Mucinous tubular and spindle cell carcinoma of the kidney: Five case reports and review of the literature

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Abstract. Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney is a rare and polymorphic tumor, which has been previously considered to be a low-grade malignancy, predominantly occurring in women. To the best of our knowledge, MTSCC with bladder metastasis has never been reported. The current study presents five adult cases of MTSCC that included three male and two female patients. Among the male cases, two were of advanced stage, one with MTSCC and renal chromophobe cell carcinoma with bladder metastasis and the other with MTSCC with invasion of the renal vein. The other three cases with small masses were at an early stage. All five cases had a good prognosis and were without recurrence after several years of follow-up. A 70-year-old male with intermittent gross hematuria, intermittent renal colic, and groin radiation pain for a year (case 1), was incidentally detected to have a left renal density mass by total abdominal enhanced computed tomography scans. In the other four cases, renal masses were found by B-ultrasound. The patient in case 1 underwent a retroperitoneal laparoscopic radical nephroureterectomy with bladder cuff resection and transurethral resection of the bladder tumor, and received gemcitabine hydrochloride via intravesical instillation therapy plus cisplatin chemotherapy every 3 months. The patient in case 2 underwent an open left radical nephrectomy and renal pedicle lymph node dissection. The other three patients underwent a laparoscopic radical nephrectomy. All five patients had no recurrence or new metastasis in other organs after follow-up. In conclusion, the incidence of MTSCC in men and women is not as disparate as reported in previous publications. The characteristics of the images of the five adult cases in the present study showed a considerable consistency, with only minor differences. The malignancy and prognosis of MTSCC are still controversial, and thus inclusion and review of more cases is required to reach a definite final conclusion. Sunitinib and gemcitabine chemotherapy in combination with cisplatin may be effective for the therapy of MTSCC patients with metastasis, but a larger range of treatments needs to be identified.

Introduction

Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney is a relatively rare tumor that was defined in the 2004 World Health Organization Classification (1). The tumor was previously believed to be low grade with a favorable prognosis (2). The origin of MTSCC is controversial and has been speculated to be either the loop of Henle or the collecting duct (3). This tumor is usually diagnosed by pathology, with tubular and spindled cords surrounded by an abundant extracellular matrix (4). However, very few cases have been classified so far as mucin-poor (5). There is no uniform standard for the diagnosis, especially the imaging diagnosis, or the treatment of MTSCC. Based on the findings of the analysis of the histological and imaging features of MTSCC, The present study provides hypotheses on the origin and growth mode of MTSCC, aimed at the identification and development of more accurate treatment methods and a precise evaluation of the prognosis of patients.

Case report

Case 1. A 70-year-old man with intermittent gross hematuria, intermittent renal colic, and radiating pain in the groin that recurred two or three times per month over a year, presented to the Third Affiliated Hospital of Soochow University (Changzhou, China) in February 2016. A physical examination revealed left lower abdominal pain and left renal percussion pain. Left ureteral calculi with left hydronephrosis were identified by B-ultrasound, and the patient reported discharging two small stones 2 days after the initiation of antispasmodic and anti-inflammatory therapy. Total abdominal enhanced computed tomography (CT) scans

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showed a 4.4x2.3-cm isodense mass with clear boundaries in the left renal pelvis (Fig. 1A and B)and a 1x1-cm isodense mass on the surface of the left kidney (Fig. 1C and D). Urine cytology showed no obvious tumor cells. Cystoscopy revealed a 1x0.8-cm gray-white mass on the left wall of the bladder, which was excised. The bladder tumor was diagnosed as MTSCC based on that Vimentin, CK8/18 and P504S showed positive expression in tumoral cells. The preoperative diagnosis was left renal pelvis carcinoma, left ureter carcinoma and MTSCC of the bladder. Retroperitoneal laparoscopic radical nephroureterectomy with bladder cuff resection and transurethral resection of the bladder tumor was performed under general anesthesia in March 2016. The dissection of the specimen revealed a pelvic mass with a size of 3x3 cm, which was dark red. A 1x1-cm grey nodule was available on the renal surface; the grey bladder tumor had a total volume of 1.5x0.8x0.4 cm. The pathological diagnosis was renal MTSCC with extensive necrosis and invasive growth, suggesting a poor prognosis. Renal chromophobe cell carcinoma (1x1-cm mass) on the renal surface and bladder MTSCC with a tendency for renal tumor metastasis were also found. The immunohistochemical results were consistent with the preoperative pathological diagnosis. The patient was transferred to the Department of Oncology, where he received chemotherapy consisting of 1.2 g gemcitabine and 60 mg cisplatin through intravenous injection every 3 months. The patient underwent chest and abdominal enhanced CT, routine blood tests, liver and kidney function and cystoscopy every 3 months. There were no signs of recurrence or metastasis in any other organs and blood tests were normal after 36 months of follow-up.

Case 2. A 61-year-old man, with left lower back pain that had lasted a year, received treatment for chronic hepatitis B and underwent B-ultrasound in March 2012. This showed a huge malignant tumor (10.7x7.4 cm) in the lower pole of the left kidney and a thrombus in the renal vein. Physical examination revealed left renal percussion pain. Enhanced CT revealed that the left kidney was significantly enlarged; the capsule was not smooth, and a cystic-solid soft mass of ~9.7x8.0 cm in size was present. The internal density was uneven with small high-density shadows, and the low-density area was considered to be the liquefaction area (Fig. 2A-D). On magnetic resonance imaging (MRI), a large 9.7x8x6-cm mass in the left kidney exhibited a mixed signal of equal height in T2-weighted imaging (T2WI), and a low-hybrid signal in T1WI (Fig. 2E and F). The left renal vein was invasive. The patient underwent an open left radical nephrectomy and renal pedicle lymph-node dissection. After the tumor was incised, a 9.7x8x6-cm nodular mass, which was grayish yellow and caseous, was found in the left renal cortex. The tumor was diagnosed as MTSCC, and the renal pedicle lymph nodes had no metastasis (0/3 lymph nodes). The patient received chest and abdominal enhanced CT, routine blood tests, liver and kidney function every 3 months during the follow-up period of 80 months, and all these examinations showed no signs of recurrence.

Case 3. A 52-year-old woman without painless gross hematuria or lower back pain, who had suffered from diabetes for 10 years, was in hospital for a 4.3-cm mass in the left lower pole of the kidney, which was found by B-ultrasound in July 2014. Physical examination revealed slight left renal percussion pain. A circular shadow with equal density and clear boundaries (Fig. 3A), which was weaker compared with that of the cortex and greater compared with that of the medulla in the arterial and venous phases, was found by enhanced CT (Fig. 3B and C). MRI revealed a circular abnormal signal shadow of ~4 cm in diameter in the left renal cortex, a moderate signal at T1, a slightly lower signal at T2, slight enhancement in the enhanced scan and a low signal in susceptibility weighted imaging (Fig. 3D-F). After a laparoscopic radical nephrectomy, the kidney was cut open, and a 4.3x3-cm gray-white mass was observed in the renal cortex. The mass were diagnosed as MTSCC. The patient, who underwent chest and abdominal enhanced CT, routine blood tests, liver and kidney function every 3 months, did not receive any other treatment, and after a 56-month follow-up period, no recurrence was found.

Case 4. A 57-year-old man were underwent a B-ultrasound, which revealed a 3.9x4-cm strong-echo mass in the upper middle segment of the left kidney. A physical examination revealed no left renal percussion pain. The shape of the mass was regular, with unclear boundaries. On MRI, a circular abnormal signal was observed in the left kidney, with an equal signal in T1WI (Fig. 4A) and a slightly higher signal in T2WI (Fig. 4B). At 3 days post-hospitalization, the patient underwent a laparoscopic radical resection of the left kidney, and a 3.7x4-cm gray-yellow mass was found. The pathological result was left renal MTSCC. Immunohistochemical results were as follows: CK19(+), CK(+), CK8/18(+), Vimentin(+), CD10(+) and Ki-67 (+). The patient, who received chest and abdominal enhanced CT, routine blood tests, liver and kidney function every 3 months, did not receive any other treatment and was without recurrence after 68 months of follow-up.

Case 5. In March 2012, a 3.6x3.3-cm mass was found in the right kidney of a 49-year-old woman who underwent B-ultrasound. The mass was regular in shape, with an unclear boundary and uneven internal echo. CT showed a 3.6x2.9-cm circular tumor in the right kidney, which had a relatively uniform density. The tumor grew into the renal pelvis and exhibited only slight enhancement (Fig. 5B). The patient underwent a laparoscopic radical resection of the right kidney at 4-days post-admission. After the dissection, a pale-yellow mass with clear boundaries was located near the renal pelvis. Finally, it was diagnosed as MTSCC. Without any other treatment after surgery, the patient, who underwent who received chest and abdominal enhanced CT, blood routine test, liver and kidney function every 3 months, showed no signs of recurrence after 65 months of follow-up.

Discussion

As revealed by previous reports, MTSCC of the kidney occurs predominantly in patients aged between 17 and 82 years, the majority of who are female (female:male, 4:1) (6,7). This result was not confirmed by the three male and two female patients described in the five cases in the present study. Although we consider that there is obvious disparity in the MTSCC sex ratio presented, further statistics are required to elucidate the sex ratio and its associations in such cases.
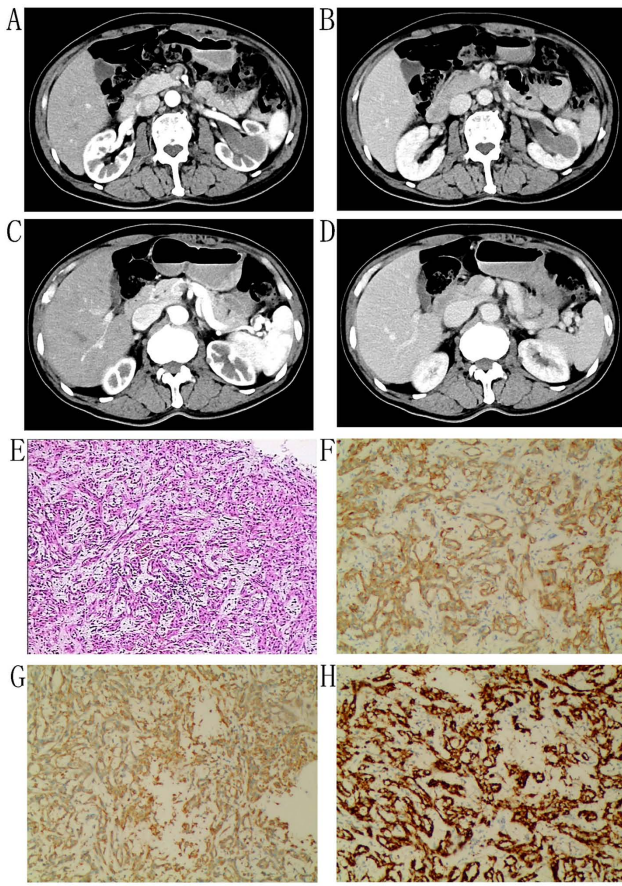
Figure 1. Case 1. (A and B) A 4.4x2.3-cm dense mass with a clear boundary was observed on computed tomography; the tumor exhibited weaker enhancement than the cortex and medulla in the arterial and venous phases. (C and D) A tumor with a size of 0.8x1 cm was located on the surface of the kidney. (E) A number of long narrow tubular epithelial cells were arranged in the sputum, which was filled with a white mucinous matrix and spindle cells (magnification, x20). (F) Positive cytoplasmic staining of vimentin (magnification, x40). (G) Positive cytoplasmic staining of CK8/18 (magnification, x40). (H) Positive cytoplasmic staining of P504s (magnification, x40).
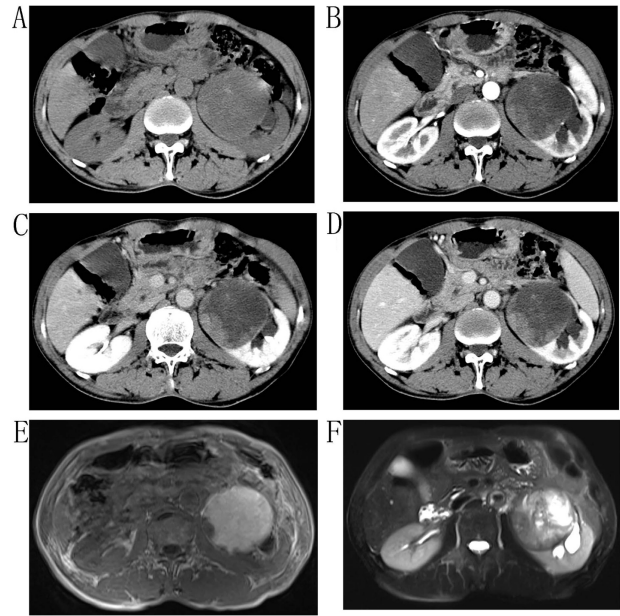

Figure 2. Case 2. (A) The left kidney was significantly enlarged, the capsule was not smooth and there was a cystic-solid soft mass of ~9.7x7 cm in size on CT. The internal density was uneven and small areas of high-density shadow were observed. (B-D) Patchy enhancement was noted in the parenchymal part of the lesion on the enhanced CT, and liquefaction necrosis was recorded in the non-enhanced area. The nodular high-density shadow was seen in the left renal collecting system. In the arterial and venous phases of enhanced CT, tumor enhancement was weaker than that in the cortex and medulla, but in the patchy enhanced zone of the tumor, the enhancement was greater than that in the medulla and lower than that in the cortex. (E and F) A large 9.1x8x6 cm mass in the left kidney showed a mixed signal of equal height in T2WI, a low-hybrid signal in T1WI and uneven enhancement on magnetic resonance imaging. The left renal vein was pressed forward. CT, computed tomography; WI, weighted imaging.

As reported by a previous study (8), no final conclusion exists as to whether MTSCC originates from the loop of Henle or the collecting duct. MacLennan *et al* (2) suggested that the tumors, which had some overlapping features between MTSCC and low-grade collecting duct carcinoma (CDC), originate from the collecting duct epithelium. However, Parwani *et al* (9) put forth the contrary view that cuboidal cells, elongated tubular glands and myxoid stroma, which are the histological features in some MTSCC cases, were associated with the loop of Henle. Epithelial neoplasms are usually polymorphic and well circumscribed. The clinical manifestations and signs of MTSCC are not significantly different from those in common renal tumors, and the imaging findings of the polymorphic tumors are not completely consistent. Thus, it is rather difficult to make a precise preoperative diagnosis. Kenney *et al* (10) reviewed, analyzed and summarized the findings of the CT images of 19 MTSCCs. It was established that the mean tumor attenuation was 36 Hounsfield units in the pre-contrast phase, 67 in the corticomedullary phase (CMP), 89 in the nephrographic phase (NP) and 76 in the excretory phase (10). In the CT imaging of eight MTSCC cases reported earlier by Wu *et al* (7), all tumors were slightly enhanced at
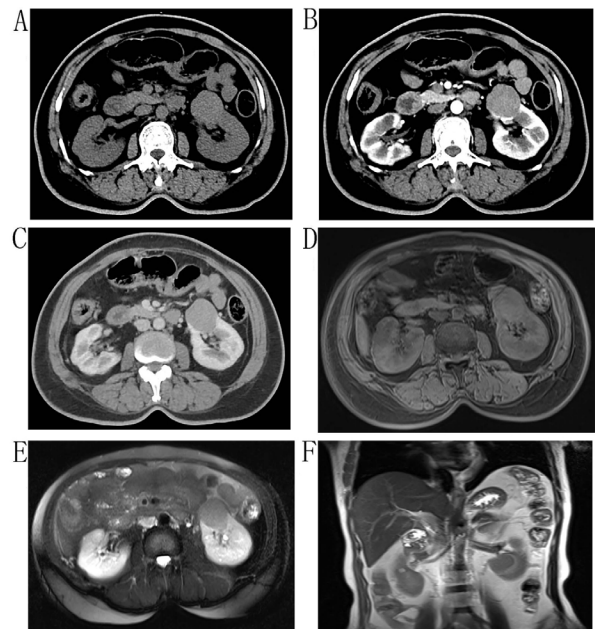

Figure 3. Case 3. (A) The attenuation value of the MTSCC was slightly higher than that of the cortex and the medulla on the computed tomography scan. (B and C) The enhancement of the MTSCC was weaker than that of the cortex and greater than that of the medulla in the arterial and venous phases. (D-F) A circular abnormal signal shadow of ~4 cm was visible in the left renal cortex, with a moderate signal on T1WI, a slightly lower signal on T2WI, slight enhancement in the enhanced scan and a low signal in the susceptibility weighted imaging. MTSCC, mucinous tubular and spindle cell carcinoma; WI, weighted imaging.
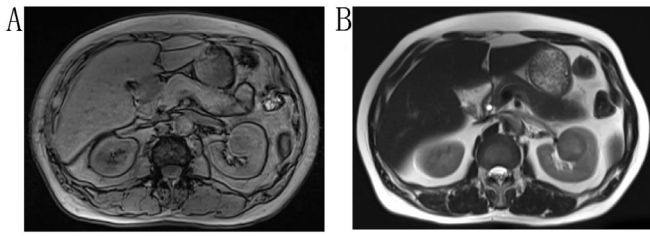
Figure 4. Case 4. (A and B) A circular abnormal signal was detected in the left kidney, with an equal signal on T1WI and a slightly higher signal on T2WI. WI, weighted imaging.
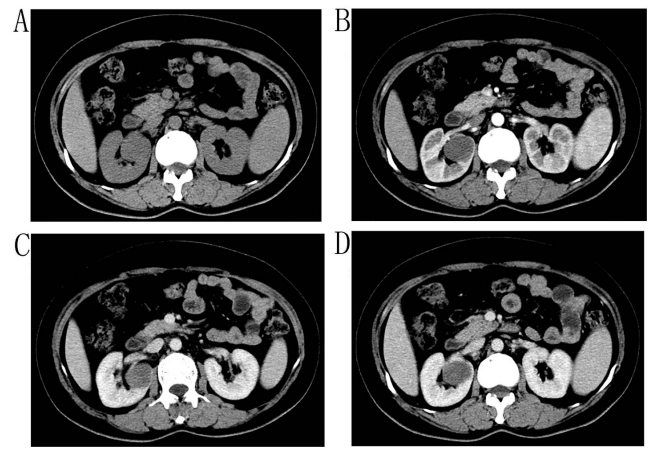

Figure 5. Case 5. (A-D) A 3.6x2.9-cm circular tumor was reported in the right kidney, with a relatively uniform density, which grew into the renal pelvis, and exhibited only slight enhancement. The attenuation value of the solid-cystic tumor was always smaller than that of the cortex and the medulla in any of the phases.

both the CMP and the NP, but less enhanced than the cortex and medulla. In another study, the attenuation of MTSCC tumors in 17 cases was close to that in the cortex and medulla in the CT plain scan, but less enhanced than the cortex and the medulla during all phases of enhanced CT (11). Wu *et al* (12) summarized the CT features of 21 MTSCC cases and 18 CDC cases, and drew the following conclusions: The attenuation value of CDC was greater than that of MTSCC on the unenhanced CT; the enhancement of MTSCC and CDC was less than that of the renal cortex and medulla; and the enhancement of MTSCC was weaker than that of CDC in all phases of enhanced CT. Yang *et al* (13) reported a CT finding of MTSCC with a pattern of 'lightly slow wash-in' in enhanced CT, which is very different from that of normal renal carcinoma. The mass showed slight enhancement, but was less enhanced than the normal renal parenchyma on the arterial and venous phases; however, some areas of the mass showed slightly patchy low attenuation (13). The MRI scan of a MTSCC case reported by Marcela *et al* (14) showed a low signal on T1WI, but some areas of the tumor had a high signal for necrosis and hemorrhage. These areas revealed classic hypervascularization after the injection of contrast medium. On T2WI, the tumor had an intermediate to high signal. In the present study, on the CT scans of cases 1, 2, 3 and 5, it was evident that the enhancement of the tumor was weaker than that of the cortex and medulla in the arterial and venous phases (Figs. 1A and B, 2A-D, 3A-C and 5A-D). The MTSCC showed a mixed signal of equal height on T2WI, a low-hybrid signal on T1WI. The left renal vein was pressed forward (Fig. 2E and F). In case 4, the tumor showed an equal signal on T1WI and a slightly higher signal on T2WI (Fig. 4A and B). It can be noted that the features of CT and MRI in the present five cases were similar to those of the cases previously reported, although some differences remained. Summarizing the CT and MRI findings of other publications and the imaging features of these five cases, it was found that the attenuation value of the tumors in the CT plain scan were close to those of the renal cortex and the medulla, and that the enhancement of the tumor was weaker than that of the cortex and the medulla in both the arterial and the venous phases. The tumors in cases 1 and 5 were endogenous, and their attenuation value was significantly lower than that of the cortex and the medulla on CT scan. Meanwhile, the other three tumors were exogenous and their attenuation values were equal to or higher than those of the cortex and the medulla. We speculate that the reason for this phenomenon is the difference in the origin of the tumor. Earlier reports showed attenuation values of CDC greater than that of MTSCC on unenhanced

CT. Therefore, we speculate that the tumors had two origins: The tumors in cases 1 and 5 originated from the loop of Henle, whereas the other three tumors originated from the collecting tube. All these conclusions are, however, speculative, and should be confirmed by more detailed pathology studies. On MRI, the MTSCCs exhibited a low signal at T1WI but a high signal at T2WI. Moreover, some areas of the tumor had a great enhancement on CT and a high signal on MRI for necrosis and hemorrhage. Although the imaging features of MTSCC have some commonalities, the disease should be diagnosed by the pathological results. As was evident in case 1, the pathological features of MTSCC are long and narrow tubular epithelial cells arranged in the sputum, filled with a white mucinous matrix and spindle cells (Fig. 1E). As reported by Sarsik *et al* (5), MTSCC is subdivided into a classical and a mucin-poor type. In another investigation, Ferlicot *et al* (15) summarized the immunohistochemical results of 15 patients with MTSCC and found that almost all cases had positive expression of epithelial membrane antigen, CK7, CK9, α-methylacyl-CoA racemase, E-cadherin and cytokeratin AE1/AE3 (14). However, in case 1 in the present study, mainly positive expression of Vimentin, CK8/18 and P504s was present (Fig. 1F-H). Sarsik *et al* (5) suggested that it was difficult to distinguish MTSCC from papillary renal cell carcinoma through immunohistochemical results. Therefore, we speculated that these differences between the expression established in previous cases and that in the present cases may be due to the different origins of the tumors. Therefore, there may be multiple origins possible for MTSCC.

MTSCC is a rare kidney tumor, and its main treatments are radical nephrectomy or partial nephrectomy. For patients with metastatic renal cell carcinoma, subtractive nephrectomy plus cytokine therapy is the first choice (16). Retroperitoneal laparoscopic radical nephroureterectomy with bladder cuff resection and transurethral resection of the bladder tumor was therefore performed for case 1; after the surgery the patient received intravesical instillation therapy consisting of gemcitabine hydrochloride and cisplatin chemotherapy every 3 months. In addition, it is still controversial whether

renal pedicle lymph-node dissection is needed for patients for localized renal cell carcinoma and locally advanced renal cell carcinoma. A study by Blom *et al* (17) showed that regional lymph-node dissection did not significantly improve the incidence of complications, overall survival time or disease progression time in patients with localized renal cell carcinoma, and thus it was concluded to be unnecessary. Renal cancer is not sensitive to either radiotherapy or chemotherapy, and there is currently no standard adjuvant treatment for radical nephrectomy. Simon *et al* (18) reported a case in which a patient with MTSCC and two other lesions in the thoracic vertebral bodies received radiotherapy after tumor embolization and radical nephrectomy with vertebral body resection. However, the treatment effect was not ideal, and the patient died with additional vertebral body lesions and liver lesions 3 weeks postoperatively (18). The patients in the present study in cases 2, 3, 4 and 5, who did not receive additional radiotherapy or chemotherapy, had a good prognosis. For patients with metastatic renal cell carcinoma, radical nephrectomy and metastasis are feasible, and postoperative medical treatments include molecular targeted therapy and chemotherapy. As reported previously in 2010, sunitinib was effective for the treatment of a patient with MTSCC (19). Another study (20) administered Proleukin to an MTSCC patient for 3 months, and they remained alive with no recurrence at 9-years of follow-up (20). However, another study indicated that pazopanib was ineffective for MTSCC (21). A further study (22) suggested that patients should receive specific therapies depending on their condition. Molecular targeted therapy with oral sorafenib was administered to an old woman , who had a 7-cm solid mass in the left kidney with pulmonary metastases and a shrunken right kidney, and she had no disease progression for 5 years Additionally, a 49-year-old male with a 19-cm left renal mass and multiple other metastases, received pazopanib for 6 months to reduce the renal tumor volume and underwent a left radical nephrectomy (22). In the same study, the patient diagnosed as MTSCC and metastasis of the bladder received postoperative chemotherapy with gemcitabine in combination with cisplatin, and had no recurrence within a 32-month follow-up period.

As a rare low-grade and indolent renal tumor, MTSCC is considered to have a good prognosis. All five cases included in the present study had a good prognosis. However, increasingly more cases of MTSCC with distant metastases are reported, some of which have a poor prognosis. In an earlier study (21), mucin-poor MTSCC with multiple osseous metastases without sarcomatoid differentiation was found two years after bilateral nephrectomy. The patient received treatment with pazopanib and focal radiotherapy to the lumbar and cervical vertebrae metastases, but the effect was poor, and hepatic and pulmonary metastases were recorded after 3 months of treatment. The patient died a few months later. In another investigation, Sakatani *et al* (23) reported that the CT scan showed para-aortic lymph node metastasis and hepatic metastasis 5 months after radical nephrectomy. The patient received treatment with sunitinib but succumbed to a brain metastasis (23). In a study by Shiro *et al* (24), distant metastases were revealed in the liver and bone by CT imaging after partial nephrectomy, and the patient, who received molecular targeted therapy and irradiation, succumbed due to tumor progression (24). Patients with MTSCC and sarcomatoid changes are considered to have a poor prognosis, with previous evidence showing that three out of five patients developed fatal distant metastasis (25,26). A study by Ged *et al* (27) included 25 cases of MTSCC, and found 3-year overall survival data for 22 cases, while the remaining three cases succumbed to metastasis within 3 years of being diagnosis (27). Although the review of certain cases with distant metastasis would lead us to the conclusion that MTSCC is a tumor with a high degree of malignancy and a poor prognosis, other cases have revealed that MTSCC is indolent and has a good prognosis (2,7,27).

In conclusion, most patients with MTSCC have a good prognosis, but mucin-poor MTSCC with distant metastases or multiple metastases has a bad prognosis. MTSCC may have unconfirmed subtypes, therefore its origin is controversial. The CT features associated with MTSCC include the weaker enhancement of the tumor compared with that of the cortex and medulla in the arterial and venous phases. Surgery is preferred for localized or progressive MTSCC, and progressive cases should receive molecular targeted therapies depending on the condition of the patient, as this may be effective.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable requests.

Authors' contributions

RX, TD, SY and XH analyzed and interpreted the patient data regarding the renal cell carcinoma. PG, QZ and XW performed the histological examination of the kidney, and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committees of The First People's Hospital of Changzhou (Changzhou, China), and all participants provided written informed consent to participate.

Patient consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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