Case Report

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Immunotherapy treatment for sarcomatoid renal cell carcinoma: case report and literature review

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Introduction: Sarcomatoid renal cell carcinoma (SRCC) is clinically rare, accounting for ~1.0–1.5% of renal parenchymal tumors. Although the concept of SRCC was proposed in 1968, the molecular mechanisms and immunological characteristics of sarcomatoid changes remain unclear. In the era of targeted therapy, the overall survival (OS) of patients with SRCC is typically less than 12 months.
Case presentation: This article reports a case of SRCC in an 81-year-old male. Progression-free survival (PFS) was as long as 25 months and OS was 30 months after immunotherapy and the effect was significant. This is the first report of successful use toripalimab in the treatment of SRCC.
Clinical discussion: SRCC is a rare type of renal cancer with no obvious specific clinical manifestations or imaging findings, and the diagnosis of the disease is based on pathological examinations. SRCC has a high degree of malignancy, progresses rapidly, and has a poor prognosis. The effect of traditional treatment is limited, and immune checkpoint inhibitors may have therapeutic potential.
Conclusions: Toripalimab may be effective and further exploration is anticipated to advance a new period of SRCC.

Keywords: case report, immune checkpoint inhibitors, immunotherapy, sarcomatoid renal cell carcinoma, toripalimab

Introduction

Sarcomatoid renal cell carcinoma (SRCC) is the most fatal type of renal cell carcinoma (RCC) and is histologically characterized by the presence of spindle-shaped mesenchymal-like cells in any RCC subtype. Sarcomatoid changes indicate an increased frequency of aggressive behavior of the tumor, including rapid progression and poor prognosis. The natural history and prognosis of SRCCs are poor, as ~60–80% of patients present with advanced or late-stage disease[1]. Median overall survival (OS) is ~6–13 months, and a higher percentage of sarcomatoid dedifferentiation on histology has been reported to confer a worse prognosis[2–4]. Kawakami *et al*.[5] proved that SRCC showed higher PD-L1 expression and higher PD-1- and CD8-positive cell density; the results indicate a notable immunosuppressive environment in SRCC and suggest PD-1/PD-L1 blockade therapy as a potential therapeutic approach for SRCC. Toripalimab is a humanized recombinant anti-PD-1 IgG4 antibody that selectively blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2, and promotes antigen-specific T cell activation. The present report describes a case of SRCC with significant benefits after immunotherapy. Immunotherapy improved the prognosis of this patient, and immune checkpoint inhibitors (ICIs) may impact SRCC management in the future. This case report is reported according to Surgical CAse REport (SCARE) guidelines[6].

HIGHLIGHTS

- Sarcomatoid renal cell carcinoma (SRCC) is a rare entity.
- To accurately diagnose the condition and give the patient a fair prognosis, a multidisciplinary approach involving oncologists, pathologists, and internists is advised.
- The traditional treatment of SRCC has limited efficacy, while immune checkpoint inhibitors may have therapeutic potential.

Case report

An 81-year-old male patient with a medical history of hypertension, benign prostatic hyperplasia, and coronary heart disease was admitted to a hospital in another province due to the discovery of a soft tissue mass in the left renal pelvis during B-ultrasonography for one week after a laparoscopic total length left nephroureterectomy performed in May 2019. There was no history of cancer in the family. Postoperative pathological immunohistochemical diagnosis of sarcomatoid carcinoma indicated the following: CK, vimentin, CK7, and GATA-3 were partially positive; CK20, uroplakin II, and P53 were negative; and Ki-67 (localized, ~50% +). Subsequently, postoperative intravesical instillation with mitomycin was performed four times. No further antitumor therapy was given. Re-examination

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by positron emission tomography/computed tomography (PET/CT) in November 2019 showed a soft tissue mass in the left kidney and ureter, and tumor recurrence was suspected. In addition, soft tissue thickening of the posterior and right sidewalls of the nasopharyngeal roof was considered a nasopharyngeal carcinoma. Multiple lymph node metastases were observed in the left supraclavicular area, right behind the diaphragmatic angle and abdomen, and adjacent to the common iliac vessels. Nasopharyngeal laryngoscopy revealed squamous cell carcinoma: immunohistochemistry results indicated AE1/AE3, CK5/6, P63, P40, and epidermal growth factor receptor (EGFR) were positive (3+); P16, vascular endothelial growth factor (VEGF), and Epstein-Barr encoding region were negative; and Ki-67 (~30%+). A biopsy of the left supraclavicular lymph node revealed a malignant tumor, and renal tumor metastasis was considered. Due to intermittent pain on the left side of the abdomen, hearing loss, and nasal congestion during the treatment period in our hospital from February 2020 to March 2022, the patient received toripalimab successfully (36 times) but suspended due to elevated myocardial enzymes and brain natriuretic peptide, and finally passed away in August 2022. Notably, during periodic review, imaging indicated stable disease (SD) in renal tumors (Fig. 1), partial response (PR) in nasopharyngeal tumor (Fig. 2), and the progression-free survival (PFS) was up to 25 months, and overall survival (OS) was up to 30 months.

Discussion

In 1968, Farrow *et al.*[7] found a type of renal cancer with a mixture of pleomorphic spindle cells and giant cells under the microscope, which was similar to sarcoma, and named it SRCC. Later studies found that sarcomatoid components can be found in the traditional histological types of renal cancer. Therefore, the American Joint Committee on Cancer removed SRCC from the histological types of renal cancer as a separate subtype in 1997, and it is now regarded as a special pathological feature of renal cancer. Only a proportion of sarcomatoid components in each subtype of tumor tissue has been described, and almost all sarcomatoid components are unclassified kidney cancers. Compared with other subtypes of RCC, SRCC progresses rapidly and has poor prognosis; the higher the proportion of sarcomatoid dedifferentiation, the worse the prognosis[1,8].

Clinical manifestations of SRCC

SRCC is more common in middle-aged and elderly people (median age of onset: 60 years) than other age groups and is slightly more common in men than in women (1.6:1). It is often unilateral. The clinical manifestations of SRCC are closely related to the clinical staging at the time of consultation. It is often asymptomatic in its early stages and not easily detected. However, 90% of patients are mostly in the late stage at the time of consultation, with clinical symptoms such as abdominal pain on the affected side, waist mass, and hematuria. The most common metastatic sites of SRCC are the lungs, lymph nodes, bones, liver, and brain. For every 10% increase in the proportion of sarcomatoid dedifferentiation compared with non-SRCC, the risk of death increases by ~6%. Most patients with a survival period of more than 1 year are in the early stages of the disease (T1 and T2 stages) when they are diagnosed, and 60–80% of patients with SRCC have lymphatic invasion and distant metastasis at the time of diagnosis. The median OS (mOS) was 6–13 months, and the median PFS (mPFS) was 3.5–5.8 months[9]. The PFS and OS of this patient were as long as 25 and 30 months after immunotherapy, and the effect was significant.

SRCC imaging

There is no obvious capsule formation in the tumor during the plain CT scan, but the tumor shows infiltrative growth with unclear boundaries. Cystic degeneration and tumor necrosis are common in the inner and central regions of tumors, showing the appearance of cystic and solid tumors. Enhanced CT shows heterogeneous enhancement of the tumor, which is lower than that of the normal renal cortex. The larger the diameter of the tumor, the greater the probability of lesion necrosis. Necrosis is more uneven, mainly due to ischemia caused by the extrusion and rupture of blood vessels; however, regardless of the reason, tumor blood vessels can still cater to a small part of the cancer nest. Therefore, necrosis is incomplete and may result in 'necrotic intra-enhancing foci' seen on imaging. The sensitivity and accuracy of MRI in the diagnosis of SRCC are similar to those of CT, but MRI is superior to CT in showing involvement of the renal vein or inferior vena cava, invasion of surrounding organs, and differentiation from benign tumors or cystic masses. The enhanced CT of the case showed cystic low-density foci with enhanced edges, uniform inner density, and calcification. SRCC lacks specific imaging manifestations and cannot be correctly

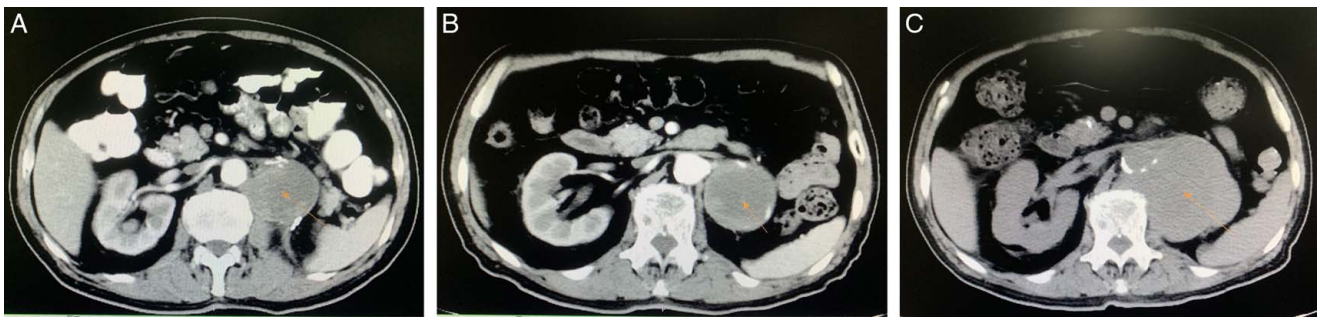

Figure 1. Dynamic changes in computed tomography imaging of the renal tumor during treatment: (A) before immunotherapy (2020-02-15, 4.6×4.5 cm); (B) after four immunotherapy treatments [2020-05-11, 5.5×5.4 cm, indicating stable disease (SD)]; (C) after 36 immunotherapy treatments [2022-03-13, 8.4×8.0 cm, indicating progressive disease (PD)].

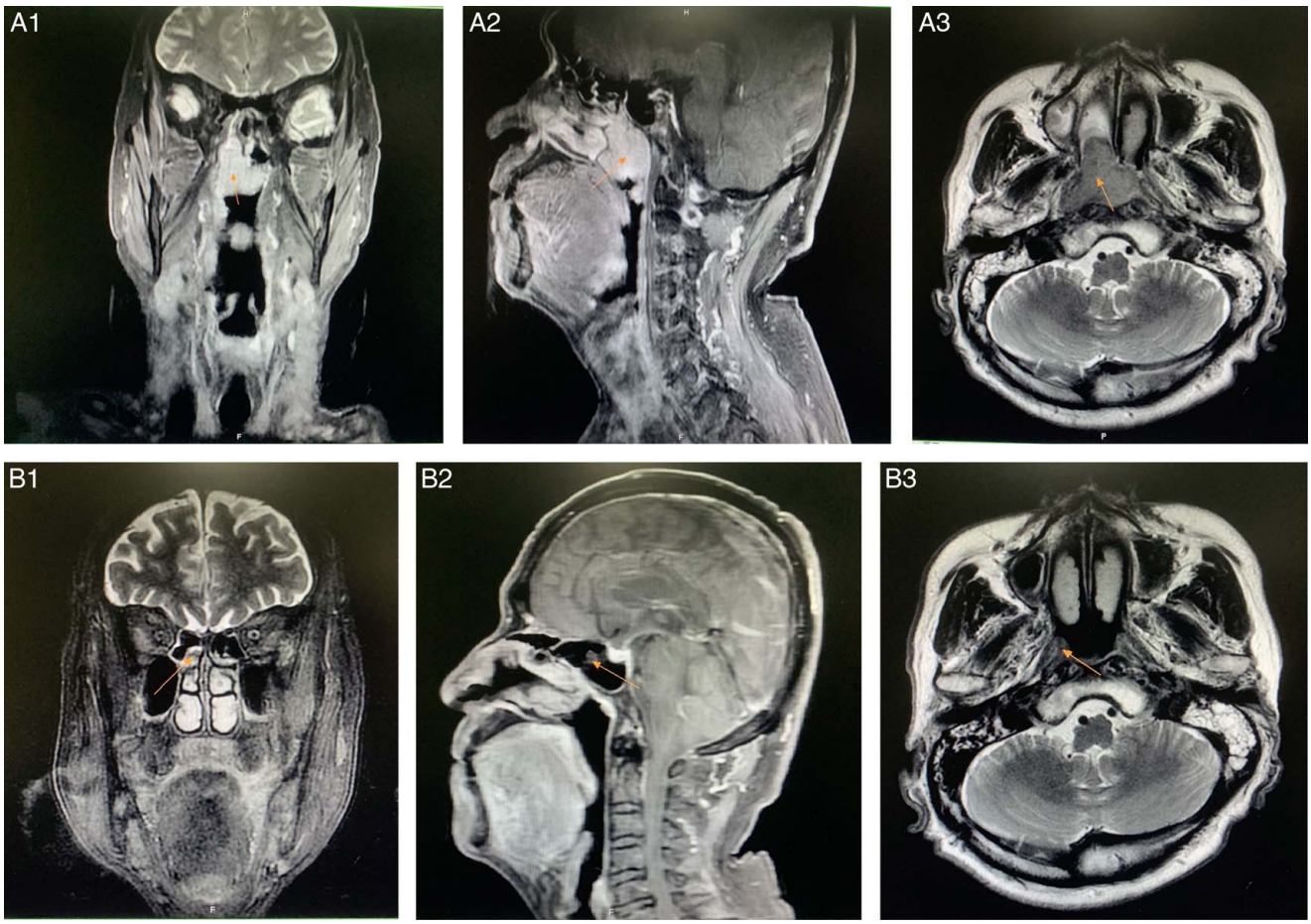

Figure 2. Dynamic changes in MRI of the nasopharynx during treatment: (A1/A2/A3) before immunotherapy (2020-02-15, 3.2 × 3.1 × 3.7 cm) and (B1/B2/B3) after four immunotherapy treatments [2020-05-10, 0.6 × 0.8 × 2.0 cm, indicating partial response (PR)].

diagnosed before surgery; diagnosis depends on postoperative pathological and immunohistochemical examinations.

Pathological features of SRCC

SRCC can originate from various RCC subtypes, such as clear cell carcinoma, papillary RCC, and chromophobe RCC. SRCC is dominated by tumor necrosis and cystic degeneration, and its diagnosis depends on the presence of cord-like spindle cells in the sarcomatoid component area[10,11]. Of note, SRCC is derived from epithelial tissue, but there are two types of epithelial and mesenchymal differentiation in its morphology. Sarcomatoid carcinomas express both epithelial markers, such as CK18, CK7, EMA, and mesenchymal markers (vimentin, S-100, etc.)[12]. The sarcomatoid component of carcinosarcoma only expresses mesenchymal markers. Immunohistochemistry results of the this patient indicated: AE1/AE3, CK5/6, P63, P40, and EGFR were positive (3 +); P16, VEGF, and Epstein-Barr encoding region were negative; and Ki-67 (~30% +).

Treatment of SRCC

The results of some studies showed that surgery[1,3,13,14], chemotherapy[15], or targeted therapy[16–19] were not effective in patients with advanced SRCC. Approximately 77–80% of patients who receive nephrectomy with curative intent for localized SRCC recur within 5–26 months[3,13]. mOS was not more than 1 year in patients who underwent cytoreductive nephrectomy[1,14]. A prospective phase II clinical trial[14] evaluated the efficacy of a combination of doxorubicin and gemcitabine in patients with previously untreated SRCCs, mOS, and mPFS at 8.8 and 3.5 months, respectively. Keskin *et al.*[16] noted a 12-month OS benefit in patients with SRCC treated in the targeted therapy era, which assessed sunitinib, sorafenib, bevacizumab, etc. In a larger retrospective series[17], VEGF inhibitor therapy in 230 patients with metastatic SRCCs, objective response rate (ORR) was 20%, mPFS and mOS were 4.5 and 10.4 months. A phase II trial[18] with metastatic SRCCs was conducted to explore the use of combination chemotherapy with targeted therapy agents, ORR was 20%, mPFS and mOS were 5.5 and 12 months. Another trial[19] presented that mPFS and mOS were 5.29 and 9.43 months for sunitinib plus gemcitabine, and 2.99 and 7.59 months for sunitinib.

Zhao *et al.*[20] collected 59 patients diagnosed with SRCC between 2012 and 2022, the positive expression of PD-1 and PD-L1 was 57.6% and 62.7%, respectively. OS was shorter in the subgroup of patients with PD-L1-positive SRCC compared with the PD-L1-negative subgroup. Toripalimab, a humanized anti-programmed cell death protein 1 (PD-1) IgG4κ antibody[21], is

approved in China for the treatment of six cancer indications, including melanoma[22], urothelial cancer[23], non-small-cell lung cancer[24], and esophageal squamous cell cancer[25], among others. In a phase I trial[26], single-agent toripalimab showed promising clinical activities for patients with previously treated advanced RCC, with an ORR of 33.3% and a disease control rate (DCR) of 50%. To our knowledge, this is the first case report of the use of toripalimab for the treatment of SRCC. Other immunotherapy trials related to SRCC, such as the Checkmate-214 and 016 trials[27–29], compared nivolumab combined with ipilimumab and sunitinib for the first-line treatment of advanced intermediate and high-risk renal cancer. Patients with SRCCs treated with ipilimumab plus nivolumab had improved mPFS (26.5 vs. 5.1 months), complete response rates (CRR) (18.9% vs. 3.1%), partial response rates (PRR) (41.9% vs. 20.0%) and mOS (not reached vs. 14.2 months) compared with those treated with sunitinib. Therefore, it is recommended by major guidelines as the first-line treatment option for SRCC. The KEYNOTE-426 study[30–32] compared pembrolizumab combined with axitinib and sunitinib as first-line treatment for advanced RCC. The results showed that the ORR (58.8% vs. 31.5%), complete CRR (11.8% vs. 0), and 1-year tumor PFS (57% vs. 26%) in the combination group were improved compared with those in the control group. Phase III clinical trials support its use as a first-line treatment option for SRCC. The AVELIN Renal 101 study[33] compared the efficacy of avelumab combined with axitinib and sunitinib in the treatment of SRCC, and the results showed that for PD-L1-positive patients, the combination group could significantly improve the mPFS and ORR compared with the control group (13.8 vs. 7.2 months and 46.8% vs. 21.3%, respectively)[34]. The phase III clinical trial, IMmotion151 study[35–37], compared atezolizumab combined with bevacizumab and sunitinib as first-line treatment for SRCC. The ORR of the combination group and the control group was 49% and 14%, and the mPFS was 8.3 and 5.3 months, respectively; these results support its use as a first-line treatment option for patients with advanced SRCC. In conclusion, the combination of ICIs and targeted drugs prolong OS in patients with advanced SRCC compared with targeted therapy. The patient was diagnosed as having SRCC with multiple lymph node metastases. After toripalimab immunotherapy, the PFS and OS were 25 and 30 months, respectively, and its curative effect was significant.

Conclusion

SRCC is a rare entity. The effect of traditional treatment is limited, and ICIs may have therapeutic potential. Importantly, our patient obtained PFS for up to 25 months while OS for up to 30 months through the application of ICIs. However, because this is a single case report, it is necessary to further expand the sample size in clinical practice to confirm its therapeutic value.

Ethical approval

Not required.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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This study did not receive any sources of funding.

Author contribution

H.S. and G.S.: drafted the manuscript and the collation of the case; X.M.: critically revised the paper; X.Y. and C.Y.: participated in the collection and sorting of images and the format editing of the article. All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not required.

Guarantor

Hui Su, the corresponding author.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Hui Su, upon reasonable request.

Provenance and peer review

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