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Tislelizumab combined with sunitinib in the treatment of metastatic clear cell renal cell carcinoma with renal venous tumor thrombus: A case report and literature review

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ABSTRACT

In recent years, with the in-depth study of PD-1/PD-L1 related pathways, great progress has been made in cancer immunotherapy. However, the immunotherapy regimen for mccRCC is still controversial in clinical practice.

A 50-year-old man with mccRCC complicated with renal venous tumor thrombus from 2019 to present, including surgical treatment, targeted therapy and the combined treatment regimen of "Tislelizumab combined with Sunitinib". Although he experienced a roller coaster of adverse reactions during treatment, the patient's prognosis was good.

Tislelizumab combined with Sunitinib is safe and effective in the Treatment of mccRCC.

1. Introduction

Renal Cell Carcinoma (RCC) is one of the most common tumors of the urinary system, accounting for 2–3% of adult malignancies, and the fatality rate is the first among urinary system malignant tumors.[1] 10% RCC patients had renal vein or inferior vena cava tumor thrombus, of which 1% extended to the right atrium. In untreated RCC patients with venous tumor thrombus, one-year disease-specific survival was 29%.[2]

As an adjunctive therapy for metastatic RCC(mRCC), surgery includes tumor reduction surgery for primary lesions and palliative resection of metastatic lesions, and some patients can achieve long-term survival through surgery. Studies have shown that Cytoreductive Nephrectomy (CN) treatment can prolong the survival time of mRCC patients.[3] Radical Nephrectomy (RN) and Thrombectomy significantly improved survival for RCC patients with venous tumor thrombus.[4,5] There are several subvariants of RCC, and approximately 65–75 percent of individuals are diagnosed with clear cell RCC(ccRCC).[6,7] Although ccRCC is a disease that can be caught early and successfully treated with surgical or ablative strategies, up to a third of cases will present with or develop metastases.[8] However, the treatment of metastatic ccRCC (mccRCC) is still controversial.

Programmed cell death 1(PD-1) binds to ligands on tumor cells and inhibits T cells through a negative feedback loop, resulting in immune response evasion.[9] Targeting PD-1/PD-L1 antibodies block this inhibitory signaling pathway and reactivate the anti-tumor immune response. In recent years, with the in-depth study of PD-1/PD-L1 related pathways, cancer immunotherapy has made great progress. Currently, based on clinical data from many clinical trials, anti-PD-1 or anti-PD-L1 agents are part of the standard of treatment for most advanced malignancies.[10,11] As a new immunosuppressant of PD-1, Tislelizumab was approved by National Medical Products Adminisration(NMPA) in 2020 for the treatment of patients with locally advanced or metastatic uroepithelial carcinoma (UC) with high PD-L1 expression who have failed chemotherapy with platinum-containing drugs, including progression within 12 months after neoadjuvant or adjuvant chemotherapy. However, the application in patients with mccRCC is rarely studied, and its clinical efficacy remains unclear.

We reviewed a case of a patient with mccRCC whose metastatic lesions were well controlled after the treatment of Tislelizumab combined with Sunitinib, which had a poor therapeutic effect after the treatment of Axitinib and Pazopanib. In the meantime, we reviewed the relevant literature and reported as follows.

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2. Case presentation

The patient, a 50-year-old middle-aged male with a history of hypertension for many years, has not regularly taken medication and monitored blood pressure. On July 22, 2019, the patient was admitted to the respiratory department because of chest tightness and asthma. Chest CT showed soft tissue shadow of the right kidney, multiple nodules in both lungs, and lymph nodes in the right hilar was enlarged. After admission, enhanced CT examination (Fig. 1A–C) showed renal cancer with multiple metastasis to both lungs, lymph node metastasis to right hilar lung, and tumor thrombus formation to right renal vein. Therefore, the diagnosis was considered as follows: 1.Right kidney cancer with multiple metastasis(T3aN1M1); 2.Multiple pulmonary embolism; 3. Pulmonary hypertension; 4.Hypertension. After consultation with our department, the patient was transferred to our department for further specialized treatment.

After the patient was transferred to our department, auxiliary examinations such as blood routine examination, complete coagulation, biochemical electrolyte examination and cardiac ultrasound were completed, and no obvious surgical contraindications were found. According to guidelines, laparoscopy-assisted radical nephrectomy of right kidney conbined with removal of renal vein tumor thrombus was performed under general anesthesia on August 01, 2019. During the operation, a mass was found at the lower pole of the right kidney, with a range of about 12*10*8cm. The tumor adhesion with the surrounding tissue was heavy, and the renal pedicle vessels were carefully dissociated, one renal artery was found. The tumor thrombus was touched in the right renal vein, and the severed renal vein was ligated from the place where the renal vein entered the inferior vena cava. Blunt and sharp dissociation of the kidney and perirenal fat along the perirenal fascia was performed. The ureter was severed, and the tumor and the right kidney were completely removed. The operation was successfully completed, which lasted 6 hours and 15 minutes. 5.5U of MAP and 400ml of fresh frozen plasma were transfused during the operation. 4 months after the operation, CT reexamination showed that right renal tumor and renal venous carcinoma thrombus were completely resected compared with that before the operation (Fig. 1D–F). Postoperative pathology indicated clear cell renal cell carcinoma of right kidney, WHO/ISUP grade: grade 3, involving renal capsule, ureter stump, renal artery and vein stump and perirenal adipose tissue were not involved (Fig. 2A–E). The clinical stage of the patient was pT4NxM1 stage IV. The patient's treatment process was shown in Fig. 2F.

According to international guidelines, surgical treatment was better than drug therapy for single metastases, and combination therapy was recommended for patients with medium or high risk of IMDC(International Metastatic Renal Cell Carcinoma Database Consortium). The patient had multiple systemic metastases, and the risk of IMDC was classified as medium-risk. After full communication with the patient, no surgical treatment was performed on the metastases, and the patient refused the combined treatment for fear of greater side effects. After weighing the pros and cons, the patient had been receiving oral targeted drug therapy since September 2019. 3 months after the use of Axitinib, chest CT was reviewed, and it was found that bilateral pulmonary nodules in the patient were increased and enlarged, cavities were found

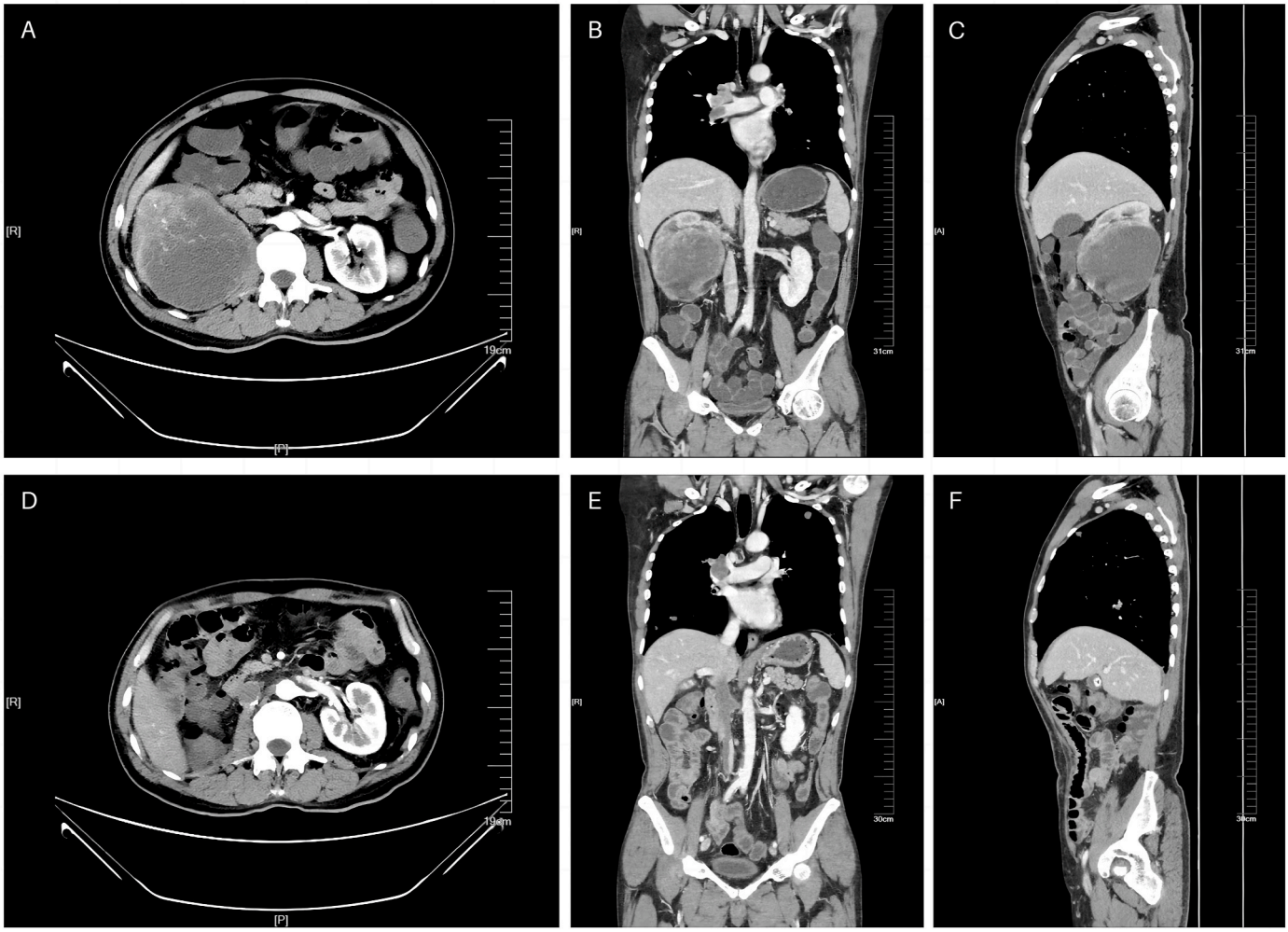

Fig. 1. Preoperative(A-C) and postoperative(D-F) CT examination results of the patient.

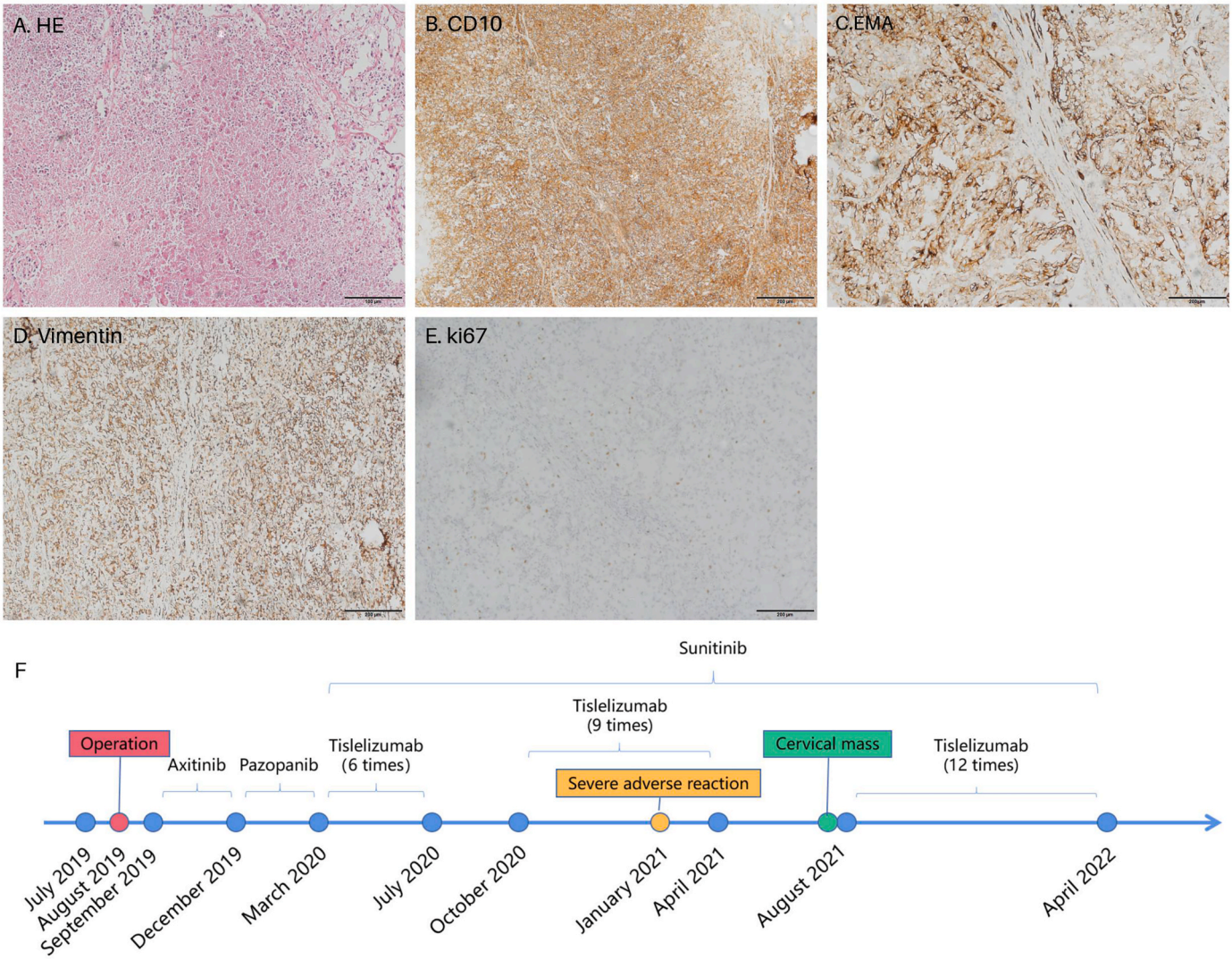

Fig. 2. Postoperative pathological sections and timeline of the patient. A:H&E B-E:Immunohistochemistry F:Timeline of patient's main management.

in some nodules, and lymph nodes in the mediastinum and bilateral hilar were enlarged compared with before (Fig. 3A–C). Therefore, Pazopanil was taken orally for 3 months, and chest CT was reexamined again. It was found that bilateral pulmonary nodules increased, hilar lymph nodes in mediastinum and on both sides increased, and nodules around quadratus lumborum increased (Fig. 3D–F).

After 6 months of postoperative treatment with targeted drugs (Axitinib and Pazopanib), the efficacy was not good, and the lung metastases increased rapidly. The MDT(Multidisciplinary Team) of our hospital (including the department of urology, oncology, radiotherapy, etc.) carried out multidisciplinary comprehensive discussion and fully communicated with the patient, and the combination of immunotherapy and targeted drugs was decided: Tislelizumab(200mg, three times a week) combined with Sunitinib(50mg, 4 weeks of treatment and 2 weeks of withdrawal were divided into one cycle). After the first round of 6 times, the second round of 9 times, and the third round of 12 times of immunotherapy combined with targeted drugs, chest CT reexamination showed that bilateral pulmonary nodules were significantly reduced, and the mediastinal and bilateral hilar lymph nodes were reduced. The low density foci under the capsule of the right lobe of the liver and the nodules beside the quadratus lumborum were significantly smaller than before (Fig. 4).

After oral targeted drug therapy, the number of white blood cells of the patient decreased gradually. After treatment with Recombinant Human Granulocyte Colony-Stimulating Factor, the number of white blood cells increased and fluctuated to the lower limit of normal reference value (Fig. 5A). Since January 2021, the patient's general condition was poor and hematologic examinations showed significant abnormalities, such as decreased white blood cell count, decreased platelet count, hypothyroidism, and increased creatinine(Fig. 5B–F). After multidisciplinary consultation in the department of urology, ICU and Oncology of our hospital, we decided to postpone the current immunotherapy combined with targeted drug therapy. The patient's symptoms improved after one week of treatment with methylprednisolone, Recombinant Human Granulocyte Colony-Stimulating Factor, Recombinant Human Thrombopoietin(15,000 U), platelet infusion and oral thyroxine tablet. The treatment regimen(Tislelizumab combined with Sunitinib) was continued as before. In August 2021, the patient found an enlarged neck mass for more than 3 months and was advised to undergo surgery, but the patient refused.

To date, the patient is continuing to receive immunotherapy combined with targeted drug therapy(Tislelizumab combined with Sunitinib), and recent CT findings confirm that the patient is in good condition. Compared to 2021, the metastatic lesions are stable and neck mass has not grown further.

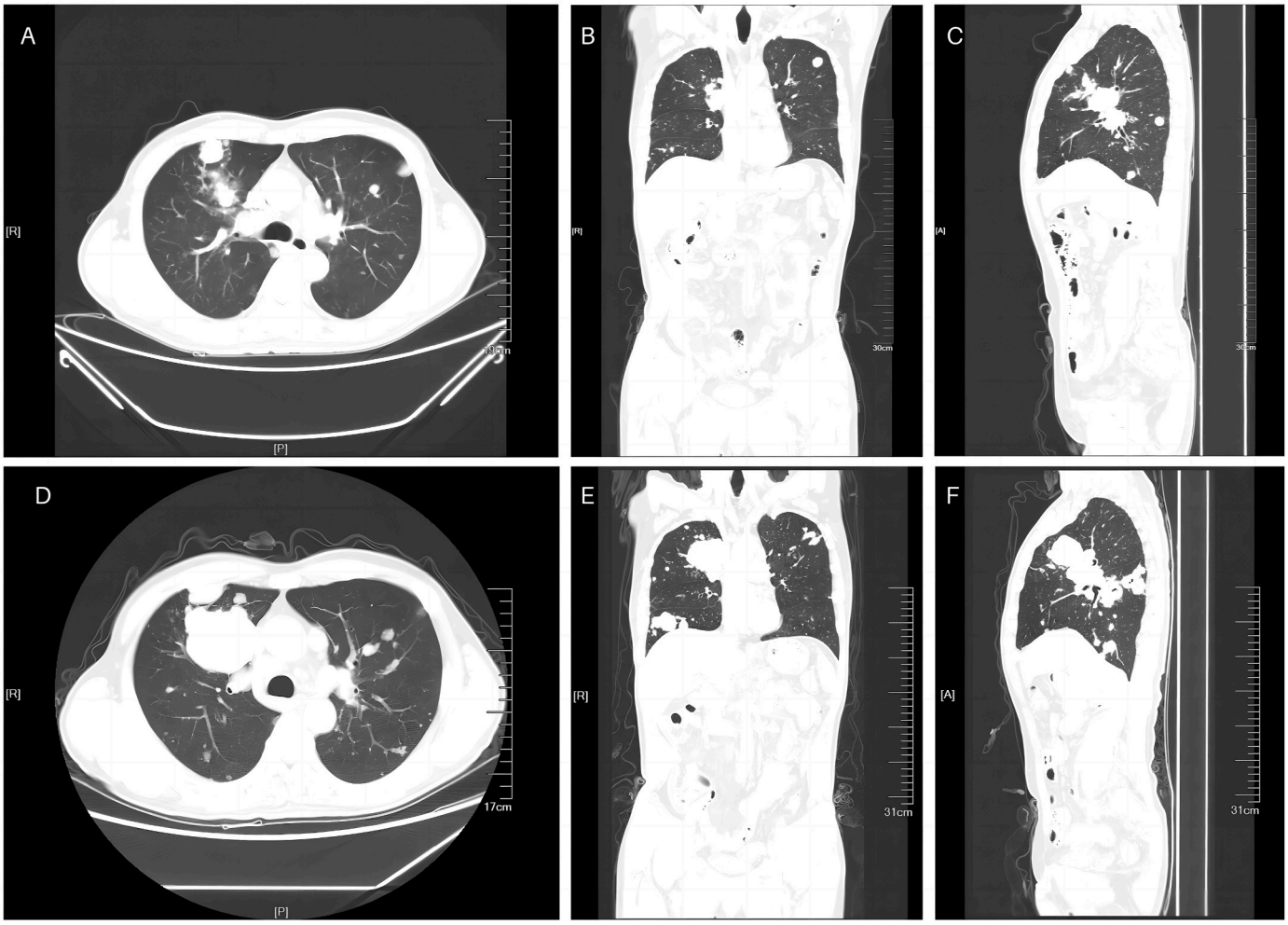

Fig. 3. Poor treatment of patients with oral targeted drugs. A–C 2019.12.03, 3 months after the use of Axitinib, the maximum diameter of lung metastases was about 28mm. D–F: 2020.03.10, 3 months after the use of Pazopanib, the maximum diameter of lung metastases was about 58mm.

3. Discussion

For patients with advanced RCC, the tumor has spread and metastasized, and surgery is no longer able to achieve the goal of radical cure. Moreover, the effect of traditional radiotherapy and chemotherapy is poor, and the survival prognosis of patients is not good. Since 2015, a large number of clinical studies have confirmed that single drug therapy or combination therapy with ICIs(Immune Checkpoint Inhibitors) can achieve significant survival benefit for patients with mRCC, and has therefore been included in the first and second line therapy in various international guidelines.[12–14] The first-line therapy for advanced ccRCC approved by FDA(Food and Drug Administration) mainly consists of mTOR (Mammalian target of rapamycin) inhibitors, angiogenesis inhibitors (VEGFR) and checkpoint inhibitors (ICIs).At present, NCCN, EAU, CUA and CACA - GU and other domestic and international guidelines recommend the first-line treatment of advanced ccRCC schemes are mainly TKIs(tyrosine kinase inhibitors) class targeting single drug therapy and immune targeted therapy two broad categories. In recent years, a number of international multi-center clinical trials have shown that immunotherapy combined with targeted therapy is better than targeted or immunomonotherapy for advanced ccRCC, especially for patients with moderate or poor prognosis in the IMDC score.[15–17]

Besides, immunotherapy has become a new force in the treatment of advanced renal clear cell carcinoma, which makes people have a new understanding of the treatment of renal cancer. Tislelizumab, a humanized IgG4 monoclonal antibody against PD-1, was approved by the National Medical Products Administration (NMPA) on December 26, 2019 for the treatment of patients with typical Hodgkin's lymphoma. In April 2020, tirelizumab was approved by NMPA for the treatment of patients with locally advanced or metastatic PD-L1 high expression of urothelial carcinoma (UC) who have failed chemotherapy regiments containing platinum-based drugs, including progression within 12 months after neoadjuvant or adjuvant chemotherapy. Tislelizumab is the first PD-1 mab approved for urothelial carcinoma in China. The latest study shows that Tislelizumab has shown a meaningful clinical benefit with a manageable safety profile in previously treated patients with locally advanced or metastatic PD-L1 positive urothelial carcinoma.[18] After reviewing the literature, we found that there are few studies on the application of Tislelizumab in patients with metastatic clear cell renal carcinoma. Fanjie Qu[19] et al. first reported a case of efficacy observation of Tislelizumab plus Apatinib in patients with advanced ccRCC in 2022, and the patient achieved stage results after treatment. A retrospective study in 2022 showed that Tislelizumab plus Axitinib significantly increased ORR (59.1% vs. 40.7%) and DCR (81.8% vs. 66.7%) in patients with advanced renal clear cell carcinoma compared with acitinib monotherapy.[20] However, there are limited clinical data on the efficacy of Tislelizumab in patients with mccRCC. Further observation and accumulation of more experience are needed to conduct further clinical studies on the efficacy and safety of this combination regimen.

To review our case of ccRCC with multiple lung metastases and renal

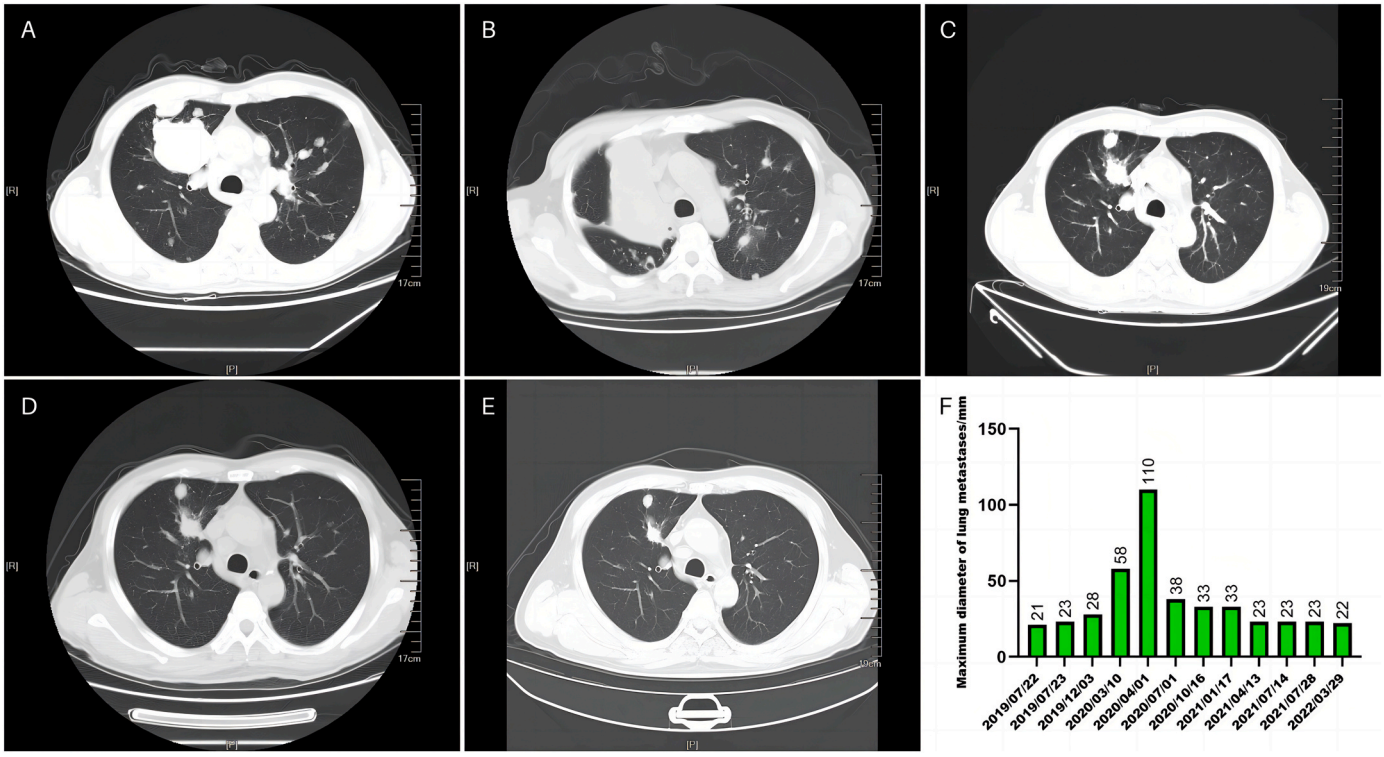

Fig. 4. Efficacy of immunotherapy combined with targeted drugs of the patient. A:2020.03.10, the maximum diameter of lung metastases was about 58mm, the patient was treated by "Tislelizumab + Sunitinib". B:2020.04.01, the maximum diameter of lung metastases was about 110mm. C–E: After the first round of 6 times (C: 2020.07.01), the second round of 9 times(D: 2021.04.13), and the third round of 12 times(E: 2022.03.29) of immunotherapy combined with targeted drugs, chest CT was reviewed. F:The trend chart of the maximum diameter of lung metastases in this patient during immunotherapy combined with targeted drugs.

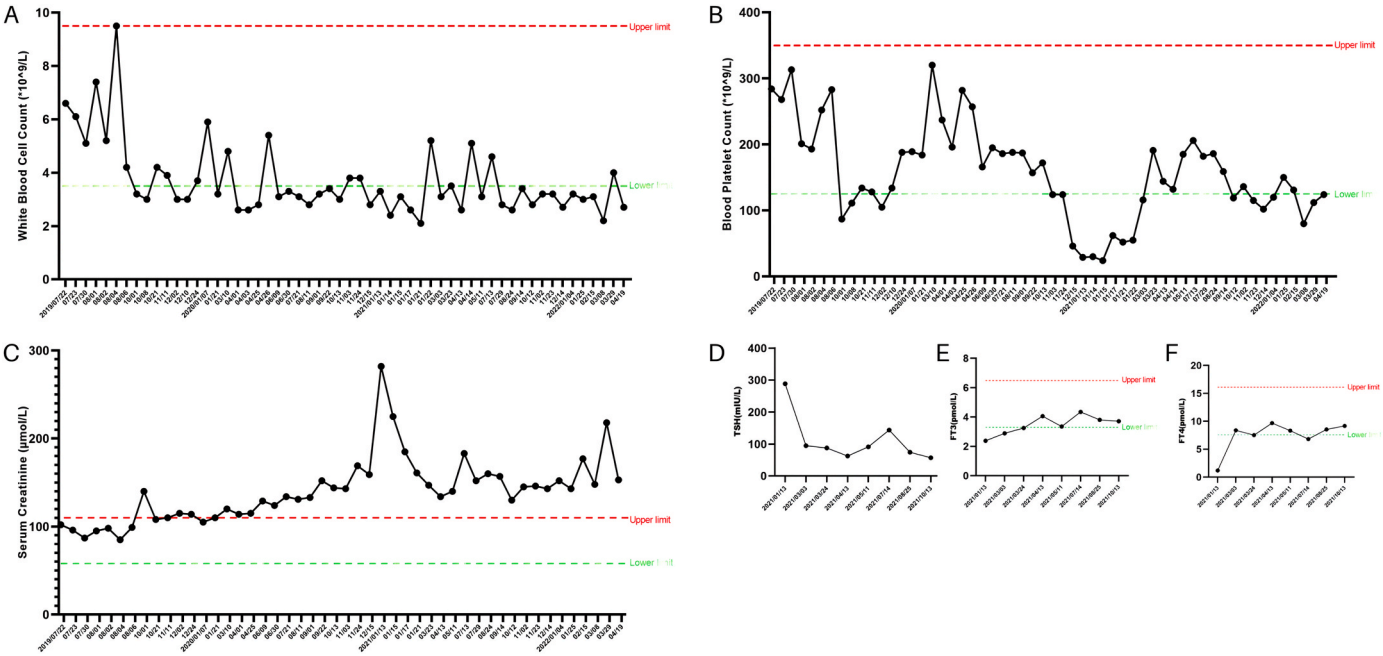

Fig. 5. Adverse reactions of immunotherapy combined with targeted drugs of the patient. A:The cure of white blood cell count over time. B:The cure of platelet count over time. C:The cure of serum creatinine over time. D-F.Thyroid function(FSH、FT3、FT4) curve of the patient.

venous carcinoma thrombus formation, the renal tumor and renal venous tumor thrombus were removed surgically. Postoperative treatment with targeted drugs (Axitinib and Pazopanib) alone has a poor efficacy, and Tislelizumab combined with Sunitinib has a definite efficacy, and the pulmonary metastases were controlled. The adverse reactions of the patient, such as hematopoietic function inhibition, renal hypofunction and thyroid dysfunction, were improved after conservative treatment, and the patient is now in better condition.

4. Conclusion

In addition, aggressive surgical intervention is necessary for patients with mccRCC if they can tolerate surgery. Besides, the combined treatment regimen of Tislelizumab combined with Sunitinib was effective in our patient with mccRCC, and the patient achieved good outcome. However, Tislelizumab, as a new immunosuppressant of PD-1, has been rarely applied in advanced RCC and has not been recommended by various guidelines. However, since only one patient with mccRCC complicated with renal venous thrombus was observed in this report, the clinical data was very limited, and further observation and accumulation of more experience should be required.

Ethics approval and consent to participate

We obtained patient consent to treatment and Informed consent was obtained from the patient for the publication of the case reports and accompanying images. We have de-identified all patient details.

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CRediT authorship contribution statement

Zhixiang Gao: Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lu Jin:** Writing – review & editing, Software, Data curation. **Haijun Lv:** Validation, Software, Methodology. **Nengliang Duan:** Validation, Software, Data curation. **Guoneng Zhang:** Validation, Data curation. **Yuanshuai Ran:** Validation, Software. **Boxin Xue:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Xiaolong Liu:** Writing – review & editing, Validation, Resources, Funding acquisition, Conceptualization.

Declaration of conflicting interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this case.

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