Annals of Diagnostic Pathology 27 (2017) 48–56

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Warthin-like papillary renal cell carcinoma: Clinicopathologic, morphologic, immunohistochemical and molecular genetic analysis of 11 cases☆

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ARTICLE INFO

Keywords:
Kidney
Oncocytic papillary renal cell carcinoma
Warthin's tumor
Warthin-like
Lymphoid stroma
Immunohistochemistry
Chromosomal aberration pattern

ABSTRACT

Oncocytic papillary renal cell carcinoma (PRCC) is a distinct subtype of PRCC, listed as a possible new variant of PRCC in the 2016 WHO classification. It is composed of papillae aligned by large single-layered eosinophilic cells showing linearly arranged oncocytoma-like nuclei.

We analyzed clinicopathologic, morphologic, immunohistochemical and molecular-genetic characteristics of 11 oncocytic PRCCs with prominent tumor lymphocytic infiltrate, morphologically resembling Warthin's tumor. The patients were predominantly males (8/11, 73%), with an average age of 59 years (range 14–76), and a mean tumor size of 7 cm (range 1–22 cm). Tumors had the features of oncocytic PRCCs with focal pseudostratification in 8/11 cases and showed dense stromal inflammatory infiltration in all cases. Papillary growth pattern was predominant, comprising more than 60% of tumor volume. Tubular and solid components were present in 5 and 3 cases, respectively. Uniform immunohistochemical positivity was found for AMACR, PAX-8, MIA, vimentin, and OSCAR. Tumors were mostly negative for carboanhydrase 9, CD117, CK20, and TTF-1. Immunohistochemical stains for DNA mismatch repair proteins MLH1 and PMS2 were retained in all cases, while MSH2 and MSH6 were negative in 1 case. Tumor infiltrating lymphocytes (TILs) consisted of both B and T cells. Chromosomal copy number variation analysis showed great variability in 5 cases, ranging from a loss of one single chromosome to complex genome rearrangements. Only one case showed gains of chromosomes 7 and 17, among other aberrations. In 4 cases no numerical imbalance was found. Follow up data was available for 9 patients (median 47.6 months, range 1–132). In 6 patients no lethal progression was noted, while 3 died of disease.

In conclusion, Warthin-like PRCC is morphologically very close to oncocytic PRCC, from which it differs by the presence of dense lymphoid stroma. Chromosomal numerical aberration pattern of these tumors is variable;

☆ The study was supported by the Charles University Research Fund (project number P36) and by the grant of Ministry of Health of the Czech Republic - Conceptual Development of Research Organization (Faculty Hospital in Pilsen – FN Pl, 00669806).

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http://dx.doi.org/10.1016/j.anndiagpath.2017.01.005

only one case showed gains of chromosomes 7 and 17. Warthin-like PRCC is a potentially aggressive tumor since a lethal outcome was recorded in 3/9 cases.

1. Introduction

Renal cell carcinoma (RCC) is a highly heterogeneous group of tumors, consisting of at least 14 subtypes recognized in the latest WHO classification, and several additional tentatively distinct variants [1-3]. The subgroup of papillary renal cell carcinoma (PRCC) is further divided into type 1 and 2. Recently, a number of studies have described a small series of morphologically distinctive PRCCs, such as oncocytic, solid, biphasic squamoid alveolar, "mucin"-secreting, or clear cell types, not belonging to any of the two main types [4-9]. These tumors may be associated with foci of type 2-resembling areas and are thus often designated as such, which may contribute to the molecular-genetic heterogeneity of PRCC type 2 tumors [10]. Some of these tumors are even designated as unclassified [11]. Even though the tumor stage remains the best determinant for the survival of patients after nephron sparing surgery within the PRCC group [12], the histological variants of PRCC are important to recognize. This is due to the fact that the papillary morphology is also seen in other RCC subtypes, and thus the treatment and outcome may significantly differ in patients with variant tumors as compared with those who have two classical forms of PRCC.

Oncocytic PRCC [4,13,14] is mentioned in the 2016 WHO classification as a tumor that has a papillary architecture, and is composed of large cells with finely granular eosinophilic cytoplasm, mostly single-layered, and linearly aligned oncocytoma-like nuclei [3]. Such morphology, with addition of a prominent lymphocytic infiltrate in stroma, may commonly be seen in the papillary cystadenoma lymphomatosum (Warthin's tumor) of the salivary glands. To the best of our knowledge, carcinomas resembling benign Warthin's tumor have been described in salivary glands [15] and thyroid [16], but not in the kidney. Tumor infiltrating lymphocytes (TILs) may have prognostic value and that with the advent of novel immune mediated therapies [17], tumors with TILs could be considered for potential immunotherapy in the future. Of note, lymphoid infiltrates are frequently found in tumors of other organs associated with Lynch syndrome. However, a potential link between this hereditary syndrome and lymphoid infiltrates in some renal tumors has not been explored.

The aim of this study was to analyze the clinicopathologic, morphologic, immunohistochemical and molecular-genetic characteristics of 11 oncocytic PRCCs with prominent lymphoid stroma (Warthin-like papillary renal cell carcinoma - WPRCC), morphologically reminiscent of Warthin's tumor.

2. Materials and methods

2.1. Case selection and routine microscopy

There were 1147 in-house and consultation cases of PRCC in Plzen Tumor Registry. We searched the database for keywords "oncocytic, papillary, kidney, lymphoid stroma", and reviewed 147 tumors. We subsequently selected 11 cases with predominant oncocytic cytology and abundant intratumoral lymphocytic infiltrate. All the cases were reviewed by three pathologists (FS, MU, OH). There were 1–10 tissue blocks available for each case, and 1–2 representative blocks were selected for immunohistochemical and molecular–genetic studies. Clinical, gross and follow-up data were collected by review of the institutional medical records and by contacting the consulting pathologists.

Tissue for light microscopy was fixed in 4% formaldehyde, embedded in paraffin using routine procedures. 5 μm thin sections were cut and stained with hematoxylin and eosin. Special stain technique for evaluation of mucin was performed using mucicarmine, periodic acid - Schiff (PAS) and alcian blue at pH 2.5. We evaluated percentages of papillary, tubular, cystic, and solid architectural patterns, abundance of TIL with reference to index case, nuclear grade according to the guidelines of ISUP (International Society of Urologic Pathology), nuclear pseudostratification, single versus multiple cell layers forming papillae, presence of foamy macrophages, and microscopic necrosis.

2.2. Immunohistochemistry

Immunohistochemical study was performed using primary antibodies recognizing following antigens: racemase/AMACR (13H4, monoclonal, Dako, Glostrup, Denmark, 1:200), carbonic anhydrase IX (rhCA9, monoclonal, RD systems, Abingdon, GB, 1:100), vimentin (D9, monoclonal, NeoMarkers, Westinghouse, CA, 1:1000), OSCAR (OSCAR, monoclonal, Covance-SpinChem, San Diego, CA, 1:500), PAX-8 (polyclonal, Cell Marque, Rocklin, CA, 1:25), cytokeratin 7 (OV-TL12/30, monoclonal, Dako, 1:200), cytokeratin 20 (M7019, monoclonal, Dako, 1:100), cytokeratins (AE1-AE3, monoclonal, BioGenex, San Ramon, CA, 1:1000), CD117 (CD117, polyclonal; Dako, Glostrup, Denmark; RTU), EMA (E29, monoclonal; DakoCytomation, Carpinteria, CA; 1:1000), CD10 (56C6, monoclonal; Novocastra, Newcastle upon Tyne, UK; 1:50), TTF-1 (SPT24, monoclonal; Novocastra, 1:400), *anti*-mitochondrial antigen (MIA, monoclonal; BioGenex; 1:100), CD3 (monoclonal, LN10, Novocastra, 1:50), CD5 (monoclonal, 4C7, Novocastra, 1:50), CD20 (monoclonal, L26, DakoCytomation, RTU), MSH2 (monoclonal, G219-1129, Cell Marque, RTU), MSH6 (monoclonal, 44, Ventana, Manheim, Germany, RTU), PMS2 (monoclonal, EPR 3947, Cell Marque, RTU), MLH1 (monoclonal, G168-728, Cell Marque, RTU). The primary antibodies were visualized using the supersensitive streptavidin-biotin-peroxidase complex (BioGenex). Appropriate positive controls were employed for all assays. Immunohistochemical staining was recorded negative if no staining, or less than 5% of staining was observed; as weak (+) for staining of up to 25% of tumor cells; moderate (++) for staining 25–50% of tumor cells; and strong (+++) for staining in more than 50% of tumor cells.

2.3. DNA extraction

DNA was extracted using the QIAsymphony DSP DNA Mini Kit on automated extraction system QIAsymphony SP (QIAGEN, Hilden, Germany) according to the manufacturer's supplementary protocol for FFPE samples. Concentration and purity of isolated DNA were measured using the NanoDrop ND-1000 (NanoDrop Technologies, Inc., Wilmington, DE, USA). DNA integrity was examined by multiplex PCR amplification of five fragments of lengths ranging from 100 to 600 base pairs (bp) [18].

2.4. Low pass whole genome analysis

All samples were tested for copy number variations (CNV) in all chromosomes using low pass whole genome sequencing on Ion Torrent PGM platform using kits and software from Life Technologies (Thermo Fisher Scientific, Waltham, MA USA). The extracted DNA (100 ng) was enzymatically fragmented using a shear enzyme mix contained in Ion Xpress Plus Fragment Library Kit. Samples with DNA integrity control result of 600 bp were sheared 10 min, and samples with lower integrity were sheared 5 min. Sequencing adapters were ligated and the sequencing library was size-selected for 200 bp. Final libraries were