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# Mucinous tubular and spindle cell carcinoma with Fuhrman nuclear grade 3: A histological, immunohistochemical, ultrastructural and FISH study

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Summary. Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney generally shows low nuclear grade. MTSCC with high nuclear grade is relatively rare. In this article, we report two cases of MTSCC with Fuhrman grade 3. One case occurred in a 57-year-old Japanese female and the second case in a 49-year-old Caucasian female. Histologically, the tumors were composed of neoplastic cells with cuboidal or columnar and spindle morphology, and Fuhrman nuclear grade 3. The myxoid stroma was also observed. This stroma was positive for Alcian blue stain. Immunohistochemically, neoplastic cells of both cases were positive for AMACR, but negative for CD10 and RCC Ma. Ultrastructurally, tumorous cells of one case contained numerous mitochondria. In FISH analysis, many neoplastic cells of both cases demonstrated monosomy of chromosomes 15 and 22 and disomy of chromosomes 7 and 17. One of the two patients died of respiratory failure due to pleuritis carcinomatosa 48 months postoperatively. Finally, the pathologist should recognize that high grade MTSCC exists despite its rare frequency. FISH analysis may be helpful in establishing the diagnosis of this entity. Furthermore, we present the first report of a patient with MTSCC dying of distant metastasis.

**Key words:** Kidney, High grade, Mucinous tubular and spindle cell carcinoma, Renal cell carcinoma, FISH, Chromosome 15, Chromosome 22

## Introduction

Mucinous tubular and spindle cell carcinoma (MTSCC) has newly been added into the recent WHO classification published in 2004 (Srigley, 2004). The majority of previously reported cases have been considered as low nuclear grade renal cell carcinoma (RCC) (He et al., 1998; Otani et al., 2001; Parawani et al., 2001; Hes et al., 2002; Rakozy et al., 2002; Weber et al., 2003; Aubert et al., 2004; Kuroda et al., 2004, 2005; Fine et al., 2006; Paner et al., 2006). Recently, six cases of MTSCC with high nuclear grade (more than Fuhrman grade 3) features have also been reported (Shen et al., 2006). However, the genetic features of high nuclear grade MTSCC remain unknown. In this article, we report two cases of high nuclear grade MTSCC, with the focus on morphological and genetic aspects.

## Materials and methods

#### Archive materials

One case originated in the Department of Pathology, Maizuru Kyosai Hospital, Kyoto, Japan, and the other case was retrieved from consultation files of one of the authors (OH). One case is a 57-year-old Japanese female. She presented with macroscopic hematuria. Ultrasound sonography, CT scan and MRI examinations disclosed a solid tumor with cystic change. Radical nephrectomy was performed on the basis of the diagnosis of renal cancer. The tumor stage corresponded to Stage I (T1bN0M0). During her follow-up, pleuritis carcinomatosa was detected 28 months after the operation. She died of respiratory failure 48 months postoperatively, but an autopsy was not performed. The

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other case is a 49-year-old Caucasian female. She presented with acute renal colic and macroscopic hematuria. Ultrasound sonography disclosed the renal tumor. Radical nephrectomy was performed. The tumor stage corresponded to Stage II (T2N0M0). She was alive and well nine months after the operation.

## Histological examination, histochemistry and immunohistochemistry

Renal tumor tissues obtained from nephrectomy were fixed in 10% formalin and embedded in paraffin. Three-micron thick sections were stained with hematoxylin-eosin, periodic acid-Schiff (PAS) and Alcian blue stain. In the present study, a 4-tiered nuclear grading system was used (Fuhrman et al., 1982). Additionally, immunohistochemical staining was performed using a Histofine Simple stain-PO (multi) kit (Nichirei, Tokyo, Japan). Antibodies against AMACR (P504S)(13H4, 1:100, DAKO, Glostrup, Denmark), CD10 (56C6, prediluted, Novocastra Laboratories, Newcastle, UK), RCC Ma (66.4.C2, 1:100, Novocastra Laboratories), Ki-67 (MIB-1, 1:100, DAKO) and p53 (DO-7, 1:50, Novocastra Laboratories) were employed in the present study. For Ki-67 and p53, positive cells in nuclei of neoplastic cells were counted in different three cluster fields of one hundred cells and the range and average of percentages of positive cells were evaluated.

#### Electron microscopy

Small sections retrieved from paraffin-embedded tissues were deparaffinized and fixed with 2.5% glutaraldehyde and postfixed with 0.8% osmium tetroxide in phosphate buffer for one hour at room temperature. After dehydration in graded ethanol, they

were embedded in Epon 812. The ultrathin sections were cut with a Reichert microtome (Reichert Jung, Heidelberg, Germany), stained with uranyl acetate and lead citrate, and examined with an electron microscope (JEM-100S; JEOL Ltd, Tokyo, Japan).

### Fluorescence in situ hybridization (FISH)

FISH was performed using centromeric probe (D15Z1) (Vysis Inc, Downers Grove, IL, USA) and LIS Digeorge/VCFS region probe (TUPLE 1, 22q11.2, red color and ARSA, 22q13.3, green color) (Vysis Inc, Downers Grove, IL, USA) for chromosomes 15 and 22, respectively. The FISH for chromosomes 15 and 22 was performed in Cytogenetic Testing Group, Molecular Genetic Testing Department, Clinical Testing Center, Mitsubishi Chemical Medience Corporation, Kyoto, Japan. For the results of chromosomes 15 and 22, more than 400 neoplastic cells were evaluated and percentages of one, two and three signals per cell were calculated. Additionally, two centromeric probes (Vysis Inc, Downers Grove, IL, USA) were used for the analysis of chromosomes 7 and 17. FISH for chromosomes 7 and 17 was performed in Charles University Hospital, Plzen, as previously described (Hes et al., 2006). Signals from about 200 neoplastic cells were counted and the numbers one, two and three signals per cell were expressed as percentages.

#### Results

## Macroscopical findings

In case no.1, the tumor measuring 5cm in maximum diameter was observed in the lower portion of the right kidney. The cut surface of the tumor showed a whitish

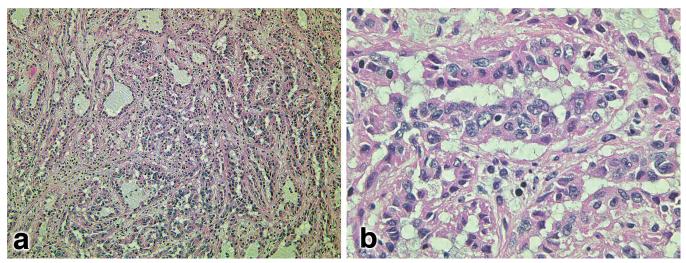


Fig. 1. Histological findings of case no. 1. a. Tumorous areas of both low (left side) and high nuclear grades (right side) are observed. b. The proliferation of neoplastic cells with enlarged nuclei and prominent nucleoli is seen in high nuclear grade area. a, x 40; b, x 400

aspect in color and prominent cystic change. Neither hemorrhage nor necrosis was seen in the cut surface. In case no.2, a tumor measuring 7.3cm in its largest dimension was observed in the right kidney. The cut surface of the tumor disclosed a solid consistency with focal necrosis.

## Microscopical findings

In case no.1, tubular neoplastic cells predominantly proliferated on the myxoid background. Elongated tubules were cystically dilated and intermingled with spindle cells. These neoplastic cells had the area of Fuhrman nuclear grades 2 (Tumorous cells have finely "open" chromatin but inconspicuous nucleoli) and 3 (Tumorous cells have unequivocally recognizable nucleoli), and a transitional zone between neoplastic cells of two nuclear grades was observed (Fig. 1a). In total, neoplastic cells with Fuhrman nuclear grade 3 predominanted (Fig. 1b). Tumorous cells with clear and oncocytic change of the cytoplasm were also occasionally seen. Necrosis with cholesterol deposition, hemosiderin-laden macrophages and multinucleated giant cells were also observed.

In case no.2, neoplastic cells with tubular and papillary configurations proliferated. Spindle cells and

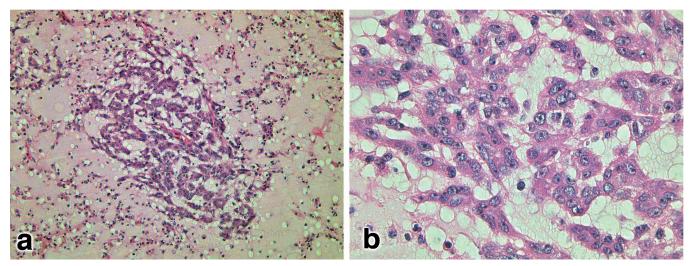


Fig. 2. Histological findings of case no. a. The mixed proliferation of spindle cells and interconnecting tubules is observed on the background of myxoid stroma. b. Tumorous cells with enlarged nuclei and prominent nucleoli are seen in high nuclear grade area. a, x 40; b, x 400

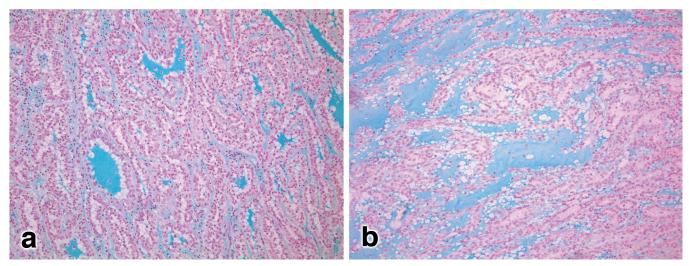


Fig. 3. Histochemical findings. The myxoid stroma is positive for Alcian blue stain. a. Case no. 1. b. Case no. 2. x 40

interconnecting tubules were also mixed (Fig. 2a). The tumor stroma demonstrated a myxoid appearance. The nuclear grade of tumorous cells corresponded to Fuhrman grade 3 (Fig. 2b) and typical Fuhrman grade 2 areas were also focally observed.

#### Histochemical findings

The tumorous stroma of both cases was positive for Alcian blue stain (Fig. 3a,b).

#### Immunohistochemical findings

Immunohistochemical results are summarized in Table 1. In both cases, neoplastic cells were diffusely positive for AMACR in Fuhrman nuclear grade 2 areas and focally positive for AMACR in Fuhrman nuclear grade 3 areas (Fig. 4a,b). However, both tumors were completely negative for CD10 and RCC Ma. In both tumors, the positive rate for Ki-67 was higher in Fuhrman nuclear grade 3 areas than in Fuhrman nuclear grade 2 areas. The p53 expression in nuclei of neoplastic cells was observed only in Fuhrman nuclear grade 3

Table 1. Immunohistochemical results of two cases.

	AMACR	CD10	RCC Ma	Ki-67	p53
Case no.1 low grade area	d+	-	-	1-2%	0%
high grade area	f+	-	-	5-10%	2%
Case no. 2					
low grade area	d+	-	-	1-2%	0%
high grade area	f+	-	-	3-10%	2%

d, diffuse; f, focal; +, positive; -, negative.

areas.

#### Ultrastructural findings

Tumorous cells with tubular and spindle cell morphology contained abundant mitochondria in case no.1 (Fig. 5).

#### FISH findings

The results of FISH findings of chromosomes 15 and 22 are summarized in Table 2. In case no.1, one, two and three signals of chromosome 15 in neoplastic cells comprised 86.3%, 13.7% and 0%, respectively. Additionally, one, two and three signals of chromosome 22 occupied 87.7%, 12.3% and 0%, respectively. In case no.2, one, two and three signals of chromosome 15 in tumorous cells accounted for 90.1%, 9.9% and 0%, respectively (Fig. 6a). Furthermore, one, two, three signals of chromosome 22 comprised 90.8%, 9.2% and 0%, respectively (Fig. 6b). We finally considered that

Table 2. FISH results of chromosomes 15, 22, 7 and 17.

	15	22	7	17
Case no.1				
Total cells	431	511	214	206
one signal	372 (86.3%)	448 (87.7%)	18 (8.4%)	26 (12.6%)
two signals	59 (13.7%)	63 (12.3%)	180 (84.1%)	170 (82.5%)
three signals	0 (0%)	0 (0%)	16 (7.5%)	10 (4.9%)
Case no.2				
Total cells	527	568	210	199
one signal	475 (90.1%)	516 (90.8%)	36 (17.1%)	28 (14.1%)
two signals	52 (9.9%)	52 (9.2%)	160 (76.2%)	156 (78.4%)
three signals	0 (0%)	0 (0%)	14 (6.7%)	15 (7.5%)

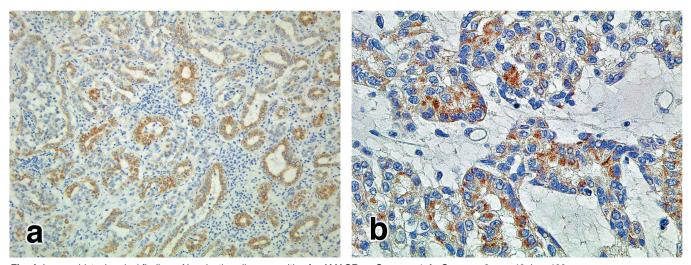


Fig. 4. Immunohistochemical findings. Neoplastic cells are positive for AMACR. a. Case no. 1. b. Case no. 2. a, x 40; b, x 400

both tumors showed a monosomy of both chromosomes 15 and 22. The results of FISH analysis of chromosomes 7 and 17 are also shown in Table 2. In case no.1, one, two and three signals of chromosome 7 in neoplastic cells counted 8.4%, 84.1% and 7.5%, respectively. Furthermore, one, two and three signals of chromosome 17 occupied 12.6%, 82.5% and 4.9%, respectively. In case no.2, one, two and three signals of chromosome 7 in tumorous cells comprised 17.1%, 76.2% and 6.7%, respectively. Additionally, one, two and three signals of chromosome 17 accounted for 14.1%, 78.4% and 7.5%, respectively. According to the criteria adapted from Hopman et al. (1994), we concluded that both tumors showed a disomy for chromosome 7 and 17 (Hopman et al., 1994).

## Discussion

MTSCC has been described morphologically in detail many times (He et al., 1998; Otani et al., 2001; Parawani et al., 2001; Hes et al., 2002; Rakozy et al., 2002; Weber et al., 2003; Aubert et al., 2004; Kuroda et al., 2004, 2005; Fine et al., 2006; Paner et al., 2006). According to the previous reports, the majority of MTSCC show low nuclear grade. Several reports dealing with chromosomal abnormalities of MTSCC have been published. Using comparative genomic hybridization (CGH) in five cases of MTSCC with low nuclear grade, Rakozy et al. (2002) have reported combined losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15 and 22. Weber and Srigley have found the combined losses of 1, 4, 6, 8, 13 and 14 and gains of chromosomes 7, 11, 16 and 17 using CGH and FISH of 21 cases of low nuclear grade MTSCC (Weber et al., 2003; Srigley, 2004). According to the previous CGH analysis, clear cell RCC shows the gain of chromosome 5q and losses of chromosomes 3p,

8p, 9, 14 and 18. In papillary RCC, gains of 7, 17, 16, 3 and 12 are often observed. The losses of chromosomes 1, 2, 6, 10, 13, 17 and 21 are characteristic of chromophobe RCC. Collecting duct carcinoma (CDC) is frequently associated with gains of chromosomes 16 and 20, and losses of chromosomes 1, 2, 9, 11 and 18. Losses of chromosomes 1 and 14 are frequently seen in oncocytoma (in Table 3 of Kuroda et al., 2007). Losses of chromosomes 15 and 22 seem to be relatively specific in MTSCC among primary renal tumors. However, there have been no FISH studies on chromosomes 15 and 22 on high nuclear grade MTSCC to date. Accordingly, we selected chromosomes 15 and 22 in the present study. On the one hand, recent WHO classification has shown that MTSCC is a distinct entity from papillary RCC (Srigley, 2004). On the other hand, some authors have

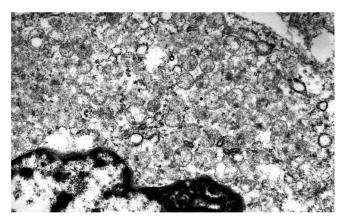


Fig. 5. Ultrastructural findings of oncocytic cells in case no. 1. Tumorous cells contain numerous mitochondria. x 8,000

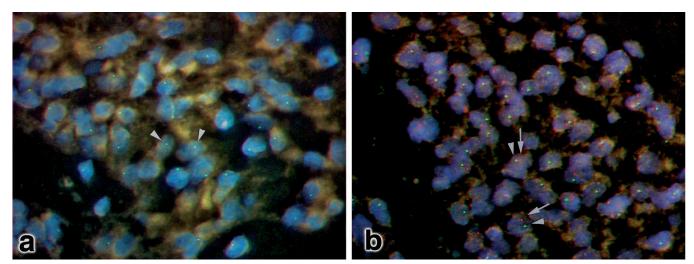


Fig. 6. Fluorescence *in situ* hybridization findings of case no. 2. Many neoplastic cells show the monosomy of chromosomes 15 and 22. A. Chromosome 15. B. Chromosome 22. x 1000.

recently described the close relationship between MTSCC and papillary RCC in the histological, immunohistochemical and genetic aspects, because of AMACR expression and abnormalities of chromosomes 7 and 17 (Weber et al., 2003; Srigley, 2004; Brandal et al., 2006; Paner et al., 2006; Shen et al., 2006) However, Cossu-Rocca et al. (2006) have reported that MTSCC lacks the gains of chromosomes 7 and 17 and losses of Y chromosome that are prevalent in papillary RCC. Therefore, we believe that RCC with losses of chromosomes 15 and 22 and without polysomy of chromosomes 7 and 17 may be true MTSCC, and the examination of chromosomes 7, 15, 17 and 22 may contribute to distinction of MTSCC from papillary RCC. Among several reports on chromosomal changes in CDC, we found three tumors with monosomy of chromosomes 15 and 22 associated with disomy of chromosomes 7 and 17 by cytogenetic study (Fuzesi et al., 1992; Shoenberg et al., 1995; Gregori-Romero et al., 1996; Polascik et al., 1996; Steiner et al., 1996). Additionally, some investigators have suggested that some MTSCCs might originate from the colleting duct system (Rakozy et al., 2002; Kuroda et al., 2004). However, whether the origin of MTSCC is Henle loop or collecting duct system is now debatable (Parawani et al., 2001; Hes et al., 2002). Accordingly, further examinations will be required in order to elucidate the relationship between MTSCC and CDC.

Shen et al. (2006) have recently reported six cases of MTSCC with high nuclear grade (Fuhrman grade 3), however, no cytogenetic data were provided in this article. In the present study, we confirmed a monosomy of chromosomes 15 and 22 in two cases of MTSCC with Fuhrman grade 3.

The histologic spectrum of MTSCC is considerably wide. Fine et al. have reported two cases of MTSCC with oncocytic tubules (Fine et al., 2006). In the present study, we ultrastructurally found many mitochondria in oncocytic cells of high nuclear grade MTSCC. Therefore, this is the first report where the presence of oncocytic cells in MTSCC was ultrastructurally confirmed.

To the best of our knowledge, there are no reports on patients with MTSCC that died of distant metastasis. Therefore, this is the first case of tumor death of MTSCC, and urologists and pathologists should recognize that some MTSCCs with high nuclear grade may pursue an aggressive clinical course.

Conclusions: We report two cases of high nuclear grade MTSCC with a monosomy of chromosomes 15 and 22 and disomy of chromosomes 7 and 17. The presence of myxoid stroma, cuboidal and spindle cells with high nuclear grade, associated with immunohistochemical expression of AMACR, monosomy of chromosomes 15 and 22, and disomy of chromosomes 7 and 17 may be important for establishing the diagnosis of high nuclear grade MTSCC. Also, this is the first report of a patient with MTSCC who died of distant metastasis. Acknowledgements. The author is grateful to Kumiko Hayashi, Cytogenetic Testing Group, Molecular Genetic Testing Department, Clinical Testing Center, Mitsubishi Chemical Medience Corporation, Kyoto, Japan for her technical assistance.

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