Annals of Diagnostic Pathology 19 (2015) 226–231

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Mucinous spindle and tubular renal cell carcinoma: analysis of chromosomal aberration pattern of low-grade, high-grade, and overlapping morphologic variant with papillary renal cell carcinoma☆,☆☆

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ARTICLE INFO

Keywords:
Kidney
Mucinous spindle and tubular cell carcinoma
Chromosomal aberration
aCGH

ABSTRACT

The chromosomal numerical aberration pattern in mucinous tubular and spindle renal cell carcinoma (MTSRCC) is referred to as variable with frequent gains and losses. The objectives of this study are to map the spectrum of chromosomal aberrations (extent and location) in a large cohort of the cases and relate these findings to the morphologic variants of MTSRCC. Fifty-four MTSRCCs with uniform morphologic pattern were selected (of 133 MTSRCCs available in our registry) and divided into 3 groups: classic low-grade MTSRCC (Fuhrman nucleolar International Society of Urological Pathology grade 2), high-grade MTSRCC (grade 3), and overlapping MTSRCC with papillary renal cell carcinoma (RCC) morphology. Array comparative genomic hybridization analysis was applied to 16 cases in which DNA was well preserved. Four analyzable classic low-grade MTSRCCs showed multiple losses affecting chromosomes 1, 4, 8, 9, 14, 15, and 22. No chromosomal gains were found. Four analyzable cases of MTSRCC showing overlapping morphology with PRCC displayed a more variable pattern including normal chromosomal status; losses of chromosomes 1, 6, 8, 9, 14, 15, and 22; and gains of 3, 7, 16, and 17. The group of 4 high-grade MTSRCCs exhibited a more uniform chromosomal aberration pattern with losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22 and without any gains detected. (1) MTSRCC, both low-grade and high-grade, shows chromosomal losses (including 1, 4, 6, 8, 9, 13, 14, 15, and 22) in all analyzable cases; this seems to be the most frequent chromosomal numerical aberration in this type of RCC. (2) Cases with overlapping morphologic features (MTSRCC and PRCC) showed a more variable pattern with multiple losses and gains, including gains of chromosomes 7 and 17 (2 cases). This result is in line with previously published morphologic and immunohistochemical studies that describe the broad morphologic spectrum of MTSRCC, with changes resembling papillary RCC. (3) The diagnosis of MTSRCC in tumors with overlapping morphology (MTSRCC and PRCC) showing gains of both chromosomes 7 and 17 remains questionable. Based on our findings, we recommend that such tumors should not be classified as MTSRCC but rather as PRCC.

1. Introduction

Mucinous spindle and tubular renal cell carcinoma (MTSRCC) is a relatively rare but distinctive subtype of renal cell carcinoma (RCC). The tumor is characterized by proliferation of cuboidal and spindle cells of low nuclear cytology which are arranged in cords and tubules,

☆ The study was supported by the Charles University Research Fund (Project No. P36) and by the project CZ.1.05/2.1.00/03.0076 from European Regional Development Fund.
☆☆ Disclosure of conflict of interest: All authors declare no conflict of interest.
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http://dx.doi.org/10.1016/j.anndiagpath.2015.04.004
1092-9134/

typically within a myxoid background [1]. Some cases seem to show certain morphologic similarities to papillary RCC (PRCC) [2–4]. The chromosomal numerical aberration pattern in MTSRCC is usually referred to as variable with frequent gains and losses. However, few studies have been published, thus far, making it difficult to establish a precise description of the genetic profile [2, 5–10]. The objectives of this study were to map the spectrum of chromosomal aberrations (extent and location) in a large cohort of cases and to relate these findings to the morphologic variants of MTSRCC; special emphasis was placed on the differential diagnosis between PRCC and MTSRCC.

2. Materials and methods

Fifty-four cases of MTSRCC with uniform morphologic pattern were selected of 133 MTSRCCs available in the Pilzen Tumor Registry. Pathologic examination of routine hematoxylin-eosin–stained sections was performed on each case by at least 2 pathologists (K.P. and O.H.). Cases were reevaluated and further histologic patterns were described. For each case, 1 to 4 tissue blocks were available for further study. All cases were divided into 3 groups: classic low-grade (CLG; Fuhrman International Society of Urological Pathology [ISUP] nucleolar grade 2), high-grade (HG; Fuhrman nucleolar ISUP grade 3), and cases with morphologic features overlapping with PRCC morphology (OPM). Array comparative genomic hybridization (aCGH) analysis was applied to 16 cases with well-preserved DNA.

2.1. Molecular study

Tumor areas of the formalin-fixed, paraffin-embedded samples were determined using hematoxylin-eosin–stained slides and macrodissected. The procedures of DNA purification, integrity control, array CGH, and fluorescent in situ hybridization (FISH) analysis were described previously [11]. Required integrity of DNA was 400 base pairs. Array CGH analysis was performed using CytoChip Focus Constitutional (Illumina, San Diego, California). Several chromosomal aberrations from each group were confirmed by FISH analysis.

3. Results

The clinical and pathological features of the cases are summarized in Table 1. All 16 cases were divided into 3 groups: CLG mucinous spindle cell and tubular RCC (Fuhrman ISUP nucleolar grade 2), OPM, and HG (Fuhrman ISUP nucleolar grade 3) MTSRCC.

The group of 5 analyzable CLG MTSRCCs was composed of 4 men and 1 woman, with ages ranging from 51 to 60 years (mean, 56.4 years; median, 57 years). Tumor size ranged from 3.2 to 12.5 cm (mean, 6.44 cm; median, 6 cm). Follow-up information was available for 2 patients, both of which were alive and well at last clinical examination. Histologically, the tumors showed a predominantly tubular architectural pattern composed of tubules and cords lined by cuboidal cells with pale to eosinophilic cytoplasm admixed with spindle cell proliferation foci, all set in a loose fibrotic and, in 2 of 5 cases, myxoid stroma. Tumor cells of both cuboidal and spindle cell populations were generally bland in appearance. The nuclei were uniform in size, with rounded contours and occasional distinct nucleoli. Mitoses were infrequently observed and abnormal mitotic figures were not identified. None of the tumors displayed necrosis (Fig. 1A + B).

The group of 6 OPM MTSRCCs included 3 male and 3 female patients, with ages ranging from 47 to 71 years (mean, 57.83 years; median, 56.5 years). The tumor size ranged from 1.2 to 11 cm (mean, 4.62 cm; median, 3.5 cm). Follow-up was available for 2 patients with no signs of progression at the last clinical examination in either case. Histologically, the tumors showed areas compatible with the diagnosis of MTSRCC, composed of elongated tubules and streams (Fig. 2A + B). There was both a spindle cell component and a cuboidal cell component within the myxoid stroma. Neoplastic cells were generally of low to intermediate grade; however, cells with larger nucleoli, consistent with grade 3 (Fuhrman nucleolar), were also observed. In some areas, structures strongly resembling PRCC with predominantly papillary architecture, rare foamy macrophages, and occasional psammoma bodies were also seen. Myxoid changes in the interstitium were present in 2 of 6 cases.

Table 1
Basic clinicopathologic data

Case number	Age (years)	Sex	Size (cm)	Follow up (years)	Myxoid changes in interstitium
1	59	M	6	LE	Present
2	51	M	4.5	6 AW	Present
3	55	M	12.5	LE	Absent
4	60	F	6	LE	Absent
5	57	M	3.2	6 AW*	Absent
6	59	F	11	1 AW	Present focally
7	51	F	6.5	LE	Present
8	54	F	2	5 AW	Absent
9+	65	M	4	1 AW	Absent
10+	71	M	1.2	LE	Absent
11	47	M	3	5 AW	Absent
12	60	F	5.5	5 AW	Present
13	40	F	3.4	6 AW	Present
14	42	M	1.3	2 AW	Absent
15	57	M	??	5 AW	Absent
16	83	M	5.6	9 AW	Absent

Yellow represents classic MSTRCC; green, overlapping morphology between MSTRCC and PRCC; blue, HG MSTRCC; +, tumors were reevaluated as PRCC.
Abbreviations: AW, alive and well; LE, lost of evidence.
[a]Patient subsequently underwent kidney transplantation.

The third group included 5 cases of MTSRCC with HG morphology. Patient age (3 men and 2 women) ranged from 40 to 83 years (mean, 56.4 years; median, 57 years), and tumor size ranged from 1.3 to 5.6 cm (mean, 3.95 cm; median, 4.45 cm). Follow-up was available for all 5 patients, all of whom were alive with no evidence of disease. Tumors were morphologically characterized by the intermixing of spindle and cuboidal cells within predominantly loose, fibrous stroma. Myxoid stromal changes were present in 2 of 5 cases. The architecture was similar to that of the low-grade group (Fig. 3). Nevertheless, in some areas, neoplastic cells showed HG nuclear features, that is, nuclear pleomorphism and enlarged nucleoli (Fuhrman nucleolar grade 3).

3.1. Molecular study

Results of the aCGH are summarized in Table 2. The aCGH analysis was successful for 4 of 5 CLG MTSRCCs. In these 4 cases, aCGH data indicated multiple losses, mostly involving chromosomes 1, 4, 8, 9, 14, 15, and 22, with no detected gains in any of the studied tumors (Fig. 4A).

From the group of 6 cases designated as OPM MTSRCCs, 4 were analyzable. Array comparative genomic hybridization analysis revealed a more variable pattern in this group: 1 case showed a normal chromosomal status; 1 case presented with losses of chromosomes 1, 4, 6, 8, 9, 10, 14, 15, and 22; and in 2 cases, multiple gains (chromosomes 3, 7, 16, and 17) were detected (Fig. 4B).

Array comparative genomic hybridization results from 4 analyzable cases of HG MTSRCC demonstrated a more uniform chromosomal aberration pattern with losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22. There were no areas of gain detected in any of these cases (Fig. 4C).