Case Report

Small cell carcinoma of the kidney treated with immune checkpoint inhibitor/tyrosine kinase inhibitor

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Abbreviations & Acronyms
CT = computed tomography
EPSCC = extra-pulmonary small cell carcinoma
ICI = immune checkpoint inhibitor
irHLH = immune-related hemophagocytic lymphohistiocytosis
OS = overall survival
SCC = small cell carcinoma
SCLC = small cell lung cancer

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Introduction: Small cell carcinoma (SCC) of the kidney is extremely rare. Although the majority of patients with advanced renal small cell carcinoma were treated with a combination of cisplatin and etoposide, the efficacy was limited. We report the first case with renal small cell carcinoma who received nivolumab and cabozantinib.

Case presentation: A 57-year-old woman was referred to our hospital with a massive left kidney mass and several bone, lymph nodes, liver, and lung metastases. A left renal mass biopsy made the diagnosis of small cell carcinoma. Nivolumab and cabozantinib were used in combination therapy. The tumors were stable during the treatment for 4 weeks. However, the treatment was halted due to a serious adverse event, immune-related hemophagocytic lymphohistiocytosis. Although immune-related hemophagocytic lymphohistiocytosis was resolved with corticosteroids, the patient died 3 months after the initiation of nivolumab and cabozantinib.

Conclusion: We reported the first case of renal small cell carcinoma treated with nivolumab and cabozantinib.

Key words: nivolumab, non-cabozantinib, small cell carcinoma, small cell carcinoma kidney.

Keynote message

We present the first instance of renal SCC treated with nivolumab and cabozantinib. It might be treatment options in patients with unresectable or metastatic renal SCC.

Introduction

SCC primary developing in the kidney is extremely rare. SCC occurs most commonly in the lungs, but EPSCC is a well-recognized disease because of its aggressive disease nature. Due to its rarity, there is no standard of care and optimal treatment has been extrapolated from outcomes for patients with SCLC. So far, the majority of patients with advanced EPSCC were treated with cisplatin and etoposide; however, the efficacy was limited. Recently, ICIs have entered the treatment armamentarium for SCLC, and in NCCN guideline version 2.2022, combination of ICIs plus chemotherapy is said investigational for all patients with EPSCC.[1] So far, no case of renal SCC have treated with ICI plus chemotherapy. We report the first case of a renal SCC treated with nivolumab and cabozantinib who could not undergo chemotherapy because of poor general condition.

Case presentation

A 57-year-old woman went to the orthopedics office with lower back pain. CT revealed multiple bone metastases and a left renal mass, and the patient was referred to our hospital. A big (16 cm × 11 cm × 20 cm) left kidney tumor with late enhancement was identified by contrast-enhanced CT (Fig. 1). Multiple para-aortic and renal hilus lymph nodes, liver, and lung metastases were present. Uptake was seen in the lumber spine (L3/L4), right ilium,

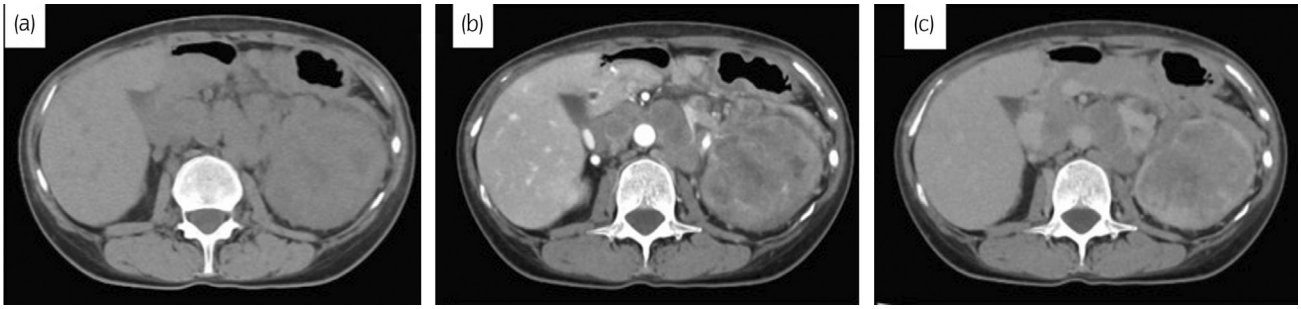

Fig. 1 CT shows a large (16 cm × 11 cm × 20 cm) heterogeneous left renal mass with late enhancement. (a: plain CT, b: early arterial phase, c: excretory phase) and the central low-density area suggests necrotic tissue. The renal hilus lymph nodes were enlarged.

femur, and humerus during the bone scan. A biopsy of the left kidney tumor was conducted using ultrasound guidance. Pathologically, carcinoma cells were arranged in cords and rosette-like growth patterns. Immunohistochemistry revealed the presence of synaptophysin, chromogranin A, and insulinoma-associated protein 1, all of which are linked with small cell neuroendocrine carcinoma (Fig. 2). Furthermore, because of the positive finding of CA9 and CD10, which are specific markers of renal cell carcinoma, a diagnosis of renal SCC was made. The serum concentrations of gastrin-releasing peptide and neuron-specific enolase were 7210 pg/mL (less than 81.0 pg/mL) and 246.7 ng/mL (less than 16.3 ng/mL), respectively.

As first-line therapy, combination therapy with nivolumab (240 mg/body, every 2 weeks) and cabozantinib (40 mg/body) was used. 4 weeks after starting the combination therapy, main lesion and lung metastases tumors shrank by 15% and 16%, while liver and lymph node metastasis enlarged by 19% and 2% on CT (Fig. 3).

Pancytopenia was discovered 6 weeks after the therapy began. The other hematological findings such as elevated ferritin, lactic acid dehydrogenase, and triglyceride levels were also observed. A bone marrow biopsy demonstrated blood cell phagocytosis, leading to the diagnosis of irHLH. Nivolumab and cabozantinib were stopped, and she was given intravenous hydrocortisone (125 mg/body) for the first day,

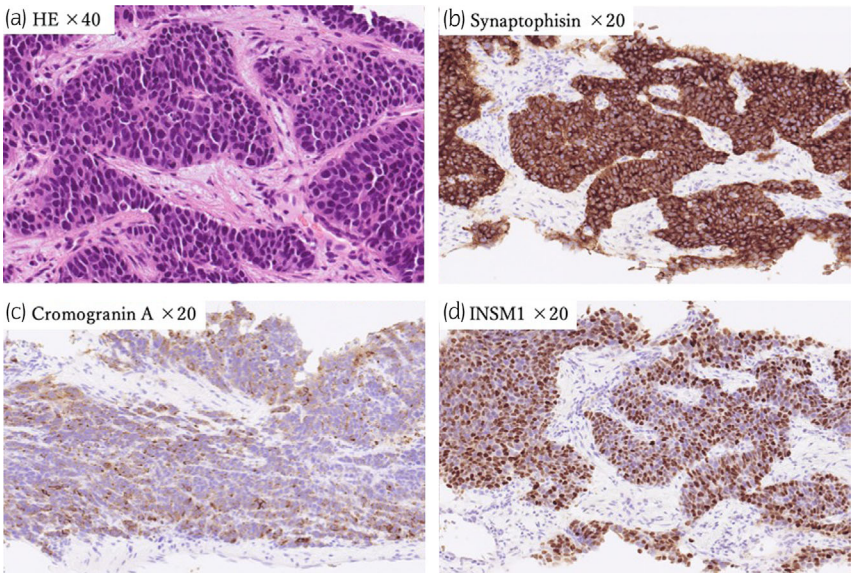

Fig. 2 Histologically, hematoxylin and eosin staining showed that carcinoma cells were arranged in cords and rosette-like growth patterns (a). Immunohistochemistry study showed positivity for general neuroendocrine markers such as synaptophysin (b) and chromogranin A (c), insulinoma-associated protein 1 (d).

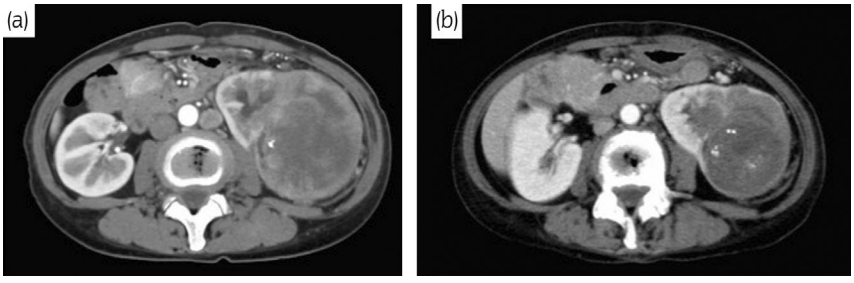

Fig. 3 CT shows a reduction of left renal mass 4 weeks after the initiation of the combination therapy (a: before the treatment, b: 4 weeks after the therapy).

followed by oral prednisolone (1 mg/kg). Laboratory data for irHLH returned to normal ranges in 2 weeks, and prednisolone was reduced to 10 mg per week, nonetheless, her overall condition deteriorated. Furthermore, CT showed obvious progression in all of the metastatic sites. 3 months after starting nivolumab and cabozantinib, the patient died of acute respiratory distress.

Discussion

Renal SCC is extremely rare, with only a few case series found in the literature. Due to its rarity, no standard of care for renal SCC has been established. According to the treatment of SCLC, the majority of advanced renal SCC were treated with cisplatin-based combination chemotherapy. While these chemotherapies produced some examples of tumor response,[2,3] the prognosis is generally poor. A review reported the median OS of 9.31 months.[4]

SCLC is the most prevalent type of SCC. The prognosis is exceedingly dismal, with a median OS of 10.1 months reported for extensive-disease SCLC treated with cisplatin and etoposide combination treatment.[5] Recently, ICIs have entered the treatment armamentarium for SCLC. There are three large phase 3 studies which showed improved OS by adding immunotherapy to first-line chemotherapy. According to the IMpower 133 study, atezolizumab plus carboplatin and etoposide combination treatment enhanced OS compared to carboplatin and etoposide combination chemotherapy (12.3 vs. 10.3 months).[6] Food and Drug Administration approves carboplatin, etoposide, and atezolizumab as the first-line therapy for SCLC. In the phase 3 CASPIAN trial, the addition of durvalumab to chemotherapy was also evaluated in treatment-naive patients with metastasized SCLC. First-line durvalumab plus chemotherapy significantly improved OS (22% after 24 months) in patients with advanced SCLC compared with chemotherapy alone.[7,8] In the phase 3 Keynote-604 study, OS was prolonged in the pembrolizumab plus chemotherapy arm compared with chemotherapy alone.[9]

Because of the rarity and the characteristics of widely distributed throughout the body, SCC originated in except lung are recognized as EPSCC. Recently, according to the development of the treatment for advanced SCLC, EPSCC treatment has been changed. In NCCN guideline version 2.2022, it is said combination of ICIs plus chemotherapy is investigational for all patients with EPSCCs.[1] Although, there was no case with renal SCC treated with neither ICI alone nor ICI plus chemotherapy, ICI was considered as one of valuable treatment options. Unfortunately, because of her bad general condition, intolerability to chemotherapy was expected in this case. Therefore, combination of ICIs or ICI-TKI was considered as the 1st line therapy according to RCC treatment. Physician and patient discussed and decided to treat with nivolumab and cabozantinib which may occur less irAEs than ICIs combination therapy.

To our knowledge, this is the first case of renal SCC treated with ICI and tyrosine kinase inhibitor (TKI) combination therapy. Unfortunately, due to significant irAE, the therapy had to be discontinued in this case. However, 4 weeks of the treatment made the renal mass and lung metastasis decrease in size. As a result, a combination of ICI and TKI may be one of the treatments for patients with renal SCC.

In this case, HLH, an extremely rare irAE, was observed. HLH-2004 diagnostic criteria are used to diagnose HLH. However, exclusion of severe infection and cancer progression is required because of the absence of specific symptoms or laboratory evidence. Hyperferritinemia, on the other hand, with ferritinemia more than 10,000 μg/L having a sensitivity of 90% and a specificity of 96% for HLH diagnosis.[10]

Based on HLH-94 and 2004 protocols, high-dose glucocorticoids, etoposide, methotrexate, and cyclosporine are major components of the treatment regimen of HLH.[11–13] An analysis of 22 instances with irHLH found that the majority of cases were successfully treated with corticosteroids alone or in combination with corticosteroids and etoposide.[14] Some cases who did not respond to corticosteroids were treated with tacrolimus[15] and combination of corticosteroids and mycophenolate motif.[16]

Conclusion

We reported the first case of renal SCC treated with nivolumab and cabozantinib. Although the treatment was stopped after a short amount of time due to irHLH, disease control was achieved during the treatment. Therefore, ICI combination therapy might be treatment options in patients with unresectable or metastatic renal SCC.

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Author contributions

Mirii Harada: Conceptualization; data curation; writing – original draft. Ikko Tomisaki: Conceptualization; writing – review and editing. Shohei Shimajiri: Investigation. Keisuke Kuretake: Data curation. Kenichi Harada: Conceptualization. Naohiro Fujimoto: Supervision; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Not applicable.

Registry and the Registration No. of the study/trial

Not applicable.

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