Renal Replacement Therapy

CASE REPORT

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High-grade mucinous tubular and spindle cell carcinoma of the kidney in a patient on hemodialysis: a case report and literature review

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Abstract

Background End-stage renal disease is a risk factor for renal cell carcinoma. However, mucinous tubular and spindle cell carcinoma of the kidney is rare. We report a patient on hemodialysis who had high-grade mucinous tubular and spindle cell carcinoma of the kidney.

Case presentation A 62-year-old Japanese woman had end-stage renal disease and had been on hemodialysis for the previous 4 years. However, periodic imaging examinations to detect kidney cancer had not been conducted. The patient visited our department of urology complaining of general fatigue and dyspnea. Computed tomography with enhancement revealed a solid renal mass with a diameter of 66 mm. It had invaded the right psoas muscle and had multiple lymph node metastases. In addition, the patient had massive ascites and right-sided predominant pleural effusion. We drained the pleural effusion, but she died 11 days after admission. An autopsy was performed. Pathological examination revealed high-grade mucinous tubular and spindle cell carcinoma of the right kidney; multiple organ metastases to the bilateral lungs, liver, gall bladder, uterus, ovary, and inferior vena cava; cancerous pleuritis; and cancerous peritonitis. Our case indicates that high-grade mucinous tubular and spindle cell carcinoma emerging in end-stage kidney causes a detrimental clinical course.

Conclusion High-grade mucinous tubular and spindle cell carcinoma of the kidney had a severe clinical course. We recommend periodic screening of patients with end-stage renal disease, using computed tomography or ultrasound.

Keywords Carcinoma, End-stage renal disease, Hemodialysis, Kidney

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Background

End-stage renal disease (ESRD) is a risk factor for renal cell carcinoma (RCC). Compared with the general population, patients on dialysis with acquired cystic kidney disease have an up to 50-fold increased risk of developing RCC [1]; therefore, clinicians should check the findings of imaging modalities, such as computed tomography (CT) or ultrasound, for patients with ESRD.

Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney is rare; MTSCC constitutes 0.53% of RCC

cases [2]. MTSCC is divided into "high-grade" and "low-grade"; high-grade MTSCC has an aggressive clinical course [3].

We report a case of high-grade MTSCC of the kidney in a patient who was on hemodialysis. The patient died approximately 2 weeks after admission.

Case presentation

In 2020, the patient, a Japanese woman, was 59 years old. She had ESRD due to chronic glomerulonephritis and underwent hemodialysis. Imaging findings such as CT or ultrasound had not been regularly checked to detect RCC at her hemodialysis clinic. When she was 62 years old, the patient visited our hospital with general fatigue and dyspnea. Her vital signs were as follows: systolic blood pressure was 118 mmHg, heart rate was 96 beats per min, body temperature was 36.5 °C, and saturation of percutaneous oxygen was 96%. The blood analysis findings were as follows: the serum creatinine level was 7.12 mg/dL and hemoglobin was 12.4 g/dL. CT with enhancement revealed a solid renal tumor with a diameter of 66 mm (Fig. 1A), tumor invasion of the psoas muscles (Fig. 1B), multiple lymph node metastases, ascites, and pleural effusion in the right lung (Fig. 1C). Her clinical stage was cT4N1M1.

After her admission into our department of urology, a tumor biopsy was performed to check the pathological findings, and the pleural effusion was drained. The cytologic examination of the pleural effusion revealed the presence of atypical cells with enlarged nuclei and increased chromatin. These findings were diagnosed as class V. After drainage of pleural effusion was performed, her blood pressure was decreased, even after using vasopressor drug. She died 11 days after admission.

A pathologic autopsy was performed. On macroscopic observation, the right retroperitoneum had a huge renal tumor (13 cm × 11 cm × 9 cm, 675 g). The tumor had entirely replaced the whole renal parenchyma and exhibited extensive necrosis and areas of hemorrhage (Fig. 2A and B). Numerous disseminated tumor nodules were diffusely scattered throughout the adipose tissue of the retroperitoneum. The total amount of pleural effusion in the left thoracic cavity (drainage done before her death) was 400 mL and ascites was 1200 mL.

The tumor was histologically composed of an aggregation of fused and elongated tubules (Fig. 3A). At higher magnification, these neoplastic cells had poor cell-to-cell adhesion and had large and irregularly shaped nuclei with prominent nucleoli (Fig. 3B). In addition, the tumor comprised spindle-shaped tumor cells, analogous to sarcomatoid RCC cells, arranged in a vague fascicular architecture (Fig. 3C). These proliferated spindle cells also showed marked atypia (Fig. 3D). Mucinous stroma was not confirmed. Extensive lymph vascular invasion was observed.

Immunohistochemistry revealed a patchy positive reaction for α-methylacyl coenzyme A racemase (AMACR) and vimentin in the cytoplasm and diffuse nuclear expression of paired box 8 (PAX8). Carbonic anhydrase IX (CA9), cytokeratin 7 (CK7), high molecular weight CK (HMWCK), and GATA-binding protein 3 were negative (Fig. 4A–F). Methylthioadenosine phosphorylase (MTAP) cytoplasmic staining was absent (Fig. 4G). The nuclear expression of p16 was entirely absent (Fig. 4H).

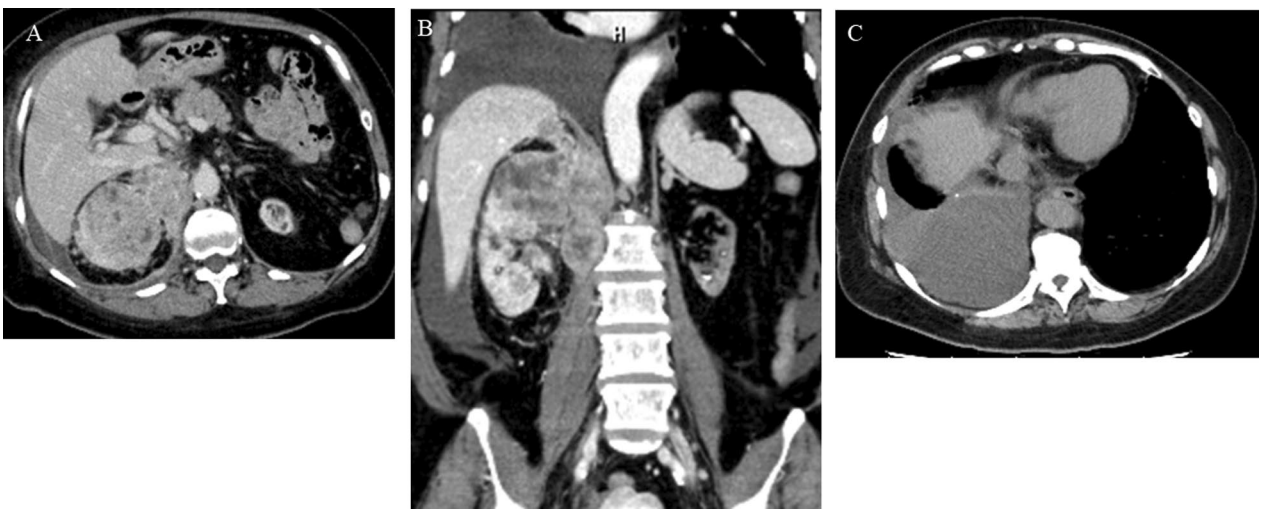

Fig. 1 Computed tomography findings. **A** The enhanced image shows a solid renal tumor with a diameter of 66 mm. **B** The solid renal tumor has invaded the psoas muscles. **C** Pleural effusion in the right lung

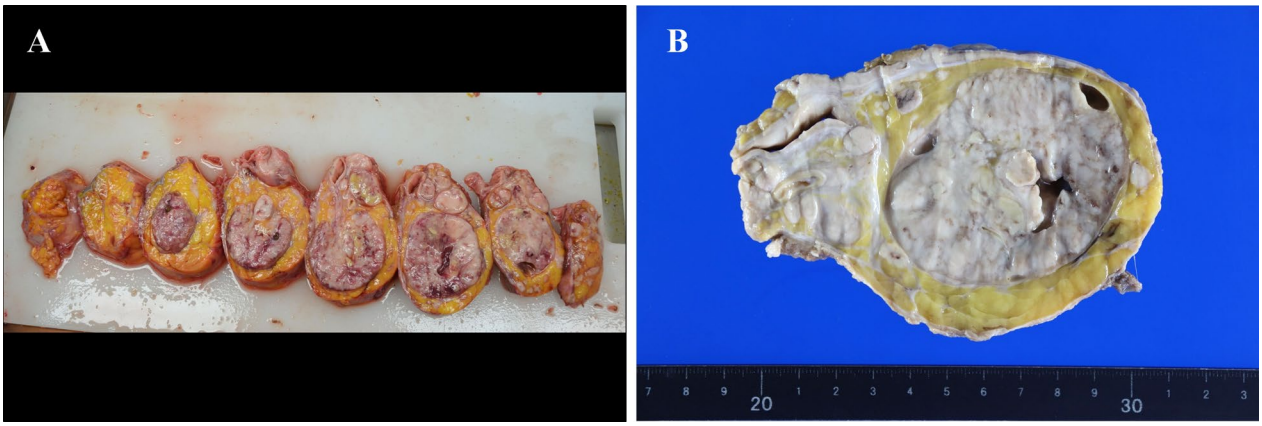

Fig. 2 Gross appearance. **A** Consecutive sections of the right kidney. **B** On the cut surface after formalin fixation, the renal parenchyma has virtually disappeared because of the tumor. Numerous tumor nodules are in the adipose tissue of Gerota's fascia around the main tumor

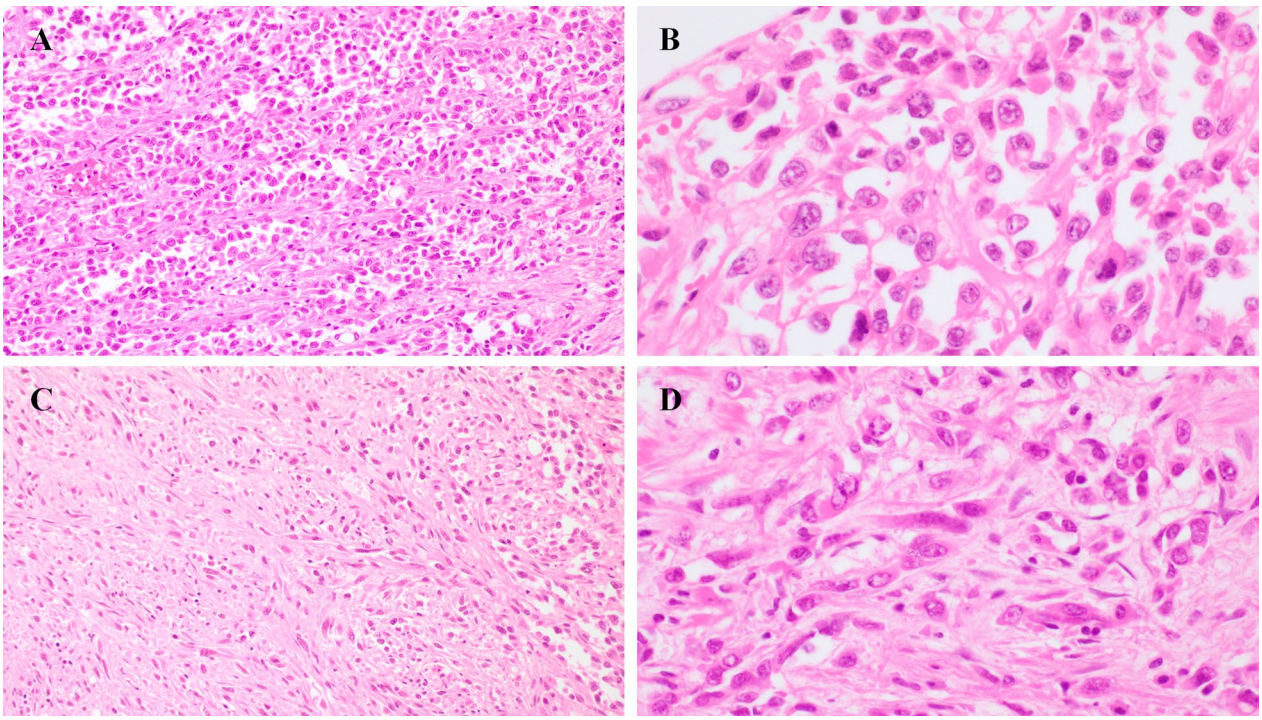

Fig. 3 The microscopic photographs show the histological findings (hematoxylin and eosin staining). **A** The accumulation of complex tubules is visible at low magnification. **B** Tumor cells show distinct cytological atypia with nuclear pleomorphism at high magnification. **C** Stromal spindle cells are arranged in a fascicular pattern at low magnification. **D** The neoplastic cells also have marked atypia at high magnification.

Pathological findings revealed MTSCC (high-grade transformation), grade 4 [based on World Health Organization/International Society of Urological Pathology (ISUP) classification]. The high-grade tumor cells, which were positive for PAX8 expression, were also recognized in the lymph nodes. These cells were compatible with metastasis of MTSCC (high-grade transformation, grade 4). Furthermore, multiple organ metastases to the bilateral lungs, liver, gall bladder, uterus, ovary, and inferior vena cava were also confirmed. The cytology of the pleural and peritoneal effusion was also examined. Numerous epithelial cells with marked atypia were in the cell block of both effusion specimens. This finding was considered cancerous peritonitis. Therefore, we diagnosed MTSCC (high-grade transformation) of the kidney: pT4N1M1, stage IV. We concluded that the patient's

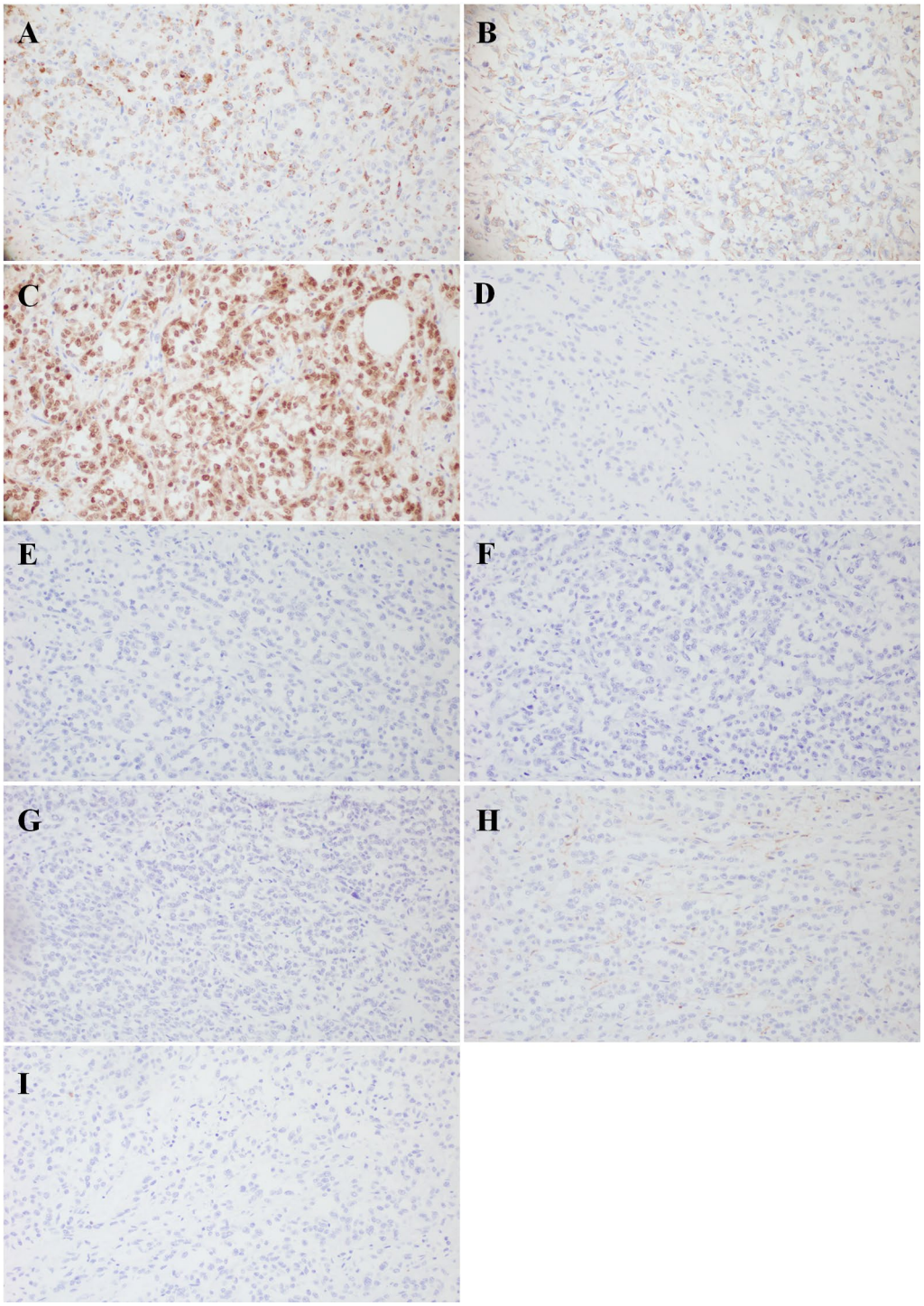

Fig. 4 Immunohistochemistry findings. Tumor cells show partial cytoplasmic positivity for **A** α-methylacyl coenzyme A racemase (AMACR) and **B** vimentin. **C** Diffuse nuclear positivity for paired box 8 (PAX8). **D**–**G** Neoplastic cells are negative for carbonic anhydrase IX (CA9), cytokeratin (CK) 7, high molecular weight CK (HMWCK), and GATA-binding protein 3 (GATA3), respectively. **H**, **I** Methylthioadenosine phosphorylase (MTAP) cytoplasmic staining and p16 nuclear staining are both absent

cause of death was cancerous pleuritis due to rapidly progressive MTSCC (high-grade transformation).

Discussion and Conclusion

MTSCC of the kidney is an uncommon subtype of RCC. MTSCC accounts for 0.53% of all RCCs [2]. Kondo et al. [4] classified pathological examinations of the specimens after radical nephrectomy for RCC in 378 patients with ESRD; the histological subtypes of RCC showed clear cell RCC in 43.6% (165 of 378 patients), acquired cystic disease-associated RCC in 29.6% (112 of 378 patients), papillary RCC in 16.1% (61 of 378 patients), chromophobe RCC in 2.9% (11 of 378 patients), clear cell papillary RCC in 2.1% (8 out of 378 patients), microphthalmia (MiT) family translocation RCC in 0.7% (3 of 878 patients), and unclassified RCC in 4.7% (18 of 378 patients). MTSCC belongs to the unclassified RCC classification, and the frequency of MTSCC may be less than approximately 5% among RCC in patients with ESRD.

Gross images of MTSCC usually show a well-circumscribed mass with solid and gray to tan cut surfaces. Typical MTSCC is histologically composed of elongated and anastomosing tubules and bland spindle cells in the myxoid stroma. Tumor cells generally have low-grade nuclei with infrequent mitosis. The differential diagnosis of MTSCC includes papillary RCC, sarcomatoid RCC, mesenchymal tumors, and metanephric adenoma. Immunohistochemical findings of this subtype typically have positive expression for AMACR, CK7, PAX8, CD10, vimentin, AE1/AE3, and epithelial membrane antigen [5].

In general, high-grade transformation of MTSCC has previously been reported to have the characteristics of distinct nuclear pleomorphism, prominent nucleoli (i.e., WHO/ISUP grade 3), brisk mitosis or sarcomatoid features (i.e., WHO/ISUP grade 4), infiltrative tumor border and vascular invasion, and necrosis. These features are associated with distant metastasis and rapid tumor proliferation and expansion.

Based on genetic aspects, the combination of MTAP and p16 immunohistochemical deficiency is used as a surrogate marker for *CDKN2A/B* homozygous deletion in other histopathological types of tumors such as mesothelioma and glioma [6, 7]. Immunohistochemical co-deficient MTAP and p16 may imply *CDKN2A/B* homozygous deletion. This type of genetic alteration has been detected in high-grade transformation of MTSCC [8]. In the present case, neither MTAP nor p16 was expressed, based on immunohistochemistry findings. Furthermore, behavioral aggressiveness was consistent with that of high-grade MTSCC. In summary, we finally diagnosed MTSCC (high-grade transformation) of the kidney (tumor stage: pT4N1M1, stage IV).

Cases of MTSCC in the background of ESRD have been reported. We have summarized a literature review of six case reports with MTSCC in ESRD [9–13] (Table 1). The average age of the patients with MTSCC was 52.6 years (age range, 39–63 years), the average duration between the year of hemodialysis or kidney transplantation and the year of the surgery for MTSCC was 14.5 years (range, 3–25 years). Nouh et al. [14] reported a relationship between histological type and duration of dialysis; MTSCC was relatively common in patients with more than 10 years on dialysis. However, in our patient, the time from the onset did not match that of previous research. This discrepancy is presumedly associated with high-grade transformation. MTSCC is divided into high-grade and low-grade [3, 14]. High-grade MTSCC has an aggressive clinical course. Yang et al. [3] reported that 8 of 10 cases of locally advanced/metastatic MTSCC (pT3 or N1 or M1) was high-grade MTSCC.

Treatment for MTSCC may involve partial or radical nephrectomy with complete or adequate excision [15]. The consensus about the treatment for locally advanced/metastatic MTSCC has not been reached, to the best of our knowledge. Kenny et al. [16], reported four patients with advanced/metastatic MTSCC who underwent systematic therapy; the patients received vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) therapy with sunitinib, pazopanib, and sorafenib in the first- and second-line therapies, and checkpoint inhibitor therapy with nivolumab in the third-line therapy. However, two of the four patients died when the report was published.

With regard to treating MTSCC in patients with ESRD, Kobari et al. [9] prescribed pazopanib for the first-line therapy, axitinib for the second-line therapy, and cabozantinib for the third-line therapy for multiple metastases; radiation for metastases in the right adrenal gland, para-aortic lymph node, right hip muscle, shoulder muscle, and sigmoid mesocolon; and metastasectomy of back skin metastasis for the treatment of MTSCC in a patient with a transplanted kidney. However, the patient died 7 years after radical nephrectomy. Sokolakis et al. [12] prescribed pazopanib for lumbar and cervical vertebrae metastases to treat MTSCC in a patient with ESRD on hemodialysis. However, the patient died 2 years after undergoing radical nephrectomy.

Hemodialysis is a risk factor for RCC. Compared with the general population, patients on dialysis with acquired cystic kidney disease have up to a 50-fold increased risk of RCC and patients on dialysis have a standardized incidence ratio (SIR) of 3.7 for kidney cancers [1]. Ito [17] recommend that dialysis patients undergo a CT or ultrasound examination at least once annually to detect renal tumors. Patients who have been on dialysis for more

Table 1 Summary of the reported clinical cases of MTSCC in patients with ESRD

Author [reference no.] (publishing year)	Age at surgery for RCC, years/sex	Kidney replacement therapy	Location of RCC	Primary stage	Surgery for RCC/diameter of RCC	Metastasis to other organs	Treatment of other organs	Outcome
Kobari et al. [9]	53/M	Hemodialysis (duration of 24 years), living-related kidney transplantation (8 years ago)	Native kidney	pT3aN0M0	Radical nephrectomy/115 mm × 95 mm × 70 mm	Back skin, para-aortic LN, adrenal gland, hip muscle, shoulder muscle, trapezius, axillary soft tissue, liver, sigmoid mesocolon	Pazopanib, axinib, cabozantinib, radiation, metastasectomy	Died 7 years after radical nephrectomy
Dincer et al. [10]	39/M	Kidney transplantation (10 years ago)	Transplanted kidney	pT1aN0M0	Partial nephrectomy/33 mm × 23 mm × 20 mm	No metastasis	None	3-year survival after partial nephrectomy
Sasaki et al. [11]	72/M	Hemodialysis (duration of 15 years)	Native kidney	pT1bN0M0	Radical nephrectomy/45 mm × 40 mm × 30 mm	No metastasis	None	6-month survival after partial nephrectomy
Sokolakis et al. [12]	47/M	Kidney transplantation (25 years ago), Hemodialysis (duration of 10 years)	Native kidney	pT1aN0M0	Radical nephrectomy/unknown	Lumbar and cervical vertebrae, liver, lung	Pazopanib, radiation	Died 2 years after radical nephrectomy
Alexiev et al. [13]	42/M	Cadaveric kidney transplantation (10 years ago)	Native kidney	pT1bNxMx	Radical nephrectomy/47 mm × 46 mm × 29 mm	Unknown	Unknown	Unknown
Our case (2024)	63/F	Hemodialysis (duration of 3 years)	Native kidney	T4aN1M1	Inoperable/200 mm	Multiple LNs, ascites, pleural effusion on the right-side lung	Palliative treatment	Died 11 days after admission

MTSCC, mucinous tubular and spindle cell carcinoma; ESRD, end-stage renal disease; RCC, renal cell carcinoma; M, male; F, female; LN, lymph node

than 20 years are at high risk for RCC; Ito [17] recommends checking CT or ultrasound images of patients at least every 6 months. Karami et al. [18], report that kidney transplant recipients have an SIR of 5.68 for kidney cancers. Therefore, we recommend checking CT or ultrasound images at least once annually for patients on dialysis and for kidney transplant recipients to detect renal tumors and consulting with urologists if a CT or ultrasound image exhibits a possible renal tumor.

In conclusion, ESRD is a risk factor for RCC. High-grade MTSCC of the kidney is rare, but it may have a severe clinical course. We recommend checking CT or ultrasound images of patients with ESRD to detect RCC early. An early diagnosis may result in a suitable treatment and a favorable prognosis for patients with ESRD.

Abbreviations

ESRD	End-stage renal disease
RCC	Renal cell carcinoma
CT	Computed tomography
MTSCC	Mucinous tubular and spindle cell carcinoma
SIR	Standardized incidence ratio

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Not applicable.

Author contributions
K.Y. and K.Y. were major contributors in writing the original manuscript. T.S., S.K., and T.S. were involved in the patient's clinical care. K.Y., Y.N., and T.N. performed the pathological examination. T.N., Y.N., and M.I. supervised the manuscript.

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Availability of data and materials
Our data cannot be shared openly.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Consent for publication was obtained from the patient's family.

Competing interests
The authors declare that they have no competing interests.

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References

1. Shirazian S, Starakiewicz P, Latcha S. Cancer screening in end-stage kidney disease. Adv Chronic Kidney Dis. 2021;28:502–8.
2. Adamane SA, Menon S, Prakash G, Bakshi G, Joshi A, Popat P, et al. Mucinous tubular and spindle cell carcinoma of the kidney. A case series with a brief review of the literature. Indian J Cancer. 2020;57:367–81.
3. Yang C, Cimera RS, Aryeequaye R, Jayakumaran G, Sarungbam J, Al-Ahmadie MA, et al. Adverse histology, homozygous loss CDKN2A/B, and complex genomic alterations in locally advanced/metastatic renal mucinous tubular and spindle cell carcinoma. Mod Pathol. 2021;34:445–56.
4. Kondo T, Sassa N, Yamada H, Takagi T, Iizuka J, Kobayashi H, et al. Comparable survival outcome between acquired cystic disease associated renal cell carcinoma and clear cell carcinoma in patients with end-stage renal disease: a muti-institutional central pathology study. Pathology. 2021;53:720–7.
5. Shen SS, Ro JY, Tamboli P, Truong LD, Zhai Q, Jung SJ, et al. Mucinous tubular and spindle cell carcinoma of kidney is probably a variant of papillary renal cell carcinoma with spindle cell features. Ann Diagn Pathol. 2007;11:13–21.
6. Maragkou T, Reinhard S, Jungo P, Pasquier B, Neuenshwander MN, Schuchat P, et al. Evaluation of MTAP and p16 immunohistochemical deficiency as surrogate marker for CDKN2A/B homozygous deletion in gliomas. Pathology. 2023;55:446–77.
7. Brcic L, Stang NL, Gallob F, Pissaloux D, Sequeiros R, Paindavoine S, et al. A combination of MTAP and p16 immunohistochemistry can substitute for CDKN2A fluorescence in situ hybridization in diagnosis and prognosis of pleural mesotheliomas. Arch Pathol Lab Med. 2023;147:313–22.
8. Yang C, Cimera RS, Aryeequaye R, Jayakumaran G, Sarungban J, Al-Ahmadie HA, et al. Adverse histology, homozygous loss of CSKN2A/B, and complex genomic alterations in locally advanced/metastatic renal mucinous tubular and spindle cell carcinoma. Mod Pathol. 2021;34:445–56.
9. Kobari Y, Yoshida K, Minoda R, Fukuda H, Hata K, Unagami K, et al. Long-time survival of a renal transplant recipient with metastatic mucinous tubular and spindle cell carcinoma: a case report. In Vivo. 2023;37:1394–8.
10. Dincer E, Ipek OS, Kayipmaz AA, Akca O. Solid renal mass in a transplanted allograft kidney: mucinous tubular and spindle cell renal cell carcinoma. JCPSP Case Rep. 2022;32:192–4.
11. Sasaki Y, Shiozaki K, Nakanishi R, Izaki H, Kanda K, Ishikawa E, et al. Mucinous tubular and spindle cell carcinoma in a patient on hemodialysis: a case report. Hinyokika Kiyo. 2018;64:365–8.
12. Sokolakis I, Kalogirou C, Frey L, Oelschlager M, Krebs M, Riedmiller H, et al. Mucin-poor mucinous tubular and spindle cell carcinoma of the kidney presented with multiple metastases two years after nephrectomy: an atypical behaviour of a rare, Indolent Tumour. Case Rep Urol. 2017;2017:6597592.
13. Alexiev BA, Burke AP, Dranchenberg CB, Richards SM, Zou YS. Mucious tubular and spindle cell carcinoma of the kidney with prominent papillary component, a non-class morphologic variant. A histologic, immunohistochemical electron microscopic and fluorescence in situ hybridization study. Pathol Res Pract. 2014;210:454–8.
14. Nouh MAAM, Kuroda N, Yamashita M, Hayashida Y, Yano T, Minakuchi J, et al. Renal cell carcinoma in patients with end-stage renal disease: relationship between histological type and duration of dialysis. BJU Int. 2009;105:620–7.
15. Nathany S, Monappa V. Mucinous tubular and spindle cell carcinoma a review of histopathology and clinical and prognosti implications. Arch Pathol Lab Med. 2020;144:115–8.
16. Kenny PA, Vikram R, Prasad SR, Tamboli P, Matin SF, Wood CG, et al. Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney: a detailed study of radiological, pathological and clinical outcomes. BJU Int. 2015;116:85–92.
17. Ito K. Renal cell carcinoma in hemodialysis patients. J Natl Def Med Coll. 2022;47:28–37.
18. Karami S, Yanik EL, Moore LE, Pfeiffer RM, Copeland G, Gonsalves L, et al. Risk of renal cell carcinoma among kidney transplant recipients in the United States. Am J Transplant. 2016;16:3479–89.

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