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# Immunotherapy Treatment for Sarcomatoid Renal Cell Carcinoma: Case Report and Literature Review

*Su H[1,2]*, Ma X[2], Yu C[3], Yu X[4] and Sun G[1]*

[1]*Department of Oncology, Liaocheng People's Hospital, China*

[2]*The Affiliated Qingdao Central Hospital of Qingdao University, Qingdao Cancer Hospital, China*

[3]*Department of Orthopedics, Liaocheng People's Hospital, China*

[4]*Department of Radiotherapy, Liaocheng People's Hospital, China*

## Abstract

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. SRCC is clinically rare, accounting for approximately 1.0% to 1.5% of renal parenchymal tumors. Sarcomatoid changes indicate increased frequency of aggressive behavior of the tumor, including rapid progression and poor prognosis. 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. Considering that the positivity rate of Programmed Death Ligand 1 (PD-L1) is higher in SRCC subgroups, Immune Checkpoint Inhibitors (ICI), especially Programmed cell Death 1 (PD-1) inhibitors, have considerable therapeutic potential. 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. Immunotherapy improved the prognosis of this patient, and ICI may impact SRCC management in the future.

**Keywords: Sarcomatoid renal cell carcinoma; Immunotherapy; Toripalimab; Immune checkpoint inhibitors**

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***Correspondence:***
*Hui Su, Department of Oncology, Liaocheng People's Hospital, and The Affiliated Qingdao Central Hospital of Qingdao University, Qingdao Cancer Hospital, Qingdao 266042, Shandong, China, Tel: +8619963506113*

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## Case Summary

An 81-year-old male patient was admitted to Xuanwu Hospital of Capital Medical University due to discovery of a soft tissue mass in the left renal pelvis for one week after a laparoscopic total length left nephroureterectomy performed in May 2019. 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, approximately 50% +). Subsequently, postoperative intravesical instillation was performed while no other anti-tumor therapy was administered. Re-examination 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 EBER were negative; and Ki-67 (approximately 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), and finally passed away in August 2022. Notably, during periodic review, imaging indicated Stable Disease (SD) in renal tumors (Figure 1), Partial Response (PR) in nasopharyngeal tumor (Figure 2), and the PFS was up to 25 months, OS was up to 30 months.

## Discussion

In 1968, Farrow et al. [1] found a type of renal cancer with a mixture of pleomorphic spindle

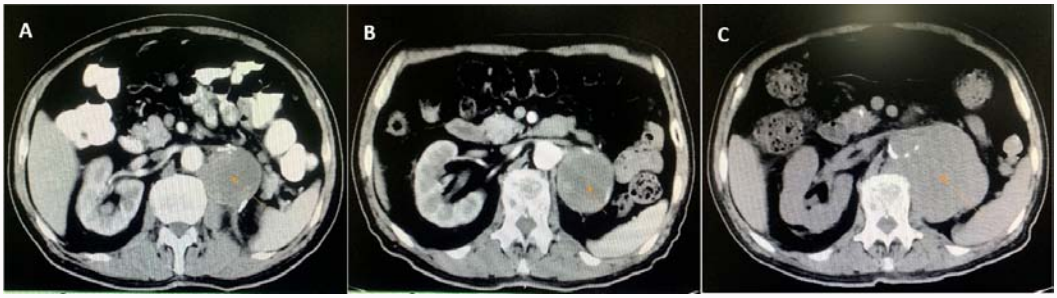


**Figure 1:** Dynamic changes in CT imaging of the renal tumor during treatment.
A: Before immunotherapy (2020-02-15, 4.6 cm × 4.5 cm)
B: After four immunotherapy treatments (2020-05-11, 5.5 cm × 5.4 cm, indicating SD)
C: After 36 immunotherapy treatments (2022-03-13, 8.4 cm × 8.0 cm, indicating Progressive Disease (PD))

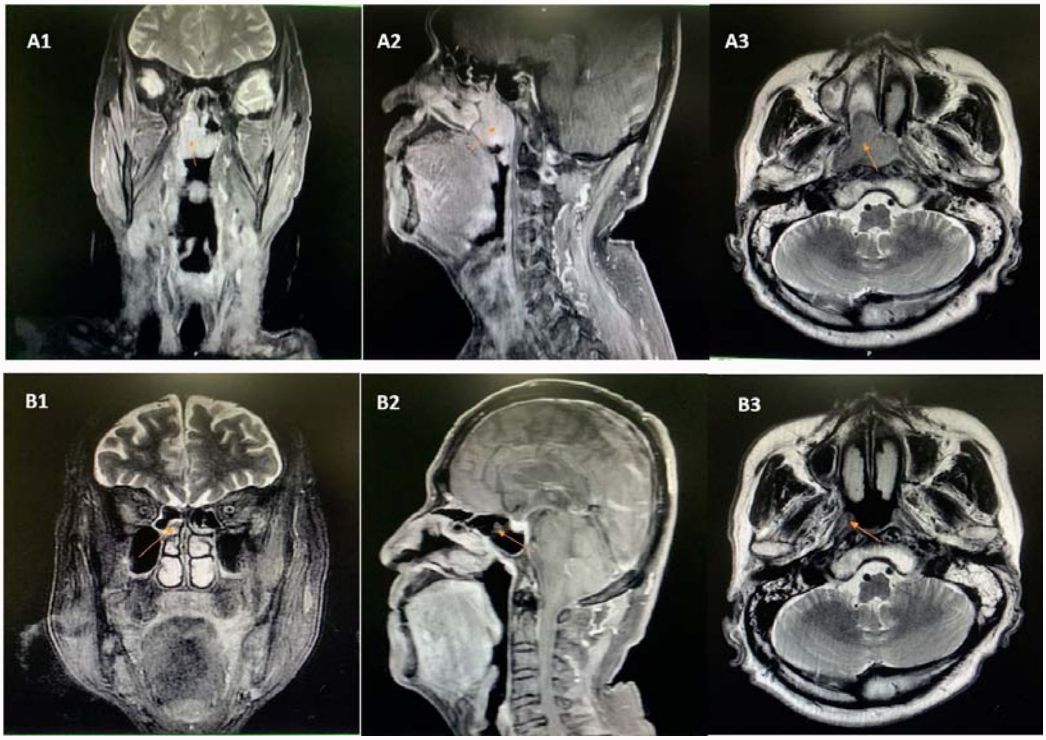


**Figure 2:** Dynamic changes in MRI of the nasopharynx during treatment.
A1/A2/A3: Before immunotherapy (2020-02-15, 3.2 cm × 3.1 cm × 3.7 cm)
B1/B2/B3: After four immunotherapy treatments (2020-05-10, 0.6 cm × 0.8 cm × 2.0 cm, indicating PR)

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 [2,3].

## 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. Among 108 patients with SRCC reported by Mian et al. [4], 25 had tumors confined to the kidney, while 83 had distant metastases. Tumors are mostly invasive and expansive and can grow to a large volume in a short period of time. Invasion of adjacent tissues and organs, the renal capsule, and distant metastases are also common. 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 approximately 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% to 80% of patients with SRCC have lymphatic invasion and distant

metastasis at the time of diagnosis. The median OS (mOS) was 6 to 13 months, and the median PFS (mPFS) was 3.5 to 5.8 months [5]. 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 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 [6,7]. 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.) [8]. The sarcomatoid component of carcinosarcoma only expresses mesenchymal markers. Immunohistochemistry results of this patient indicated: AE1/AE3, CK5/6, P63, P40, and EGFR were positive (3+); P16, VEGF, and EBER were negative; and Ki-67 (approximately 30% +).

### Treatment of SRCC

The results of some studies showed that cytoreductive surgery [9-11], chemotherapy [12], or targeted therapy [13-15] were not effective in patients with advanced SRCC. In-depth research on the pathogenesis and molecular biological characteristics of SRCC revealed that the expression levels of PD-1 and PD-L1 were higher than those of other pathological subtypes [16,17]. Therefore, ICI or immunotherapy combined targeted therapy constitute the first-line treatment. 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. 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 [18-20], compared nivolumab combined with ipilimumab and sunitinib for the first-line treatment of advanced intermediate and high-risk renal cancer. The results showed that the Objective Response Rate (ORR) of the combination group and the control group was 42% and 27% (P<0.0001), and the mPFS was 11.6 and 8.4 months respectively (P=0.0031). Patients in the combination group did not reach the median OS, but their results were significantly better than that in the sunitinib control group. Therefore, it is recommended by major guidelines as the first-line treatment option for advanced renal cancer with an International Metastatic RCC Database Consortium (IMDC) prognostic risk score of intermediate and high risk. The KEYNOTE-426 study [21-23] 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 Response Rate (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 advanced RCC. The AVELIN Renal 101 study [24] compared the efficacy of avelumab combined with axitinib and sunitinib in the treatment of advanced RCC, 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 55.2% *vs.* 25.5%, respectively) [25]. The phase III clinical trial, IMmotion151 study [26,27], compared atezolizumab combined with bevacizumab and sunitinib as first-line treatment for metastatic RCC. 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 ICI and targeted drugs prolongs 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.

In addition, recurrence of SRCC in this patient was accompanied by nasopharyngeal carcinoma. A multicenter, open-label phase II clinical study (NCT02915432) [28] evaluated the efficacy and safety of toripalimab in patients with refractory/metastatic nasopharyngeal carcinoma. The results showed that, as of January 2019, among 135 evaluable patients, 3 CR, 31 PR, and 40 SD were observed, with an ORR of 25.2% and Disease Control Rate (DCR) of 54.8%. In subgroup analysis, the ORR of PD-L1-positive and PD-L1-negative patients was 29.8% and 22.1%, respectively, with no significant difference. After the application of toripalimab in this patient, the curative effect was evaluated by regular imaging, and the tumor was significantly reduced, which was consistent with the reports in the literature.

## Conclusion

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 ICI 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 ICI. 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.

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