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Original contribution

Papillary renal cell carcinoma with oncocytic cells and nonoverlapping low grade nuclei: expanding the morphologic spectrum with emphasis on clinicopathologic, immunohistochemical and molecular features

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Summary Papillary renal cell carcinoma (PRCC), a morphologically and genetically distinct subtype of RCC, is morphologically separated into 2 subtypes, type 1 and 2, for prognostic purposes. Type 1 PRCC (single layer of small cells, scant pale cytoplasm) is more common and has a favorable prognosis compared with type 2 (pseudostratified high-grade nuclei, abundant eosinophilic/oncocytic cytoplasm). We report the clinicopathologic, immunohistochemical, and molecular data of 7 adult papillary tumors with morphological features distinct from type 1 or 2 PRCC. All tumors demonstrated predominant papillary architecture, lined by cells with oncocytic cytoplasm, and nonoverlapping low Fuhrman grade nuclei (1 or 2). Foamy macrophages were noted in 2 of 7 tumors. No case demonstrated necrosis or psammoma bodies. Most tumors (6/7) were small (mean size, 2.0 cm; range, 0.8-5.7 cm) and limited to the kidney. No tumor recurrence or metastasis was identified (median follow-up, 22 months). All tumors demonstrated trisomy for 7 and 17 by fluorescence in situ hybridization analysis and uniform CK 7, CD10, and α-methylacyl-coenzyme A racemase expression, characteristic of PRCC. These results suggest that these tumors are distinct from type 1 (owing to oncocytic cells) and type 2 (owing to low-grade nonstratified nuclei, low stage, and good outcome). Awareness of this favorable spectrum of PRCC is important to avoid its potential misinterpretation as an aggressive type 2 PRCC (owing to oncocytic cells) or rarely as an oncocytoma (owing to oncocytic cells and low-grade nuclei). Morphologic spectrum of these PRCCs emphasizes that the future prognostic model of PRCC may need to be based primarily on the nuclear characteristics, irrespective of the cytoplasmic features.

1. Introduction

Papillary renal cell carcinoma (PRCC), first described by Mancilla-Jimenez et al [1], is a histologically distinct type of

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renal cell carcinoma (RCC) comprising 10% to 15% of all RCCs. Evolving cytogenetic and molecular data have also characterized PRCC as a genotypically distinct variant of RCC, characterized by trisomies of chromosomes 7 and 17 and deletion of chromosome Y as well as additional gains of chromosomes 3q, 12, 16, and 20 [2-4]. PRCC is morphologically characterized by a predominant papillary or tubopapillary architecture with tumor cells lining fibrovascular cores. Delahunt and Eble [5] further subdivided PRCC into 2 morphological subtypes, type 1 and 2, for its proposed prognostic implications. Type 1 PRCC is characterized by papillae lined by small cells with scant pale to basophilic cytoplasm arranged in a single layer, often with abundant foamy macrophages. Type 2 PRCC is composed of tumor cells often of high Fuhrman nuclear grade (FNG) with eosinophilic cytoplasm and pseudostratification of nuclei on papillary cores. Studies comparing these 2 types of PRCC have suggested that type 2 PRCC usually present with higher stage and are associated with poor prognosis [6,7]. The morphologic subdivision was further supported by differences at the genetic level [4,8]. Type 1 PRCC demonstrates more frequent gain of chromosomes 7 and 17 and loss of Y, but the chromosomal aberrations of type 2 PRCC were more heterogeneous than those of type 1 PRCC. Based on these observations, the 2004 World Health Organization classification now separates PRCC into 2 morphologic subtypes, type 1 and type 2 [9].

Although most PRCCs can be classified into the 2 types described, this classification remains difficult to adopt in a subset of papillary tumors, distinct from type 1 and type 2 PRCC, because of overlapping morphology and tumor biology. The classification of tumors demonstrating oncocytic (abundant eosinophilic) cytoplasm but nonoverlapping low-grade nuclei remains uncertain [7,8,10,11]. Many of these tumors could potentially be misclassified as an aggressive type 2 PRCC because of the presence of oncocytic cells. We herein describe and expand on the clinicopathologic, immunohistochemical, and cytogenetic features of a series of 7 morphologically distinct PRCCs that were difficult to classify into 2 specific proposed types, and discuss their biologic significance as well as their relationship with respect to the current classification system.

2. Materials and methods

2.1. Case selection, clinical, morphological, and immunohistochemical analysis

The files of the Department of Pathology, University of Michigan, were searched for all cases of PRCC diagnosed between January 1997 and June 2006 after resection. All hematoxylin-eosin (H & E)–stained sections were reviewed (R.B.S., L.P.K., and K.W.). All PRCCs were assigned a nuclear grade using criteria described by Fuhrman et al [12], whereas the subtype of PRCC was determined by using the criteria proposed by Delahunt and Eble [5] A total of 99 cases were evaluated, of which 65 were classified as type 1, 23 as type 2, and 4 as mixed PRCC (3 composed of type 1 PRCC admixed with oncocytic nonoverlapping low–nuclear grade cells as well as 1 case composed of a mixture of both type 1 and type 2 PRCC). Seven tumors composed exclusively of cells with oncocytic cytoplasm and nonoverlapping low-grade nuclei, which could not be definitively classified as type 1 or type 2 PRCC, were included in the current study and further analyzed.

The demographic data (age, sex) and follow-up information (presence of recurrence, metastasis, or death) were obtained from available clinical charts. All 7 tumors were staged according to the TNM staging system. Multiple pathologic parameters including tumor size, FNG, presence of foamy macrophages, necrosis, psammoma bodies, focality, and laterality were recorded for the study cases.

Immunohistochemical staining for RCC, CD10, CK 7, and α-methylacyl-coenzyme A racemase (AMACR) was performed in all cases. Representative formalin-fixed, paraffin-embedded tissue blocks were selected for immunohistochemical staining, which was performed using an avidin-biotin-peroxidase complex technique. Table 1 lists the antigen retrieval methods, dilutions, and manufacturer's information for all the antibodies. A Ventana Basic DAB Detection Kit (Ventana Medical Systems, Tucson, AZ) was used according to the manufacturer's specifications for CK 7, RCC, CD10, and P504S (AMACR); staining was performed on the Benchmark XT Ventana autostainer. Appropriate controls were tested simultaneously. Two authors (L.P.K. and R.B.S.) evaluated the immunohistochemically stained slides, which were interpreted as positive when greater than 5% of tumor cells demonstrated strong reactivity with antibody. Staining was considered diffuse when greater than 50% of tumor demonstrated reactivity, and focal when 5% to 50% cells showed reactivity.

2.2. Fluorescence in situ hybridization preparation

Fluorescence in situ hybridization (FISH) analysis was done as previously described [13-16]. Five-micrometer-thick

Table 1 Immunohistochemical antibodies used

Antibody	Type	Antigen retrieval	Dilution	Manufacturer
CK7	Mouse Monoclonal	Protease 2	1:50	Dako, Carpentina, CA
P504S (AMACR)	Rabbit Monoclonal	Citrate buffer	1:40	Zeta, Sierra Madre, CA
RCC Ag	Mouse Monoclonal	Protease 1	Predilute	Ventana, Tucson, AZ
CD 10	Mouse Monoclonal	Citrate buffer	Predilute	Ventana