Case Report

Secrets revealed by the skin: initial success of tislelizumab and targeted therapy in advanced renal cell carcinoma—a case report and literature review

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Background: In renal cell carcinoma (RCC), skin metastases (SMs) occur in only 3.3% of cases and are even rarer as an initial manifestation of the disease. Although combination therapy with immune checkpoint inhibitors (ICIs) and targeted agents is the current standard of care, access to these treatments may be limited in certain regions due to cost constraints. Tislelizumab, a structurally enhanced humanized IgG4 monoclonal antibody developed indigenously in China, has demonstrated substantial efficacy and manageable safety profiles in clinical trials across a variety of solid tumors.

Case Description: We report the case of a 46-year-old male who initially presented with painless ulcerative skin nodules on his scalp and the tip of his nose. Surgical removal of the scalp nodules led to a pathological diagnosis of metastatic clear cell RCC (ccRCC). Subsequent positron emission tomography/computed tomography (PET/CT) imaging revealed metastases in the lungs, bones, and brain. Due to financial constraints, the patient opted for combination therapy with tislelizumab and sunitinib. After one treatment cycle, the skin nodules resolved, pulmonary metastases decreased in size, and the left renal mass stabilized. However, disease progression (PD) was observed before the start of the twelfth cycle.

Conclusions: Our case demonstrates that tislelizumab combined with sunitinib exhibits potential benefits for patients with advanced RCC, particularly in regions where access to standard combination therapy is limited. However, further clinical evidence is needed to support its widespread adoption in routine clinical practice.

Keywords: Tislelizumab; skin; renal cell carcinoma (RCC); case report

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Introduction

Renal cell carcinoma (RCC) is one of the leading causes of death among urologic malignancies globally, with approximately 175,000 fatalities annually (1). RCC is often diagnosed at an advanced stage, with about one-third of patients presenting with advanced or metastatic disease at initial diagnosis (2). The location of metastatic lesions may serve as a potential prognostic factor (3). The lungs are the most common metastatic site (70%), followed by lymph nodes (45%), bone (32%), and liver (18%) (4). In contrast, skin metastases (SMs) are rare, and even more seldom do they present as the initial symptom (5).

With the advent of immune checkpoint inhibitor (ICI) combinations with targeted therapies, the treatment landscape for advanced RCC has evolved substantially. Current first-line standard-of-care regimens, including pembrolizumab plus axitinib and nivolumab plus cabozantinib, have demonstrated superior efficacy in pivotal clinical trials (6). However, the implementation of these regimens faces practical challenges in clinical settings, prompting the exploration of alternative therapeutic approaches.

Tislelizumab, a novel humanized IgG4 anti-programmed cell death 1 (PD-1) monoclonal antibody, features distinct molecular engineering characteristics. Its Fc region has been engineered to minimize binding to macrophage FcγR, thereby avoiding antibody-dependent cell-mediated phagocytosis (ADCP) (7). This design not only reduces antibody clearance but may also enhance antitumor activity. Additionally, its Fab region demonstrates high target specificity and affinity, enabling more effective PD-1 binding. While tislelizumab has demonstrated promising efficacy and safety across a range of solid tumors (8), its therapeutic potential in advanced RCC warrants further investigation.

This report describes a case of metastatic clear cell RCC (ccRCC) treated with tislelizumab in combination with sunitinib. The case demonstrates not only the therapeutic potential of this combination regimen but also provides insights into treatment alternatives. Moreover, the dynamic changes in visible cutaneous metastases offered a unique clinical window for monitoring therapeutic efficacy. We present this article in accordance with the CARE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-427/rc).

Highlight box

Key findings

- In this case, the combined treatment with tislelizumab and targeted therapy provided preliminary benefits to a patient with advanced renal cell carcinoma (RCC), achieving disappearance of skin nodules, reduction of pulmonary metastases, and stabilization of the left renal tumor. Additionally, the patient's survival exceeded the average for similar cases.

What is known and what is new?

- Skin metastases in RCC are extremely rare and usually do not present as the initial symptom. Tislelizumab has shown good efficacy and safety in a variety of solid tumors.
- This case report underscores the potential of tislelizumab combined with targeted therapies to offer significant clinical benefits in patients with advanced RCC, particularly those presenting with rare skin metastases. It adds to the growing body of evidence supporting the use of immunotherapy in treating atypical manifestations of RCC.

What is the implication, and what should change now?

- The findings from this case highlight the need for further research into the specific benefits of immunotherapy in RCC patients with unusual metastatic presentations. It suggests that such combinations might be particularly effective in cases where traditional approaches fail.
- Given the preliminary success demonstrated by the combination of tislelizumab and targeted therapy in this case, it is recommended to expand clinical trials involving such treatment combinations in patients with RCC, particularly those presenting with atypical metastases such as skin metastases. These studies should explore various drug combinations and treatment protocols to identify the most effective therapeutic approaches.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the editorial office of this journal.

A 46-year-old male, employed at a coal mining plant with a history of occupational radiation exposure and no personal or family history of cancer, self-detected a scalp nodule one month prior to seeking medical attention. The nodule, which did not cause itching or pain, gradually ulcerated and began to bleed, prompting his visit to a local hospital. Clinical examination revealed a 1 cm × 1 cm purplish-red nodular mass on the scalp, soft and not fixed to the skull. A similar nodule was also noted on the tip of his nose (*Figure 1A*,*1B*). Local excision of the scalp mass was performed with a 5 mm margin. Postoperative pathology diagnosed the lesion as metastatic renal clear cell carcinoma, Fuhrman grade III. Immunohistochemistry results showed PAX-8 (+), CD10 (+), S-100 (–), HMB45 (–), Vimentin (+), CD68 (–), and SMA (–), with Ki-67 at 70%.

Following referral to the First Affiliated Hospital of Zhengzhou University, the patient underwent a thorough physical examination and laboratory evaluation, revealing a hemoglobin level of 82 g/L, a neutrophil count of 9,800 cells/μL, a platelet count of 673×10^9/L, and a corrected calcium level of 13 mg/dL. Lactate dehydrogenase levels were within normal limits. Abdominal ultrasound and CT scans identified a solid

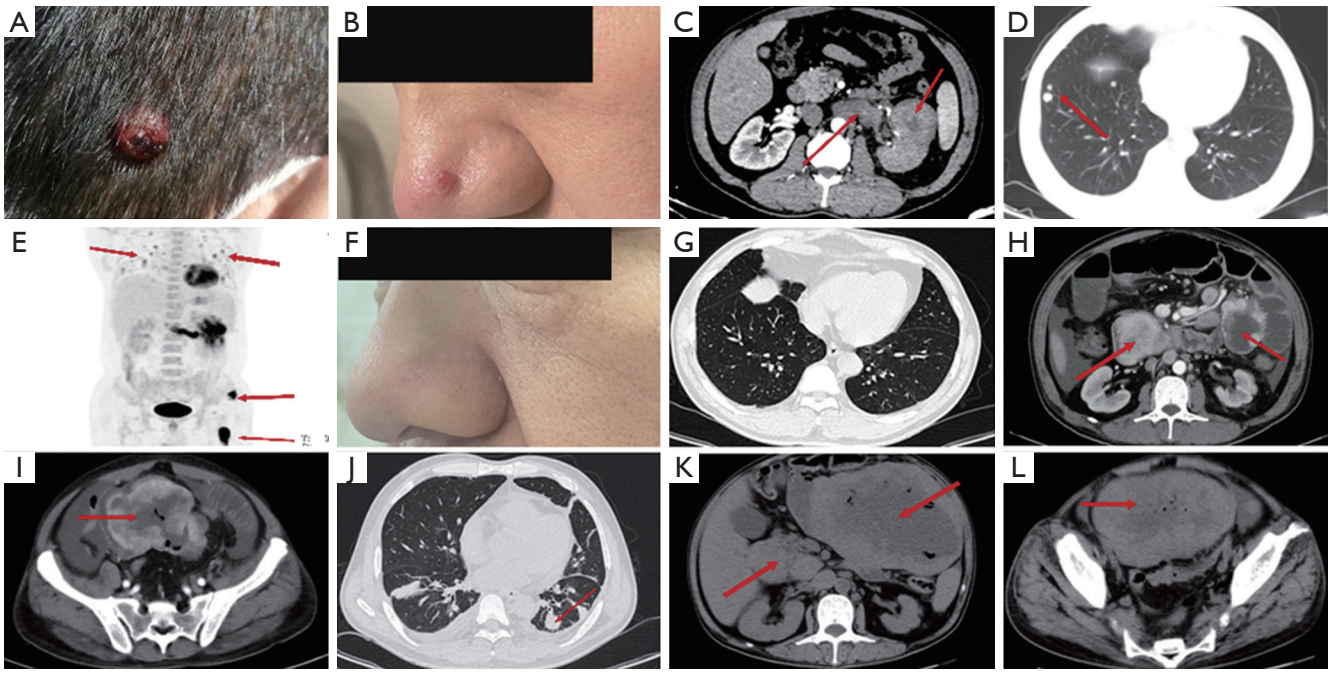

Figure 1 Clinical manifestations and treatment course of advanced renal cell carcinoma with cutaneous metastases. (A) Ulcerative metastatic nodule on the scalp at initial diagnosis. (B) Cutaneous metastasis on the nasal tip before treatment. (C) Initial contrast-enhanced abdominal CT showing primary tumor in the left kidney (right red arrow) with tumor thrombus in the left renal vein (left red arrow). (D) Initial chest CT demonstrating multiple pulmonary metastases (red arrow indicating a larger metastatic lesion). (E) Initial whole-body PET/CT revealing multiple organ metastases (upper red arrows showing pulmonary metastasis, lower red arrows showing bone metastasis). (F) Resolution of nasal tip metastasis after one cycle of combination therapy. (G) Follow-up chest CT after one cycle of combination therapy showing disappearance of larger pulmonary metastatic lesion. (H) Follow-up abdominal CT before the twelfth cycle revealing new metastases in the duodenum (left red arrow) and small intestine (right red arrow). (I) Follow-up pelvic CT before the twelfth cycle showing new metastatic lesion (red arrow). (J) Follow-up chest CT two months after change of treatment regimen demonstrating progression of pulmonary metastases (red arrow indicating new large pulmonary metastatic lesion). (K) Follow-up abdominal CT two months after change of treatment regimen showing enlarged duodenal metastasis (left red arrow) and enlarged small intestinal metastasis with necrosis (right red arrow). (L) Follow-up pelvic CT two months after change of treatment regimen revealing progressive enlargement and necrosis of metastatic lesion (red arrow). This image is published with the patient's consent. CT, computed tomography; PET/CT, positron emission tomography/computed tomography.

38 mm × 31 mm mass at the lower pole of the left kidney with a tumor thrombus in the left renal vein (*Figure 1C*). Positron emission tomography/computed tomography (PET/CT) scans confirmed widespread metastases involving the brain, lungs, lymph nodes, and bones (*Figure 1D,1E*).

Based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria, the patient was classified in the poor-risk group. Considering the high costs of imported immunotherapy in our country, along with issues regarding drug availability and health insurance policies, thorough discussions with the patient and his family led to the choice of tislelizumab combined with sunitinib as the preferred treatment regimen. Tislelizumab was administered at 200 mg every three weeks. Sunitinib was prescribed at 50 mg daily for four weeks, followed by a two-week off period. After one treatment cycle, the nasal tip nodule resolved, and significant reduction in pulmonary metastases and stabilization of the left kidney mass were observed (*Figure 1F,1G*). Laboratory tests demonstrated improvement in hemoglobin level to 98 g/L and normalization of calcium levels.

During the fourth cycle of treatment, the patient experienced dizziness and was found to have elevated blood pressure at 160/98 mmHg, considered a side effect

of sunitinib. Without reducing the dose of sunitinib, immediate administration of nifedipine extended-release at 10 mg/day effectively controlled the hypertension. No significant immune-related adverse events were observed during the combination therapy, indicating good tolerability of tislelizumab.

Prior to the twelfth treatment cycle, the patient exhibited symptoms of fatigue, nausea, abdominal bloating, and pain. Hemoglobin levels dropped to 69 g/L. Abdominal CT scans revealed multiple masses of varying sizes within the duodenum and parts of the small intestine, with the largest mass located at the pelvic inlet (*Figure 1H*,*1I*). These findings suggest disease progression (PD) and drug side effects. Given the patient's declining performance status, significant gastrointestinal symptoms, anemia, and potential decreased tolerability to the combination therapy, the therapeutic plan was adjusted to axitinib monotherapy. Axitinib is taken orally at a dose of 5 mg per day.

Two months after this adjustment, the patient's Eastern Cooperative Oncology Group (ECOG) performance status deteriorated to 4, characterized by worsening abdominal bloating, persistent abdominal pain, and difficulty eating. Chest CT revealed further enlargement and increase in lung nodules, while abdominal CT showed significant enlargement of lesions in the duodenum and small intestine, with possible areas of necrosis (*Figure 1J-1L*). To alleviate these symptoms, gastrointestinal decompression and parenteral nutrition were initiated. Pain was managed with oxycodone, dosages adjusted as necessary. Ondansetron was used to mitigate nausea and vomiting, and metoclopramide was employed to enhance gastrointestinal motility and alleviate symptoms. However, three days post-gastrointestinal decompression, a small volume of bright red gastric fluid was noted, and hemoglobin levels continued to decline, indicating possible gastrointestinal bleeding. Endoscopic examination was recommended to identify the source of bleeding and to provide hemostatic treatment. Despite this, the patient declined the procedure, and after correcting coagulation with frozen plasma, he was transferred to medical oncology for palliative care.

Unfortunately, the patient passed away 11.8 months after the initial discovery of metastatic kidney cancer.

Discussion

RCC exhibits complex and variable biological behavior, and its diverse metastatic patterns make prognostication challenging (9). To better understand the characteristics and clinical features of RCC with SM, we conducted a systematic review of the online databases PubMed and Wed of Science. The search terms used were ("Kidney Cancer" OR "Renal Cell Carcinoma") AND ("Skin" OR "Cutaneous") AND ("Metastasis" OR "Metastasis Disease") AND ("2000/01/01"[Date - Publication]: "2024/07/31"[Date - Publication]). We excluded studies related to SM occurring after renal cancer surgery, primary skin tumors, SM from other internal organ, kidney transplants, non-clear cell pathological types, and cases lacking detailed pathological information. We identified 10 cases of ccRCC with SM as the initial presentation. In *Table 1*, we summarized the age, gender, tumor characteristics, SM details, management approaches, and survival times of these patients.

Our literature review revealed that most lesions were located in the scalp and facial regions, presenting as purple-red, soft nodules. Although the skin's superficial location facilitates the detection of metastatic lesions, SM often appears as painless nodular lesions, which can easily be misdiagnosed as benign skin conditions (20). Therefore, clinicians should maintain a high index of suspicion for such atypical presentations. When suspicious skin nodules are discovered, prompt biopsy and systemic evaluation are essential, as SM often indicates PD. From a clinical perspective, however, these SM offer a unique advantage in treatment—their accessibility and visibility allow for direct monitoring of treatment response.

In this study, we employed a combination therapy of tislelizumab and sunitinib. Tislelizumab, as an innovative PD-1 inhibitor, has demonstrated promising clinical value in advanced RCC treatment. Studies have shown that combining tislelizumab with targeted therapies significantly improves clinical outcomes in patients with advanced ccRCC. Wang *et al.* reported in their retrospective study that tislelizumab combined with axitinib increased the objective response rate from 40.7% to 59.1% and disease control rate from 66.7% to 81.8% (21). Additionally, case reports have documented favorable outcomes when tislelizumab was combined with other targeted agents such as sunitinib and apatinib (22,23). For our patient, who presented with multiple metastases at initial diagnosis, we selected tislelizumab plus sunitinib as first-line treatment, considering economic factors.

According to the IMDC database, patients with intermediate to high-risk RCC treated with sunitinib alone have a median progression-free survival (PFS) of only 5.3 months (24). According to Surveillance, Epidemiology,

Table 1 Published cases of renal cell carcinoma with skin metastases as initial presentation

Author (Ref.)	Published years	Gender	Age (years)	Primary lesion			Skin metastases			Survival time from diagnosis of SM
				Subtype	Tumor stage	Original treatment	Site	Description	Treatment	
Fang *et al.* (10)	2022	M	62	Clear cell	T4	NA	Upper eyelid	Painless nodules	Excision	NA
Balawender *et al.* (11)	2022	M	68	Clear cell	T1b	RN	Scalp	Painless nodule with well-delineated	Excision	Follow 30 months
Krogerus *et al.* (12)	2020	M	65	Clear cell	T3a	RN	Scalp	Pulsating, soft and highly vascularized tumor	Excision	Follow 3 months
Mann *et al.* (13)	2020	M	51	Clear cell	T3a	IT	Scalp	Mass without painful or itchy	Excision	NA
Cui *et al.* (14)	2019	M	86	Clear cell	T1	TT	Nose	Firm nodule as big as a horsebean with tenderness	NA	NA
Mirza *et al.* (15)	2019	M	41	Clear cell	T2	NA	Scalp, chest and back	Violaceous and non-tender mass	NA	NA
Ndounga *et al.* (16)	2018	M	70	Clear cell	NA	NA	Right scalp	Painless enlarging mass	NA	NA
de Paula *et al.* (17)	2010	M	61	Clear cell	T1b	NA	Scalp, dorsum, and face	Purplish color and fibroelastic consistency regions	None	Survived 2 months
Bjurlin *et al.* (18)	2010	M	40	Clear cell	T3a	PN	Facial	NA	Excision	Follow 3 months
Porter *et al.* (19)	2006	M	36	Clear cell	T3b	RN + IT	Chin	Erythematous, tender, tense and was similar to the appearance of an abscess	Excision + RT	Follow 30 months

SM, skin metastasis; M, male; NA, not available; RN, radical nephrectomy; IT, immunotherapy; TT, targeted therapy; PN, partial nephrectomy; RT, radiotherapy.

and End Results (SEER) database analysis, patients with three or more metastatic sites had a shorter survival time, with median overall survival (OS) ranging from 6 to 7 months (25). In comparison, despite having multiple metastases including cutaneous involvement, our patient's PFS and OS significantly exceeded previously reported data through this combination approach. These results support the strategy of combining ICIs with anti-angiogenic targeted therapy.

This study provides a comprehensive literature review, detailing the clinical characteristics and prognosis of the patient, and exploring the potential mechanisms underlying cutaneous metastasis in RCC. However, several limitations exist: (I) the report is based on a single case of advanced RCC with SM treated with a novel therapeutic approach, resulting in limited clinical data. Further observation, experience accumulation, and additional clinical studies are necessary to more accurately assess the efficacy and safety of this combined therapy. (II) The cases are dispersed, making it challenging to gather comprehensive data for precise analysis, which may affect the reliability and generalizability of the results. (III) The report lacks standardized treatment guidelines, creating uncertainty in the application of this novel therapy in clinical practice.

Conclusions

Our case demonstrates that the combination of tislelizumab and sunitinib shows promising potential benefits for patients with advanced RCC, particularly in regions with

limited access to standard combination therapy. In this case, the patient presented with cutaneous and multi-organ metastases at initial diagnosis, and achieved survival benefits significantly exceeding previously reported data through this combination regimen. While these preliminary results are encouraging, more clinical evidence is needed to support its widespread implementation in routine clinical practice. Additionally, clinicians should maintain vigilance for atypical cutaneous presentations, conducting prompt biopsies and systematic evaluations to avoid delays in diagnosis and treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-427/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-427/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the editorial office of this journal.

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