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Original Article

Immunohistochemical panel for differentiating renal cell carcinoma with clear and papillary features

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ABSTRACT

Objectives: Renal cell carcinoma (RCC) in which clear cells with papillary architecture are present is a difficult diagnostic challenge. Clear cell RCC, rarely has papillary architecture. Papillary RCC rarely contains clear cells. However, two recently described types; clear cell papillary and Xp11 translocation RCC characteristically feature both papillary and clear cells. Accurate diagnosis has both prognostic and therapeutic implications. This study aims to highlight the helpful features of each of these entities to enable reproducible classification.

Methods: Sixty RCC cases with clear cells and papillary architecture were selected and classified according to The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia and graded according to The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma then stained for CK7, carbonic anhydrase IX (CA IX), α-methylacyl-CoA-racemase (AMACR) and TFE-3.

Results: The characteristic immunoprofile of Clear RCC is CK7−, AMACR−, CA IX+ and TFE3−, papillary RCC is CK7+, AMACR+, CAIX− and TFE3−, while for clear cell papillary RCC it is CK7+, AMACR−, CAIX+ and TFE3− and lastly Xp11 translocation RCC is CK7−, AMACR+, CAIX− and TFE3+.

Conclusions: Staining for CA IX, CK7, AMACR and TFE3 comprises a concise panel for distinguishing RCC with papillary and clear pattern.

1. Introduction

Renal epithelial tumors are renal neoplasms arising from renal tubules and can be classified into many major categories based on morphology [1]. Different tumor type appears to have different outcome. With increased understanding of pathogenesis of each type of tumors, new target therapy may be developed [2].

Primary renal cell carcinomas (RCCs) with both papillary architecture and cells with clear cytoplasm may be a difficult diagnostic challenge. The most common RCC, clear renal cell carcinoma, CRCC, which represent about 75% of the cases, may sometimes have papillary architecture. The second most common RCC, papillary renal cell carcinoma, PRCC which represent about 15%, may also contains clear cells [3]. However, two recently described but less-common RCCs, clear cell papillary renal cell carcinoma, CPRCC and Xp11 translocation RCC, characteristically feature both papillary architecture and cells with clear cytoplasm. Accurate diagnosis of these distinct entities has prognostic and therapeutic implications [4]. Immunohistochemical markers may be needed to establish the correct diagnosis [5].

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CPRCC is a recently recognized renal neoplasm, composed of an admixture of cystic, glandular, and papillary components, all lined by cells with clear cytoplasm, usually of low nuclear grade. The nuclei are characteristically located away from the basement membrane to show a "piano-key-like" pattern [3]. The outcome data are limited; however, the available data suggest that this type of tumor usually have a good prognosis. Originally they were discovered in a background of end-stage renal disease and acquired cystic kidney disease [6].

Xp11 translocation RCC was initially described in children and young adults. Recently, the term "MiTF/TFE family translocation-associated carcinoma" has been proposed for tumors that have translocations involving TFE3. TFE3 is transcription factor that belong to the same family of transcription factors that will overexpress nuclear TFE3. These immunohistochemical findings are important given the occurrence of these tumors in the adult population, as they morphologically overlap with CCRCC and PRCC. In the literature, these tumors do not appear to respond to immunotherapy [7]. Outcome data of this entity are still premature and good long-term follow-up data are necessary. Published outcome series in adults show a poor prognosis [4].

The treatment paradigm for renal tumors are changing, and these changes are in part driven by tumor classification. Traditionally, RCC has been considered a surgical disease. In some cases, surgery with its associated complications and negative impact on long-term renal function may be very harmful, so follow up after chemo radiotherapy may be used in low grade small tumors [8].

Cytokeratins are a family of intermediate filaments that characterize epithelial differentiation, There have been conflicting results on the expression of CK7 in renal epithelial tumors in the literature as some authors recognized its role in the differentiation of "non-clear cell" RCC from CRCC [9].

The most useful positive immunohistochemical stain in supporting a diagnosis of PRCC is α-methylacyl-coenzyme A racemase (AMACR). It is now recognized that AMACR can show positivity in tumors from many different organs and in several different types of renal tumors. But AMACR staining has conflicting results in CPRCC as it is often negative [10] but in other studies it is focally or, rarely, diffusely positive [6].

Carbonic anhydrase IX (CA IX) protein is thought to play a role in the regulation of cell proliferation and may be involved in oncogenesis and tumor progression. Previous immunobiochemical studies revealed that CA IX expression may be a useful diagnostic biomarker in RCC subclassification. Clinical tumor targeting studies with a monoclonal antibody to CA IX have shown that CA IX shows promise as a marker for selecting patients with advanced disease who would benefit from certain specific systemic agents, specifically interleukin-2 (IL-2) [7,11].

This work aims to highlight the helpful cytomorphologic and immunohistochemical features of each of these entities to enable reproducible classification. We examined the expression of 4 markers in a series of the 4 major renal cell tumors with clear and papillary architecture. In this study, we evaluated the expression of carbonic anhydrase IX (CA IX), α-methylacyl-CoA-racemase (AMACR), CK7 and TFE-3 for differential diagnosis and subclassification.

2. Materials and methods

2.1. Case selection and histopathological study

A retrospective study was performed on RCC cases selected from January 1, 2010 to April 30, 2014. A total of 250 cases of RCC were removed by nephrectomy either partial or radical and brought to the Department of Pathology, University of Tanta. Representative tissue sections from the surgical specimens were fixed in 10% buffered formalin and embedded in paraffin. For routine microscopy, 4 μ-thick sections were stained with Hematoxylin and Eosin (H&E). The clinical sheets for all cases were reviewed. The cases were classified according to The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia [12]. Tumors that fulfill the morphological criteria of clear and papillary renal cell neoplasms were selected. They were 60 cases. Only the selected cases were assessed for size, laterality, multifocality, presence of associated end-stage renal disease (ESRD). Then they were assessed histologically for the presence of branched tubular structures, subnuclear vacuoles, acini, thin walled sinusoid-like vessels, 'secretory' cells with nuclei aligned at the apical end of the cells, cystic components, character of the stromal compartment, presence of tumor pseudocapsule, and calcification. The selected carcinomas were later reevaluated for morphologic characteristics of those tumors that qualify them in either one of the following categories: CRCC, PRCC, CCPRCC or Xp11 translocation RCC. Specifically, the criteria used for classification of a tumor as a CCPRCC included the following: (1) diffuse cytoplasmic clarity; (2) papillary, tubular or cystic architecture; and (3) characteristic linear arrangement of the nuclei away from the basement membrane [10]. Xp11 translocation RCC cases were confirmed by TFE3 immunostaining positivity. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma grading system was applied to assess the nucleolar grades [13]. The tumors were staged according to the 2010 UICC/AJCC consensus guidelines [14].

2.2. Immunohistochemical study and evaluation

Immunohistochemical staining was performed using the following antibodies: CK7 (OV-TL 12/30, 1:100, DAKO, Glostrup, Denmark), CA IX (dilution 1:200, mouse monoclonal, Leica), AMACR (13H4, 1:100; DAKO, Glostrup, Denmark) and TFE3 (1:1500, Santa Cruz Biotechnology Inv., Santa Cruz, CA, USA).

Evaluation of the immunohistochemical staining was performed by light microscopy using a 10× objective lens with the selective use of a 20–40× objective lens for confirmation. The interpretation of immunoreactivity was performed in a semiquantitative manner by analyzing the extent of the staining positivity of the tumor cells. Immunostaining of greater than 10% of tumor cells was required for scoring as a positive case. The interpretation score was as follows: 0 or negative ≤10% tumor cell