] More cases are needed to study the molecular mechanism of CCPRCC.

The main differential diagnosis of CCPRCC is clear cell RCC, especially that with cystic changes. Some low grade clear cell RCC may have subnuclear clearing and present as linear arrangement of nuclei mimicking that in CCPRCC.[2,8] Furthermore, some cases of clear cell RCC show positivity for CK7, although mostly focal and not as strong as that in CCPRCC. However, clear cell RCC is usually CD10+, HMWK-, with a box-shaped distribution of CA-IX staining (the luminal aspects of the tumor cells are also positive for CA-IX, which is negative in CCPRCC and resulting in cup-shaped pattern) (see **Table 1**).

Table 1. Immunohistochemistry and genetic changes in CCPRCC, clear cell RCC and papillary RCC.

	CCPRCC	Clear cell RCC	Papillary RCC
CK7	+	-/+	+
CD10	-	+	-
RCC	-	+	+
AMACR	-	-	+
HMWK	+	-	-
CA-IX	+ (cup-shaped)	+ (box-shaped)	-/+
VHL	-	+	-
Trisomies 7, 17	-	-	+

Since CCPRCC has papillae as one of its manifestations, papillary RCC should also be ruled out when making a diagnosis. In contrast to CCPRCC, The lining on the papillae in papillary RCC is usually of multiple-layer of tumor cells, with abundant macrophages in the papillary core. Moreover, the tumor cells in papillary RCC are often positive for AMACR, RCC and negative for HMWK, while the converse occurs in CCPRCC (see Table 1).[9-11]

Overall, here we report a case of CCPRCC in a patient on dialysis. This low grade tumor is recently classified as a new entity with strict morphologic and immunohistochemical requirements. No pathognomonic genetic alteration has been identified. A recently gene expression profile meta-analysis of clear cell RCC identified 3 distinct subgroups. One of them corresponded to a VHL wild type pattern, which, interestingly, presenting as CCPRCC morphologically.[12] Therefore it is safe to say that many CCPRCC cases had been wrongly classified as clear cell RCC in the past. In the future, more observation and research are needed to further understand this unique entity.

CONFLICT OF INTEREST
None.

ETHICAL APPROVAL
This work meets all the ethical guidelines.

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