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# Mucinous Tubular and Spindle Cell Carcinoma of the Kidney with Aggressive Behavior: An Unusual Renal Epithelial Neoplasm – A Case Report–

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Mucinous tubular and spindle cell carcinoma is a rare low-grade renal cell carcinoma, which was first described as a new entity in the World Health Organization 2004 classification. We report here on a case of this tumor with very unusual aggressive behavior. A 73-year-old man presented with gross hematuria. A computed tomography scan demonstrated a 5 cm sized low density mass in the left kidney. The radical nephrectomy specimen grossly showed a well demarcated tumor confined to the renal parenchyma. Histologically, the tumor consisted of elongated tubules or trabeculae of oval to cuboidal cells with a low nuclear grade, and these tubules/trabeculae were separated by abundant acidic mucinous stroma. In some areas, spindle cell components were mixed with parallel tubules. Neither significant atypia nor mitosis was seen. The patient developed multiple metastatic pulmonary nodules 2 months later. Four months after the surgery, the left supraclavicular, right hilar and right subcarinal lymph nodes were also enlarged by metastasis. The patient died of respiratory failure 13 months after the operation.

**Key Words :** Carcinoma, renal cell; Kidney; Kidney neoplasms

Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare renal epithelial neoplasm. MTSCC has been reported as an unclassified renal cell carcinoma (RCC) with a characteristic histology.[1-3] Parwani *et al*.[4] reported on four cases as low-grade myxoid renal epithelial neoplasm with distal nephron differentiation and they suggested it was a distinct entity in 2001. This tumor was recently classified as a new entity in the World Health Organization (WHO) 2004 classification.[5,6] Histologically, the tumor cells are cuboidal to spindle shaped with a low nuclear grade and they are arranged in elongated tubules or trabeculae that are separated by abundant acidic mucinous stroma. Several studies have suggested that the origin of MTSCC is the distal nephron or loop of Henle based on its immunohistochemical and ultrastructural findings,[3,4,7,8] but this view is still controversial. This tumor is known to have a favorable clinical outcome.[4-6]

We describe here in a case of renal MTSCC with very unusual aggressive behavior in a 73-year-old patient.

## CASE REPORT

A 73-year-old man was hospitalized because of gross hematuria. Abdomino-pelvic contrast computed tomography (CT) revealed about 5 cm sized mass with slightly enhancing low density in the left kidney (Fig. 1A). At that time, neither lymph node enlargement nor metastatic lesion was noted. All of the laboratory data of the patient was within the normal ranges. The primary impression was RCC.

A radical nephrectomy was performed, and the specimen revealed a well demarcated mass involving the mid-portion to lower pole of the kidney, and the tumor measured 5 × 5 cm

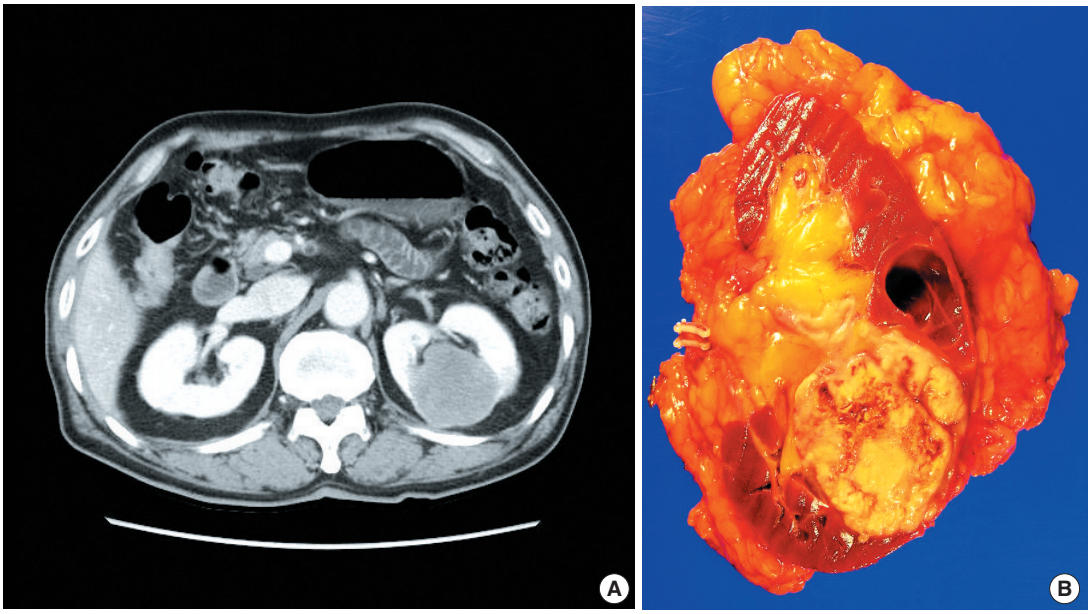


Fig. 1. The abdomino-pelvic contrast computed tomography scan and the cut surface photograph of the renal mass. (A) A 5 cm-sized subtle enhancing low density mass is found in the left kidney. (B) The nephrectomy specimen reveals a well-demarcated tumor and the cut surface is gray-yellow and solid with focal hemorrhage.

across. The mass showed a gray-yellowish solid appearance with focal hemorrhage. The tumor was pushing to the renal pelvis, but it did not involve the renal pelvic fat or renal vasculature (Fig. 1B). A simple cyst that measured 3 × 2.5 cm across was also noted. Histologically, the tumor was composed of elongated tubules or trabeculae of oval to cuboidal cells with a low nuclear grade, and the tubules/trabeculae were separated by abundant acidic mucinous stroma (Fig. 2A, B). In some areas, paralleled tubular arrays resulted in a spindle-shaped appearance with short interlacing fascicles (Fig. 2C). A focal papillary growth pattern was noted. The tumor cells had ovoid to spindle nuclei with small prominent nucleoli. Cellular pleomorphism or mitotic activity was not observed. The mucinous stroma was reactive for Alcian blue stain (Fig. 2D). Immunohistochemically, the tumor cells were diffusely reactive for vimentin, epithelial membrane antigen (EMA) and CAM5.2. Kidney specific cadherin, $\alpha$-methylacryl-CoA racemase (AMACR) (Fig. 2E), neuron-specific enolase (NSE) and p53 showed focal positivity. The tumor cells were negative for CD10 (Fig. 2F), cytokeratin (CK)7, RCC marker antigen (RCC Ma), high-molecular weight CK (34$\beta$E12) and CD15. The Ki-67 labeling index was less than 1%.

Two months after the diagnosis, multiple metastatic nodules were discovered in both lungs by a positron emission tomography-CT scan. Four months after the surgery, several metastatic lymph nodes also developed in the left supraclavicular, right hilum and right subcarinal areas. Bone metastases and pleural effusion followed in spite of two cycles of chemotherapy that included cyclophosphamide, doxorubicin, dacarbazine and vincristine.

The pleural fluid cytology showed variable sized, tight, three-dimensional clusters of round to cuboidal cells with relatively uniform round-to-ovoid nuclei and small nucleoli (Fig. 2G). The cells were morphologically similar to the main tumor cells of MTSCC, and they were immunopositive for vimentin, but negative for thyroid transcription factor-1.

The patient died of respiratory failure 13 months after the operation.

## DISCUSSION

The renal malignant tumors showing specific histologic findings have been reported as unclassified RCC.[1-3] In 2001, Parwani *et al*.[4] described four cases of low-grade myxoid renal epithelial neoplasm with distal nephron differentiation. Afterward, Hes *et al*.[9] reported on 11 cases as cuboidal and spindle cell carcinoma. Rakozy *et al*.[7] also reported on 5 cases as low-grade tubular-mucinous renal neoplasm. These tumors showed multiple losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22 by comparative genomic hybridization. Srigley *et al*.[10] described frequent losses of chromosomes 1, 4q, 6, 8p, 9q, 11q, 13,

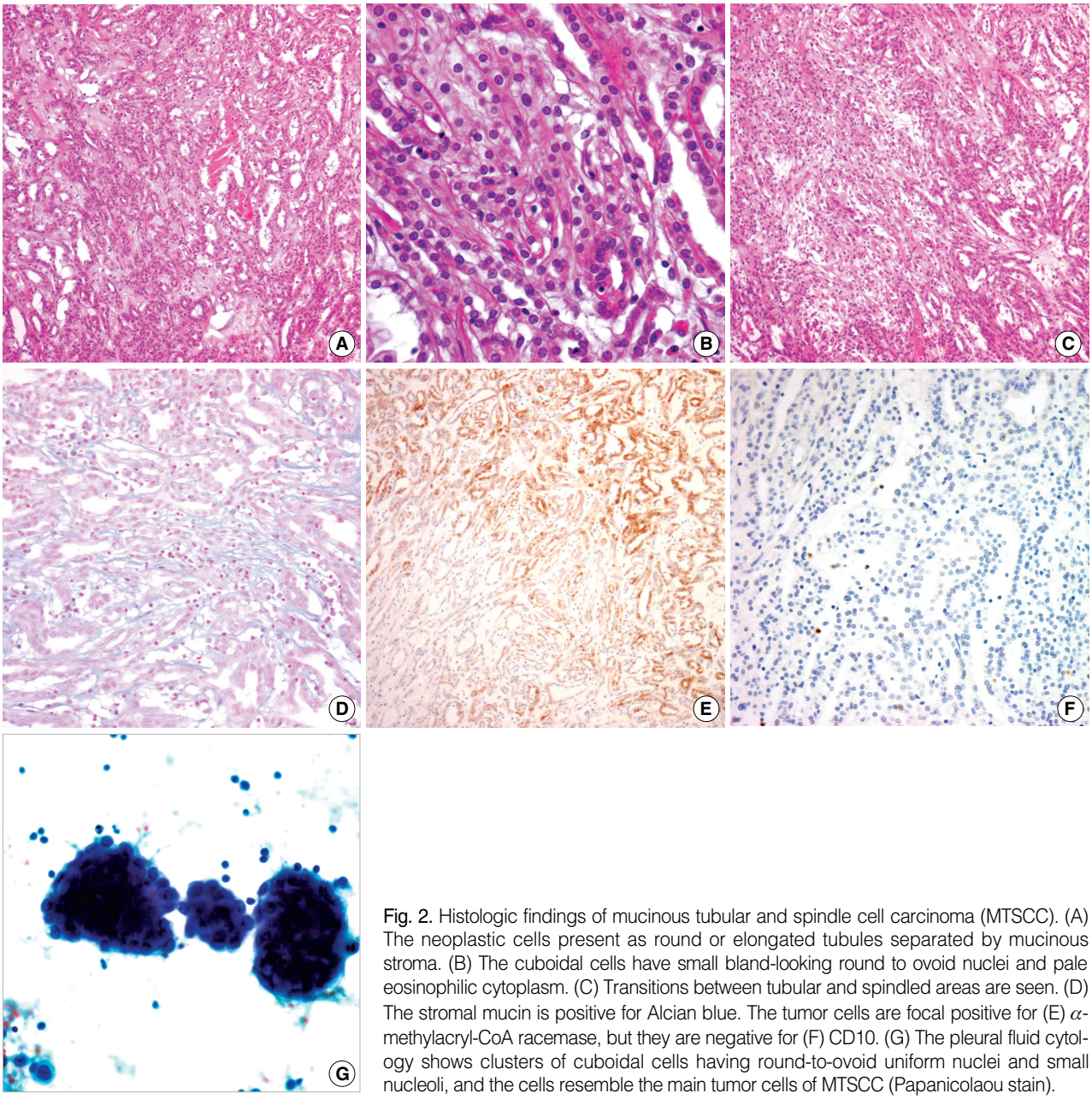


Fig. 2. Histologic findings of mucinous tubular and spindle cell carcinoma (MTSCC). (A) The neoplastic cells present as round or elongated tubules separated by mucinous stroma. (B) The cuboidal cells have small bland-looking round to ovoid nuclei and pale eosinophilic cytoplasm. (C) Transitions between tubular and spindled areas are seen. (D) The stromal mucin is positive for Alcian blue. The tumor cells are focal positive for (E) $\alpha$-methylacryl-CoA racemase, but they are negative for (F) CD10. (G) The pleural fluid cytology shows clusters of cuboidal cells having round-to-ovoid uniform nuclei and small nucleoli, and the cells resemble the main tumor cells of MTSCC (Papanicolaou stain).

14, and 15, and gains of chromosomes 11q, 12q, 16q, 17, and 20q. Due to the unique histological and genetic findings, these tumors were classified as MTSCC in the 2004 WHO tumor classification.[5,6] Case reports or small series on this tumor have been published after this.[6,8,11-17] Only four such cases have been reported in Korea.[13,15,16]

Clinically, MTSCCs have a female predisposition.[4,7,8,10] In a small series studied by Srigley *et al*.,[10] there was a wide age range of 17-82 (mean age, 53) and a study by Ferlicot *et al*.,[8] showed a age range from 21 to 81 (mean age, 53). MTSCCs usually present as asymptomatic masses.[6,10] However, some tumors may exhibit hematuria or flank pain.[4,9]

Grossly, MTSCCs are often located at the renal medulla. They are well-defined masses, but they are generally without a capsule. The tumors have firm, smooth consistency and grey or whitish cut surfaces. Necrosis or hemorrhage is rare. Involvement of extra-renal tissue or the renal vein is very rare.[6,7,9] MTSCCs are essentially epithelial neoplasms that show tubular, trabecular, cord-like or solid growth patterns. A papillary growth pattern or glomeruloid-like features may be seen.[1,6,11,12] The tumor cells

are basically cuboidal, but they may appear spindle-shaped in some areas. The cytoplasm is eosinophilic or clear, and the nuclei are uniform, round and centrally located. The intervening stroma tends to be edematous or myxoid, and it is reactive on Alcian blue and colloidal iron stains.[4,6,7]

The tumor cells usually express both epithelial markers (EMA & pan-cytokeratin) and mesenchymal markers (vimentin).[4,6,7,9] High-molecular weight CK (34$\beta$E12), CAM5.2, CK7 and CK18 are often reactive.[4,6,7,9,10] Recent studies have shown the frequent expression of neuroendocrine markers, i.e., NSE, chromogranin A and synaptophysin.[13,14] Our case also showed immunoreactivity for NSE.

Making the diagnosis of MTSCC can often be difficult. MTSCC may have papillary structures, as in the present case, with aggregates of foam cells and psammomatous calcifications, and so it resembles a papillary RCC.[15,17] The tumor papillae of MTSCC show a relatively lack of true fibrovascular cores or foam cell aggregations, but Fine *et al*.[17] described rare, well-formed papillae containing a fibrovascular core in MTSCC. CD10 immunostaining is helpful for the differential diagnosis since the majority of MTSCCs are negative for CD10, but most papillary RCCs exhibit immunoreactivity for CD10.[11,12,18] The existence of areas of spindle cells may raise the possibility of a sarcomatoid RCC. The spindle cells of MTSCC have a bland cytomorphology with a low nuclear grade,[8,18] in comparison with the atypical spindle cells with marked cytologic atypia, prominent pleomorphism and numerous mitoses of sarcomatoid RCC.[6,8]

The origin of MTSCC has been suggested to be the distal nephron. Parwani *et al*.[4] demonstrated that the cuboidal shaped cells, their elongated tubular structures and the myxoid stroma were highly suggestive of the loop of Henle. Rakozy *et al*.[7] reported that these tumors were negative for Tamm-Horsfall protein, which is a marker found in distal convoluted tubules and the ascending loop of Henle, but the tumors revealed reactivity for EMA and peanut agglutinin, which are markers of the collecting duct epithelium. Thus, they suggested that MTSCCs originated from the collecting duct epithelium.[7] However, there also have been reports showing immunohistochemical results favoring proximal tubular differentiation. Paner *et al.*[11] showed a relatively similar pattern of the AMACR, CK7 and EMA expressions between MTSCC and papillary RCC. Additionally, Shen *et al*.[12] reported the tubulopapillary growth pattern as well as the strong expression of proximal tubule markers, including RCC Ma, CD15 and AMACR, and they are suggested that MTSCC is a variant of papillary RCC. But the cytogenetic differences of MTSCC from RCC have been well demonstrated,[8,10,18,19] and MTSCC is currently considered a distinct entity, though its histogenesis remains undetermined.

Regarding the biologic behavior of MTSCCs, many researchers have reported their indolent courses.[4,6] However, a few cases with recurrences or lymph node metastases or MTSCC with sarcomatoid differentiation have been described,[7-9,20] A recent study suggested that the overexpression of Ki-67 and p53 is correlated with aggressive behavior of MTSCC.[16] Kuroda *et al*.[20] reported on two cases of MTSCC with a Fuhrman nuclear grade of 3.[19] One the 2 patients died of respiratory failure due to pleuritis carcinomatosa 48 months later. In the present case, the nuclear grade, mitotic activity, Ki-67 labeling index and p53 positivity was low in the primary tumor, but the tumor showed rapid progression after the surgery.

In summary, we report here on an additional case of MTSCC because this is a very rare renal neoplasm and a recently established entity in the WHO tumor classification. In addition, our case showed an aggressive clinical behavior, which is very different from that of the previously reported cases. The biologic nature of MTSCC still seems unclear, and so large long-term follow-up studies of MTSCC are needed.

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