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Case Report

Mucin-poor mucinous tubular and spindle cell renal cell carcinoma with sarcomatoid transformation and multiple metastases: report of a unique case and review of literature

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Abstract: Mucinous tubular and spindle cell renal cell carcinoma (MTSRCC) is an uncommon, newly recognized tumor that is histologically characterized by small, elongated tubules lined by cuboidal cells and/or cords of spindled cells separated by variable amounts of mucinous/myxoid stroma. Nonclassic morphologic variants and features of MTSRCC have not been well documented and only rarely been studied. Although initially considered to be a low-grade carcinoma with favorable prognosis, MTSRCC demonstrating sarcomatoid transformation with an aggressive behavior has recently been reported. Herein, we present a unique case of MTSRCC with a mucin-poor morphology, extensive high-grade sarcomatoid transformation, multiple metastases and a rapidly fatal clinical course in a 53-year-old man and describe its histomorphologic and immunohistochemical features as well as molecular genetic findings. Our findings further expand both the histological and behavioral spectrums encountered in MTSRCC.

Keywords: Mucinous tubular and spindle cell carcinoma, renal cell carcinoma, sarcomatoid, metastasis, FISH

Introduction

Mucinous tubular and spindle cell renal cell carcinoma (MTSRCC) is an uncommon, recently described subtype of renal cell carcinoma (RCC), which has been recognized as a distinct entity in the 2004 *World Health Organization* (WHO) tumor classification [1]. In its classic form MTSRCC is histologically characterized by an admixture proliferation of tubular cuboidal cells and spindle cells, setting in a background of variable amounts of mucinous/myxoid stroma. Cytologically, the tumor cells are usually bland-appearing with scant, pale to slightly eosinophilic cytoplasm, and the nuclei are generally round, uniform and display low nuclear grade characteristics [2]. Histological variations, such as mucin-poor histology [3, 4], oncocytic cell changes [3], and presence of focal or prominent papillations [3, 5], which could cause significant diagnostic confusions have rarely been reported in MTSRCC. With regard to biologic behavior, MTSRCC is generally a low-grade malignant tumor with a protracted clinical course. However, very few cases that demonstrated recurrence, metastasis to regional lymph nodes at the time of presentation, and distant metastases have been reported [6, 7]. Sarcomatoid transformation, which can be seen in any subtype of RCC and usually portends a worse prognosis of the tumor, has also been rarely documented in MTSRCC [8-12]. Herein, we report a unique case of MTSRCC with a mucin-poor morphology, extensive sarcomatoid transformation, multiple metastases, and a rapidly fatal clinical course in a 53-year-old man. Our aim is to further expand both the morphologic and behavioral spectrums of MTSRCC.

Case presentation

A 53-year-old Chinese man with a significant history of chronic hepatitis presented with progressive weight loss for 6 months, and fever for 5 days. Abdominal imaging studies including

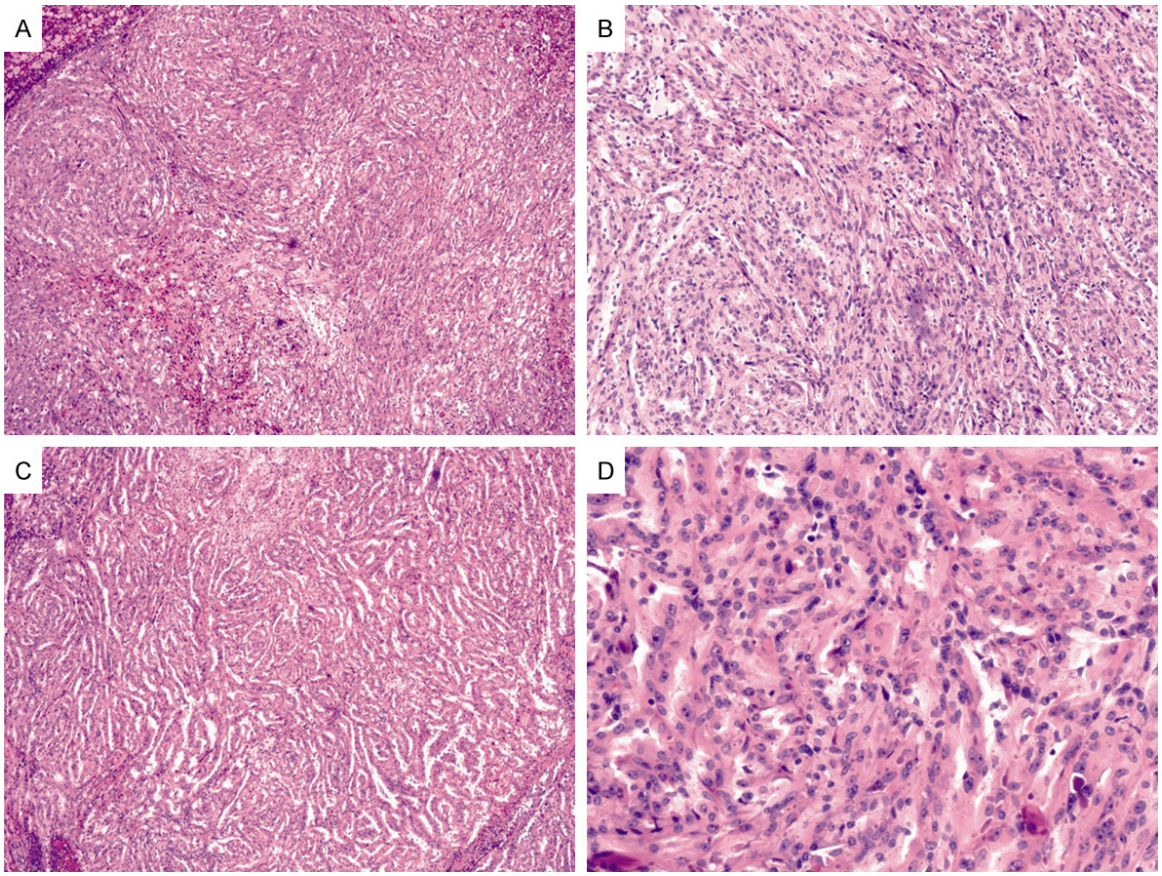

Figure 1. Low-grade MTSRCC component showed (A) tightly packed, elongated tubules and (B) spindle cells without mucinous stroma detected. (C) Focal areas showing abortive papillary structures with tumor cell tufts protruding into the tubular lumen. (D) The tumor cells were bland-appearing cuboidal to columnar with moderate amount of oncocytic cytoplasm that contained numerous hyalinized globular bodies.

ultrasonic examination and computed tomography (CT) scan revealed a 6.5 cm heterogeneous mass in the lower pole of the left kidney. Multiple abdominal and retroperitoneal lymphadenopathy was detected with the largest lymph node measuring up to 3 cm. The right kidney had multiple simple cysts. Subsequent extended CT scan demonstrated multiple mediastinal lymphadenopathy and expansile lytic lesions which involved bilateral ribs, left superior limbus of sternum and thoracic 3 vertebral body; these imaging studies were highly suspicious of metastatic diseases from the kidney. Laparoscopically radical left nephrectomy was performed; the patient succumbed to the disease at a follow-up of 11 months after the surgery.

Grossly, the resected specimen measured 15 × 12 × 9 cm and had a 7 × 6 × 6 cm, cortex-predominant tumor with partially circumscribed but focally infiltrative irregular borders. On cut surface, the tumor was extensively necrotic with some viable tan-yellow soft areas and tan-white firm nodular zones. Neither perinephric nor renal sinus fat extension of the tumor was grossly evident. No intravenous tumor embolus was noted. The adrenal gland was unremarkable without evidence of tumor involvement. Nine enlarged hilar lymph nodes with diameter ranging from 0.5 to 2 cm were detected. Morphologically, the low grade component of MTSRCC, which accounted for approximately 30% of the entire tumor, consisted predominantly of tightly packed, frequently collapsed, elongated tubules and spindle cells that often formed solid nodules and arranged in short fascicular or swirling growth patterns (**Figure 1A** and **1B**). Focal areas showing abortive papillary structures with tumor cell tufts protruding into the tubular lumen were also observed (**Figure 1C**). The tumor cells of the low grade areas

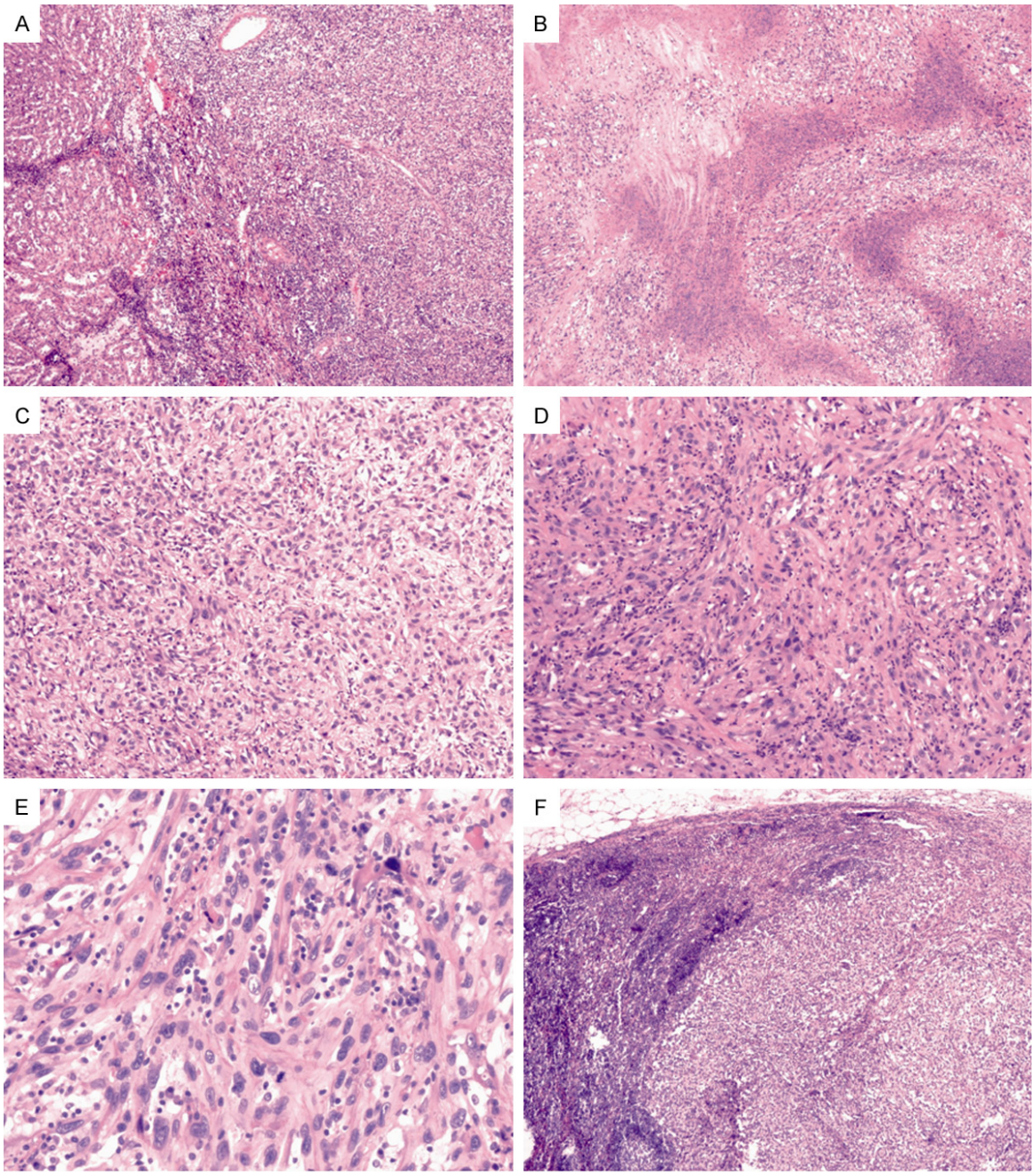

Figure 2. (A) Low grade MTSRCC component (left) displayed abrupt transition to sarcomatoid areas (right), which were (B) extensively necrotic and composed of spindle to pleomorphic, undifferentiated cells that frequently arranged in (C) solid sheets and (D) storiform growth patterns. (E) The sarcomatoid cells displayed moderate-to-severe nuclear pleomorphism with increased mitotic activity. (F) Renal hilar lymph nodes were positive with metastasis of sarcomatoid component of MTSRCC.

were cuboidal to columnar with moderate amount of oncocytic cytoplasm that contained numerous hyalinized globular bodies (**Figure 1D**). The nuclei were rounded with single small nucleoli corresponding to Fuhrman nuclear grade 2. Mitoses were very rare. Mucinous stroma was not identified by hematoxylin and eosin or Alcian blue staining. A background of variable amount of lymphocytes, plasma cells, foamy macrophages and hemosiderin depositions was present. Occupying approximately 70% of the tumor areas was an extensively

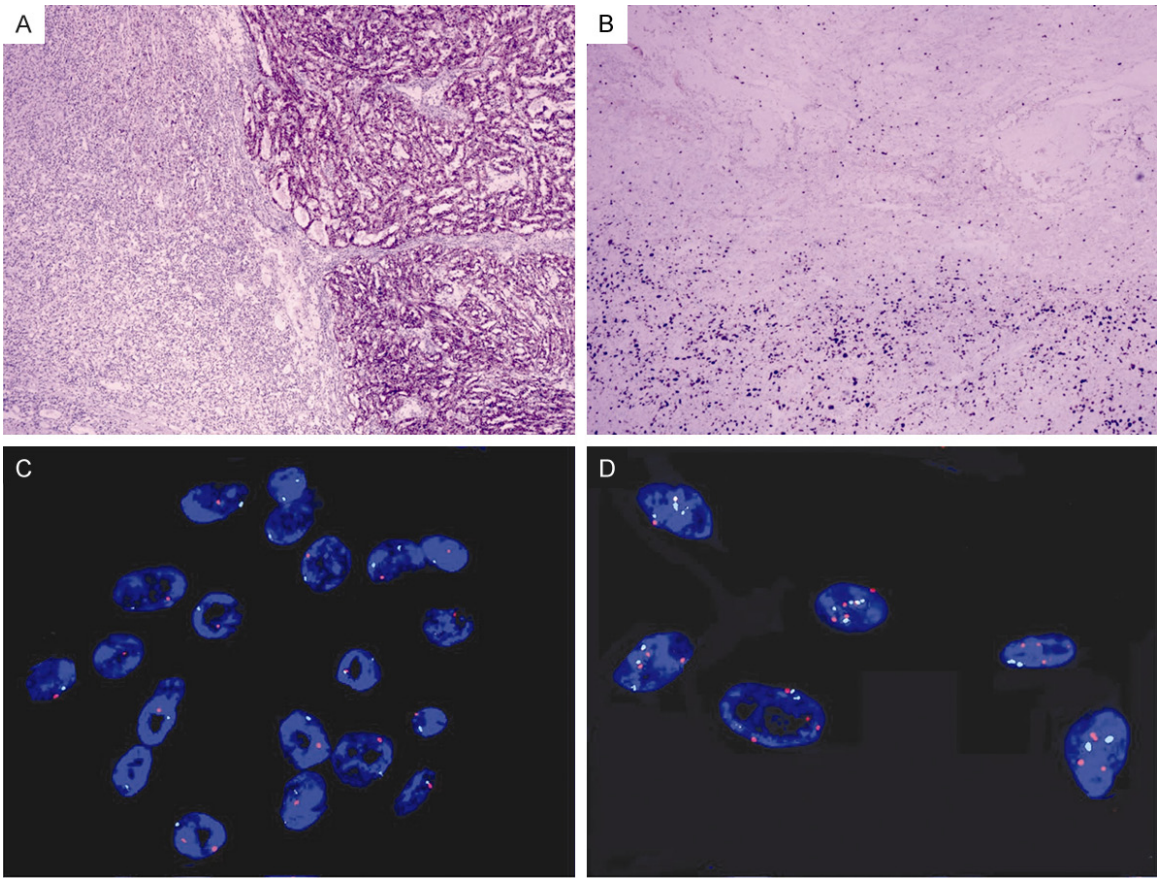

Figure 3. Immunohistochemical study showed that (A) AMACR expression was diffusely and strongly positive in the low grade component and was absent in the sarcomatoid component of MTSRCC. (B) MIB1 nuclear staining was absent to rare in the low grade component and was highly expressed in the sarcomatoid component. Fluorescence in situ hybridization analysis for chromosomes 7 (in green) and 17 (in orange) in the tumor revealing (C) one green and one orange signals in the low grade component, consistent with monosomy of chromosomes 7 and 17, and (D) three or more signals in both green and orange signals in the sarcomatoid component consistent with polysomy of chromosomes 7 and 17.

necrotic, high-grade sarcomatoid tumor that usually merged abruptly with areas of low grade MTSRCC (**Figure 2A** and **2B**). The sarcomatoid component was composed of spindle to pleomorphic, undifferentiated cells that frequently arranged in solid sheets and storiform growth patterns, set in a background of desmoplastic stroma with prominent inflammatory infiltrations (**Figure 2C** and **2D**). Mucinous stromal change was not identified. The sarcomatoid cells displayed moderate-to-severe nuclear pleomorphism with occasional prominent single-to-multiple nucleoli (**Figure 2E**). Mitotic rate varied from 0 to 6/10 high power fields (**Figure 2E**). The sarcomatoid component focally infiltrated the renal sinus adipose tissue. Four of 9 renal hilar lymph nodes were positive with metastases showing histologically only high grade sarcomatoid component (**Figure 2F**).

By immunohistochemistry, tumor cells of both the low grade and sarcomatoid component showed expression of PAX8, vimentin, cytokeratin(CK)19, and Cam 5.2. A-methylacyl-CoA racemase (AMACR) expression was diffusely and strongly positive in the low grade component and was absent in the sarcomatoid component (**Figure 3A**). MIB1 nuclear staining was absent to rare in the low grade component and was highly expressed in the sarcomatoid component (average 50% positive nuclear staining) (**Figure 3B**). Immunostains for CK7, CK34βE12, CD10, CD117, E-cadherin, renal cell carcinoma marker, P63, synaptophysin, chromogranin A and Napsin A were all negative through the tumor. Fluorescence in situ hybridization (FISH) analysis was performed with centromeric α-satellite DNA probes for chromosome 7 (CEP 7, D7Z1, Spectrum Green) and chromosome 17

(CEP 17, D17Z1, Spectrum Orange), according to the manufacturer's instructions (Abbott Molecular), and no trisomy of chromosomes 7 or 17 were detected in both the low grade and the sarcomatoid componet. The low grade component usually showed monosomy of chromosomes 7 and 17 (**Figure 3C**) while the sarcomatoid component frequently showed polysomy of both chromosomes (**Figure 3D**).

Discussion

MTSRCC is a relatively new entity among subtypes of RCC that is thought to be a low grade, relatively indolent neoplasm with a favorable prognosis [1, 2]. Classic morphologic features include low grade epithelial cells organized in tubules and spindled cords, associated with abundant myxoid or mucinous extracellular matrix. Mitoses and necrosis are uncommon. Unlike the classic MTSRCC, the current case presented as a low grade MTSRCC with depletion of extracellular mucin, and high-grade sarcomatoid transformation with extensive necrosis, multiple metastases, and a rapidly fatal clinical course.

Sarcomatoid transformation is a well-documented phenomenon of tumor progression in RCC and is generally defined histologically by the presence of high-grade spindle cells with nuclear pleomorphism, prominent nucleoli and increased mitotic activities [13]. It may arise out of a background of any histological type of RCC as a manifestation of a final common dedifferentiation pathway and has been well documented in the more common subtypes of RCC such as papillary RCC, chromophobe RCC, and collecting duct carcinoma [14]. Sarcomatoid differentiation arising in a background of low grade MTSRCC is exceptional, to our knowledge, including the current case, only seven cases have been reported in the literature to date [8-12] (**Table 1**). As with other common type sarcomatoid RCC, patients with sarcomatoid MTSRCC usually present with advanced diseases and symptoms related either to the effects of the primary tumor or, more commonly, metastasis. Multiple sites of metastasis at the time of primary treatment are commonly seen, with axial bones and lungs being the most frequent sites of secondary spread. Sarcomatoid MTSRCC pursues a rapidly fatal clinical course with five of the 7 patients dead of the disease at a follow-up ranging from 1 to 11 months. Histologically, sarcomatoid component in MTSRCC is oftentimes fibrosarcoma like with intersecting fascicles of malignant spindle cells, pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma like), or of an unclassified morphology. Necrosis is usually extensively and mitotic activity is increased. These are in striking contrast to the inherent spindle cells in low grade MTSRCC that are typically bland-appearing, arranged in parallel arrays blending with elongated and well-formed tubules. Nuclei are relatively regular and mitoses are very rare in the inherent spindle cell component of MTSRCC. By immunohistochemistry, sarcomatoid component of MTSRCC expresses at least one marker of cytokeratins and usually lacks the expression of AMACR that is typically strongly positive in the low grade component of MTSRCC. MIB1 nuclear staining shows a striking disparity in the expression between the low grade component and the sarcomatoid areas.

Molecular investigations have shown that classic MTSRCC is typically characteristic of multiple chromosomal numerical aberrations with losses of (or partly from) chromosomes 1, 4, 6, 8, 9, 13, 14, 15, 18, 22 and X, as well as gains of all or parts of chromosomes 2, 4, 7, 11, 12, 16, 17, 18, and 20 [15-18]. In the FISH analysis of the present study, we found monosomy of chromosomes 7, 17 in the low grade component of MTSRCC and polysomy of chromosomes 7 and 17 in the sarcomatoid areas. A similar result was obtained in a case of sarcomatoid MTSRCC reported by Bulimbasic et al. [11] where monosomy of chromosome 15 and polysomy of chromosomes of 7, 17, and 22 were established in the tumor by FISH study. In addition, Dhillon et al. [10] recently reported another case of high-grade (sarcomatoid) MTSRCC that genetically showed losses of chromosomes 14 and 15 and gains of chromosomes 2, 5, 7, 9, 10, 12, 17, 19, 20, 22, and X. These chromosomal abnormalities of sarcomatoid MTSRCC are generally comparable to those of low-grade MTSRCC, further confirming that the former component represents a high-grade counterpart of the latter one.

Mucinous extracellular matrix is typically a key clue to diagnosis of MTSRCC and it is present usually abundant, at least focally in most tumors. MTSRCC with little or no extracellular mucin appreciable on routine microscopy has

Table 1. Summary of the clinicopathologic and molecular characterizations of sarcomatoid MTSRCC

Author	Age (y)/ gender	Size (cm)	Presentation with metastasis	Follow-up (mo)	Percentage of SC	Histology of SC	Immunohistochemistry of SC	Molecular features of SC
Simon et al. [8]	64/M	15	Yes, thoracic vertebral body	DOD/1	>50%	Large pleomorphic cells with high grade nuclei	Positive: CKAE1/3, CK19, vimentin. Negative: EMA, CK7, CD10, AMACR	NA
Pillay et al. [9]	72/F	7	No	NED/12	33%	Pleomorphic spindle cells with fascicular and storiform growth patterns	Positive: CKAE1/3, CK7, AMACR (very weakly), MIB1 (>10%). Negative: 34BE12, desmin, MSA, S100	NA
Dhillon et al. [10], case 1	71/F	9.5	Yes, bilateral ribs, lumbar 4 vertebral body, bilateral lung	DOD/9	60%	High grade sarcoma cells with sheet like, pseudovascular, solid and storiform growth patterns	Positive: CK7, EMA, Cam 5.2, vimentin, MIB1 (46%)	Loss of chromosomes 14 and 15; gain of chromosomes 2, 5, 7, 9, 10, 12, 17, 19, 20, 22, and X
Dhillon et al. [10], case 2	80/M	11	No	NED/4	20%	Sarcomatoid spindle cells with pseudovascular and storiform patterns	Negative: CK7, AMACR	NA
Bulimbasic et al. [11]	75/M	NA	No	DOD/1	NA	Bizarre atypical cells with high nuclear polymorphism	Positive: CKAE1/AE3, CK19, vimentin, AMACR (weak). Negative: CK7, CD10	Polysomy of chromosome 7, 17, 15; monosomy of chromosome 15; no mutation of the VHL gene or LOH 3p
Arafah et al. [12]	64/M	20	No	DOD/8	20%	High-grade spindle cells with poorly formed fascicular growth pattern	Positive: CK7 (patchy), MIB1 (raised). Negative: AMACR	NA
Qi et al. (current case)	53/M	7	Yes, bilateral ribs, left superior limbus of sternum, thoracic 3 vertebral body	DOD/11	70%	Spindle to pleomorphic cells with solid sheets and storiform growth patterns	Positive: PAX8, vimentin, CK19, Cam 5.2, MIB1 (50%). Negative: CK7, AMACR, CD10, CK34βE12, CD117, E-cadherin	Monosomy of chromosomes 7, 17 in low grade MTSRCC; polysomy of chromosomes 7, 17 in SC component

Abbreviations: DOD, dead of disease; F, female; M, male; NA, not available; NED, no evidence of disease; SC, sarcomatoid component.

been referred as a "mucin-poor" variant in the literature, which could elicit a broad spectrum of differential diagnoses [3, 4]. In this setting, histochemical staining for Alcian blue can usually highlight the scant mucin in the tumor and help arrive at accurate diagnosis. Our case is unique as with thoroughly sampling of the tumor, no mucinous material was detected by hematoxylin and eosin or Alcian blue staining in the low grade component, hence, a question of possible solid variant of papillary RCC may rise. However, morphology showing tightly packed, paralleled tubules without prominent well-shaped papillae, and molecular analysis demonstrating negative for trisomy of chromosomes 7 and 17 that are characteristic of papillary RCC indicated that our case was best classified as a predominantly mucin poor subtype of MTSRCC rather than papillary RCC. Indeed, Single cases of MTSRCC with no mucin displaying a prominence of small tightly packed tubules, some of which are elongated and spindled resembling type 1 papillary RCC had indeed been reported in the literature [19]. Moreover, existence of focal mucinous/myxoid stroma has rarely been reported in papillary RCC [20]. Accordingly, mucinous stroma change is not the absolute point to distinguish MTSRCC from solid pattern papillary RCC. It is critical for pathologists to recognize that "mucin-poor" variant MTSRCC exists and entirely depletion of mucinous extracellular matrix should not necessarily exclude the diagnosis of this entity. Other entities that may enter into the differential diagnosis of sarcomatoid mucin-poor MTSRCC include collecting duct carcinoma (CDC), hereditary leiomyomatosis RCC syndrome-associated RCC (HLRCC) [2], and infiltrative urothelial carcinoma, all of which are high grade tumors with aggressive clinical course and may show some similarities to sarcomatoid mucin poor MTSCRCC either histologically or immunohistochemically. With adequate sampling and identification of a combination of features of low grade MTSRCC component, including bland-appearing cytology and the presence of transition areas between tubular and spindled morphology, and careful attention to the distinctive immunoprofile (PAX8+/AMACR+/CD10-/P63-) as well as genetically lacking of trisomy of chromosomes 7 and 17 will help to distinguish mucin-poor MTSRCC from above mentioned tumors [21].

In summary, we present a case of mucin poor MTSRCC with high-grade sarcomatoid transformation, multiple metastases, and a rapidly fatal clinical course that expands both the histological and behavioral spectrums encountered in these tumors. Awareness of variable morphologic variants of MTSRCC is critical to avoid a misdiagnosis, and identification of sarcomatoid change that may occur in MTSRCC is important because of its potential for aggressive biologic behavior.

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Disclosure of conflict of interest

None.

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