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Original article

Oncocytic papillary renal cell carcinoma: A clinicopathological and genetic analysis and indolent clinical course in 14 cases

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ABSTRACT

A sort of PRCC with distinct eosinophilic cytoplasm named Oncocytic Papillary Renal Cell Carcinoma (OPRCC) has been increasingly attracting the attention of researchers recently. However, owing to the rarity of OPRCC, the clinicopathological and genetic features of the tumor have still not been well elucidated and whether it should be regarded as an independent subtype of PRCC remains controversial. Herein, a cohort of 14 OPRCCs was studied with the aim of revealing the distinct clinicopathological features, facilitating the classification and correct diagnosis of OPRCC. Men and women each accounted for a half of the cohort with the median age of 64 years old. The majority of patients (9/14) were identified by medical examination and the remaining presented with macroscopic haematuria or lumbar pain. Grossly, tumors were well demarcated and varied from 1.5 to 9 cm in diameter. Microscopically, typical OPRCC possessed fine papillary structures with delicate fibrovascular cores, lined with a single layer cell with large, deeply eosinophilic granular cytoplasm and round or polygonal-shaped nucleus exhibiting low nuclear grade in 10 cases (WHO/ISUP grade I-II). Most cases (12/14) possessed hemosiderin-laden and foam-like cells. Focal necrosis presented in 5 cases. Furthermore, solid oncocytoma-like areas appeared in 5 cases and focal sarcomatoid differentiation was identified in 1 case. Immunohistochemically, the majority of tumors presented high expression rates of alpha-methylacylCoA racemase (AMACR), CD10 and vimentin, which were similar to type 2 PRCC. The immune markers including cytokeratin-7 (CK7), KSP-cadherin and EMA exhibited variable positive immunostaining. Genetically, FISH analysis demonstrated trisomy of chromosome 7 in 7 OPRCCs and trisomy of chromosome 17 in 6 OPRCCs. Among 7 male cases, loss of chromosome Y was revealed in 2 cases. Follow-up data was available in 13 patients and only 1 patient died of bone metastasis of the tumor. The other 12 patients were all alive uneventfully at a mean follow-up time of 37 months, indicating that OPRCC is a unique subtype of PRCC with indolent clinical behavior. In conclusion, OPRCCs show a single layer tumor cell of low nuclear grade similar to type 1 PRCC, and abundant eosinophilic cytoplasm resembling type 2 PRCC. Furthermore, the tumor presents the same immunophynotype as type 2 PRCC but the same genetic features and prognosis as type 1 PRCC. OPRCC should be classified as an independent subtype of PRCC with different features from both type 1 and type 2 PRCC.

1. Introduction

Papillary renal cell carcinoma (PRCC) is the second most frequent subtype of renal cell carcinoma (RCC), accounting for approximately 10%–15% of RCC [1] and characterized by a predominant papillary or tubular papillary architecture with tumor cells lining fibrovascular cores, as well as specific immunophenotypes. PRCCs were traditionally subdivided into two morphological types (type 1 and type 2) based on architectural and cytological features showing different biological behavior according to the WHO Classification of Tumors in 2004 [2]. However, in the newly edition of WHO Classification of Tumors of the Urinary and Male Genital Organs in 2016, it for the first time mentions the oncocytic PRCCs and described its different pathological features from type 1 and type 2 PRCC. It also said that tumors with this morphology are not yet fully characterized and ongoing studies will help further refine the characterization of tumors in this category [3]. Type1 tumor consists of delicate papillae lined by small cells with low nuclear

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Table 1
Clinicopathological features of 14 cases of OPRCC.

Case no.	Age/Sex	Diameter (cm)	Laterality	Presenting symptom	TNM stage	Surgery	Follow up (mouths)
1	59/M	9	R	MH	II	RN	43
2	73/M	2	R	ID	I	PN	34
3	67/F	3,1.5	L	ID	I	RN	19
4	67/M	4	L	ID	I	PN	12
5	50/M	4	L	Flank pain	I	PN	15
6	52/F	7	L	back pain	III	RN	8(DOD)
7	53/M	5	L	ID	I	RN	67
8	51/M	2.5	L	MH	I	RN	57
9	78/F	4	R	ID	I	RN	105
10	79/F	3.5	L	ID	I	PN	98
11	70/F	4	R	ID	I	RN	17
12	67/M	1.8	R	ID	I	RN	Lost
13	79/F	4	R	ID	I	RN	2
14	80/F	7	L	waist pain	I	PN	4

M, man; F, female; MH, Macroscopic hematuria; ID, incidental detection; RN, radical nephrectomy; PN, partical nephrectomy; DOD, die of tumor

grade and a scant pale of basophilic cytoplasm arranged in a single layer; type 2 tumor consists of broad papillae covered by pseudostratified tumor cells with eosinophilic cytoplasm. Studies suggested that type 2 PRCC had poorer prognosis than type 1, with disease-free survival rates of 44% and 92%, respectively [4]. Oncocytic PRCCs consists of a single layer of tumor cells with eosinophilic cytoplasm and low-grade nucleus. However, the prognosis of this tumor is unknown until now. Therefore, accurate subtype of PRCC is important for guiding the treatment and anticipating the prognosis of the patient.

In 2005, Lefevre et al. [5], who first reported 10 cases with acidophil form of papillary renal tumor named Oncocytic Papillary Renal Cell Carcinoma (OPRCC), put forward that OPRCC is a kind of independent variant of PRCC because the tumor presents unique morphological characteristics and immunohistochemical profiles, which are different from type 1 and type 2 PRCCs. Due to the rare reports and insufficient understanding of OPRCC, the pathological diagnosis was often misdiagnosed as type 2 PRCC and other eosinophilic renal tumors. We herein report 14 cases of OPRCC combined with related literature to uncover the clinicopathological, immunophenotype and cytogenetic features of OPRCC in order to facilitate the classification of PRCC and improve the recognization ability of diagnosis and differential diagnosis of OPRCC.

2. Materials and methods

2.1. Study population

A total of 753 cases of renal cell carcinoma were collected from the Pathology Departments of the Affiliated Hospital of Qingdao University and 401 Hospital of PLA between 2007 and 2015. Among them 14 cases of renal cell carcinoma with the presence of predominant papillary architecture, abundant oncocytic cytoplasm, and low-grade non-overlapping nuclei were enrolled into the study; and 38 cases of classic PRCC, including 24 cases type 1 and 14 cases type 2 tumors were selected as the control approximate proportion of age, gender, tumor size and follow-up procedures with OPRCCs. All specimens were reviewed by two genitourinary pathologists and diagnosed according to the 2016 World Health Organization, graded according to the WHO/ISUP (International Society of Urological Pathology) grading system and staged on the basis of the 2010 TNM staging system of renal tumor. Survival was calculated from the date of surgery to death or the last follow-up visit.

2.2. Histopathology

Tissues for all cases were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections of 3–4 μm thickness were stained by hematoxylin and eosin. The immunohistochemical staining was performed using EnVision method and the primary antibodies including alpha-methylacylCoA racemase (AMACR) (Zeta, 13H4, 1:50), vimentin (Cellmarque, V9, 1:100), cytokeratin-7 (CK7) (Cellmarque, OV-TL12/30, 1:50), CD10 (Dako, 56C6, 1:50), CD117 (Cellmarque, YR145, 1:100), epithelial membrane antigen (EMA) (Thermo, E29, 1:50), KSP-cadherin (Zymed, 4H6/F9, 1:100) and high molecular weight cytokeratin (HMW-CK) (Cellmarque, CKHMW, 1:100). All kits and antibodies were bought from Maixin Biotechnology Company (Fuzhou, China). The specificity of immunolabelling was demonstrated by the absence of labelling when the primary antibody was omitted.

2.3. Genetic analysis

Interphase fluorescence *in situ* hybridization (FISH) analysis was carried out on 3 μm paraffin sections in accordance with routine method. The CEP 7 and Y probes were green labeled and CEP 17 probe labeled with spectrum orange was diluted with tDenHyb1 (Insitus, Alburquerque, NM) in a ratio of 1:100. Olympus BX51 fluorescence microscope and CellScan Fluospot FISH system (Tokyo, Japan) were used to observe and capture images.

2.4. Interpretation standard

The interpretations of immunoreactive score were on the basis of staining intensity combined with the percentage of positive cells: no obvious positive cells was negative (0), the number of positive cells <25% was weakly positive (1+), the number of positive cells 25%–50% was moderate positive (2+), and the number of positive cells >50% was strong positive (3+).

The interpretations of FISH were as follows. Chromosomes 7, 17 and Y were green-labeled. Two green signals or one green signal of chromosomes 7 and 17 appeared in normal cells. Chromosome Y is haploid in normal cells of male. Abnormal signals in more than 10% tumor cells indicate the gain or loss of the chromosomes. Interpretation standard was according to the literature [7,9].

2.5. Statistical analysis

All statistical analyses were performed by the SPSS22.0 software using chi-square test (or Fisher's exact test) for qualitative variables. For survival analysis, only deaths for OPRCC were considered as events. Survival curves were derived from Kaplan-Meier analysis and log-rank test was used to compare survival distributions between different groups. Statistical significance was considered as p value less than 0.05.