Case Report

Metastatic mucinous tubular and spindle cell carcinoma of the kidney responding to nivolumab plus ipilimumab

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Abbreviations & Acronyms
AMACR = α-methylacyl CoA racemase
ANN = artificial neural networks
BSI = bone scan index
CT = computed tomography
FDG-PET = fluorodeoxyglucose-positron emission tomography
HLA = human leukocyte antigen
HS(n) = Hot spot number
IMDC = International Metastatic RCC Database Consortium
IO = immune-oncology
MTSCC = mucinous tubular and spindle cell carcinoma
RCC = renal cell carcinoma
TKIs = tyrosine kinase inhibitors
WHO = World Health Organization

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Introduction: Mucinous tubular and spindle cell carcinoma is a rare subtype of renal cell carcinoma. Little is known regarding the efficacy of systemic therapy on its metastatic form because of its rarity.

Case presentation: We present the case of a patient with metastatic mucinous tubular and spindle cell carcinoma who achieved durable complete remission of multiple osseous metastases after undergoing cytoreductive nephrectomy followed by combination immunotherapy (ipilimumab plus nivolumab). Immunohistochemical analyses of the primary tumor revealed the presence of the tumor-infiltrating immune cells, including activated $CD8^+$ T cells and PD-L1 expression, suggesting an immunologically hot tumor.

Conclusion: Combination immunotherapy was a viable treatment option for this disease. Immunohistochemical analyses of the tumor-infiltrating immune cells predicted the efficacy of immune checkpoint inhibitors against rare renal cancers.

Key words: cytoreductive surgery, immunotherapy, mucinous tubular and spindle cell carcinoma, nephrectomy, renal cell carcinoma.

Keynote message

- MTSCC can behave aggressively and metastasize.
- Combination immunotherapy with ipilimumab plus nivolumab was effective against metastatic MTSCC.
- Immunohistochemical analyses of tumor-infiltrating immune cells effectively predicted the efficacy of immune checkpoint inhibitors against rare renal cancers, including MTSCC.

Introduction

MTSCC, a rare subtype of RCC, was introduced in the WHO classification system in 2004.[1] MTSCC was initially considered as a low-grade subtype of collecting duct carcinoma[2] but later as an independent histological type because of its significantly favorable prognosis compared to collecting duct carcinoma. Fatal MTSCC cases involving nodal and distant metastases have been reported.[3–6] In the 2016 WHO classification, the description of MTSCC as an indolent disease was removed.[7] There is no recommended systemic therapy for metastatic MTSCC because it is rare, particularly the aggressive type with metastases.[8] We describe a patient with metastatic MTSCC who achieved durable complete remission of multiple osseous metastases after undergoing cytoreductive nephrectomy and IO drug combination therapy.

Case presentation

A 69-year-old man previously consulted for lumbar pain and weight loss visited our hospital after CT detected a large left renal tumor of 9cm in size. In contrast-enhanced CT, the tumor was located at the left kidney's upper pole. We noted slight and prolonged enhancement in

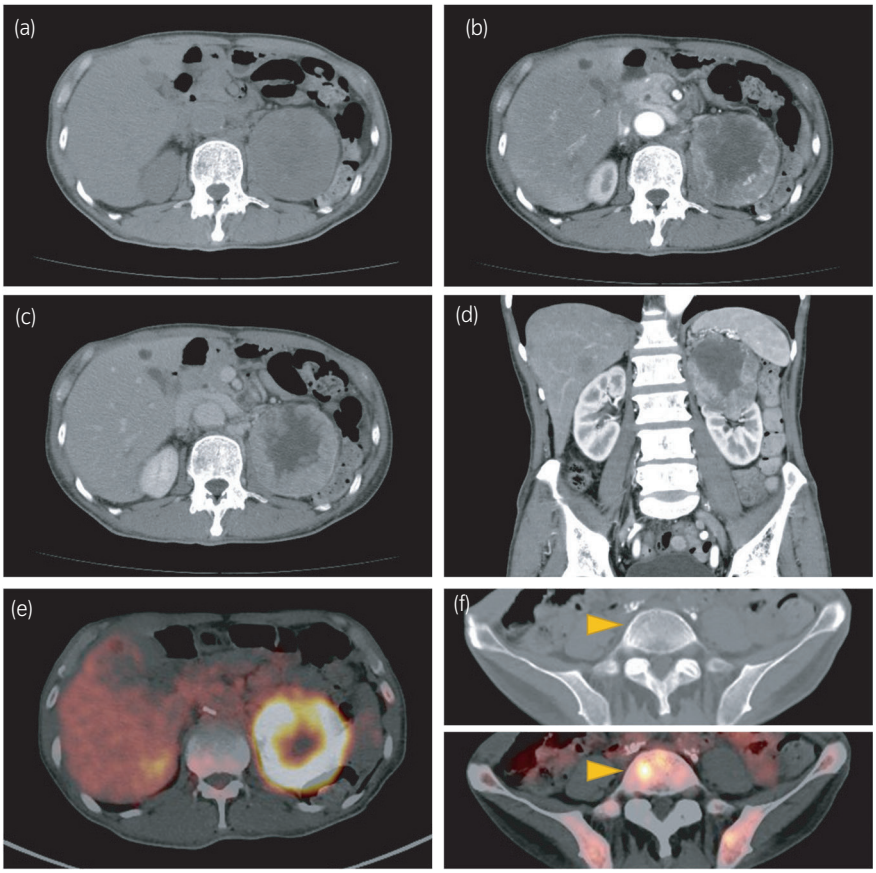

Fig. 1 Computed tomography findings of the left renal tumor and osseous lesions. (a) plain CT, (b) arterial phase, (c) venous phase, (d): Sagittal image in arterial phase, (e) FDG-PET image, (f) representative images of osseous lesions in plain CT (upper) and FDG-PET CT (bottom).

the arterial and venous phases, respectively, suggestive of non-clear cell RCC. Contrast enhancement was seen only peripherally, and the central part was considered necrotic (Fig. 1a–d). On FDG-PET-CT, the tumor's peripheral part showed abnormal FDG uptake (SUV max 11.61). FDG uptake in the central part was scarce, suggesting central necrosis (Fig. 1e). This also revealed FDG-avid multiple osseous lesions, which were difficult to identify on plain CT because they exhibited a mixed (lytic and sclerotic) or intertrabecular pattern (Fig. 1f). Bone scintigraphy could confirm only a subset of these osseous lesions. His clinical staging was T2aN0M1.

His performance status was well preserved (Karnofsky PS 80%). Laboratory test results revealed slight leukocytosis (9.0×10^9/L), neutrophilia (6.7×10^9/L), and anemia (hemoglobin 12.5 g/dL), with elevated alkaline phosphatase (729 U/L) and C-reactive protein (1.16 mg/dL) levels.

We performed an upfront cytoreductive nephrectomy for the left renal tumor. The tumor had a tubulopapillary structure lined by cuboidal cells with mucinous stroma, positive with Alcian blue (Fig. 2a,b). Although the tumor cells were uniformly small with round nuclei, the tumor contained high-grade transformation foci (Fig. 2c) and areas of invasive growth of high-grade spindle cells with intratumor hemorrhage and necrosis (Fig. 2d). On immunohistochemistry, the tumor cells were positive for AMACR (Fig. 2e), fumarate hydratase, and succinate dehydrogenase B but negative for CK7 and TFE3. The final pathological diagnosis was MTSCC, pT2a, Fuhrman grade 3. The tumor cells were strongly positive for PD-L1 (Fig. 2f) and moderately positive for HLA class I (Fig. 2g). The tumor was infiltrated by CD8+ lymphocytes (Fig. 2h) and TIA-1-positive immune cells (Fig. 2i), but FOXP3-positive cells were absent, suggesting an immunogenic tumor.

One month postsurgical laboratory test revealed normalization of neutrophilia and anemia. According to the IMDC Risk Model,[9] he was classified to be at intermediate risk (one positive risk factor: Time from diagnosis to treatment was <12 months). The patient received immunotherapy (ipilimumab and nivolumab) along with a bone-modifying agent (zoledronic acid).

No adverse events were observed. The lumbar pain disappeared after the first cycle. After 4 cycles, bone scintigraphy revealed improvement in multiple osseous metastases. The patient continued receiving nivolumab monotherapy. After 12 months of combination immunotherapy, abnormal signs were absent on bone scintigraphy and FDG-PET CT (Fig. 3), suggesting a clinically complete response. Upon counseling the patient, nivolumab and the bone-modifying agent were terminated at 15 months after combination immunotherapy. He has been under close follow-up for more than 6 months without systemic therapy, and he remained disease free.

Discussion

Not all cases of MTSCC follow an indolent course. This is the first case to report the efficacy of modern immunotherapy with IO drug combinations against metastatic MTSCC.

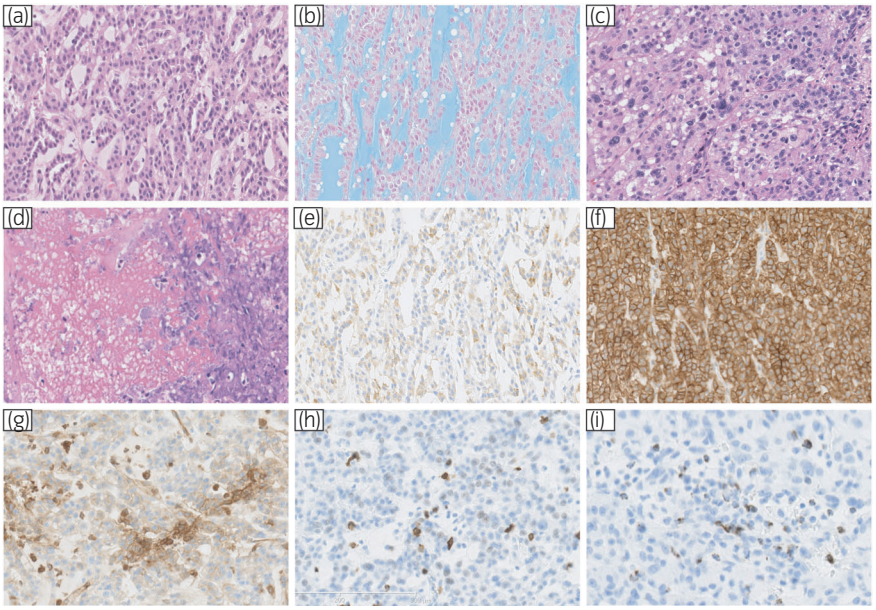

Fig. 2 Histological and immunohistochemical analyses of the primary tumor. (a) HE staining (tubulopapillary lesion), (b) Alcian blue staining, (c) HE staining (high-grade area), (d) HE staining (necrosis), (e) AMACR, (f) PD-L1, (g) HLA class I, (h) CD8, and (i) TIA-1.

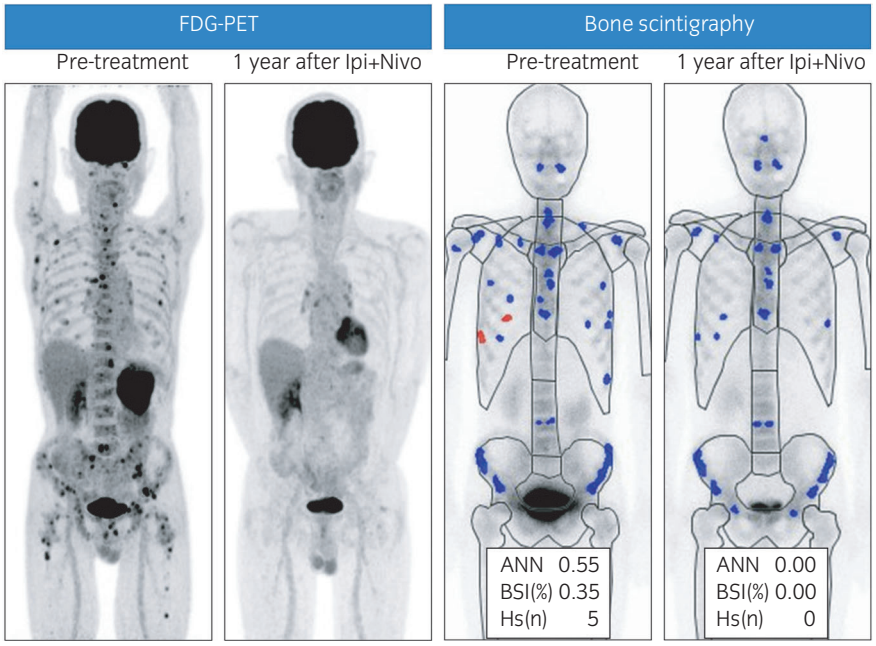

Fig. 3 FDG-PET CT and bone scintigraphy findings before cytoreductive nephrectomy and 1 year after ipilimumab plus nivolumab therapy, showing the complete remissions of multiple osseous metastases.

MTSCC possesses morphological and immunohistochemical characteristics similar to those of papillary RCC with AMACR expression,[10] indicating that MTSCC was a subtype of papillary RCC.[11] Although AMACR expression suggests that MTSCC exhibits proximal nephron differentiation, the histogenesis of MTSCC remains debatable. Our immunohistochemical study demonstrated that the tumor cells were positive for a proximal nephron marker (AMACR) but negative for a distal nephron marker (CK7). These findings suggest that MTSCC originated from the proximal nephron and was not related to collecting duct carcinoma.

In the current case, CT and bone scintigraphy could hardly detect multiple osseous lesions but was pointed out by FDG-PET because these lesions exhibited a mixed (lytic and sclerotic) or intertrabecular pattern. In particular, intertrabecular metastases have tumor cells infiltrating into the marrow space without bone trabecular destruction, therefore being invisible on conventional CT and bone scan. The use of FDG-PET/CT in detecting intertrabecular metastases was reported.[12] Since MTSCC could develop bone metastases of mixed or intertrabecular type observed in the current case, whole-body scanning with FDG-PET could be useful in the initial staging.

The primary tumor cells' immunohistochemistry results suggested that the tumor was an immunologically "hot" tumor in the current case. To have a good anticancer effect by IO drugs, a series of stepwise events, referred to as the cancer-immunity cycle,[13] must occur. The presence of tumor-

infiltrating CD8+ and TIA-1-positive cells represents successful step 5 (infiltration of T cells into tumors), and the expression of HLA class I by the tumor cells suggests successful step 6 (recognition of cancer cells by T cells). The absence of FOXP3-positive cells suggested the absence of regulatory T cells that inhibit step 7 (killing of cancer cells). RCC has been recognized as an unusual disease in which CD8+ T-cell infiltration could be related to a poor prognosis, which might be due to T-cell exhaustion. In this case, TIA-1-positive staining, induced by activated T lymphocytes, suggested that the tumor was infiltrated by activated T cells. Although, the predictive value of PD-L1 has not been revealed because IO drugs were effective irrespective of PD-L1 status, multiple studies suggested that those therapies were more effective in PD-L1-positive patients.[14]

The ideal systemic therapy for metastatic MTSCC remains unknown because most clinical trials excluded patients with non-clear cell histology. Systemic therapies that were proven efficacious against clear cell RCC have been used for metastatic MTSCC. However, these drugs' efficacy was unsatisfactory. In the contemporary series of Kenney *et al.*,[15] two metastatic MTSCC patients underwent sequential therapies with TKIs (sunitinib, sorafenib, bevacizumab), immunotherapy (interleukin-2), and cytotoxic chemotherapy (gemcitabine), which showed limited efficacy. Uchida *et al.*[16] reported a patient who received sunitinib, temsirolimus, and axitinib but showed no objective response. Larkin *et al.*[17] reported a metastatic MTSCC patient who was responsive to sunitinib. Although the efficacy of these conventional drugs needs further evaluation, a more potent therapeutic option for metastatic MTSCC is warranted.

Modern immunotherapy with immune checkpoint inhibitors, including IO drug (anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab) and TKI (axitinib) plus IO drug (anti-PD-1 pembrolizumab or anti-PD-L1 avelumab) combinations, revolutionized a first-line treatment in clear cell RCC. Two studies reported the efficacy of nivolumab monotherapy as a second-line therapy for non-clear cell RCCs, including MTSCC. According to Koshkin *et al.*,[18] one MTSCC patient had stable disease in the first month after nivolumab treatment. The disease progressed in the sixth month, and nivolumab was terminated in the eighth month. According to Chahoud *et al.*,[19] one MTSCC patient had stable disease with a progression-free survival rate of 7.4 months. In the present study, the patient received an IO combination as a first-line therapy. It achieved durable complete remission in multiple osseous metastases, suggesting that the IO combination was highly effective for metastatic MTSCC. The efficacies of the IO combination and IO-TKI combination should be evaluated in future trials. The randomized phase II trial (NCT03075423) comparing the IO combination of nivolumab plus ipilimumab against the current standard of care for previously untreated metastatic non-clear cell RCC is currently ongoing. Additionally, two prospective trials (CheckMate 374 and CheckMate 920), comparing nivolumab monotherapy against the combination of nivolumab plus ipilimumab, included patients with non-clear cell RCC. These studies provide important information regarding the efficacies of nivolumab monotherapy and nivolumab plus ipilimumab combination therapy in non-clear cell RCC, including MTSCC.

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Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Registry and the registration no. of the study/trial

Not applicable.

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