Annals of Diagnostic Pathology 35 (2018) 1–6

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Papillary renal cell carcinoma with cytologic and molecular genetic features overlapping with renal oncocytoma: Analysis of 10 cases

Kvetoslava Michalova[a], Petr Steiner[a], Reza Alaghehbandan[b], Kiril Trpkov[c], Petr Martinek[a], Petr Grossmann[a], Delia Perez Montiel[d], Maris Sperga[e], Lubomir Straka[f], Kristyna Prochazkova[g], Dana Cempirkova[h], Vladimir Horava[i], Stela Bulimbasic[j], Kristyna Pivovarcikova[a], Ondrej Daum[a], Ondrej Ondic[a], Pavla Rotterova[k], Michal Michal[a], Milan Hora[g], Ondrej Hes[a,*]

[a] Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Czech Republic
[b] Department of Pathology, Faculty of Medicine, University of British Columbia, Royal Columbian Hospital, Vancouver, BC, Canada
[c] Department of Pathology and Laboratory Medicine, University of Calgary, Calgary Laboratory Services, Calgary, Canada
[d] Department of Pathology, Institute Nacional de Cancerologia, Mexico City, Mexico
[e] Department of Pathology, Rigas Stradins University, Riga, Latvia
[f] Department of Pathology, Alpha Medical, Presov, Slovakia
[g] Department of Urology, Charles University, Medical Faculty and Charles University Hospital Plzen, Czech Republic
[h] Department of Pathology, Regional Hospital Jindrichuv Hradec, Czech Republic
[i] Department of Pathology, Regional Hospital Fridek Mistek, Czech Republic
[j] Department of Pathology, Clinical Hospital Center Zagreb, Zagreb, Croatia
[k] Biopticka laborator, Plzen, Czech Republic

ARTICLE INFO

Keywords:
Kidney
Papillary renal cell carcinoma
Oncocytic
Oncocytoma
High grade
FISH
Chromosomal aberration pattern

ABSTRACT

Background: We present a series of papillary renal cell carcinomas (PRCC) reminiscent of so-called "oncocytic variant of papillary renal cell carcinoma" (OPRCC), included in the 2016 WHO classification as a potential type 3 PRCC. OPRCC is a poorly understood entity, cytologically characterized by oncocytic cells with non-overlapping low grade nuclei. OPRCC is not genotypically distinct and the studies concerning this variant have shown an inconsistent genetic profile. The tumors presented herein demonstrated predominantly papillary/tubulopapillary architecture and differed from OPRCC by pseudostratification and grade 2–3 nuclei (Fuhrman/ISUP). Because there is a morphologic overlap between renal oncocytoma (RO) and PRCC in the cases included in this study, the most frequently affected chromosomes in RO and PRCC were analyzed.

Materials and methods: 147 PRCC composed of oncocytic cells were retrieved from our registry in order to select a group of morphologically uniform tumors. 10 cases with predominantly papillary, tubulopapillary or solid architectural patterns were identified. For immunohistochemical analysis, the following antibodies were used: vimentin, antimitochondrial antigene (MIA), AMACR, PAX8, CK7, CK20, AE1-3, CAM5.2, OSCAR, Cathepsin K, HMB45, SDHB, CD10, and CD117. Enumeration changes of locus 1p36, chromosomes 7, 14, 17, X, Y and rearrangement of *CCND1* were examined by FISH. For further study, only tumors showing karyotype similar to that of RO were selected. The tumors exhibiting either trisomy of chromosomes 7, 17 or gain of Y, thus abnormalities characteristic for PRCC, were excluded.

Results: There were 5 males and 5 females, with patient age ranging from 56 to 79 years (mean 66.8 years). The tumor size ranged from 2 to 10 cm (mean 5.1 cm). Follow-up was available for 8/10 patients (mean 5.2 years); one patient died of the disease, while 7 of 8 are alive and well. Immunohistochemically, all cases were reactive for AMACR, vimentin, PAX8, OSCAR, CAM5.2, and MIA. SDHB was retained in all cases. 9/10 cases were positive for CD10, 7/10 cases reacted with CK7, 4/10 with Cathepsin K, and 2/10 with AE1-3. None of the cases were positive for CD117, HMB45 and CK20. All 10 cases were analyzable by FISH and showed chromosomal abnormalities similar to that usually seen in RO (i.e. loss of 1p36 gene loci, loss of chromosome Y, rearrangement of *CCND1* and numerical changes of chromosome 14).

Conclusions: We analyzed a series of renal tumors combining the features of PRCC/OPRCC and RO, that included pseudostratification and mostly high grade oncocytic cells lining papillary/tubulopapillary structures, karyotype characterized by loss of 1p36, loss of chromosome Y, rearrangement of *CCND1* gene and numerical changes of chromosome 14. Despite the chromosomal numerical abnormalities typical of RO, we classified these tumors as

* Corresponding aurthor at: Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Plzen, Czech Republic.
E-mail address: hes@medima.cz (O. Hes).

https://doi.org/10.1016/j.anndiagpath.2018.01.010

part of the spectrum of PRCC because of their predominant papillary/tubulopapillary architecture, immunoprofile that included reactivity for AMACR, vimentin and lack of reactivity for CD117, all of which is incompatible with the diagnosis of RO. This study expands the morphological spectrum of PRCC by adding a cohort of diagnostically challenging cases, which may be potentially aggressive.

1. Introduction

Oncocytic papillary renal cell carcinoma (OPRCC) was first described in a series of 10 cases in 2005 [13], followed by a series of 12 cases published a couple months later [7]. Since then, several studies on OPRCC have been published [12,15,16,18,19,26]. These tumors characteristically show solid to papillary architecture with low grade non-stratified neoplastic cells strikingly resembling renal oncocytoma (RO). There are several aspects of these tumors which are still poorly understood. The cytogenetic results on OPRCC remain controversial in the studies published to date, as some cases show trisomy of chromosome 7 and 17, while others do not [7,12,15,18,19].

We analyzed a cohort of 10 cases selected from a group of morphologically straightforward papillary RCCs composed of oncocytic cells, which we descriptively called “papillary renal cell carcinoma with features of renal oncocytoma” (PRCCRO). PRCCRO differed from “classic” OPRCC mostly by the presence of pseudostratification and high grade nuclei in some cases. With respect to the overlapping features between PRCCRO and OPRCC, we used the same cytogenetic approach when analyzing PRCCRO as in OPRCC. Because of the lack of a comprehensive chromosomal analysis of OPRCC, we decided to evaluate the most frequently affected chromosomes in RO and papillary renal cell carcinoma (PRCC). The goal of this study was to potentially elucidate a morphologic subset of PRCC demonstrating immunohistochemical features of PRCC, but cytogenetic features of RO.

2. Materials and methods

The Pilsen tumor registry was searched using the following keywords “papillary-renal-carcinoma-oncocytic”. Of 1563 PRCCs, 147 OPRCCs met the search criteria, during the period 1993–2017. All 147 cases were reviewed by two pathologists (K.M. and O.H.) and subsequently 56 morphologically uniform cases of PRCCs with oncocytic cytoplasm were selected. DNA quality was tested in all OPRCCs and ultimately, 23 cases with good quality of DNA were selected. In order to present as consistent series as possible, we excluded the cases showing either trisomy of chromosomes 7 and 17, chromosomal abnormalities characteristically encountered in PRCC. Within this group, we selected for further analysis 10 cases of PRCC with oncocytic cells which exhibited copy number variation status similar to RO. The clinical information was extracted from the registry records and follow-up data were obtained by contacting the attending clinicians. The tissues for light microscopy was fixed in 4% formaldehyde and embedded in paraffin, using a routine procedure. 5 μm thick sections were cut from the tissue blocks and were stained with hematoxylin and eosin (H&E). One to 18 blocks were available for evaluation per case.

2.1. Immunohistochemistry

The immunohistochemical (IHC) analysis was performed using a Ventana BenchMark ULTRA (Ventana Medical System, Inc., Tucson, Arizona). The following primary antibodies were used: racemase/AMACR (13H4, monoclonal, DAKO, Glostrup, Denmark, 1:200), cytokeratin (CK) 7 (OV-TL12/30, monoclonal, DakoCytomation, Carpinteria CA, USA, 1:200), CK20 (Ks20.8, monoclonal, DAKO, Glostrup, Denmark, 1:100), AE1-3 (AE1/AE3 & PCK26, monoclonal, Ventana Medical Systems, RTU), OSCAR (OSCAR, monoclonal, Covance, Herts, UK, 1:500), (CAM5.2, monoclonal, Ventana, RTU), vimentin (V9, monoclonal, Ventana Medical Systems, RTU), PAX 8 (MRQ-50, monoclonal, CellMarque, Rocklin, CA, RTU), anti-mitochondrial antibody (113-1, monoclonal, Biogenex, San Ramon, CA, 1:500), HMB45 (HMB45, monoclonal, DAKO, Glostrup, Denmark, 1:400), CD117 (polyclonal, DAKO, Glostrup, Denmark, 1:800), CD10 (56C6, Novocastra, Burlingame, CA, 1:20), SDHB (polyclonal, Sigma Aldrich, St. Luis, MS, 1:200), Cathepsin K (3F9, monoclonal, Abcam, Cambridge, UK, 1:100). Antibodies were visualized using the enzymes alkaline phosphatase or peroxidase as detecting systems (both purchased from Ventana Medical System). Appropriate positive controls were used.

2.2. Molecular genetic analysis

2.2.1. Fluorescence in situ hybridization

The enumeration changes of locus 1p36, chromosomes 7, 14, 17, X, Y and rearrangement of *CCND1* (BCL1ba) were examined by Fluorescence In Situ Hybridisation (FISH). In brief, 4-μm-thick formalin fixed paraffin embedded section, were placed on a positively charged slide. Tissues were deparaffinized in xylene two times for 5 min and were washed twice in 96% ethanol and once in deionized water for 5 min. The slides were then heated in the 1× Target Retrieval Solution (pH 6) (DAKO, Glostrup, Denmark) for 40 min at 95 °C and were cooled for 20 min at room temperature in the same solution. The slides were washed in deionized water for 5 min and digested in protease solution with pepsin (0.5 mg/mL) (Sigma Aldrich) in 0.01 M HCl at 37 °C for 15 min. The slides were then placed into deionized water for 5 min, dehydrated in a series of ethanol solution (70%, 85% and 96% for 2 min each) and air dried. An appropriate amount of FISH probe was diluted according to manufacturer's instructions, and applied onto each

Table 1
Clinicopathologic data.

Case No	Age	Sex	Size (cm)	Follow-up	Pattern	WHO/ISUP nucleolar grade	Stage
1	69	M	10	AW 6 yr; dg of AML	Papillary, compressed papillae	2	NA
2	61	F	7	AW 6 yr	Tubulopapillary	2	NA
3	56	F	2	DOD 4 yr after surgery	Papillary	2	NA
4	65	F	3.5	AW 6 yr	Papillary	2	pT1a
5	68	F	4	AW 1.5 yr	Tubulopapillary	2	pT1a
6	58	F	5	AW 13 yr	Papillary	3	pT1b
7	79	M	9	AW 3 yr	Compressed papillae	2	pT2
8	73	M	3	AW 2 yr	Tubulopapillary	3	pT1a
9	76	M	NA	NA	Papillary	2	NA
10	63	M	3.5	NA	Papillary	3	pT1b

AW alive and well; DOD death of disease; NA not available; yr years, year, dg diagnosis, AML acute myeloid leukemia.